FDG PET for Gauging of Sarcoid Disease Activity

Human Adams, MD1,2 Ruth G. Keijsers, MD, PhD2 Jan C. Grutters, MD, PhD1,3

1 Department of Pulmonology, Center Interstitial Lung Diseases, St. Antonius Hospital, Nieuwegein, The Netherlands
2 Department of Nuclear Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands
3 Division of Heart and Lung, UMC Utrecht, Utrecht, The Netherlands

Address for correspondence Jan C. Grutters, MD, PhD, Department of Pulmonology and Center of Interstitial Lung diseases, St Antonius Hospital, Postbus 2500, 3430 EM Nieuwegein, The Netherlands (e-mail: j.grutters@antoniusziekenhuis.nl).

Abstract

Fluorodeoxyglucose (FDG), labeled with a positron emitting fluorine-18 (18F), is a synthesized glucose analogue and is well known for its application in a wide variety of clinical conditions such as cancer. Visualizing metabolic activity of inflammation is another application of FDG in positron emission tomography (PET). Here, active granulomas appear to have a high affinity for FDG, which is reflected in a high sensitivity of FDG PET imaging. This has led to novel applications of FDG PET in sarcoidosis diagnosis and management. Although chest radiography and high-resolution computed tomography are still the cornerstones of diagnosing pulmonary involvement, FDG PET appears to be superior to both techniques in imaging active sites of disease. FDG PET also correlates well with serum biomarkers such as soluble interleukin-2 receptor in symptomatic patients, and even visualizes active lesions in the context of normal serum biomarkers. Moreover, FDG PET activity in lung parenchyma correlates with decrease of lung function values over time. Also in cardiac involvement in sarcoidosis, FDG PET is a promising technique complementary to magnetic resonance imaging, especially in guiding treatment. New developments, such as applications for quantitative organ-specific measurement, are proceeding and will probably enhance the clinical implementation of FDG PET in sarcoidosis.

Keywords
- fluorodeoxyglucose
- PET/CT
- sarcoidosis
- biomarker
- pulmonary function test
- imaging
- cardiac
- treatment monitoring
- SUV

The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiological findings, histologic evidence of noncaseating granulomas, and exclusion of other conditions. Symptoms of sarcoidosis are not very specific for the presence of disease and a reliable marker for monitoring disease activity is lacking. In the majority of patients, granulomas may resolve spontaneously, but in others on-going inflammation may lead to irreversible organ function loss. Gauging the activity and extent of granuloma accumulation in such organs is a challenge for clinicians involved in the management of this disease.

Organ-specific assessment of sarcoidosis activity and estimation of the extent of granuloma accumulation throughout the body has become a step closer as a result of the technological developments in molecular imaging over the past decade. Especially, fluorodeoxyglucose (FDG) positron emission tomography (PET) has emerged to be a very promising tool. FDG PET studies have shown a high signal-to-noise ratio and deliver high contrast images in active granulomatous disease. Compared with a standalone PET scanner, the PET combined with computed tomography (CT) provides a more detailed PET image through complementary CT information. This combined PET/CT delivers several advantages of which are fusion of function and structure and better spatial resolution. In addition, this technique provides possibilities for robust quantitative assessment. In the future, magnetic resonance imaging (MRI) can be used for simultaneous PET/MRI scanning. This might become an alternative imaging modality for sarcoidosis, especially in cases with suspected cardiac involvement. However, PET/MRI has to overcome important
FDG PET for Gauging of Sarcoïd Disease Activity, Adams et al. 353

technical limitations and feasibility issues before routine clinical implementation. The current FDG PET/CT scanning protocols are optimized for lower radiation dose. Scans are able to deliver relatively low radiation exposures of 4 to 5 mSv but may also reach to 10 mSv depending on the size and weight of the patient as well as the administered $^{18}$F-FDG dosage. However, with lower FDG dose and three-dimensional time-of-flight PET/CT scanners lower radiation burdens may be achieved. Whole body acquisition radiation dose can be equal to (or lower than) a single contrast-enhanced chest CT.  

In this article, we will discuss the current position of FDG PET in imaging in sarcoïdosis and highlight its potential role in the diagnostic work-up. In this light, we will compare FDG PET with several other imaging techniques and discuss correlations of FDG PET with biomarkers, lung function changes, and staging of the disease. Moreover, the implementation of FDG PET in special forms of sarcoïdosis (cardiac sarcoïdosis [CS] and neurosarcoidosis) is underlined. Eventually, this will lead to the evaluation of the usefulness of FDG PET in the clinical setting, accompanied by recommendations for future improvement. To clarify the technique of FDG PET, we will first explain the uptake mechanism of FDG PET in sarcoïdosis.

**FDG PET: Uptake Mechanism in Sarcoïdosis**

PET relies on the use of positron emitting tracers. $^{18}$F-FDG is a molecular tracer which is a glucose analogue that is transported through the cell membrane to become phosphorylated by hexokinase as $^{18}$F-FDG-6-phosphate. The latter molecule is trapped inside the cell because it cannot be metabolized. Simultaneously, it radiates positron emissions which can be detected currently up to 5 mm resolution. $^{18}$F-FDG is a well-studied and practical tracer with broad applications in medicine, without the need for an onsite cyclotron generator. In sarcoïdosis, it is known that activated macrophages and CD4+ T-lymphocytes are contained within the granulomas. Macrophages and lymphocytes express high levels of glucose transporters, specifically the glucose transporter 1 and 3 isoforms (GLUT-1 and GLUT-3), to regulate and facilitate cellular functions. Analogous to glucose, in vitro studies have shown that also FDG is transported into macrophages through GLUT-1 and GLUT-3 glucose transporters. This mechanism enables PET imaging in sarcoïdosis and other granulomatous diseases.

In addition, we like to point out that the standardized uptake value (SUV) has been introduced as a formula to calculate activity amounts and FDG PET scans are performed following a standardized protocol. The SUV represents the amount of glucose (i.e., disease) activity, which could be helpful for prognosis and response assessment.

**Chest Radiography Compared with FDG PET**

The first technique FDG PET will be compared with is chest radiography. Chest radiography is still frequently used in the diagnosis of sarcoïdosis. It is widely available; cost effective and abnormalities can be found in 85 to 95% of patients. The most common finding is bilateral hilar adenopathy, while pulmonary parenchymal involvement is present in 20 to 50%. However, one of the limitations of chest radiography is the lack of correlation between radiological findings based on the descriptive classification by Scadding (stages 0, I–IV) and actual disease activity imaged by FDG PET, even during follow-up. FDG PET can be positive at any stage, but the majority (85%) of the positive FDG PET scans were found in patients with stages I and II disease, followed by IV. Of note, 93% PET positivity was found in patients with stage IV and 20% in stage 0. Also, compared with patients with other stages, patients with stage IV most frequently demonstrated pulmonary parenchyma FDG PET activity (87% stage IV). However, stage 0 does not exclude pulmonary inflammatory activity on FDG PET. From this, it may be concluded that FDG PET is superior to chest radiography in the evaluation of active parenchymal and/or lymph node involvement of sarcoïdosis.

**High-Resolution Computed Tomography Compared with FDG PET**

Second, FDG PET is compared with high-resolution CT (HRCT). Significant advances in CT technology have made it possible to take volumetric, multiplanar HR lung images within a single breath-hold. By this means not only morphological information is captured but also the possibility of performing inspiratory and expiratory volumetric scanning is delivered. The most characteristic HRCT findings in sarcoïdosis are micronodules; small nodules which can represent microscopic granulomas, ground glass opacities, honeycombing, distortion, septal thickening, and consolidation. More specific are the “sarcoïd galaxy sign,” “cluster sign,” and “reversed halo sign,” suggestive for granulomatous disease. The loss of pulmonary function is highly associated with the degree of pulmonary involvement on HRCT. In selected cases, HRCT has also shown diagnostic value in the discrimination between reversible alveolitis and fibrosis. However, recently, a 2-year follow-up study did not find a predictive value of parenchymal opacities detected on HRCT in stage I sarcoïdosis.

So far, comparative studies between HRCT and FDG PET in sarcoïdosis are limited. HRCT patterns associated with increased FDG uptake are parenchymal consolidations in 48%, lymph nodes in 25%, intraparenchymal nodules in 21%, septal and nonseptal lines in 4%, and pleural thickening in 2% of the patients. FDG PET may also show high metabolic activity in areas adjacent to consolidations, in areas with sparse nodules. In exploring signs of fibrosis on HRCT, FDG PET regularly shows metabolically active lung parenchyma. Although the amount of uptake is variable, it is much higher than observed in idiopathic pulmonary fibrosis (IPF). It is speculated that the significantly higher amount of metabolism observed in sarcoïdosis mainly represents inflammation, whereas in IPF slightly increased FDG activity is the result of increased fibroblast glucose metabolism. The notion that not all fibrotic changes on HRCT show FDG activity supports the concept that HRCT cannot distinguish areas of on-going fibrogenesis from end-stage fibrotic lesions.
Gallium Scintigraphy—An Obsolete Technique?

Furthermore, we like to compare FDG PET with gallium scintigraphy. $^{67}$Gallium scintigraphy is a previously, widely used functional imaging tool for sarcoidosis. $^{67}$Gallium acts as a ferric iron analogue in the body and shows radioactive isotope accumulation in several nonspecific inflammatory processes, most importantly the activated macrophages, T-lymphocytes to a lesser degree, which can be found in granulomas. Specificity of the study is part dependent on the pretest likelihood, while some features of the scan can be suggestive of the disease such as the so-called “panda sign” or “lambda sign,” it is however not specific for sarcoidosis. The classical “panda sign” pattern (reflecting symmetrical inflammation to the lacrimal and parotid glands) is known from gallium scintigraphy, and typically found in Scadding stages I and II sarcoidosis. This pattern, however, does rarely appear on FDG PET. Another molecular imaging pattern is classically known as “lambda sign,” and reflects a bilateral mediastinal inflammation on gallium scintigraphy. This pattern is also found on FDG-PET; however, FDG PET is more sensitive. $^{67}$Ga scintigraphy also shows unrelated high uptake in organs such as in liver, spleen, and bone marrow. Despite the lower specificity of approximately 50%, lack of reliable method for quantification of findings and the relatively high radiation burden, $^{67}$Ga scintigraphy still showed some promise as a staging and monitoring tool. However, the clinical prognostic value $^{67}$Ga scintigraphy was limited in sarcoidosis. Moreover, many studies have demonstrated superiority of FDG PET/CT over $^{67}$Ga scintigraphy in both sensitivity and clinical value. In combination with higher radiation exposure in $^{67}$Ga scintigraphy, this makes FDG PET the imaging technique of first choice.

Is There a Role for Staging with FDG PET Imaging?

Now that the position of FDG PET in comparison with the other techniques of imaging is clear, one may discuss the role of FDG PET in the diagnostic work-up. During the work-up, imaging techniques play an important part in evaluating patterns of involvement of sarcoidosis. Staging and categorizing the disease activity based on imaging patterns has become common practice. Whether or not specific PET sub-patterns exist in sarcoidosis is debatable. To date, no scientific
Correlation of FDG PET with Biomarkers

In addition to imaging techniques, measurement of biomarkers and assessment of lung function play an important role during the work-up of sarcoidosis. In this paragraph, the correlation of FDG PET with biomarkers is discussed. The correlation with lung function will be the topic of the next paragraph.

Recently, FDG PET activity has been associated with several biomarkers measured either in bronchoalveolar lavage (BAL) fluid or blood. In BAL, inflammatory cells are known to be highly associated with disease severity. For example, a CD4/CD8 ratio higher than 3.5 shows a high specificity of 93 to 96% for sarcoidosis. In addition, the study of Keijser et al showed that an increased CD4/CD8 ratio found with BAL also correlates with increased pulmonary FDG PET activity. The latter finding has been confirmed by Mostard et al. Another biomarker in BAL is CD103. CD103 is also known as αEβ7 integrin and can be found on CD4+ T-lymphocytes in bronchi. A low ratio of CD4+ T cells expressing CD103 (CD103+CD4+) in BAL is found in sarcoidosis and this low ratio appears to correlate well with metabolic activity on FDG PET.

In addition, serum and blood biomarkers were studied with a focus on angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R). A study with newly diagnosed sarcoidosis showed that an increased concentration of ACE and sIL-2R levels correlated with a positive FDG PET in 92 and 94%, respectively. Also, Vorselaars et al demonstrated a significant correlation between mediastinal high metabolic activity and levels of sIL-2R. In another study by Sobic-Saranovic et al, the amount of positive FDG PET cases with normal ACE levels was 51% (38 patients). Therefore, FDG PET seems to reflect active disease more accurately than particular serum markers, such as ACE. These findings of a higher accuracy were also confirmed in serum sIL-2R, neopterin, and ACE levels. Normal biomarkers may not exclude the presence of inflammation, which is supported in several PET positive cases with a negative ACE (78%), CRP (68%), and to a lesser extent sIL-2R (32%) and neopterin (36%). These comparative studies demonstrate the potential use of FDG PET as a most sensitive biomarker for disease activity.

FDG PET and Pulmonary Function

Likewise to biomarkers, assessment of lung function is essential during the work-up of sarcoidosis. This paragraph sheds light to the correlation of pulmonary function tests (PFTs) and FDG PET. As granulomatous inflammation of lung tissue may lead to pulmonary function decline, PFTs are imperative in the evaluation of sarcoidosis. So far, a relation between PFT and HRCT findings has been established. HRCT patterns such as ground glass opacities, consolidation patterns, and honeycombing correlate with vital capacity (VC), and diffusion capacity of the lung for carbon monoxide (DLCO). HRCT adds to PFT in staging of disease severity and by visualizing fibrotic changes and complications such as aspergiloma. However, both PFT and HRCT need repeated measurements to detect change: both improvement as well as progressive disease. In addition to HRCT, FDG PET can demonstrate sites of ongoing granulomatous inflammation in the lung. As a consequence, a high metabolic pulmonary activity...
will be identified at an early stage in particular patients who are at increased risk of PFT decrease over time and/or development of fibrosis.

Keijsers et al. demonstrated this possibility using FDG PET in newly diagnosed sarcoidosis patients (with and without immunosuppressive treatment) and a control group. The VC, forced expiratory volume (FEV1), and DLCO were analyzed at baseline and after 1 year of follow-up. A significant decrease over a 1-year period in DLCO was found to be correlated with a decrease in DLCO after 1 year, when left untreated. DLCO, diffusion capacity of the lung for carbon monoxide; FDG, fluorodeoxyglucose; PET, positron emission tomography.

FDG PET in Cardiac Sarcoidosis

Apart from diagnostic and prognostic value, FDG PET is also beneficial in special forms of sarcoidosis, such as CS. In CS, pathology studies demonstrate myocardial involvement in predominant sites: the left ventricular wall followed by the papillary muscles, the interventricular septum, the right ventricular wall, and the atria. Although the updated guidelines of the Japanese Ministry of Health and Welfare for the diagnosis of CS do not include FDG PET in the work-up, FDG PET has shown to be a strong and promising tool to evaluate cardiac involvement. Images demonstrating CS on FDG PET are shown in Figs. 4 and 5. The focal appearance of FDG uptake strongly suggests cardiac involvement. However, either the diffuse or focal uptake pattern may represent CS. Sensitivity of diagnosis of CS with FDG PET has been reported to be high. A recent meta-analysis study showed a pooled estimate of 89% sensitivity and 78% specificity. In a cardiac MRI comparison study, FDG PET demonstrated a favorable sensitivity over MRI of 87.5 versus 75%, respectively. This is in line with the study by Mehta et al that showed a higher sensitivity of FDG PET over MRI (86 vs. 36%, respectively). Both MRI and PET scanning may be indicated in patients in whom the diagnosis of CS is uncertain.

In addition, an abnormal FDG PET scan is associated with an increased risk of major cardiac events. Japanese criteria demonstrated poor sensitivity and had no significant association with adverse events, suggesting an important added value of FDG PET beyond the Japanese guidelines. In CS patients with implantable cardioverter-defibrillators (ICD), positive FDG PET scans for CS in combination with positive MRI predicted a higher ventricular tachycardia and
FDG PET has not only been proven to be of significant value in detecting and monitoring CS but it has also been suggested to detect active neurosarcoïdosis. Nevertheless, large studies comparing FDG PET versus MRI in neurosarcoïdosis patients are lacking and it is unlikely that these will be performed in the future. First because the high metabolic activity of normal brain tissue limits the detection of small lesions, making FDG PET unfit as a routine measurement technique. Notwithstanding, it should be noted that FDG PET should not be excluded from the work-up in complex clinical cases, especially in complicated cases. The added value of FDG PET may become apparent when MRI is indecisive of the activity of suspected cerebral lesions. It is recommended that a MRI should be used as a baseline for anatomical comparison. This is also applicable to spinal cord sarcoidosis when establishing a definite diagnosis with MRI is problematic: patterns may well resemble spondylotic myelopathy or other noninflammatory spinal cord lesions. A retrospective study has demonstrated that spinal FDG PET uptake may then be helpful. On FDG PET, the lesions in spinal neurosarcoïdosis showed a significantly higher metabolic activity with a SUV than in other noninflammatory conditions.

FDG PET in Therapeutic Decision Making

As already indicated in CS, FDG PET may be of help in monitoring the effects of therapeutic interventions. The remission or normalization of abnormal FDG PET scans after therapy may then serve as a marker for treatment effect. It is shown that decline in uptake of FDG after corticosteroid therapy correlate well with clinical remission, more than radiological remission or serum ACE levels. In the same studies, FDG PET appeared to have significant influence on therapeutic decisions making: a negative FDG PET scan allowed physicians to decrease existing corticosteroid dose or discontinue them completely. There was a significant change in clinical management demonstrated in this study population: the therapy was initiated or changed in 81% of patients over the course of follow-up. However, this extent of impact on clinical management by FDG PET depends on the patient population, as a 57% change in the management is found in another study. Most patients with a positive FDG PET received higher doses of corticosteroids or another medication: methotrexate. Thus, it seems that persistent FDG PET activity during immunosuppressive treatment, despite normal ACE, could be used as an indicator for timing and/or adjusting immunosuppressive therapy.

Besides monitoring the clinical effects in immunosuppressive therapy, FDG PET has also been studied in patients treated with biologicals. First of all, patients with severe sarcoidosis, treated with adalimumab, showed a significant decrease in FDG uptake. In another study in patients with infliximab treatment, PET proved to be helpful in determining the response. The changes in lung parenchymal activity correlated significantly with the improvement in lung function, especially in VC. A larger infliximab study in 47 patients with severe sarcoidosis (87% stage IV) demonstrated high mediastinal activity on FDG PET which appeared to be a significant predictor for relapse, even more than when compared with serum levels of sIL-2R. A FDG PET scan could prove beneficial at baseline of therapy to predict relapse after discontinuation of infliximab. The changes on FDG PET after infliximab treatment. Overall, FDG PET shows potential in the clinical management and especially in therapeutic decision making when continuation of medication or treatment strategy is disputable.
Clinical Value of FDG PET Measurements

SUV has been introduced as a formula to calculate activity amounts and FDG PET scans are performed following a standardized protocol. The SUV represents the amount of glucose (i.e., disease) activity, which could be helpful for prognosis and response assessment.

In a study with infliximab (N = 12), the overall decrease in SUV (maximum value) from baseline was 55% (± 35). Patients with a normalization or improvement showed a decrease of 63% (± 22) with a range of −12 to −83%. The lung parenchyma showed a 26% improvement and was correlated with an improvement of VC. Parameters such as DLCO, ACE, or sIL-2R did not correlate with SUVmax. Another infliximab study (N = 47) demonstrated that patients with mediastinal SUVmax scores ≥ 6.0 have a significantly higher chance of relapse than patients with SUVmax scores < 6.0 (p < 0.001; HR, 3.77). In a study in refractory sarcoidosis treated with adalimumab, the SUV decreased significantly with a positive effect on the physical quality of life in majority of patients after treatment. These findings demonstrate that SUV measurements on FDG PET could be helpful for response assessment.

Fig. 6 Maximum intensity projections of a patient with severe, refractory sarcoidosis before (A) infliximab treatment and thereafter (B). Picture A demonstrates a highly metabolically active lung parenchyma as well as multiple affected lymph nodes, while after 1 year follow-up after treatment complete normalization on FDG PET is shown in picture B. This patient also showed biochemical and clinical response. The bottom line shows transverse fusion images.

Recommendations Based on Our Experience in the St. Antonius Hospital Nieuwegein (NL)

Based on the current literature and our experience of the application of the FDG PET in diagnostic work-up and management of sarcoidosis in our hospital (a tertiary referral institution), we would like to propose several recommendations for the implementation of FDG PET. Table 1 summarizes how FDG PET may contribute at the different stages in the clinical work-up. When diagnosing sarcoidosis, FDG PET appears to be more sensitive marker for disease activity than serum biomarkers such as sIL-2R, ACE, or neopterin. This is supported by the fact that when all routine findings are normal, FDG PET is still able to detect active inflammation in symptomatic patients with sarcoidosis. Another useful contribution of combined FDG PET/CT can be in finding occult organ localizations when biopsy is needed. FDG PET has expressed good sensitivity and specificity in these cases. When FDG PET demonstrates active lung inflammation and uptake in thoracic lymph nodes, these findings are associated with a higher probability of extrathoracic involvement. Active
Table 1 Summary of clinical value of FDG PET/CT in sarcoidosis

<table>
<thead>
<tr>
<th>Clinical context</th>
<th>Contribution of FDG PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>FDG PET/CT appears to be more sensitive than serum biomarkers for active disease</td>
</tr>
<tr>
<td></td>
<td>FDG PET/CT detects inflammation in symptomatic patients when all routine findings are normal</td>
</tr>
<tr>
<td></td>
<td>FDG PET/CT can be useful in finding occult organ localizations when biopsy is not available</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>Diffuse lung parenchymal activity in FDG PET/CT is associated with loss of pulmonary function after 1 year</td>
</tr>
<tr>
<td>Treatment decisions</td>
<td>Lung uptake values for FDG correlate with lung functional improvement upon increase of immunosuppressive treatment</td>
</tr>
<tr>
<td>Monitoring of specific organ involvement</td>
<td>FDG PET/CT can be used for organ-specific monitoring of disease activity in cardiac sarcoidosis, especially in patients with a pacemaker or ICD</td>
</tr>
</tbody>
</table>

Abbreviations: FDG, fluorodeoxyglucose; ICD, implantable cardioverter-defibrillators; PET, positron emission tomography.

Concluding Remarks

The past decade, FDG PET has emerged as a powerful tool to detect and help therapeutic decision making in sarcoidosis. In our tertiary referral institution, the position of FDG PET in the clinical decision making of complex sarcoidosis is evident. Based on our experience, FDG PET has a facilitating role in diagnosis, risk assessment, therapeutic decision making, and monitoring of specific organ involvement. We specifically recommend implementation of FDG PET to localize occult granuloma sites, to assess disease activity in symptomatic patients with normal biomarkers, longstanding sarcoidosis and/or stage IV disease, and to assess the presence of active CS.

References

360 FDG PET for Gauging of Sarcoid Disease Activity, Adams et al.


47 Costabel U, Bonella F, Ohshima S, Guzman J. Diagnostic modalities in sarcoidosis: BAL, EBUS, and PET. Semin Respir Crit Care Med 2010;31(4):404–408


52 Sobic-Saranovic D, Grozdic I, Vidović-Ivanov J, et al. The utility of 18F-FDG PET/CT for diagnosis and adjustment of therapy in


58 Doughan AR, Williams BR. Cardiac sarcoidosis. Heart 2006;92(2):282–288


79 Sakushima K, Yabe I, Shiga T, et al. FDG-PET SUV can distinguish between spinal sarcoidosis and myelopathy with canal stenosis. J Neurol 2011;258(2):227–230


