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Emerging role of whole-body ^{18}F-fluorodeoxyglucose positron emission tomography as a marker of disease activity in patients with sarcoidosis: a systematic review

G. Treglia, S. Taralli, A. Giordano
Institute of Nuclear Medicine, Department of Bioimages and Radiological Sciences, Catholic University of the Sacred Heart, Rome, Italy

Abstract. *Objective:* This study was designed to systematically review the emerging role of whole-body positron emission tomography (PET) with ^{18}F-Fluorodeoxyglucose (FDG) in patients with sarcoidosis. *Design:* A comprehensive literature search of published studies through December 2010 in PubMed/MEDLINE and Embase databases regarding whole-body FDG-PET and PET/CT in patients with sarcoidosis was performed. *Results:* Ultimately, we identified nine studies comprising a total of 379 patients with sarcoidosis. Main findings of the included studies are presented. *Conclusions:* from this systematic review we can summarize that: 1) positive FDG-PET findings should be interpreted with caution in differentiating sarcoidosis from other inflammatory diseases and malignant abnormalities; 2) FDG-PET seems to be a very useful molecular imaging method in assessing disease activity, in staging and identifying occult sites, and in monitoring treatment response in patients with sarcoidosis; 3) FDG-PET shows a better diagnostic accuracy compared to ^{67}Ga scintigraphy in patients with sarcoidosis, because of a better sensitivity of FDG-PET (mainly due to the high quality of FDG-PET images with superior contrast and spatial resolution compared to ^{67}Ga scintigraphy) in addition to several practical advantages (less radiation exposure, shorter time between injection and imaging). *(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 87-94)*

Key words: positron emission tomography, ^{18}F-FDG, sarcoidosis

Introduction

Imaging methods may play a role in diagnosis and treatment strategy plan in patients with sarcoidosis at both primary staging and follow-up.

Chest radiography and computed tomography (CT) may support the diagnosis of sarcoidosis. Bilateral pulmonary hilar and mediastinal lymphadenopathy is the most common radiological finding, often associated with pulmonary infiltrates (1-5).

About functional imaging methods, Gallium-67 (^{67}Ga) scintigraphy is not routinely used in patients with sarcoidosis. This method has several limitations: a) it is a time consuming method (patients must be injected at least 48-72 hours before image acquisition); b) there is a significant interobserver variability in image interpretation; c) the overall sensitivity and specificity values are highly variable between different studies; d) this scintigraphic method yields a high radiation exposure (3, 6, 7).

While whole-body ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is reported to be a sensitive technique in oncological

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Correspondence: Dr. Giorgio Treglia,
Institute of Nuclear Medicine,
Positron Emission Tomography Centre, Department of Bioimages and Radiological Sciences,
Catholic University of the Sacred Heart
Largo Gemelli, 8 - 00168 Rome, Italy
Tel. 00390630154978
Fax 0039063013745
E-mail address: giorgiomednuc@libero.it

imaging, it is well known that inflammatory and infectious lesions may cause false positive results (8, 9). Inflammatory cells such as macrophages, lymphocytes and neutrophil granulocytes as well as fibroblasts have shown to avidly take up FDG. Therefore, FDG may also be used as a tracer of inflammation (6, 7, 10, 11).

FDG enters the cell by the same membrane transport mechanism as glucose. After penetration of the cellular membrane via glucose transporters, both FDG and glucose are phosphorylated by an hexokinase. Unlike glucose-6-phosphate, FDG-6-phosphate is not a substrate of glucose-6-phosphate isomerase and does not undergo further metabolism in the glucose pathway; FDG is therefore trapped within cells.

Autoradiographic studies of FDG uptake in sarcoidosis are lacking and the specific cell type(s) remain unknown, although it is well known that FDG is incorporated in inflammatory cells.

Disease activity in sarcoidosis can be assessed by detecting and quantifying the degree of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body. The ability to visualize FDG accumulation by activated inflammatory cells makes whole-body FDG-PET a promising modality for assess disease activity in patients with sarcoidosis, as first described by the report of Lewis and Salama in 1994 (12).

Several studies have shown the potential role of whole-body FDG-PET in evaluating disease activity in patients with sarcoidosis. However, a systematic review of published data in this field is lacking.

Methods

Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE and Embase databases was conducted to find relevant published articles about whole-body FDG-PET in patients with sarcoidosis. We used a search algorithm that was based on a combination of the terms: a) "Sarcoidosis" AND b) "Positron Emission Tomography" OR "PET". No beginning date limit was used; the search was updated until 31 December 2010. To expand our search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets in studies investigating the potential role of whole-body FDG-PET in patients with sarcoidosis were eligible for inclusion. Review articles, editorials or letters, comments, conference proceedings, case reports and preclinical studies were excluded from this review.

Only those studies or subsets in studies that satisfied all of the following criteria were included: a) FDG-PET performed in patients with histologically confirmed sarcoidosis; b) sample size of at least ten patients with sarcoidosis; c) whole-body PET studies performed.

The exclusion criteria were: a) FDG-PET not performed in patients with histologically confirmed sarcoidosis; b) sample size of less than ten patients with sarcoidosis; c) no whole-body FDG-PET studies performed (for example cardiac studies); PET studies without FDG.

Two researchers (GT and ST) independently reviewed titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data extraction

For each included study, information was collected concerning basic study (authors, journal, year of publication, country of origin), patient characteristics (number of patients with sarcoidosis, sex and mean age, chest radiographic stage), technical aspects (PET technique, tracers used). Finally, the main findings of the articles included in this review have been reported.

Results

Literature search

The comprehensive computer literature search from the PubMed/MEDLINE and Embase databases revealed 264 articles (Figure 1). Reviewing ti-

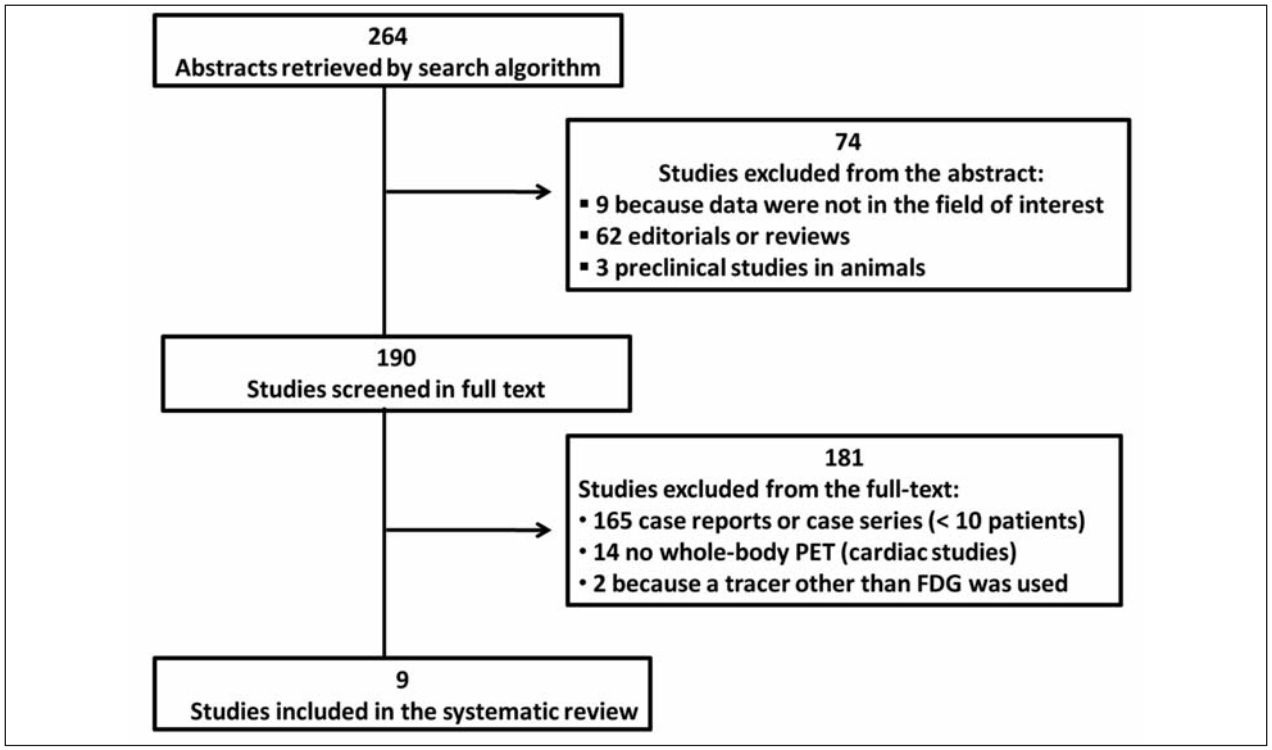

Fig. 1. Flow chart of the search for eligible studies about the role of FDG-PET in patients with sarcoidosis.

tles and abstracts, nine articles were excluded because data were not within the field of interest of this review; 62 articles were excluded because editorials or reviews; three articles were excluded because preclinical studies in animals. Reviewing the full text of the remaining 190 articles, 165 were excluded because case reports or case series (less than ten patients with pathologically confirmed sarcoidosis); 14 articles were excluded because no whole-body PET studies were performed (cardiac PET studies); two articles were excluded because PET with a tracer other than FDG was performed.

Finally, nine articles were selected (13-21). These nine studies were retrieved in full text version; no additional studies were found screening the references of these articles. The characteristics of the included studies are presented in Table 1.

Literature data discussion

In 1998 Yamada et al (13) evaluated the role of different PET tracers, FDG and ^{11}C-Methionine (Met), an amino acid tracer, in clinical assessment of thoracic lymph nodal involvement in 31 patients with pulmonary sarcoidosis. Clinical reassessment of sarcoidosis was made at least one year after the first PET examination. Overall sensitivities of FDG and Met-PET in detecting thoracic lymphadenopathy were both 97% (30/31 patients). The mean FDG uptake value was significantly higher than mean Met uptake value ($p<0.01$). Dividing the patients into two groups, the FDG-dominant group (FDG/Met uptake ratio ≥ 2), and the Met-dominant group (FDG/Met uptake ratio < 2) there was a significant linear correlation between FDG and Met uptake values in each group (FDG-dominant group, $r=0.93$, $p<0.01$; Met-dominant group, $r=0.41$, $p<0.01$). Patients did not receive any treatment after the PET scan. The FDG-dominant group showed a significantly greater remission incidence of thoracic lymphadenopathy compared to the Met-dominant group (78% versus 33%; $p<0.05$). The incidence of unchanged lymphadenopathy plus that of the appearance of pulmonary involvement, assessed by CT,

Table 1. Characteristics of the included papers

Authors	Year	Country	No. of sarcoidosis patients who performed PET	Sex (% male)	Mean age (years)	Chest radiographic stage (n° of patients)	PET technique	PET tracers used	Other tracer used
Yamada Y et al (13)	1998	Japan	31	61%	N.R.	I (18); II (13)	PET	FDG + Met	^{67}Ga
Nishiyama Y et al (14)	2006	Japan	18	33%	59	0 (1); I (13); II (4)	PET	FDG	^{67}Ga
Kaira K et al (15)	2007	Japan	24	37%	43	I (11); II (13)	PET	FDG + FMT	-
Teirstein AS et al (16)	2007	USA	137	52%	50	0 (11), I (18); II (15); III (7); IV (22)	PET/CT	FDG	-
Prager E et al (17)	2008	Austria	24	46%	52	N.R.	PET	FDG	^{67}Ga
Braun JJ et al (18)	2008	France	20	55%	51	I (2); II (3); III (1); IV (7)	PET/CT	FDG	^{67}Ga
Keijsers RG et al (19)	2008	Netherlands	12	50%	44	I (3); II (6); III (2); IV (1)	PET	FDG	-
Keijsers RG et al (20)	2009	Netherlands	36	44%	39	0 (1), I (18); II (11); III (5); IV (1)	PET	FDG	-
Keijsers RG et al (21)	2010	Netherlands	77	58%	39	0 (4), I (31); II (30); III (9); IV (3)	PET	FDG	-

Legend: N.R.: not reported; FDG: ^{18}F-fluorodeoxyglucose; FMT: ^{18}F-methyltyrosine; Met: ^{11}C-methionine; ^{67}Ga: Gallium-67

was higher in the Met- (67%) than in the FDG-dominant group (22%). These findings suggest that: 1) both FDG and Met are accumulated in mediastinal and hilar lymph nodes in patients with sarcoidosis, suggesting that sarcoid lymph nodes have a high metabolic demand for both glucose and amino acids; 2) the different uptake of FDG and Met in thoracic lymph nodes would provide information about short term prognosis for sarcoidosis patients: the disease activity seems to decrease over time without treatment giving a good prognosis for the FDG-dominant group; on the other hand, the disease activity is likely to continue, resulting in pulmonary involvement, and giving a poor prognosis for the Met-dominant group.

In 2006 Nishiyama et al (14) compared FDG-PET and ^{67}Ga scintigraphy in the evaluation of pulmonary and extrapulmonary involvement in patients with sarcoidosis. Eighteen patients with sarcoidosis were examined; FDG and ^{67}Ga uptake were visually and semiquantitatively evaluated. The presence of pulmonary and extrapulmonary lesions was evaluated by histopathology or radiological findings. Five patients had only pulmonary lesions, 12 patients had both pulmonary and extrapulmonary lesions, and one patient had only extrapulmonary lesions. Both planar and tomographic (SPECT) ^{67}Ga images detected 17 of 21 (81%) clinically observed pulmonary sites. Planar ^{67}Ga images detected 15 of 31 (48%) clinically observed extrapulmonary sites. FDG-PET detected all 21 (100%) clinically observed pulmonary sites and 28 of 31 (90%) clinically observed extrapulmonary sites. When correlated with clinical and radiological follow-up, FDG or ^{67}Ga uptake in pulmonary and extrapulmonary lesions was decreased after corticosteroid therapy. These results suggest that FDG-PET can detect pulmonary lesions to a similar degree as ^{67}Ga scintigraphy in patients with sarcoidosis. However, FDG-PET appears to be more accurate and contributes to a better evaluation of extrapulmonary involvement in patients with sarcoidosis. FDG-PET appears to be preferable in patients with sarcoidosis, compared to ^{67}Ga scintigraphy, because of at least comparable and perhaps even better sensitivity of FDG-PET in addition to several practical advantages (less radiation exposure, shorter time between injection and imaging).

In 2007 Kaira et al (15) investigated the usefulness of PET with ^{18}F-methyltyrosine (FMT), an amino acid tracer used for detecting neoplasms, in combination with FDG-PET for the diagnosis of sarcoidosis in patients with suspected malignancy. Twenty-four sarcoidosis patients with suspected malignancy underwent FDG and FMT-PET. The study included 17 patients with extrapulmonary le-

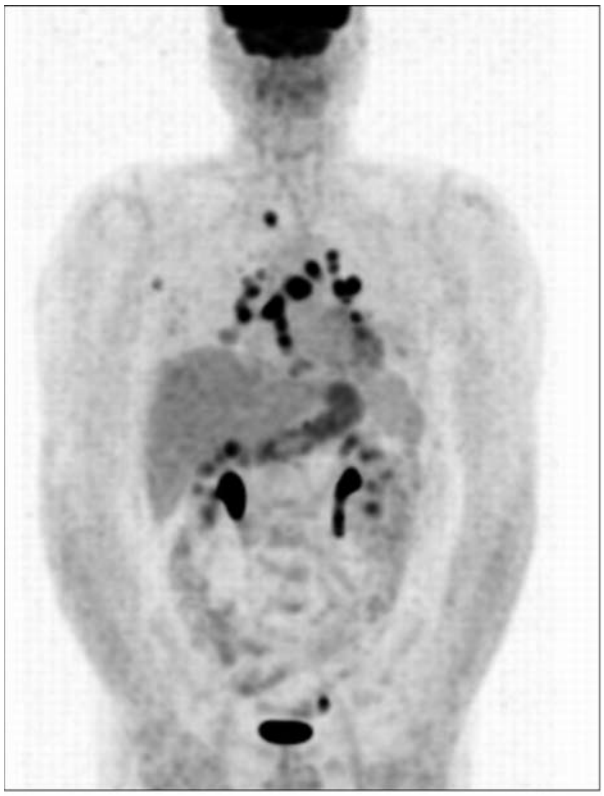

Fig. 2. FDG-PET in a 35 y.o. patient showing increased FDG uptake in bilateral pulmonary hilar and mediastinal lymph nodes; histological examination confirmed the presence of sarcoidosis

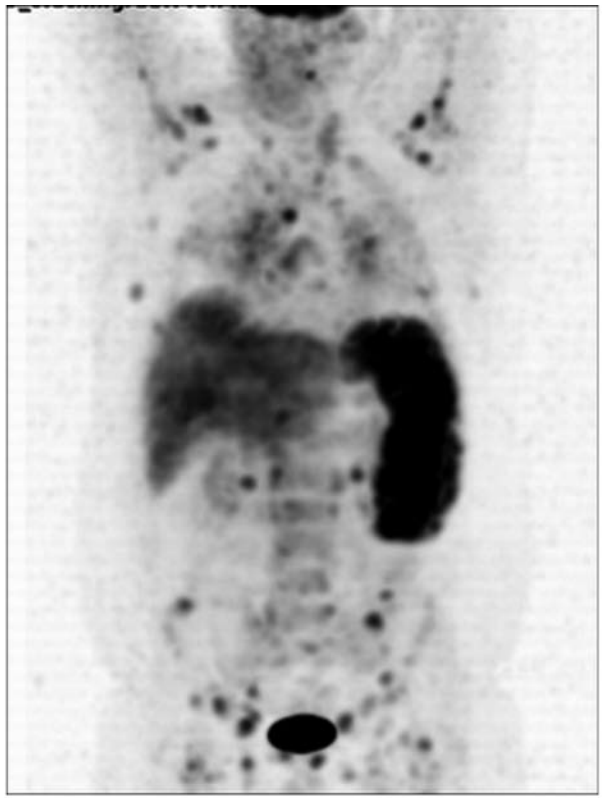

Fig. 3. FDG-PET in a 40 y.o. patient showing increased multiple foci of increased FDG uptake in the liver, spleen, multiple thoracic and abdominal lymph nodes, multiple skeletal segments; histological examination confirmed the presence of sarcoidosis.

sions mimicking malignant disease, three patients with occurrence of bilateral hilar lymphadenopathy, and four patients with multiple nodules mimicking pulmonary metastasis. All patients showed increased FDG uptake and no increased FMT uptake in their lymphadenopathies. All extranodal lesions such as liver, spleen, and bone were visually positive on FDG-PET and negative on FMT-PET. No neoplasm was confirmed in all patients. These results suggest that FDG-PET is positive in sarcoid lesions, and therefore this method could not differentiate sarcoidosis from malignant disease. Use of FMT-PET in combination with FDG-PET may be the effective method to distinguish sarcoidosis from malignancy.

In 2007 Teirstein et al (16) studied the role FDG-PET in the identification of occult sites and reversible granulomatous disease in patients with sarcoidosis. A total of 188 FDG-PET scans performed in 137 patients with proven sarcoidosis were retrospectively reviewed. A total of 139 of 188 FDG-PET scans (74%) were positive. The most common positive sites were mediastinal lymph nodes (54 scans), extrathoracic lymph nodes (30 scans), and lung (24 scans). Twenty occult disease sites were identified. A total of 36 patients were treated, but only 11 patients exhibited decreased FDG uptake with corticosteroid therapy. The positive pulmonary FDG-PET scan findings occurred in two-thirds of patients with radiographic stage II and III sarcoidosis. Negative pulmonary FDG-PET scan findings were common in patients with radiographic stage 0, I, and IV. These findings suggest that FDG-PET is a valuable tool in identifying occult sites in patients with sarcoidosis and in assessing residual activity in patients with fibrotic pulmonary sarcoidosis.

In 2008 Prager et al (17) analyzed possible advantages of FDG-PET over ^{67}Ga scintigraphy during the primary assessment of patients with sar-

coidosis. Twenty-four patients with histologically proven sarcoidosis were investigated with both methods. There was a significant difference in the detection of pulmonary and extrapulmonary sarcoidosis lesions between planar ^{67}Ga scintigraphy and FDG-PET images ($p<0.002$): a total of 64 lesions were detected with ^{67}Ga scintigraphy in the thorax and elsewhere, while 85 lesions were found with FDG-PET. There was complete agreement between FDG-PET and ^{67}Ga scintigraphy in thoracic manifestations in four (16.6%) patients, and in non-thoracic manifestations in five (20.8%) patients. In 10/24 (41.6%) patients, FDG-PET revealed more affected foci in thoracic sarcoidosis than ^{67}Ga scintigraphy, in non-thoracic disease in 7/24 (29.1%) patients. In conclusion ^{67}Ga and FDG are useful tracers for diagnostic evaluation of thoracic sarcoidosis, but FDG seems to be more suitable for imaging the mediastinum, the bi-hilar lymph nodes, the posterior regions of the lungs and non-thoracic lesions.

In 2008 Braun et al (18) evaluated the role of FDG-PET/CT for diagnosis and therapeutic follow-up of patients with sarcoidosis. Twenty patients with biopsy-proven sarcoidosis were retrospectively included, in particular, 13 and seven cases of thoracic and extra-thoracic sarcoidosis, respectively. All patients underwent FDG-PET/CT, and 12 of them also ^{67}Ga scintigraphy. Both FDG-PET/CT and ^{67}Ga scintigraphy highlighted multiple extra-thoracic foci of pathological tracer uptake, suggesting the presence of active granulomatous disease, which was not previously detected by conventional evaluation. Considering both thoracic and extra-thoracic sarcoidosis localizations, FDG-PET/CT sensitivity was 78% (28 out of 36 biopsy-proven sites of sarcoidosis were correctly identified). For thoracic, sinonasal, and pharyngolaryngeal localizations, FDG-PET/CT sensitivity was 100%, 100%, and 80%, respectively. Considering only the 12 patients who underwent both scintigraphic examinations, overall sensitivity of ^{67}Ga scintigraphy and FDG-PET/CT was 58% and 79%, respectively and improved to 67% and 86% after excluding all sites of skin involvement. To evaluate the efficacy of corticosteroid treatment, five enrolled patients underwent a second FDG-PET/CT. Complete regression of all foci of pathological tracer uptake was showed in two cases, allowing therapy withdrawal; improvement but incomplete regression of mediastinal-pulmonary disease occurred in two patients; disease progression was assessed in one patient. These results suggest that FDG-PET/CT allows to obtain a complete morpho-functional map of inflammatory active localizations and to follow treatment efficacy in patients with sarcoidosis, particularly in atypical, complex, and systemic forms. The better quality of imaging, the less technical constraints and better sensitivity are in favor of FDG-PET/CT compared to ^{67}Ga scintigraphy in this field.

In 2008 Keijsers et al (19) correlated FDG-PET with standard sarcoidosis activity parameters during infliximab treatment (anti-TNF-α therapy) in order to illustrate that FDG uptake represents active disease and might be used to monitor therapeutic effects. Twelve patients with refractory sarcoidosis were treated with 6 cycles of infliximab. Pre- and post-therapy FDG-PET was visually and semiquantitative evaluated: standardized uptake value (SUVmax) was measured. In addition, the effect of infliximab was evaluated by changes in symptoms, angiotensin converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), vital capacity (VC), diffusion capacity of the lung for carbon monoxide (DLCO) and chest radiography. SUVmax and conventional parameters were correlated. Clinical improvement as judged by conventional parameters was seen in all patients, though with a minor response in one. Symptoms improved in 11/12 patients while chest radiographic stages did not change. Pre-infliximab FDG-PET was abnormal in all patients: involvement of the pulmonary tract was seen in all 12 patients, while eight patients showed extrapulmonary involvement. Post-infliximab FDG-PET revealed either improvement or normalization in 11/12 (92%) clinically responding patients. The overall decrease in SUVmax was 55% ($p<0.01$); the patient with a limited response showed a 34% increase of SUVmax. A decrease in SUVmax of the lung parenchyma correlated with an improvement of VC ($r=-0.75$, $p<0.01$). No significant correlation between SUVmax and other parameters was found. These results suggest that changes imaged by FDG-PET during infliximab treatment in patients with sarcoidosis correlate with signs of clinical improvement, which supports the hypothesis that FDG uptake represents disease activity and may be used to monitor therapeutic effects.

In 2009 Keijsers et al (20) determined the sensitivity of FDG-PET in active sarcoidosis and its correlation with serological markers widely used for determining sarcoidosis activity, angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R). This retrospective study included 36 newly diagnosed, symptomatic sarcoidosis patients. FDG-PET was visually and semiquantitatively evaluated: maximum and average standardized uptake values (SUVmax and SUVavg) were compared with ACE and sIL-2R. FDG-PET was found positive in 34 of 36 patients (94%). Of the 32 patients with pulmonary involvement, extrapulmonary lesions were seen in 19 patients. Two patients had extrapulmonary lesions without pulmonary involvement. Thus, a total of 21 patients (58%) had extrapulmonary involvement. Thirteen patients (36%) showed an increased ACE value; seventeen patients (47%) showed an increased sIL-2R value. No correlation was found between SUV and ACE or sIL-2R values. Of the 34 patients with a positive FDG-PET result, 12 patients showed an increased ACE value (35%) and 16 patients showed an increased sIL-2R value (47%). Fourteen patients had a negative ACE as well as sIL-2R value (41%). Of 13 patients with an increased ACE value, 12 showed a positive FDG-PET (92%); of 17 patients with an increased sIL-2R value, 16 showed a positive FDG-PET (94%). These findings demonstrated that-FDG-PET is a very sensitive technique to assess disease activity in sarcoidosis, in contrast with ACE and sIL-2R values, suggesting a pivotal role for FDG-PET in sarcoidosis assessment. Positive ACE and sIL-2R correlate well with FDG-PET, suggesting that FDG-PET might be omitted when these serum markers are elevated.

In 2010 Keijsers et al (21) compared FDG-PET with bronchoalveolar lavage (BAL) cell profiles patterns to assess whether metabolic activity imaged by FDG-PET represents disease activity as reflected by BAL. A total of 77 newly diagnosed pulmonary sarcoidosis patients underwent BAL and FDG-PET. Based on FDG-PET, patients were diagnosed with exclusively mediastinal/hilar activity (group A) and activity in the lung parenchyma (group B). Per group, BAL lymphocytes (%), CD4/CD8 ratio, $CD103^{+}CD4^{+}/CD4^{+}$ ratio and neutrophils (%) were compared with the extent of metabolic activity expressed as the maximum standardized uptake value (SUVmax). Additionally, SUVmax and BAL parameters per radiographic stage were analysed. FDG-PET was positive in 75 patients (97%) and 73 of them demonstrated thoracic involvement (95%). Mediastinal/hilar activity was present in all 73 patients, which was accompanied by parenchymal activity in 50 patients. There were no patients with increased activity in the lung parenchyma without mediastinal/hilar involvement. Group A (exclusively mediastinal/hilar activity) consisted of 23 patients. Group B (increased metabolic activity in the lung parenchyma) consisted of 50 patients. Overall, SUVmax in the lung parenchyma significantly correlated with the percentage of neutrophils ($r=0.38$, $p<0.01$); SUVmax of the mediastinum/hila significantly correlated with the CD4/CD8 ratio ($r=0.39$, $p<0.01$); a negative correlation between the SUVmax of the mediastinum/hila and the $CD103^{+}CD4^{+}/CD4^{+}$ ratio ($r=-0.39$, $p<0.01$) was found. The SUVmax of the lung parenchyma was positively related to the radiographic stage, while the SUVmax of the mediastinum/hila and CD4/CD8 ratio were inversely related. These results suggest that FDG-PET correlates with the CD4/CD8 ratio and neutrophils, suggesting that FDG-PET represents this specific cell profile in BAL. High SUVmax values of the lung parenchyma may correlate with more severe parenchymal involvement, particularly when accompanied by a low SUVmax of the mediastinum/hila.

Problems and limitations

Literature findings support current concepts which are integrated in clinical practice and management in patients with sarcoidosis.

Sarcoidosis has an interesting geographic distribution relative to other diseases such as tuberculosis, fungal infections as well as clinical and radiologic presentation patterns. These characteristics decrease specificity of FDG-PET for sarcoidosis and makes interpretation of PET images difficult.

Furthermore FDG-PET cannot distinguish between inflammatory and malignant lesions, both usually characterized by increased FDG uptake. For these reasons FDG-PET is best used to monitor the disease in patients with proven sarcoidosis, while diagnosis always requires histologic confirmation.

It should be considered that FDG-PET is an imaging method characterized by relatively higher

costs and lower availability compared to other imaging methods such as CT.

In this review only whole-body PET studies in patients with sarcoidosis were included; studies about the role of FDG-PET in patients with cardiac sarcoidosis were not included. Currently, there are not validated studies of FDG-PET in cardiac sarcoidosis; the main problem is the physiologic uptake of FDG in myocardium, perhaps solved by a carbohydrate restricted diet.

Another problem is the lack of sufficient studies that evaluated the role of FDG-PET in detecting sarcoidosis in certain organs (for example skin, liver, gastrointestinal tract, nervous system), potential sites of missed sarcoidosis lesions with FDG-PET.

A possible limitation of this review is the small number of studies and the small number of patients included in each study which may influence the conclusions. Also, to date, Medicare decided to not reimburse FDG-PET for the assessment of sarcoidosis, based on insufficient data. Further studies with a larger patient population are needed to correctly define the role of FDG-PET in patients with sarcoidosis.

Conclusions

From this systematic review of the literature about the role of FDG-PET in patients with sarcoidosis we conclude that:

1) Positive FDG-PET findings should be interpreted with caution in differentiating sarcoidosis from other inflammatory diseases and malignant abnormalities;
2) FDG-PET seems to be a very useful molecular imaging method in assessing disease activity, in staging and identifying occult sites, and in monitoring treatment response in patients with sarcoidosis;
3) FDG-PET shows a better diagnostic accuracy compared to ^{67}Ga scintigraphy in patients with sarcoidosis, because of a better sensitivity of FDG-PET (mainly due to the high quality of FDG-PET images with superior contrast and spatial resolution compared to ^{67}Ga scintigraphy) in addition to several practical advantages (less radiation exposure, shorter time between injection and imaging).

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