Assessment of inflammatory activity in Takayasu's arteritis: performance of clinical scores and common biomarkers *versus* 18F-FDG PET/CT

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Abstract

Objective

There is no consensus on how to evaluate inflammatory activity in Takayasu's arteritis (TAK). Here we compare biochemical tests and three clinical scores, which evaluate inflammatory activity (IA) in TAK, versus quantitative ^{18}F-FDG PET/CT as the gold standard.

Methods

This prospective study included patients with TA diagnosed according to the American College of Rheumatology (ACR) criteria. IA was assessed through laboratory tests, clinical scores of the National Institute of Health (NIH), Dabague-Reyes (DR) and the Indian Takayasu Clinical Activity Score 2010 (ITAS2010), and the result of these assessments was compared against ^{18}F-FDG PET/CT Standardised Uptake Values (SUVmax).

Results

A total of 35 patients were studied, 86% were women. SUVmax had positive correlations with acute phase reactants and DR and NIH. Agreement of ^{18}F-FDG PET/CT was significant with erythrocyte sedimentation rate (ESR) and DR score. Receiver Operating Characteristic (ROC) curve analysis showed diagnostic value for inflammatory activity in ESR, DR and NIH scores, which had higher specificity when they were estimated with new cut-off points for the Mexican population.

Conclusion

ESR and other phase reactants have good sensitivity but low specificity to evaluate IA in TAK when compared against ^{18}F-FDG PET/CT. Among all the clinical scores, DR had the best diagnostic value, with strong potential as a clinical tool to define the inflammatory status in TAK patients when the study image is not available. However, in complex TAK cases with doubtful diagnosis after assessment by clinical scores or laboratory, ^{18}F-FDG PET/CT remains mandatory.

Key words

Takayasu's arteritis, positron emission tomography, ^{18}F-FDG PET/CT, vasculitis, inflammatory activity biomarkers, scores, clinical art

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Introduction

Takayasu's arteritis (TAK) is a rare disease which affects the aorta and its main branches with chronic and progressive inflammation leading to fibrosis in the compromised arteries (1, 2). The diagnosis of TAK is based on the American College of Rheumatology (ACR) criteria. The assessment of inflammatory activity (IA) is essential for the initiation and monitoring of medical treatment (3). Evaluation of IA by imaging is expensive, therefore simple clinical scoring methods have been proposed as an alternative method to identify increased IA (4).

The arterial damage pattern in TAK may include irregularities in the vessel wall, stenosis, post-stenotic dilatation, aneurysms, or occlusion (5). There is no current consensus on how to evaluate IA. Several common tools and non-specific markers are used to assess IA in TAK, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (6), neutrophil-to-lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) (7). Other less common biomarkers have been proposed, such as IL-18 (8) and IL-6 (9, 10), matrix metalloproteinases (11), and pentraxin-3 (PTX3) (12). Laboratory tests are limited since histopathologic studies have demonstrated a progression in the IA of TAK patients despite normal acute phase reactants (13, 14).

Moreover, there are several clinical constructs to evaluate IA. The National Institutes of Health (NIH) score includes systemic and/or vascular symptoms, ESR, and typical angiographic TAK characteristics; IA is defined by two or more points (13). The Dabague-Reyes (DR) score includes clinical and laboratory variables and considers IA with 5 points (15). The Indian Takayasu Clinical Activity Score (ITAS) evaluates systemic and organic signs and symptoms, in peripheral and central vessels (ITAS2010), with a limit of 2 points for IA (16). The ITAS algorithm score includes acute phase reactants, named ITAS-A and the cut-off is 5 points (17). Other indexes are The Birmingham Vasculitis Activity score (BVAS) (18), the Small Vessel Vasculitis score (19), the Vasculitis Damage Index (20), the Disease Extent Index for Takayasu's arteritis (DEI.Tak) (21), and the Paediatric Vasculitis Activity score (22).

Imaging techniques allow initial evaluation and monitoring of vascular damage progression in TAK (23). Magnetic resonance imaging (MRI) can identify structural and functional morphologic changes and thickening of the aortic wall (24). Integral TAK evaluation is feasible with the combination of PET scanning and computerised tomography (CT) (25, 26).

Since biopsy in arteries involves a high risk of bleeding and complications, using histopathology as a gold standard against image and all the scores and biomarkers is impossible. Most studies based on imaging and biomarkers considered the clinical assessment (*i.e.* the physician's global assessment PGA or NIH) as the gold standard, but none of them have been tested against histopathology. ^{18}F-FDG-PET/CT seems useful for the diagnosis and evaluation of IA in TAK (27, 28), and for vascular diseases diagnosis (29, 30). ^{18}F-FDG combined with hybrid PET/CT integrates functional and anatomical images, allowing anatomical location of the inflamed site and providing quantitative information to better assess IA than other methods (except histopathology).

The main aim of this study was to explore the performance of clinical scores and laboratory tests for the evaluation of IA *versus* quantitative ^{18}F-FDG PET/CT SUVmax. Secondarily, we explore the agreement and correlations between the clinical scores and absolute SUVmax units from ^{18}F-FDG PET/CT.

Materials and methods

Patients

This prospective study included 35 patients with TAK enrolled consecutively between 2010 and 2019 at a national reference Cardiology Centre in Mexico. TAK was classified according to the American College of Rheumatology (ACR) criteria (31).

^{18}F-FDG PET/CT scanning was performed only in subjects with stable renal function. We consider the maximum Standardised Uptake value (SUVmax) with a cut-off point of 2.2 to establish IA according to Tezuka *et*.

al. (28). Exclusion criteria: creatinine >1.5 mg/dl, haemodynamic instability, iodine allergy, pregnancy, and serum glucose >120 mg/dl. The included patients had glucose levels of 74±8 mg/dl and creatinine clearance of 0.7±0.2 mL/min/1.73m^2.

Laboratory tests included ESR, CRP, fibrinogen, platelet count, haemoglobin, and leukocyte quantification. We calculated the NLR and PLR indexes. Clinical criteria were collected to calculate the DR (15), NIH (32), ITAS2010 and ITAS-A scores. Localisation and extension of vascular involvement were classified into 6 types according to Hata *et al*. (Supplementary Fig. S1) (33).

^{18}F FDG PET/CT scanning

– Image acquisition.

^{18}FDG-PET/CT studies were performed using a Biograph 64 PET/CT scanner by Siemens. One hour prior to scanning, the patients received an intravenous injection of 10±5 mCi (370±185 MBq). The patients had more than 6 hours of fasting. Capillary glycaemic levels before ^{18}F-FDG were below 140 mg/dL. TC studies were obtained helicoidally with the aid of Care Dose 4D (mA), 120 kV, in 3 mm slides, with pitch values of 0.75 and 0.5 second rotation, FOV 500 mm from the craneal convexity down to the upper third of the thigh with an empty bladder and normal, peaceful breathing. Iodated non-ionic hydrosoluble contrast medium was administered. Patients were hydrated orally with 1L of water. CT was used to correct for attenuation and anatomic co-register in fusion images. Afterwards, a 3D craneo-caudal PET acquisition for 2 minutes per bed in 7 to 8 beds per patient over a 168 x 168 pixels matrix was performed. A late acquisition was performed for the regions of interest 90 minutes after injection. PET data were built iteratively (4 iterations by 14 sub-iterations) with and without attenuation correction based on the CT and reoriented towards axial, sagittal, and coronal images were also done.

– Interpretation and analysis of ^{18}F-FDG-PET/CT images

The interpretation was made by two radiologists trained in PET/CT and one expert in nuclear medicine. A comparison of SUV max was made to a reference organ (liver) as a negative control. Background uptake was also measured, and it was defined as uptake in tissue adjacent to the region of interest in the arterial wall. With this, we calculated an index of uptake/background.

A visual PET analysis was first performed for interpretation. SUVmax was measured in those patients who were visually positive by selecting a region of interest (ROI) for semi-quantification. The ROI was manually drawn with a diameter larger than 1 cm. In patients with multi-systemic disease, several ROIs were selected, and the largest uptake for each region was considered (*e.g*. thoracic aorta, abdominal aorta, renal artery).

A region of interest (ROI) was measured in the lesion and SUVmax was defined as the higher value in the ROI. Focal uptake was also evaluated in the arterial wall. After visual inspection, it was decided that a positive study (case) of active TAK was found if SUVmax was equal or greater than the one from the liver. The goal of final acquisition in the late stage was used to avoid overfitting by attenuation in contrast studies. SUVmax was defined for every patient. All cases were evaluated by using CareStream PACS/RIS v. 11.0.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The Institutional Review Board approved the study (protocol UNAM 0682011).

This article does not contain any studies with animals performed by any of the authors.

Statistical analysis

Bivariate correlation analyses between ^{18}F-FDG PET/CT and laboratory tests were performed with the Pearson or Spearman methods. The agreement about IA classification between ^{18}F-FDG PET/CT and ITAS2010/ITAS-A, DR, NIH scores and phase reactants was performed using the Kappa index. Median values of the clinical activity scores and laboratory tests were compared between active or inactive patients (*i.e*. ^{18}F-FDG PET/CT activity) with Mann-Whitney tests.

The diagnostic value of the laboratory tests and clinical scores was tested against ^{18}F-FDG PET/CT as the gold standard through receiver operating characteristic (ROC) curves analysis. Optimal cut-off values were estimated with the minimum orthogonal distance between the ROC curve points and the optimum point (0, 100). The power of the ROC curve analysis of each parameter was verified with a *post-hoc* computation of achieved power. A p-value <0.05 was considered as statistically significant. Computer programs SPSS version 19 (IBM Statistics, Armonk N.Y.), Prisma v. 8, and G Power v. 3.1 were used.

Results

Thirty participants (86%) out of 35 were women (male to female ratio was 7:1). The average of age was 30±15 years old. Table I shows the clinical characteristics of all patients and the doses of medical treatment they received at the time of the study.

According to the Numano classification (Suppl. Fig. S1), the classification of the arterial lesion was: Type I=2 (6%), IIa=3 (9%), IIb=3 (9%), IV=1 (3%) and type V=26 (74%). Coronary damage was observed in 6 patients (17%) and pulmonary damage in four patients (11%). Seventeen patients (49%) had a recent diagnose of TAK and 18 (51%) had a long evolution time of the disease when the ^{18}F-FDG PET/CT was carried out and at the time of the score evaluation. The median time between both testes was of 2 months with a range of (1–6) and 72 (12–76), respectively.

The average dose of the drugs the patients were receiving at the moment of the study in recently diagnosed and long evolution patients was of: prednisone 0 (0–10) mg and 5 (0-–0), methotrexate 0 (0–12.5) and 8.7 (0–15) mgs, azathioprine 0 and 0 (0-–00) mg, my-

Table I. Clinical characteristics and scores in each patient and doses of treatment at the moment of the study.

No.	Sex	Age	Arterial lesion	Evolution mo.	PD mg	MTX mg	AZA mg	MF mg	NIH	DR	ITAS	ITAS.A	CT-PET SUV Unit	Comorbidity and mortality
1	W	35	V	1	0	0	0	0	4	2.5	0	0	0.0	**Hypertension, aortic abdominal dilatation, occlusion left renal artery. Post-operate of Bentall and Bono and Mitral valve
2	W	32	V+C	256	5	0	0	0	3	6	0	0	2.9	Myocardial infarct and pituitary adenoma
3	W	12	V	2	0	0	0	0	3	5			0.0	Dilated cardiomyopathy, mitral and tricuspid regurgitation
4	W	24	V	120	5	0	50	0	4	6.5	2	2	3.1	Kidney left exclusion, aortic regurgitation
5	W	63	V	276	2.5	0	50	0	1	1	3	3	0.0	Hypertension
6	W	19	V	18	7.5	10	50	0	4	5.5	1		4.6	Hypertension and gallstones kidney
7	W	26	V	120	5	12.5	50	0	4	5.5	7	9	7.9	Hypertension
8	W	25	V	1	7.5	12.5	0	0	3	1	12	12	1.3	Hypertension
9	W	32	V	2	7.5	7.5	0	0	3	1			2.8	Without morbidities
10	W	36	V	6	0	0	0	0	3	6.5	0		5.2	Myocardial infarct, dilated cardiomyopathy, death
11	W	48	III+C+P	12	10	12.5	0	0	2	3.5			0.0	Hypertension
12	W	5	V	2	0	0	0	0	4	8	11	13	1.5	Aortic regurgitation
13	W	32	V	72	10	10	0	0	2	1	0	0	2.3	Hypertension
14	W	41	IIa	2	5	7.5	0	0	2	5	8		2.5	Epilepsy
15*	M	28	V	48	40	10	0	0	3	4	19	20	1.9	Cerebral ischaemic, haemolytic anaemia, death
16	W	59	V	2	0	0	0	0	4	5	11	14	2.2	Myocardial infarct, death
17[¥]	M	5	V	4	10	0	0	0	4	5.5	7	8	0.0	Rheumatoid arthritis
18	W	35	V+C	1	0	0	0	0	4	6	19	19	5.0	**Aneurysm ascending aorta, bicuspid aortic valve, cardiogenic shock, death
19	W	21	V	180	2.5	10	50	0	2	4.5	0	0	0.0	Hypertension
20	W	12	V	1	5	0	0	0	1	1.5	10	11	1.8	Without morbidities
21	W	28	V	156	2.5	7.5	50	0	3	1.5			0.0	Hypertension
22	W	39	V	12	0	0	0	0	1	4.5	20	24	3.3	Complete A-V block
23	M	56	IIa	2	0	0	0	0	4	5.5	3	4	4.1	Hypertension
24	W	30	V	1	0	0	0	0	3	5	2	3	3.1	Hypertension
25[£]	W	18	V+ P	108	10	0	0	1000	4	7.5	9	10	2.5	Pulmonary arterial hypertension, death
26	W	19	IIa	18	0	0	0	0	4	6.5	0	0	2.4	Hypertension, hypertensive retinopathy
27	W	34	V+C	2	1	0	0	0	2	4.5	13	16	0.0	Myocardial infarct, familial hypercholesterolemia, death
28	W	27	V	60	15	15	100	0	4	4.5	0	0	2.9	Cerebral ischaemic, hypertension, death
29	W	39	I	204	0	7.5	0	0	0	1	8	9	2.0	Asymptomatic
30	M	10	I	4	0	0	0	0	1	2.5	0	0	0.0	Aortic stenosis
31	W	24	IIb	1	0	0	0	0	4	6.5	4	4	3.8	Without morbidities
32	W	27	V+P	24	20	12.5	0	0	1	3.5	7	8	0.0	Pulmonary arterial hypertension
33	W	64	V	2	0	0	0	0	4	5	7	8	0.0	Hypertension
34	W	20	IIb	48	15	0	0	0	2	3.0	0	0	0.0	Descendant aorta stent
35	M	26	V1	10	0	7.5	0	0	2	4.5			0.0	Without morbidities

*the patient received 2 bolus of cyclophosphamide before the PET-CT study; [¥]this patient received methotrexate treatment three years prior to the study; [£]the only patient who received 1 gram of mycophenolate; **patients described in the text. All patients under methotrexate treatment received folic acid.

cophenolate 0 and 0 (0–1) grams, having a statistically significant difference between the groups ($p \leq 0.01$). None of the patients was receiving biological, and only one had received CFM and another mycophenolate. All patients that were receiving methotrexate were also taking folic acid.

A total of 14 (40%) of the patients had no treatment with steroids or immunosuppressants, of whom 11 had a recent diagnosis.

The average in ESR in mmhr between both groups was of 22 (11–71) and 23.5 (7–40) RCP mgdL and of 9.2 (0.6–87.2) and 7.3 (1.2–51) without there being statistical differences.

The duration of the disease had a median of 12 months (range between 1 and 276 months). The most frequent symptoms were headache 19 (54%), arterial hypertension 15 (43%), claudication of extremities 14 (40%), dyspnea 11 (31%), dizziness 8 (23%), palpitations 7 (20%) and syncope 5 (14%).

The distribution of the arterial lesions were thoracic aorta (63%), abdominal aorta (56%), carotid (51%), subclavian (42%), ascending aorta (49%), renal arteries (39%), brachiocephalic trunk (34%), coeliac trunk (13%), and iliac artery (10%). Seventeen patients (49%) were positive for IA (*i.e.* they had ^{18}F-FDG PET/CT SUV max >2.1).

Seven patients died (20%), all of whom had complex vascular pathology. Five of them (71%) had IA by ^{18}F-FDG PET/CT. The other two deceased patients had no IA prior to surgery,

The first patient was a 35-year-old female who was diagnosed with an abdominal aorta aneurism, dilation of the brachiocephalic trunk and decreased left renal caliber in 2010. She underwent surgery with Bentall and Bono and two years later, she was sent to the Immunology Clinic. The TAK Type V diagnosis was made and she fulfilled the classification criterion. She was sent to a study of PET/CT where there was no inflammatory activity, therefore there was controversy over the diagnosis. The treating doctor decided to monitor the patient in his office and in 2014 the patient returned with complete occlusion of both renal arteries and nephritic syndrome, endocarditis, with vegetations in the mitral valve, and she died a day after hospitalisation. The other patient died due to heart failure after surgery. The patient was a 35-year-old woman with classification of Type V + C arterial injury demonstrated by magnetic resonance imaging. This patient was sent from the start for evaluation by 18F-FDG PET/CT, where 6 SUV units were found, and all scores were positive. She received initial treatment with steroids and cyclophosphamide. During her study and comprehensive management, she presented sudden chest pain at home and in the hospital there was an evolving AMI and cardiorespiratory arrest. She was attended and taken to catheterisation, total ostial occlusion of the main coronary was found and resolved with the installation of a STENT. She remained in a coma for a month, after which she had a full neurological recovery. She had a LVEF of 20%, remained under medical management and survived 6 years. She died in 2018, after she had received supervised multidisciplinary management.

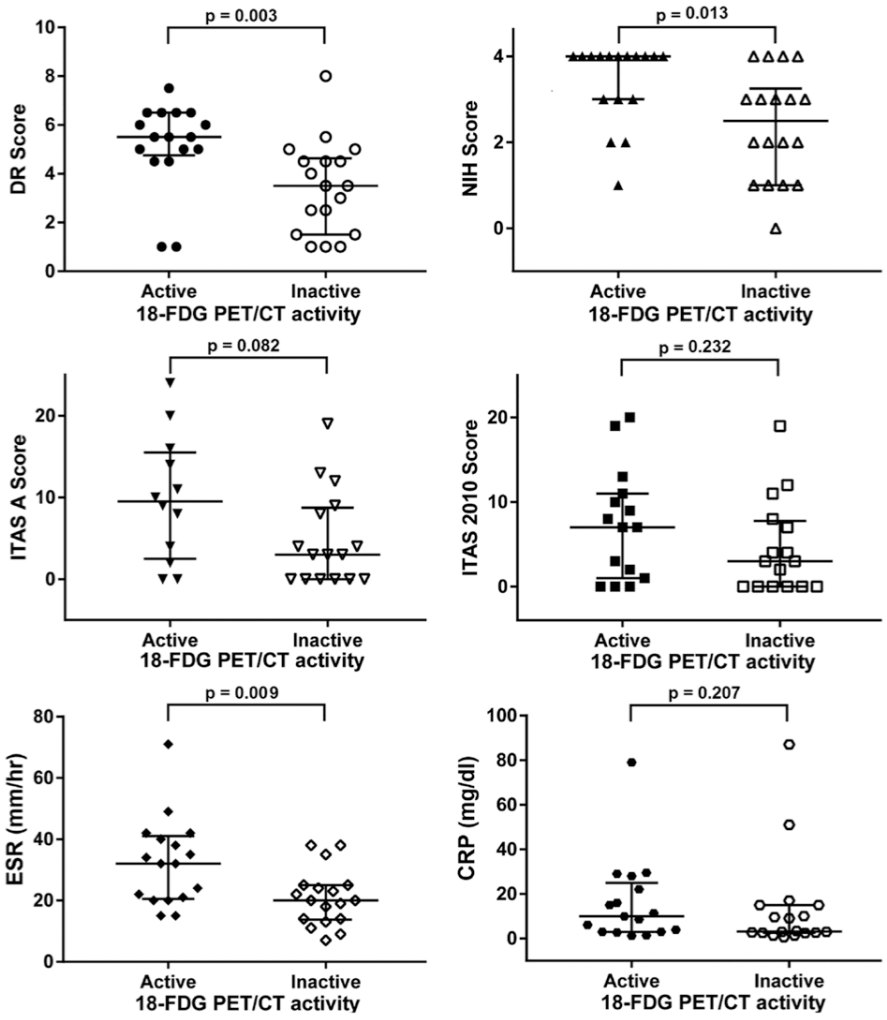

Fig. 1. Comparisons of median and quartile range of all clinical scores and acute phase reactants from TA patients with inflammatory activity (N = 17) or without inflammatory activity (N = 18) according to PET ^{18}F-FDG.

Positive correlations of ^{18}F-FDG PET/CT SUV units were found with ESR (r=0.44, *p*=0.008), fibrinogen (r=0.520, *p*=0.001), and platelets (r=0.395, *p*=0.01), while inverse correlation was found with haemoglobin (r=-0.45, *p*=0.006). There was no correlation between ^{18}F-FDG PET/CT SUV units and the NLR index (r=0.23, *p*=0.21), PLR index (r=0.32, *p*=0.07), and CRP (r=0.286, *p*=0.096). There was moderate correlation between ^{118}F-FDG PET/CT and DR (rho=0.51, *p*=0.002) and ITAS-A (rho 0.432, *p*=0.022), while there was no correlation with ITAS 2010 (rho=0.26, *p*=0.26).

When correlations were made in patients with and without treatment, between ^{18}F-FDG PET/CT SUV and ESR the result was (0.34 *p*=0.12 and r=0.59 *p*=0.02), between 18F-FDG PET/CT SUV and fibrinogen (r=0.44 *p*=0.04 and r=0.60 *p*=0.02), and between 18F-FDG PET/CT SUV and platelets(r= 0.24 *p*=0.28), and r=0.57 *p*=0.03). There was an inverse correlation with haemoglobin (0.41 *p*=0.3 and r=0.49 *p*=0.02 and r) and there was no correlation with CRP (r=0.02 *p*=0.90 and r=0.15 *p*=0.60). There was no relationship with NLR and PLR. The results of the correlations between ^{18}F-FDG PET/CT and scores in patients with or without treatment were: with the DR score (r=0.36 *p*=0.10 and r=0.39 *p*=0.16), with NIH (r=0.48 *p*=0.02 and r=0.37 *p*=0.18, with ITASA (r= 0.32 *p*=0.23 and r=0.41 *p* 0.18, ITAS 2010 (r=0.22 *p*=0.37 and r=0.12 *p*=0.69).

There was agreement between ^{18}F-FDG PET/CT and DR (kappa = 0.542, *p*=0.001), but not with NIH (kappa= 0.215, *p*=0.086), ITAS 2010 (kappa=0.133, *p*=0.430) and ITAS-A (kappa=0.33 *p*=0.08). There was agreement between ^{18}F-FDG PET/CT and fibrinogen (kappa=0.486, *p*=0.004), as well as with haemoglobin (kappa=0.364 *p*=0.019), while there was no agreement with platelets (kappa=0.243 *p*=0.061), ESR (kappa=0.207 *p*=0.19), and CRP (kappa=0.205, *p*=0.214).

When these agreements were evaluated between ^{18}F-FDG PET/CT and

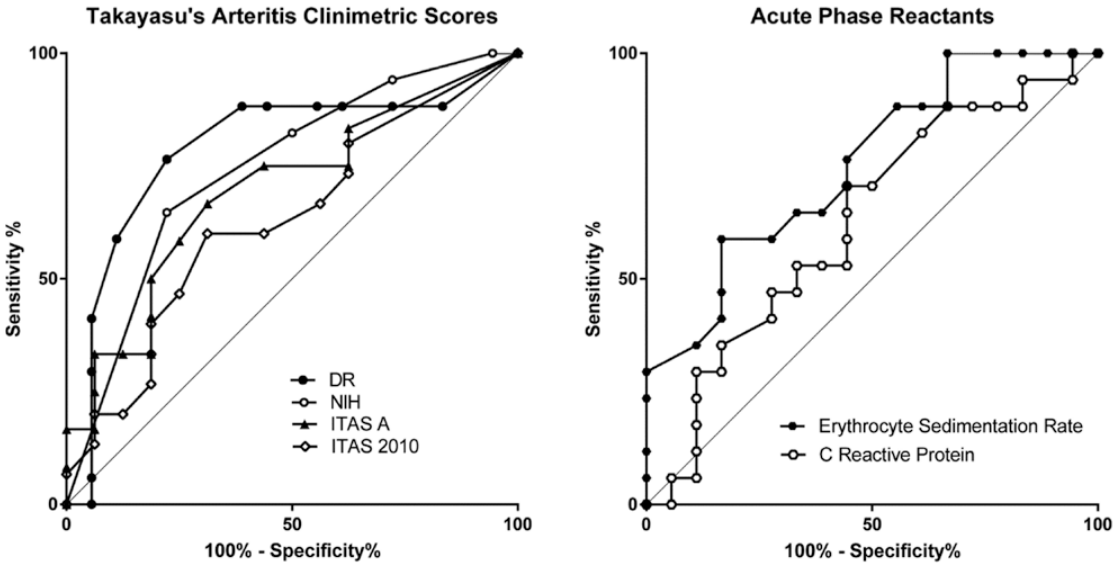

Fig. 2. ROC curve analysis of all clinical scores and acute phase reactants with activity defined by PET/CT 18F-FDG as the gold standard.

	AUC (CI 95%)	*p*	Original cut-off points	Sensitivity % (CI 95%)	Specificity % (CI 95%)	New cut-off points	Sensitivity % (CI 95%)	Specificity % (CI 95%)
DR	0.817 (0.636 - 0.997)	0.005	5	76 (56 – 97)	78 (59 – 97)	4.75	76 (56 – 97)	78 (59 – 97)
NIH	0.756 (0.568 - 0.943)	0.025	2	94 (83 – 100)	28 (7 – 48)	3.5	65 (42 – 87)	78 (59 – 97)
ITAS A	0.697 (0.493 - 0.901)	0.083	5	60 (35 – 85)	67 (43 – 91)	6	60 (35 – 85)	67 (43 – 91)
ITAS 2010	0.675 (0.468 - 0.882)	0.124	2	83 (62 – 100)	40 (15 – 65)	5.5	43 (17 – 69)	46 (19 – 73)
ESR (mm/hr)	0.819 (0.662 - 0.977)	0.005	20	88 (73 – 100)	44 (21 – 67)	28	59 (35 – 82)	83 (66 – 100)
CRP (mg/dl)	0.631 (0.413 - 0.848)	0.252	3	82 (65 – 100)	39 (16 – 61)	3.6	71 (49 – 92)	56 (33 – 79)

DR scores in patients with and without treatment there was a kappa= 0.50 p=0.02 and a kappa=0.55 p=0.03 respectively. There was agreement between with NIH (kappa=0.3 p=0.12 and kappa=0.21 p=0.19), ITAS 2010 (kappa= 0.068 p=0.77 and kappa 0.19 p=0.41), ITAS A (kappa 0.28 p=0.26 and kappa 0.33 p=0.22), respectively.

TAK patients with IA disease had a higher DR score, NIH and ESR than those without activity (Fig. 1).

Figure 2 shows that the ROC curves of two clinical scores (DR and NIH) and ESR had a significant area under the curve difference (AUC). Based on the original cut-off points, only the DR score had high sensitivity and specificity, while all other scores and acute phase reactants had high sensitivity but low specificity. New cut-off points for all clinical scores and laboratory parameters were estimated for our Mexican population (Fig. 2, bottom panel). Sensitivity remained similar in the DR score and decreased in both the NIH and ESR. Meanwhile, the specificity increased in all variables with significant AUC (DR, NIH and ESR). Detailed diagnostic values test of all clinical scores in acute phase reactants are in the (Table II). The *post-hoc* achieved power of the ROC curve analysis in all parameters ranged between 0.68 and 0.89 (Table III).

Figure 3 shows images of ^{18}-FDG PET/CT from two TAK female patients with IA disease in the descending aorta (Panels A, B, and C), the ascending aorta (Panels F and G) and the pulmonary torso (Panels F, G, and H).

Discussion

Currently, among all clinical scores, imaging methods or laboratory tests, none has adequate sensitivity or specificity to replace histopathology in the assessment of IA in TAK patients. The main problem of not having a universal consensus is that the therapeutic decisions in patients with TAK depend on an accurate assessment of IA.

In clinical practice, IA is defined by clinical signs and symptoms, laboratory assessment and vascular imaging, or a combination of them. However, the scores have disadvantages that preclude their wide acceptance among the clinical community. First, PGA, which has been used as the gold standard for IA in TAK, is feasible in flare and remission moments, but it has not been validated *versus* histopathology (34). Second, the BVAS score is used primarily for the assessment of IA in small-sized and medium-sized vasculitis (18). However, small-vessel arterial disease is rare in TAK, and therefore BVAS use can lead to unnecessary organ evaluation and incomplete cardiovascular damage assessment in TAK patients (35, 36). Third, the DEI.Tak was developed to re-

Table II. Diagnostic values of clinical scores and laboratory tests for TAK activity estimated from 35 Mexican patients compared against PET classification as gold standard. Results are expressed as percentage with a 95% confidence interval.

	Original cut-off points				New cut-off points			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
DR	76 (56 – 97)	78 (59 – 97)	76 (56 – 97)	78 (59 – 97)	76 (56 – 97)	78 (59 – 97)	76 (56 – 97)	78 (59 – 97)
NIH	94 (83 – 100)	28 (7 – 48)	55 (37 – 73)	83 (54 – 100)	65 (42 – 87)	78 (59 – 97)	73 (51 – 96)	70 (50 – 90)
ITAS A	60 (35 – 85)	67 (43 – 91)	64 (39 – 89)	63 (39 – 86)	60 (35 – 85)	67 (43 – 91)	64 (39 – 89)	63 (39 – 86)
ITAS 2010	83 (62 – 100)	40 (15 – 65)	53 (30 – 75)	75 (45 – 100)	43 (17 – 69)	46 (19 – 73)	46 (19 – 73)	43 (17 – 69)
ESR (mm/hr)	88 (73 – 100)	44 (21 – 67)	60 (41 – 79)	80 (55 – 100)	59 (35 – 82)	83 (66 – 100)	77 (54 – 100)	68 (49 – 88)
CRP (mg/dl)	82 (65 – 100)	39 (16 – 61)	56 (37 – 75)	70 (42 – 98)	71 (49 – 92)	56 (33 – 79)	60 (39 – 81)	67 (43 – 91)

DR: Dabague-Reyes Score; NIH: National Institutes of Health Score; TAK: Takayasu's arteritis; ITAS A: Indian Takayasu's Arteritis Activity Score-A; ITAS 2010: Indian Takayasu's Arteritis Activity Score 2010; ESR: erythrocyte sedimentation rate; CRP: C reactive protein.

Table III. Power analysis of area under the curve (AUC) for each clinical score and laboratory test (n = 35).

	ROC curve analysis			Achieved power (post-hoc)	Required sample size (a priori)	
Variable	AUC	SD	*p*		*p*=0.05 power=0.84	*p*=0.01 power=0.99
DR	0.82	0.54	0.005	0.78	22	65
NIH	0.76	0.57	0.025	0.75	35	107
ITAS A	0.70	0.62	0.083	0.69	69	211
ITAS 2010	0.68	0.63	0.124	0.70	87	268
ESR (mm/hr)	0.82	0.47	0.005	0.89	17	50
CRP (mg/dl)	0.63	0.66	0.252	0.69	181	561

ROC: receiver-operator characteristic; SD: standard deviation; DR: Dabague-Reyes Score; NIH: National Institutes of Health Score; ITAS A: Indian Takayasu's Arteritis Activity Score A; ITAS 2010: Indian Takayasu's Arteritis Activity Score 2010; ESR: erythrocyte sedimentation rate; CRP: C reactive protein.

cord the extent of disease and assigned greater weight to items related to larger arterial disease. Unlike the NIH criteria, the DEI.Tak does not include laboratory tests or imaging and has been compared only against the PGA (37). Furthermore, although the ITAS2010 and ITAS-A scores had good inter-rate agreement with the BVAS and PGA, the ITAS-A scores did not decrease accordingly in patients considered to have inactive disease by PGA after therapy (34). The DR score includes clinical symptoms along with acute phase reactants easily available from the laboratory results, has good performance in assessing IA, but it has not been validated against other constructs or with imaging methods (15). Finally, the most used measure is the NIH criteria, but it has not been validated against histopathology (13).

Considering that validation of any method against histopathology is unfeasible and unethical, imaging-based methods could be considered the closest to a gold standard. However, a judicious use of various imaging methods can complement the PGA and serologic tests. Currently, many imaging techniques are used including high-resolution ultrasound (US), magnetic resonance angiography (MRA), computed tomography (CT), angiography, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET), ^{18}F-FDG-PET/CT (23), and hybrid positron-emission tomography/magnetic resonance imaging (PET/MRI) (3). These imaging methods are occasionally combined to assess IA. High-resolution Doppler US combined with flow-velocity determination can assess both vessel anatomy and luminal status and may demonstrate early vessel wall alterations before detectable lumen changes on angiography (38). Continuous Doppler US has limited costs, requires a short time, does not involve radiation, but is highly operator-dependent (39). Also, US assessment of the proximal subclavian and distal internal carotid arteries is limited (40). Carotid contrast-enhanced ultrasound (CEUS) has a high predictive value for TAK disease in arterial lesions of Numano type I (41).

Assessment of IA with MRI is feasible since both cardiac morphology and function can be measured with better accuracy and reproducibility, providing information of special value in coexistent aortic regurgitation. MRI also can evaluate IA in TAK through measurement of the aortic wall thickness (42), which allows follow-up of the response to treatment (43). Although MRI is reliable in identifying vascular lesions, the measurement of the arterial wall thickness is unreliable in vessels of smaller caliber (23). MRI is time-consuming, is not readily available, has a high cost, and cannot be used to scan claustrophobic patients or those wearing metallic clips, pacemakers, and other devices.

Whole-body contrast-enhanced magnetic resonance angiography (CE-MRA) has been proposed to assess TAK activity in follow-up examinations, with moderate correlations between CE-MRA with NIH, ITAS 2010, ITAS/ ESR, ITAS/CRP, PTX3, ESR, and RCP (44). CE-MRA of the vessel walls seems useful to identify vessel wall inflammation and luminal changes. IA of TAK has been measured by hybrid positron-emission tomography/ magnetic resonance imaging (PET/ MRI) in large-vessel vasculitis, using as a gold standard of IA the presence of clinical signs, CRP >10 mg/L, and a NIH score >2 (3). The utility of ^{18}FFDG-PET/CT scanning to assess IA

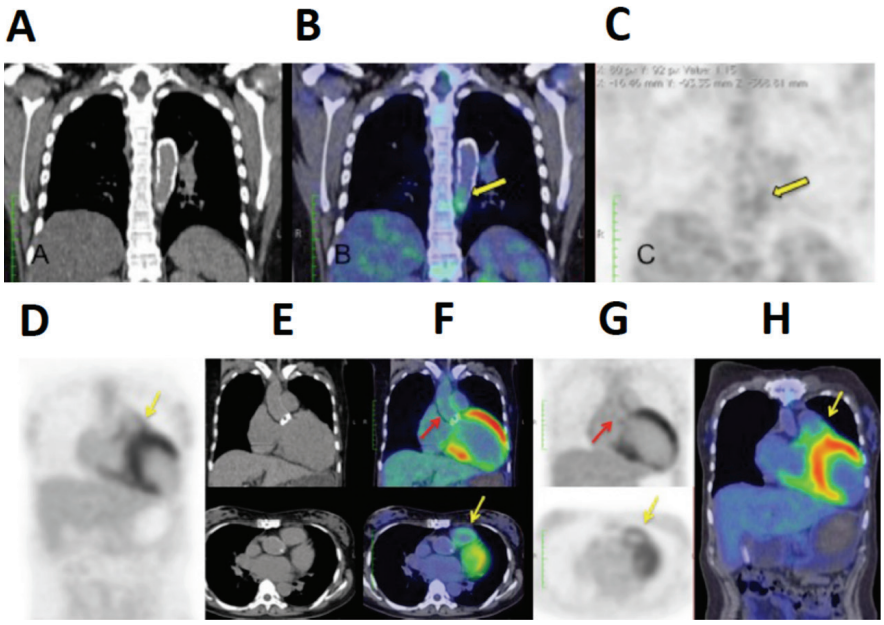

Fig. 3. Images from a 32-year-old female patient with long evolution TAK presenting calcification of the wall: Coronal projection of simple phase CT (**A**), fusion (**B**) and PET ^{18}F-FDG (**C**), all consistent with active disease in the descending thoracic aorta (yellow arrow). Images from a 36-year-old woman with Numano V TA with local ^{18}FDG capture in the aortic root (**D**), ascending aorta (red arrows **F** and **G** panels) as well as the pulmonary torso (yellow arrows) in panels **D**, lower **G** and **H** compatible with active disease.

in TAK has been previously tested (26, 45, 46). The combined studies of both PET/CT and PET/MRI is able to quantify inflammation in vasculitis.

The imaging methods to measure IA seemed to be complementary tools to each other and they should be used judiciously during the clinical art of evaluating each TAK patient, given that each imaging method has advantages and disadvantages including radiation exposure, contrast medium, and a high cost. Moreover, definitive evaluation of the diagnostic value of all proposed methods is still pending, and none of them can be used as the gold standard.

Once we consider all these tools used to assess IA, it is evident the great divergence among them, and that each method has been compared against different gold standards. Most studies have considered some clinical scores as the gold standard, such as the NIH score, which combines clinical items, some acute phase reactants, and anatomical evidence of vessel lesion by an imaging method (13). The assessment of IA with the NIH score would probably improve if the imaging methods included quantitative evaluation of the vessel wall thickness. In any case, a definite evaluation of the diagnostic value of NIH score to identify IA against the true gold standard (*i.e.* histopathology), is still lacking.

Regarding the acute phase reactants, CRP and ESR are commonly used to monitor progression of IA in TAK (6). Neither of them is specific and therefore they have no optimal accuracy to evaluate IA in TAK (6, 47). ESR has a sensitivity of 72% and specificity of 56% for active TAK, which is similar to our finding. However, ESR cannot be considered a reliable surrogate marker of IA in TAK (13). In another study, ESR and CRP had no correlation with IA confirmed by autopsy (14). Ishihara measured circulating levels of high-sensitivity CRP (hsCRP), PTX3, MMP-2, MMP-3, and MMP-9, finding that CRP had good sensitivity and specificity (71.4% and 100%, respectively) (48). However, they considered the patients' clinical symptoms as the gold standard and were limited by small sample size and lack of confirmation with histological studies (48). Regarding PTX3, one study reported good sensitivity (between 82 and 89%) and specificity (87–94%). However, they are not yet ready for clinical use (49).

Analysis of the components of the complete blood count (CBC) is inexpensive, includes parameters of inflammation, and can be used to assess IA (50). Recent findings showed that in patients with TAK, the C-reactive protein (CRP) to albumin ratio, the red cell distribution width (RDW), the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), the monocyte/lymphocyte ratio (MLR), and the mean platelet volume could be potential parameters for IA. They are proposed to determine remission of IA, and CRP/albumin ratio, albumin, and mean platelet volume may be useful markers for evaluating IA of TAK.

In the present study, we evaluated several clinical scores and phase reactant agents against one imaging method (^{18}F-FDG-PET/CT) as the gold standard. ESR and other phase reactants showed good sensitivity but low specificity to evaluate IA in TAK. It is worth mentioning that in the correlation between 18F-FDG-PET/CT and biomarkers or clinical scores in patients who did not have treatment and in those who did have it at the time of the study, the correlation was better in patients who did not have treatment, although there was no significant statistical difference. However, a better correlation was found with the NIH score in the patients receiving treatment, for which we have no explanation. We attribute it to the fact that this score showed greater sensitivity and less specificity.

Among all clinical scores, DR had the best diagnostic value, with strong potential as a clinical tool to define IA in TAK patients for follow up, surgical, and intervention decisions when the study image is not available. However, in complex TAK cases with doubtful diagnosis after testing with clinical scores or laboratory, ^{18}F-FDG-PET/CT remains mandatory. Moreover, further studies are required to demonstrate the reproducibility of our findings in other populations.

The limitations of this study include only the evaluation of biochemical parameters commonly applied throughout the world for their low cost and accessibility. It would be useful to assess other laboratory parameters such as

pentraxine 3, interleukins, and matrix metalloproteinase. The evaluation of NLR and PLR indexes requires a specific study in this context, considering the therapeutic procedures and the morbidity conditions. We could not do correlation studies of the wall thickness by MRI in our patients because a long time elapsed between the MRI and the ^{18}F-FDG-PET/CT study. We did not have all of the data on the physician's assessment of disease activity (PGA) to make the evaluation. A specific sample size is necessary in the study of each biomarker and clinical score, and when compared with this imaging method we show the power that each one achieved.

Conclusions

Compared to ^{18}F-FDG-PET/CT as the gold standard, some acute phase reactants (*e.g.* ESR) and some clinical scores (*e.g.* DR) showed good diagnostic value to assess IA in TAK patients. The inflammatory processes accompanying TAK are highly heterogeneous, and there is confusion in the interpretation of the results obtained with the use of different measuring tools. Evaluation based on imaging techniques allows us to have a closer view of inflammatory activity, when it is used in conjunction with laboratory tests and true *clinical art,* which should lead to a trustworthy patient follow-up. In this regard, ^{18}F-FDG-PET/CT can become a determinant auxiliary tool for the specific diagnosis, thus improving therapeutic decisions in complex cases of TAK.

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