Implementation of positron emission tomography with ^{18}F-fluorodeoxyglucose associated with computed tomography in patients with sarcoidosis

Its effect on disease staging and the therapeutic approach

ISABEL DOMÍNGUEZ-OSORIO, DAVID BELLIDO-PASTRANA (BD) • CIUDAD REAL (ESPAÑA)
ABEL GONZÁLEZ-GONZÁLEZ • VALLADOLID (ESPAÑA)

DOI: https://doi.org/10.36104/amc.2023.2778

Abstract

Objetives: to evaluate the benefit of implementing ^{18}F-FDG PET/TC in the staging and treatment adjustment of patients with sarcoidosis, compared with the signs and symptoms and complementary test results usually employed.

Materials and methods: an observational, analytical electronic chart review of a retrospective cohort of patients seen for sarcoidosis in the internal medicine department of a Spanish university hospital.

Results: a total of 31 patients (18 males) were evaluated, with an average age of 54.6±14.71 years and 11±5.75 years since their sarcoidosis diagnosis. In the 84.6% of the reviews, positive uptake was objectified on the ^{18}F-FDG PET/TC. In the 42.3% of the occasions, the objectified finding allowed restaging of the patient. The ^{18}F-FDG PET/TC result justified the choice of treatment in the 71% of the reviews.

Conclusions: ^{18}F-FDG PET/TC provided additional advantages in the staging and therapeutic management of patients with sarcoidosis, compared with the evaluation of signs and symptoms and other clinical tests usually employed in follow up, due to its greater accuracy in determining the activity and extension of the disease. **(Acta Med Colomb 2022; 48. DOI: https://doi.org/10.36104/amc.2023.2778).**

Keywords: *sarcoidosis, inflammation, positron emission tomography, computed tomography, ^{18}F-fluorodeoxyglucose*.

Dra. Isabel Domínguez-Osorio: Servicio de Medicina Interna. Hospital Santa Bárbara, Ciudad Real; Dr. David Bellido-Pastrana (BD): Servicio de Medicina Interna. Hospital General Universitario de Ciudad Real; Dr. Abel González-González: Servicio de Endocrinología y Nutrición. Hospital Universitario Río Hortega. Valladolid. España.
Correspondencia: Dra. Isabel Domínguez-Osorio. Puertollano, Ciudad Real (España).
E-Mail: isabeldominguezosorio@gmail.com
Received: 21/XI/2022 Accepted: 13/III/2023

Introduction

Sarcoidosis is a multisystemic granulomatous disease of uncertain etiology. It is a diagnostic and treatment challenge since, even today, none of the tests generally used for its clinical management can be considered tests of choice and its course is, in many cases, unpredictable (1-4).

Its incidence and prevalence are not precisely known. In our country, the mean annual incidence rate is 1.37 per 100,000 inhabitants, although recent studies seem to raise that figure (5, 6).

The mean age at diagnosis is 40 years, with a slight predominance of the female sex. It is a complex disease, highly suspected to have a genetic predisposition (1, 5, 7).

At a clinical level, it has miscellaneous symptoms, with pulmonary manifestations being the most common, although extrapulmonary involvement may also be found (7, 8).

The cells that make up the sarcoid granuloma capture ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and may be quantified. The algorithm most often used is the Standardized Uptake Value (SUV). These SUV variations allow hidden disease or disease located in uncommon locations to be detected, aiding diagnosis and the taking of biopsies (9). Furthermore, they make it possible to monitor the disease's activity and the response to treatment more accurately than clinical signs and symptoms, improving the performance of the usual monitoring tests (10). Thus, despite its lower availability and higher cost, the high sensitivity (90-100%) of ^{18}F-FDG together with computed tomography (^{18}F-FDG PET/CT) is making it an essential tool for managing patients with sarcoidosis (11-13).

The objective of this study was to evaluate the benefit of using ^{18}F-FDG PET/CT (due to its ability to identify inflammatory activity in the sarcoid granuloma) for restratification and treatment adjustment compared with the signs and symptoms and tests commonly used for following patients with sarcoidosis.

Materials and method

An observational, analytical study was conducted of a retrospective cohort of patients treated for sarcoidosis in the internal medicine department of Hospital General Universitario de Ciudad Real (HGUCR), a referral hospital for a health catchment area of 191,468 patients.

The source of information was the patients' electronic medical records.

All patients diagnosed with sarcoidosis who were over the age of 18, had at least one ^{18}F-FDG PET/CT during their clinical follow up and signed informed consent were included. The analyzed study period went from the first available electronic medical records at this center (in 2010) through May 2021. Patients who were not followed by internal medicine and those whose medical records did not include the minimum data needed for analysis were excluded.

The diagnosis of sarcoidosis was based on compatible anatomic pathology results (sarcoid granuloma) and/or compatible signs and symptoms. All cases were tested for tuberculosis and cancer. All patients were followed by the same internal medicine specialist (BD).

Sociodemographic data (age, sex, race, usual residence, occupation and work exposure, smoking and family history of autoimmune disease) and clinical signs and symptoms (asthenia, dyspnea and pain) were analyzed.

Analytical data were also evaluated (with angiotensin converting enzyme [ACE] levels), along with pulmonary function tests (PFTs), considering the percentages of forced vital capacity (FVC) and the diffusing capacity of the lungs for carbon monoxide (DLCO), as well as radiological study results (the Scadding Staging System [SSS] stages (14) using simple x-rays and CT) and nuclear medicine (^{18}F-FDG PET/CT). Dermatological, ophthalmological and/or echocardiographic assessments were not routinely performed except in cases with symptoms suggestive of skin, eye or heart involvement.

All clinic visits in which an ^{18}F-FDG PET/CT was performed, and the reason for ordering it, were reviewed. The positive ^{18}F-FDG PET/CT findings (with a pulmonary SUV range from 1.7 to 15.8) were analyzed, along with their location. Furthermore, the results were compared with the rest of the tests (described above) ordered simultaneously or most recently, whether during diagnosis or follow up. For staging, equivalence was established with the pulmonary radiology studies.

Additionally, the treatments used for managing the disease were collected, as well as their modifications and the reasons for the modifications. The changes compared with the beginning of treatment (increases or additions) were motivated by ^{18}F-FDG PET/CT uptake or in light of symptoms and increased SUV levels compared with prior ^{18}F-FDG PET/CTs (when possible). On the other hand, the lack of uptake or decreased SUV levels justified dose reduction or discontinuation.

The variables were shown using the descriptive statistics appropriate for the nature of each variable: measures of central tendency (mean) and dispersion (standard deviation) for quantitative variables and absolute and relative frequencies (percentages) for qualitative variables.

Results

Thirty-one patients (18 men and 13 women) aged 54.6±14.71 years, who had had sarcoidosis for 11±5.75 years, were evaluated. The rest of the main sociodemographic characteristics collected are shown in Table 1.

Twenty-eight diagnostic biopsies were found, 17 taken from enlarged mediastinal lymph nodes. In 20 patients (64.5%), the histological study was confirmatory. In the remaining patients, the diagnosis was based on clinical criteria. None of the patients were diagnosed with cancer and those with a positive tuberculosis screening had received treatment.

The 52 clinical reviews in which an ^{18}F-FDG PET/CT was performed were analyzed. The reasons for ordering the test were to help in diagnosis and to evaluate inflammatory activity in patients with reiterated symptomatic complaints and standard tests which were inconclusive for active disease. An average of 1.67 ^{18}F-FDG PET/CTs were ordered per patient. The three most common symptoms were asthenia (78.8% of the cases), pain (46.2%) and dyspnea (38.5%). Besides the ^{18}F-FDG PET/CTs, 41 PFTs were performed. Altogether, 17.3% had decreased DLCO and 23% had reduced FVC. The concentration of ACE was measured on 48 occasions

Table 1. *Percentages of the study patients' main sociodemographic variables.*

Variables	N (%), Except prevalence (‰)
Individuals	31
Sex	
Male	18 (58.1)
Female	13 (41.9)
Mean age/years since onset	54.6±14.71/11±5.75
Autoimmune history*	
Yes	2 (6.45)
No	25 (80.65)
NA/DK**	4 (12.9)
Race	
Caucasian	29 (93.5)
Other	2 (6.5)
Chemical exposure	
Yes	19 (61.29)
No	9 (29.03)
NA/DK	3 (9.68)
Prior infection	
Yes	5 (16.13)
No	21 (67.74)
NA/DK	5 (16.13)
Smoking	
Yes	12 (38.71)
No	16 (51.61)
NA/DK	3 (9.68)
Sarcoidosis prevalence	16.19

AI: autoimmune. NA/DK (no answer/does not know).*

and was elevated in 53%. Five cases had a high-resolution CT (HRCT).

A total of 84.6% of the reviews in which an ^{18}F-FDG PET/CT was performed showed positive uptake. These results were compared with those found in previous radiological tests. The stages (by equivalence with radiological tests) were: Stage II (SII) in 44%, SI in 25%, S0 in 17.3% and SIII in 13.5%. All patients staged as SIV by radiology had ^{18}F-FDG PET/CT activity. 42.3% of the time, the objectified finding allowed patient restaging compared to the result obtained by other radiological studies. In 15 of these follow ups, the ^{18}F-FDG PET/CT staging was lower than what was established by the other radiological tests reported (Figure 1).

In 44 of the 52 clinical follow ups, the patients were on some type of pharmacological treatment for the disease. The most commonly used drugs for monotherapy were corticosteroids (44.2%) and the most frequent combined therapy joined corticosteroids with methotrexate (13.5%). The ^{18}F-FDG PET/CT result justified the choice of treatment in 37 of the 52 reviews. The treatment modifications are presented in Figure 2.

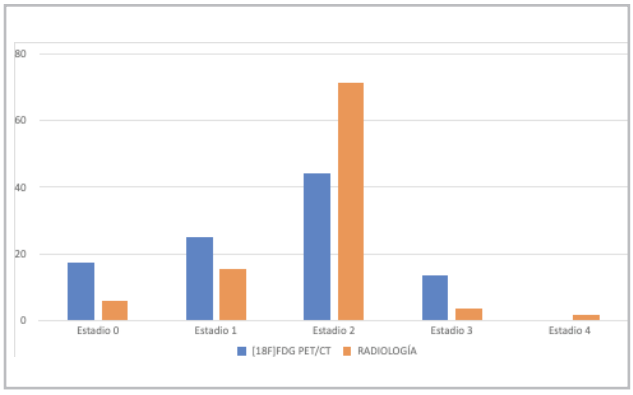

Figure 1. *Percentage distribution of the stages according to the technique used.*

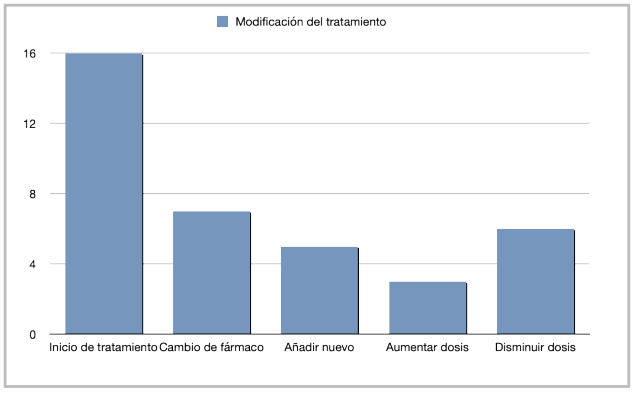

Figure 2. *Type of treatment change (in absolute values) made in the clinical reviews, motivated by the [^{18}F]FDG PET/CT result.*

Discussion

Recent papers have objectivized the high sensitivity of ^{18}F-FDG PET/CT for identifying inflammation, with positive uptakes in most of the analyzed reviews and mostly coinciding with radiological Stages II and III (11, 15). The results in our series of patients (greater than 80% uptake) appear to confirm this data. In this vein, and similar to Mostard et al.'s results, in our sample, all patients classified as SIV by radiology had ^{18}F-FDG PET/CT activity and, therefore, would benefit from a treatment adjustment (15). This supports the fact that ^{18}F-FDG PET/CT can identify active disease in patients with sarcoidosis who have persistent symptoms but little variation in the usual laboratory, imaging and respiratory tests used (16).

The most notable results in this study regarding the role of ^{18}F-FDG PET/CT were related to disease monitoring and treatment adjustments. ^{18}F-FDG PET/CT provided greater accuracy and objectivity in determining activity, changes in activity and disease extension, compared with other tests routinely ordered in our hospital for periodic follow up of these patients (15, 17). This had significant therapeutic implications, which have already been described by other authors, like Sobic-Saranovic et al., whose positive ^{18}F-FDG PET/CT results justified treatment changes in more than 70% of the reviews, with treatment onset in a significant number of cases (highlighting patients with radiological SIV and a positive PET) (17).

The main weakness of this study is that the data was obtained retrospectively from medical records in which some results and tests (like HRCT) were not available in all cases. On the other hand, the positive points to be noted are the adequate sample size, compared with other similar studies (11) and that the ordering of diagnostic tests and treatment decisions in all patients were done by a single professional (BD), which provides homogeneity in the results.

We coincide with Treglia et al. in the need to delve deeper in cost-benefit studies (18). Therefore, it would be relevant to evaluate the performance of ^{18}F-FDG PET/CT in monitoring sarcoidosis, trying to determine the most cost-efficient test or adapted algorithm, not only to improve the quality of care, but also to optimize the available resources. In this regard, ^{18}F-FDG PET/CT could play a key role, as it is able to determine the degree of disease activity more accurately.

Conclusions

^{18}F-FDG PET/CT provides additional benefits in sarcoidosis staging and therapeutic management, compared to signs and symptoms and other clinical tests commonly employed in follow-up, due to its greater accuracy in determining the disease's activity and extension.

Further study is needed of the markers which could provide greater specificity to this test and/or treatment regimens that would optimize the available resources and provide an excellent approach to patients with sarcoidosis. This opens the door to continue new studies.

References

1. **Baughman RP, Valeyre D.** Sarcoidosis. A Clinician's Guide. 1st ed. Missouri: Elsevier; 2018. 313 p.
2. **Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al.** Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;**201**(8):e26-e51.https://doi.org/10.1164/rccm.202002-0251ST.
3. **Culver DA, Judson MA.** New advances in the management of pulmonary sarcoidosis. *BMJ*. 2019;**367**:l5553. https://doi.org/10.1136/bmj.l5553.
4. **Denny MC, Fotino AD.** The Heerfordt-Waldenström syndrome as an initial presentation of sarcoidosis. *Proc Bayl Univ Med Cent*. 2013;**26**(4):390-2.
5. **Arkema EV, Cozier YC.** Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. *Curr Opin Pulm Med*. 2020;**26**(5):527-34. https://doi.org/10.1097/MCP.0000000000000715.
6. **Fernández-Ramón R, Gaitán-Valdizán JJ, Sánchez-Bilbao L, Martín-Varillas JL, Martínez-López D, Demetrio-Pablo R, et al.** Epidemiology of sarcoidosis in northern Spain, 1999-2019: A population-based study. *Eur J Intern Med*. 2021;**91**:63-9. https://doi.org/10.1016/j.ejim.2021.05.011.
7. **Judson MA, Boan AD, Lackland DT.** The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;**29**(2):119-27.
8. **Judson MA.** The Clinical Features of Sarcoidosis: A Comprehensive Review. *Clin Rev Allergy Immunol*. 2015;**49**(1):63-78. https://doi.org/10.1007/s12016-014-8450-y.
9. **Akaike G, Itani M, Shah H, Ahuja J, Yilmaz Gunes B, Assaker R, et al.** PET/CT in the Diagnosis and Workup of Sarcoidosis: Focus on Atypical Manifestations. *Radiographics*. 2018;**38**(5):1536-49. https://doi.org/10.1148/rg.2018180053
10. **Chen H, Jin R, Wang Y, Li L, Li K, He Y.** The Utility of 18F-FDG PET/CT for Monitoring Response and Predicting Prognosis after Glucocorticoids Therapy for Sarcoidosis. *Biomed Res Int*. 2018;2018:1823710. https://doi.org/10.1155/2018/1823710.
11. **Keijsers RGM, Grutters JC.** In Which Patients with Sarcoidosis Is FDG PET/CT Indicated? *J Clin Med*. 2020;**9**(3):890. https://doi.org/10.3390/jcm9030890.
12. **Barahona ZD.** When should a PET/CT be requested in sarcoidosis?. Rev Med Chil. 2019;147(10):1308-14. https://doi.org/10.4067/s0034-98872019001001308.
13. **Schimmelpennink MC, Vorselaars ADM, Veltkamp M, Keijsers RGM.** Quantification of pulmonary disease activity in sarcoidosis measured with 18F-FDG PET/CT: SUVmax versus total lung glycolysis. *EJNMMI Res*. 2019;**9**(1):54. https://doi.org/10.1186/s13550-019-0505-x.
14. **Scadding JG.** Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. *Br Med J*. 1961;**2**(5261):1165-72. https://doi.org/10.1136/bmj.2.5261.1165
15. **Mostard RL, Vöö S, van Kroonenburgh MJ, Verschakelen JA, Wijnen PA, Nelemans PJ, Erckens RJ, et al.** Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. *Respir Med*. 2011;**105**(12):1917-24. https://doi.org/10.1016/j.rmed.2011.08.012.
16. **Teirstein AS, Machac J, Almeida O, Lu P, Padilla ML, Iannuzzi MC.** Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. *Chest*. 2007;**132**(6):1949-53. https://doi.org/10.1378/chest.07-1178.
17. **Sobic-Saranovic D, Grozdic I, Videnovic-Ivanov J, Vucinic-Mihailovic V, Artiko V, Saranovic D, et al.** The utility of 18F-FDG PET/CT for diagnosis and adjustment of therapy in patients with active chronic sarcoidosis. *J Nucl Med*. 2012;**53**(10):1543-9. https://doi.org/10.2967/jnumed.112.104380.
18. **Treglia G, Annunziata S, Sobic-Saranovic D, Bertagna F, Caldarella C, Giovanella L.** The role of 18F-FDG-PET and PET/CT in patients with sarcoidosis: an updated evidence-based review. *Acad Radiol*. 2014;**21**(5):675-84. https://doi.org/10.1016/j.acra.2014.01.008.