Role of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography in Focal and Generalized Infectious and Inflammatory Disorders

Athar Haroon,1 Alimuddin Zumla,2 and Jamshed Bomanji1

1Institute of Nuclear Medicine, University College London Hospitals NHS Trust, and 2Department of Infection, Division of Infection and Immunity, University College London Medical School, United Kingdom

Several advances in imaging have become part of the work-up for localization, diagnosis, and management of infectious diseases and inflammatory disorders. Utility of multiple imaging modalities is a time-consuming step, and significant numbers of patients remain undiagnosed despite utilization of series of tests. Inflammatory cells have avidity for fluorine 18–labeled fluorodeoxyglucose (18F-FDG), and thus positron emission tomographic–computed tomographic (PET-CT) hybrid imaging provides anatomical and metabolic information that can be used to define the extent of infectious and inflammatory diseases and assess response to treatment. PET-CT provides a “one-stop test” in which use of hybrid imaging provides anatomical and metabolic information. The extent of disease is defined quickly, and response to treatment can be assessed. This modality also helps define the metastatic and/or septic foci where there is lack of localizing symptoms. More recently, there is increasing awareness among clinicians regarding the ability of PET-CT to help in diagnosing, characterizing, and assessing inflammatory disorders. This article reviews the usefulness of this imaging modality.

Recent advances in molecular imaging have significantly improved diagnostic capabilities, patient management, and monitoring of treatment response. Positron emission tomographic–computed tomographic (PET-CT) hybrid imaging provides a “one-stop test” that can provide information on anatomy, physiology, and pathology. It is increasingly used to image infectious and/or inflammatory disorders; for example, it has shown promising results in patients with fever of unknown origin (FUO) and has gained much popularity for the identification of inflammatory foci in soft tissues or bone structures. Interventional radiologists and vascular surgeons use PET-CT with fluorine 18–labeled fluorodeoxyglucose (18F-FDG) to exclude vascular graft infection, and its ability to “localize” enables accurate differentiation between graft and soft-tissue infection [1]. This review covers the role of 18F-FDG PET-CT in focal and generalized infectious and inflammatory disorders, with emphasis on those in which PET-CT has had a significant impact.

SEARCH STRATEGY

We searched PubMed for literature published from December 1990 through December 2010. Our search terms were “PET/CT in infection” and “PET/CT in inflammation,” either as single terms or using MESH (861 articles, of which the 75 most relevant were selected). The search included case reports with clinical importance, review articles, and reports of false-positive or false-negative PET-CT results in inflammation, advantages and limitations of PET-CT in acute and chronic infections, and the role of PET-CT in...
differentiating pathological processes in patients with malignant neoplasms and superimposed infection.

**MOLECULAR AND PRACTICAL BASIS FOR THE USE OF \(^{18}\text{F}\)-FDG PET-CT**

Malignant cells exhibit enhanced glycolysis [2] because of increased glucose transport proteins or enhanced hexokinase activity [3, 4]. The same principle applies to infection and inflammation. The following mechanisms play an important role: (1) a cascade of inflammatory reaction in response to a stimulus, which results in enhanced glycolysis [5]; (2) an increased number of glucose transporters in the cells; and (3) enhanced affinity of glucose transporters for FDG [6–8].

Facultative glucose transporters (GLUT-1 through GLUT-7) mediate the transport of glucose and FDG into cells. Of these transporters, GLUT-1 has the highest affinity for FDG and is vital to the supply of glucose. Within the cell, GLUT-1 transporters are located at the plasma membrane and in intracellular vesicles. Upon stimulation, there is translocation of the GLUT-1 pool to the cell membrane. Lymphocytes demonstrate this effect within 30 minutes of stimulation [9], which explains the utility of \(^{18}\text{F}\)-FDG PET-CT in early inflammation and the attractiveness of the modality for clinicians.

Calculation of serial standardized uptake values (SUVs) helps differentiate inflammatory and benign processes from malignant processes. Some tumors with high SUVs tend to develop a more aggressive pattern of growth with further increase in SUVs, whereas inflammatory processes display a reduction in SUV on resolution. Benign lesions usually demonstrate low SUVs [10]. Fluorine 18 FDG PET-CT has certain advantages over morphological imaging modalities: (1) it detects metabolic activity at the cellular level and does not rely on nonspecific signs, such as edema or increased perfusion; (2) it provides whole-body imaging in a single session; and (3) it is not contraindicated by the presence of metal implants [11]. It also entails an acceptable radiation dose and offers high spatial and contrast resolution [10]. PET imaging has progressed from PET-only, scanners to hybrid PET-CT scanners, which enable anatomical localization of lesions, to hybrid PET-CT scanners, which enable anatomical localization of lesions. Table 1 lists radiopharmaceuticals for imaging infection and their uptake mechanisms.

**RESPIRATORY SYSTEM DISEASES**

**Sarcoidosis**

Sarcoidosis is a multisystem disease of unknown etiology that involves the formation of noncaseating granulomas. Initially there is nodal involvement, and later there is involvement of the lung parenchyma. In sarcoidosis, \(^{18}\text{F}\)-FDG PET-CT has better sensitivity than gallium 67 (\(^{67}\text{Ga}\)) scintigraphy and can detect early therapeutic response. Its use is recommended especially in atypical and advanced cases, in which distribution of disease and stage can be assessed with one test [12]. The various appearances of the disease hinder differentiation from metastatic disease or lymphaema, and detailed knowledge of these appearances is vital in accurately identifying multisystem involvement (Figure 1) [13]. Chowdhery et al [14] have described a “sarcoid-like reaction” to malignant neoplasms on \(^{18}\text{F}\)-FDG PET-CT, in which noncaseating granulomas may develop in patients with underlying cancer. Another recent study [15] suggested the value of combined \(^{18}\text{F}\)-FDG and \(^{18}\text{F}\)-fluorothymidine (\(^{18}\text{F}\)-FLT) PET in differentiating sarcoidosis from malignancy. Multiple FDG-avid nodes with mild \(^{18}\text{F}\)-FLT accumulations support sarcoidosis.

Correct assessment of disease activity is vital for patient management as the spectrum of disease ranges from mild and self-limiting to (rarely) death soon after diagnosis [16]. It has been reported that \(^{18}\text{F}\)-FDG PET identifies 15% more disease sites than conventional imaging modalities, such as CT [17], and it has been found to be useful in cases with osseous, neurological, and cardiac involvement [18–20].

In summary, \(^{18}\text{F}\)-FDG PET-CT is a promising technique for metabolic evaluation of this multisystem disease. It can identify more disease sites and is of value in identifying potential biopsy sites and treatment response. It should be noted, however, that positive \(^{18}\text{F}\)-FDG PET-CT findings in isolation do not constitute an indication for treatment [17].

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**Table 1. Radiopharmaceuticals for Imaging Infection and Uptake Mechanisms**

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Uptake Mechanism</th>
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<tr>
<td>(^{67}\text{Ga})-citrate</td>
<td>Transferrin and lactoferrin receptor binding</td>
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<tr>
<td>(^{99}\text{Tc})-nanocolloids</td>
<td>Nonspecific via capillary permeability and active uptake in activated endothelial cells</td>
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<tr>
<td>(^{99}\text{Tc})- or (^{111}\text{In})-labeled human immunoglobulin</td>
<td>Nonspecific via increased capillary permeability</td>
</tr>
<tr>
<td>(^{111}\text{In})-oxine or (^{99}\text{Tc})-HMPAO</td>
<td>Specific chemotactic activation</td>
</tr>
<tr>
<td>(^{99}\text{Tc})-labeled granulocytes</td>
<td>Increased capillary permeability and specific binding or uptake as antibody-labeled granulocytes</td>
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<tr>
<td>(^{18}\text{F})-fluorodeoxyglucose</td>
<td>Up-regulated glucose transporter 1 in activated granulocytes, lymphocytes, and monocytes</td>
</tr>
</tbody>
</table>

Abbreviations: \(^{18}\text{F}\), fluorine 18; \(^{67}\text{Ga}\), gallium 67; \(^{99}\text{Tc}\), technetium 99m; \(^{111}\text{In}\), indium 111; HMPAO, Hexamethylpropyleneamine Oxime.
Tuberculosis
Fluorine 18 FDG PET-CT can be used to detect active tuberculosis in asymptomatic and extrapulmonary disease [21]. Malignancies and immunosuppressive therapy carry a risk of reactivation and progression of tuberculosis [22], but in patients with malignant neoplasms there is a danger of late diagnosis because lymphadenopathy may be due to the malignancy itself. Fluorine 18 FDG PET-CT has facilitated the diagnosis of tuberculosis in patients with malignant neoplasms such as non-Hodgkin lymphoma and lung and colon tumors [23]. It has been suggested that multifocal pathological processes in patients with malignant neoplasms from certain geographic regions should raise the possibility of tuberculosis [21]. There may be overlap of SUVs in malignant neoplasms and tuberculosis, and dual-point 18F-FDG PET-CT may help differentiate benign from malignant disease [24]. In tuberculosis, antimicrobials are prescribed for longer periods, and conventional imaging modalities may show persistent abnormalities. In such cases, PET-CT can monitor the metabolic response and help in analyzing the response to treatment [25]. In clinical scenarios such as chronic granulomatous disease, PET-CT findings can be useful in determining the appropriate duration of treatment [21]. PET-CT also helps localize and define disease extent at extrathoracic sites. Latent infection in high-risk patients should be confirmed with culture-positive disease. Treatment may be initiated if the patient is symptomatic, because there is a risk of drug resistance [26].

Fungal Infections
The main challenge for clinicians in the management of immunocompromised patients is appropriate adjustment of the therapeutic regimen. Lesions in patients with chronic focal [27] and disseminated fungal infections may persist long after completion of treatment [28], and CT plays only a limited role in assessing therapeutic response that is further hampered by the complications associated with antifungal agents. Fluorine 18 FDG PET-CT may offer a solution because it provides metabolic information of value in monitoring response to antifungal treatments and guiding the adjustment and termination of those treatments. Xu et al [29] have demonstrated that changes in FDG activity (SUV max) on PET imaging are a more accurate reflection of disease activity than are changes in lesion size, and they observed that an increase in SUV was associated with disease progression, and vice versa.

Miscellaneous Chest Disorders
Fluorine 18 FDG PET-CT can assist in localizing various inflammatory conditions of the thoracic cavity, including lung abscess [30], pneumonia [31], aspergillosis [32], local allergen-invoked inflammation in asthma [33], and mediastinitis [34].

PLEURA AND PLEURAL CAVITY
PET-CT is helpful in interpreting whether the pleura is involved by inflammation or malignancy and can provide metabolic information on pleural effusion, which can be primary (in cases of bacterial infection or neoplasia) or secondary (as a complication of underlying disease). Plain radiography, ultrasound, and CT of the chest are routinely used to evaluate the pleural cavity, with CT being the most effective. As in the case of lymph nodes, malignant neoplasms and infections of the pleural cavity display overlapping features. Moreover, empyema may resolve and leave fibrotic changes simulating malignancy. Recently, a role for 18F-FDG PET has also been described for malignant neoplasms associated with chronic empyema [35], such as non-Hodgkin lymphoma, squamous cell carcinoma, malignant mesothelioma, liposarcoma, and hemangoendothelioma [36, 37].

Focally increased FDG uptake (malignant portion) in conjunction with scant FDG uptake in the surrounding empyema is suggestive of malignancy with background low-grade inflammation [35]. A recent study by Duysinx et al [38] found that 18F-FDG PET has a sensitivity and specificity of 96.8% and 88.5%, respectively, for differentiating benign pleural diseases from malignancy. In this study of 98 patients, 4 lesions with benign etiologies were found to have intense FDG uptake whereas low-grade uptake was observed in 2 of 50 malignant pleural lesions. All mesotheliomas were intensely FDG avid. The authors admitted that “moderate uptake of FDG” is a poor

Figure 1. Coronal fused fluorine 18–labeled fluorodeoxyglucose (18F-FDG) positron emission tomographic (PET)–computed tomographic (CT) (A) and coronal 18F-FDG PET (maximum intensity projection) (B) images of a patient with visceral involvement by sarcoid. Sarcoid is a multisystemic disease; this patient has cardiac, splenic, and liver involvement. Abbreviations: L, left; R, right.
discriminator. On the other hand, lack of FDG uptake should generally allow clinicians to avoid invasive tests (exceptions being asbestos-related effusions and pleural tuberculosis).

Another study by Kramer et al [39] suggested PET to have a 92% negative predictive value for discrimination of benign and malignant pleural thickening. They suggested that patients with pleural thickening and negative PET findings should be followed up by CT only, whereas a positive PET finding should be verified by tissue diagnosis.

**MUSCULOSKELETAL SYSTEM**

**Osteomyelitis**

Findings of morphological imaging with radiography, ultrasound, CT, and magnetic resonance (MR) imaging is non-specific in cases in which active infection has to be differentiated from postoperative complications of reparative work, and artifacts associated with metallic implants further complicate diagnosis. In the absence of single photon emission CT (SPECT–CT), conventional nuclear medicine techniques (eg, 3-phase scintigraphy and gallium scintigraphy) have poor spatial resolution. Fluorine 18 FDG PET-CT has been found to show high sensitivity and specificity in localizing musculoskeletal infections and evaluating chronic osteomyelitis (Figure 2), spinal infections, and acute and chronic infections in the axial and appendicular skeleton [40]. In posttraumatic osteomyelitis, Hartmann et al found 18F-FDG PET-CT to have a sensitivity, specificity, and accuracy of 94%, 87%, and 91%, respectively, for the whole group, 88%, 100%, and 90% for the axial skeleton, and 100%, 85%, and 91% for the peripheral skeleton [41]. Guhlmann et al [42] reported that 18F-FDG PET-CT was superior to technetium 99m (99mTc)–labeled anti-granulocyte antibody scintigraphy for detecting chronic osteomyelitis in the axial skeleton.

**Diskitis**

Degenerative changes in the spine are most commonly described according to the Modic-type end-plate change, that is, type 1 (decreased signal intensity on T1-weighted and increased signal on T2-weighted images) or type 2 (increased on T1-weighted and isointense or slightly increased signal on T2-weighted images) [43], based on the MR imaging classification system. Early degenerative changes may simulate infection. Because stimulation of granulocytes and macrophages is not a feature of degenerative disease process, there is less FDG uptake than in cases of infection. Although MR imaging is highly accurate and sensitive in detecting vertebral osteomyelitis, 18F-FDG PET may help differentiate degenerative and infectious end-plate abnormalities [44, 45]. The authors of the latter study demonstrated that even in active (Modic type I) degenerative changes, 18F-FDG PET-CT did not demonstrate increased avidity.

**Metal Implants**

Conventional imaging modalities, such as CT and MR imaging, are limited after arthroplasty owing to the presence of metal artifacts. Although it is feasible to image titanium-based metal implants, the positioning of the patient and the variability of prostheses are potential limitations [46]. Use of combined Indium 111 (111In)–labeled white blood cells and 99mTc-MDP with SPECT-CT allows diagnosis of prosthetic or bone infection with sensitivity of 84%–97% and specificity of 98%–100%. Although 18F-FDG PET has good sensitivity (91%–100%) in patients with metal implants, its specificity is variable [47]. Manthey et al [48] have used 18F-FDG to differentiate between active infection, loosening, and synovitis. High-grade uptake of FDG was associated with infection, intermediate uptake with aseptic loosening, and low-grade uptake with synovitis.

**Diabetic Foot**

MR imaging demonstrates precise anatomical details but is technically limited in differentiating bone marrow edema and infection. Clinically suspected osteomyelitis in diabetic foot and abnormal radiographs still warrant MR imaging, but if MR imaging findings are positive, 18F-FDG PET-CT is indicated.
owing to its far greater specificity [49]. It is anticipated that in the future, combined MR imaging–PET will show improved specificity and sensitivity, avoiding the need for invasive procedures.

**CARDIOVASCULAR SYSTEM**

**Infective Endocarditis**

The incidence of systemic embolization is increased in patients with mobile vegetations of >1 cm [50], and PET-CT can be of value in imaging such vegetations (Figure 3). Metastatic infection can involve any organ, including skin, with rapid onset and deterioration. When the utility of 18F-FDG PET-CT was studied within 2 weeks after diagnosis of infective endocarditis [51], its diagnostic accuracy was found to be superior to that of high-dose CT for metastatic infection. Only 1 false-positive finding was reported. Among 25 patients, PET-CT had therapeutic implications in 7 patients (4 patients underwent operation based on PET-CT findings with concordance between PET-CT results and surgical findings).

**Pericarditis**

Myocardial tracer uptake limits the role of FDG. Incidental findings of pericarditis have been reported when patients with FUO have been investigated with 18F-FDG PET-CT [52]. Fluorine 18 FDG PET-CT helps assess the degree of inflammatory activity around the pericardium, without requiring additional invasive procedures. Pericarditis may occur in isolation or with myocardial involvement (perimyocarditis) [53]. Whole-body imaging with 18F-FDG PET-CT facilitates identification of spread of disease from the lungs and assessment of therapeutic response [54].

**VASCULAR DISORDERS**

**Vasculitis**

18F-FDG PET-CT has been reported to demonstrate vasculitis in cases in which 67Ga imaging has not shown any abnormality [52, 55–58]. There have been varying reports with regard to different types of vasculitis. The main value of 18F-FDG PET-CT is in the diagnosis of large-vessel vasculitis (Figure 4); specificities of 89% and 100%, respectively, have been reported for giant cell arteritis and Takayasu arteritis [55]. Uptake along the arterial wall in a linear configuration is the typical pattern, but patchy uptake along the vessel wall has also been described. There are varying and conflicting reports regarding the relation between the SUV and inflammatory activity. Koyabashi et al [59] found that although the SUV does not seem to correlate with disease activity, it is useful in monitoring treatment response. Giant cell arteritis and polymyalgia rheumatica demonstrate increased uptake in the aortic arch, subclavian artery, and lower-limb vessels [60–62], whereas in
Takayasu arteritis, uptake is seen in the aorta and the brachiocephalic, carotid, and subclavian arteries.

Vascular Graft Infections

Acute vascular graft infections can present within 4–6 weeks after surgery as a draining fistula to the groin in patients with aortofemoral and iliofemoral grafts. Two patterns of FDG uptake have been observed after vascular graft surgery: (1) linear, along the graft wall, representing a physiological inflammatory response to foreign body, which may persist for years [1] and (2) focal, characteristic of graft infection. The combination of PET and CT helps localize infection in the graft and surrounding soft tissues [1]. False-positive results have been reported in cases of hematoma adjacent to the graft, although CT was also unhelpful in distinguishing the hematoma from the vascular wall [63].

CENTRAL NERVOUS SYSTEM

The high background metabolic activity complicates the use of 18F-FDG PET-CT in imaging brain parenchyma. Compared with malignant neoplasms, fewer data are available on the feasibility of using PET-CT to image cerebral infections. Most such infections are known to demonstrate “reduced” uptake in the brain parenchyma. Toxoplasmosis demonstrates reduced tracer uptake on 18F-FDG PET-CT, whereas cerebral lymphoma shows increased metabolic activity [64]. Mascarenhas et al [65] provided 2 possible explanations for reduced uptake in infection: (1) administration of antibiotics prior to PET-CT and (2) presence of a weak immune system in immunocompromised patients. Varying patterns of uptake have been described, including focal, as in Nocardia infection [65], ring enhancing, as in Corynebacterium infection [66], and diffuse and hypometabolic, as in Lyme disease [67]. Overall, 18F-FDG PET has a rather limited role owing to the excellent anatomical detail provided by MR imaging and CT.

FEVER OF UNKNOWN ORIGIN

Fever of unknown origin (FUO) has been defined as a “sustained febrile illness (body temperature ≥38°C) exceeding 3 weeks in duration without diagnosis after 1 week of investigations in a hospital or in an outpatient department.” This definition has since been modified, for example, by incorporating 3 outpatient visits [16].

Fluorine 18 FDG PET-CT is replacing conventional scintigraphic investigations, including 67Ga- and 111In-labeled leukocyte scintigraphy, for imaging of FUO [16]. It was found to be useful in 50% of cases investigated for FUO [68], with a range of 16%–69% [69]. In patients with a normal clinical examination, the probability of reaching a diagnosis was higher if 18F-FDG PET findings were abnormal [70].

There are structured algorithms for the investigation of FUO. Fluorine 18 FDG PET has been tried as a first-line investigation and proved useful in 33% of cases [71]. It has been recommended that chest and abdominal CT should be performed as first-line investigations, with use of PET-CT as a second-line investigation if these results are inconclusive. The aim should be to avoid invasive investigations [68]. A study by Bleeker-Rovers et al [69] reported that 18F-FDG PET yields false-positive results in only 1% of patients with FUO.

A variety of pathological processes have been detected by 18F-FDG PET in patients with FUO, including multisystem inflammatory conditions such as vasculitis [72], osteomyelitis [42] (Figure 5), pelvic inflammatory disease [73], infections in immunocompromised patients, (eg, respiratory tract infections) (Figure 6), and nonspecific lymphadenopathy (Figure 7).

ALTERNATIVES TO 18F-FDG

Although 18F-FDG is among the most commonly used PET probe [74], other emerging tracers target different cell
processes, such as hypoxia ($^{18}$F-fluoromisonidazole), apoptosis ($^{18}$F-labeled annexin) and angiogenesis ($^{64}$Cu-DOTAPEGE [c(RGDyK)]₂ and $^{18}$F-Galacto-RGD) [75]. These provide information about lesions, disease establishment, progression, and treatment.

CONCLUSIONS

Anatomical delineation of infection with precise localization of involved abnormal areas is a significant challenge for which PET-CT, as an evolving novel technique, holds promise. Whole-body imaging, correct anatomical localization, metabolic information, and high spatial resolution are some of the advantages offered by PET-CT in comparison with conventional nuclear medicine and radiology techniques. Indications for $^{18}$F-FDG PET-CT are well established in sarcoidosis, tuberculosis, osteomyelitis, endocarditis, vasculitis, vascular graft infections, and FUO. The role is debated in fungal infections, asbestosis, pericarditis, and central nervous system infections. The aim of the diagnostic pathway should be to detect infection before tissue necrosis and abscess formation set in. With evolving trends in PET imaging it is anticipated that PET–MR imaging will combine excellence in radiology and nuclear medicine, thus improving sensitivity and specificity.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


Figure 6. Fused coronal fluorine 18–labeled fluorodeoxyglucose positron emission tomographic–computed tomographic image showing diffuse increased uptake in trachea (arrow), extending into the proximal bronchi bilaterally, in the trachea of a patient with tracheobronchitis.

Figure 7. A, Whole-body fluorine 18–labeled fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomographic image (maximum intensity projection) of a patient with human immunodeficiency virus infection, showing increased FDG tracer uptake in the axillary lymph nodes bilaterally (arrows). B, corresponding coronal computed tomographic image showing bilaterally axillary lymphadenopathy (arrows).
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