

# Role of Modern Imaging Techniques for Diagnosis of Infection in the Era of $^{18}\text{F}$ -Fluorodeoxyglucose Positron Emission Tomography

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## INTRODUCTION

Early diagnosis or exclusion of infection and inflammation is of utmost importance for the optimal management of patients with such common disorders. However, in certain settings, these diagnoses can be made without difficulty; in most others, clinicians encounter substantial challenges in detecting and localizing the exact sites of infection. Modern imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent structural resolution for visualizing advanced diseases including those related to infection and inflammation. However, these modalities are generally of limited value in detecting early disease regardless of the cause. Therefore, functional and metabolic imaging techniques are often needed to complement the role of anatomic imaging modalities in most clinical settings.

Over the past three decades, we have witnessed the introduction of several scintigraphic techniques, particularly radiolabeled white blood cell (WBC) imaging, for examining patients with suspected infection or inflammation (13, 151). Unfortunately, these approaches suffer from substantial shortcomings. These methodologies are time-consuming, labor-intensive, and costly, and the results may not be available for at least 24 h, which may delay optimal treatment for most pa-

tients. Furthermore, the conventional planar imaging that is utilized with these techniques has a limitation for the exact localization of affected sites in most anatomic regions of the body. Moreover, the sensitivity of these methods is relatively low, and in particular, the detection of infection and inflammation in certain locations such as skeletal structures with significant red marrow activity is quite difficult. Lastly, there are concerns about the safety of these preparations because of the potential for contamination with a variety of pathogens (137). Recently introduced radiolabeled antibodies for the detection of sites of infection were withdrawn from the market because of serious side effects in patients. Therefore, there is a great desire to employ a methodology that may overcome many of these shortcomings.

The concept of positron emission tomography (PET) with  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) was born in 1973, when the feasibility of radiolabeling deoxyglucose (DG), a glucose analogue, for in vivo imaging purposes was proposed. Soon thereafter, a major initiative was undertaken to synthesize this compound for imaging brain function in healthy and disease states (7). By the mid-1970s, DG was successfully labeled with  $^{18}\text{F}$  for the external imaging of the distribution of this radiotracer in the brain and the remainder of the body. Following the first successful synthesis of FDG, the first human study was performed with this compound in 1976 at the University of Pennsylvania, which included images of both the brain and the whole body using very primitive techniques. The initial focus of research with FDG was aimed at the determination of regional

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brain function in normal subjects and in subjects following physiological activation. In addition, this agent was used to investigate the effects of a multitude of neuropsychiatric disorders on regional brain function (3, 4, 6, 8).

The introduction of whole-body imaging techniques with PET in the latter part of the 1980s opened new avenues of research for examination of glucose metabolism in other organs and anatomic sites. Based on the observations made by Warburg in the 1930s, it was known that malignant cells have significantly elevated glycolysis (132, 162). Therefore, it seemed logical that whole-body FDG-PET imaging could allow the detection and quantitative assessment of disease activity in patients with a variety of malignancies. This methodology was used for the diagnosis, staging, treatment planning, and treatment monitoring of malignant disease (49, 68, 69, 88, 89, 180). The introduction of PET/CT technology has added another dimension to FDG-PET imaging and has further enhanced its role in managing patients with cancer.

In spite of the great successes achieved by FDG-PET imaging in the evaluation of malignant disorders, the test is non-specific for cancer. In fact, soon after the introduction of this technique for human studies, it was noted that lesions with substantial numbers of inflammatory cells also take up FDG. Therefore, in the appropriate settings, FDG-PET imaging can be effectively employed to detect and characterize infectious and inflammatory processes. As such, in recent years, the range of applications for this technique has been broadened to include the evaluation of a variety of nonneoplastic disorders (56, 156). The enhanced uptake of FDG in activated inflammatory cells such as lymphocytes or macrophages is related to significantly increased levels of glycolysis as a result of increased numbers of cell surface glucose transporters, particularly after cellular stimulation by multiple cytokines (27, 111, 150, 171). Interestingly, it has been shown that malignant tissues often contain large numbers of inflammatory cells, and therefore, a fraction of FDG uptake in such tissues can be attributed to the increased glycolysis in these cells (87).

These initial observations in the literature eventually led to the systematic assessment of the value of FDG-PET in settings where the detection or characterization of infection or inflammation is the main focus of investigations. Early experience at the University of Pennsylvania and some European institutions demonstrated that FDG-PET is quite sensitive for detecting infection in complicated orthopedic conditions (40, 74, 108, 177, 178). Controlled animal experiments further clarified the phenomenon of increased glycolysis in inflamed tissues and demonstrated the superiority of FDG-PET compared to other nuclear medicine techniques in such settings (72, 84, 139, 181).

FDG-PET and FDG-PET/CT have many advantages over other nuclear medicine imaging modalities for the diagnosis of infectious and inflammatory diseases. These advantages include the feasibility of securing diagnostic results within 1.5 to 2 h, optimal spatial resolution (CT), high target-to-background contrast, and accurate anatomical localization of sites of abnormality (41). Compared to anatomical imaging modalities such as CT, MRI, and ultrasonography, FDG-PET imaging provides the following advantages: whole-body coverage, high sensitivity, lack of artifacts due to metallic hardware, and absence of reactions to administered pharmaceuticals. While hyperglycemia affects the accuracy of FDG-PET for evaluating

suspected or confirmed malignancy, mild to moderate hyperglycemia (<250 mg/dl of serum glucose) generally does not appear to have an observable effect when this technique is utilized to detect infection or inflammation (90, 95, 160, 184).

In recent years, dual-time-point imaging with FDG-PET or FDG-PET/CT has been proposed as a method to differentiate between malignant and inflammatory processes in settings where such a distinction is essential for optimal patient management. This is due to the observation that standardized uptake values (SUVs) of inflammatory and nonneoplastic lesions tend to remain stable or decrease, while those of the malignant lesions tend to increase over time (33, 169, 181).

Certain conditions have been shown to increase FDG uptake: (i) benign infection of the lungs or mediastinum (100, 102, 146, 167, 179), appendix (82), gall bladder (80, 173), and many other organs (64, 70, 114, 135, 140); (ii) inflammation without infection, including sarcoidosis (55), pulmonary artery thrombosis (50), abdominal aortic aneurysm (37), and inflammatory arthritis (75); (iii) normal variants, such as brown fat (131), ovaries during ovulation (147), calyceal diverticula (76), the postpartum uterus (93), and activated respiratory muscles in patients with chronic obstructive pulmonary disease (11) or other conditions (172); (iv) atrogenic conditions, such as those related to immunization (165), barium aspiration (51, 94), and intravenous line or pacemaker infection (110, 159); (v) trauma (67, 115), whether spontaneous or following surgery (14, 174); and (vi) benign processes such as elastofibroma dorsi (124, 163), progressive fibrosis, and benign mesenchymal tumors (30, 83, 105, 161). Although infectious or inflammatory processes frequently pose a diagnostic challenge in the evaluation of patients with cancer (148), the possibility that malignant lesions may also mimic infectious or inflammatory disease (9, 28) should not be overlooked. This is particularly important when examining a patient with fever of unknown origin (FUO).

In this review, we will focus on the utility of modern imaging modalities in the setting of suspected infection or inflammation and on the role of FDG-PET in the management of patients with suspected or confirmed infection.

### Anatomical Imaging Modalities

CT and MRI are commonly used for the detection and characterization of infectious or inflammatory conditions that may involve various organ systems of the body. Both methods have substantial strengths, which include high spatial resolution, tomographic imaging, relatively good soft tissue contrast between normal structures and diseased sites, and a short examination time (generally less than 5 to 10 min for CT and less than 20 to 30 min for MRI), and, if desired, the examination can be extended to include the entire body. However, this is not done in most clinical settings. In general, CT is better suited for an evaluation of certain structures such as the lung parenchyma, airways, bowel, and cortical bone, whereas MRI is more useful for the evaluation of internal architecture of other structures such as the bone marrow, muscles, tendons, ligaments, cartilage, and small organs such as the prostate gland, testes, cervix, and uterus (44). CT imaging is associated with substantial radiation to the organs examined, which limits its use at frequent intervals. In contrast, MRI uses electromagnetism, which is considered to be harmless with the current

techniques employed. However, both CT and MRI are generally limited by their poor sensitivity for detecting early stages of disease at the molecular and cellular levels where no alterations in gross organ and tissue structures have occurred (5). They are also limited by a lack of specificity of many of the imaging findings that are noted in the setting of infection or inflammation.

## INDICATIONS FOR FDG-PET

### Skeletal Infection

**Osteomyelitis.** Osteomyelitis is a bone infection and is usually caused by bacterial, fungal, or mycobacterial microorganisms. Osteomyelitis can be subdivided into the acute, subacute, or chronic type based on the time course of disease. Acute osteomyelitis usually does not pose a diagnostic challenge to clinicians, as systemic symptoms such as fever, fatigue, and malaise along with localized signs including reduced motion, pain, and tenderness of the involved bone usually aid in making the correct diagnosis. However, the accurate diagnosis of subacute or chronic osteomyelitis is often difficult by physical examination and existing radiological or nuclear medicine techniques, particularly when there are preexisting alterations in osseous structures due to previous trauma or surgery. Although the use of radiolabeled WBC imaging in combination with bone marrow scintigraphy has been reported to be highly accurate for detecting chronic osteomyelitis, the role of these scintigraphic techniques appears to be limited in most clinical settings.

(i) **Anatomical imaging modalities.** Plain-film radiography can show typical findings of bone destruction and soft tissue swelling, although they may not be apparent during the early phases of disease (46). It usually takes 2 to 3 weeks for an osseous lesion to become visible on plain-film radiography because significant loss of bone density must occur before such changes become apparent. This is a significant problem in the pediatric population because delayed therapy in this age group can result in the destruction of growth plates with subsequent cessation of bone growth (118). In addition, in the plain-film radiographic evaluation of chronic osteomyelitis, the signs are often not specific. Moreover, in the pediatric population, the epiphyses are only partially ossified, and therefore, epiphyseal destruction may be difficult to recognize on plain-film radiography. Similar to conventional radiography, CT detection of osteomyelitis relies on determining changes in bone structure, and therefore, it generally cannot detect early osteomyelitis. MRI has high accuracy in the evaluation of acute osteomyelitis and adjacent soft tissue infection, particularly when no prior alterations in osseous or soft structure are present. However, in patients who have undergone prior surgical intervention, MRI may not be able to distinguish between bone marrow edema or enhancement related to a reactive phenomenon and that related to infection. In addition, the diagnostic accuracies of both CT and MRI to evaluate for osteomyelitis generally decrease in the presence of metallic implants due to streak and susceptibility artifacts, respectively.

(ii) **Conventional nuclear medicine scintigraphy.** Three-phase bone scanning with  $^{99m}\text{Tc}$  methylene diphosphonate and its analogues has long been utilized to evaluate patients with

suspected osteomyelitis (36, 112, 130) with a relatively high sensitivity and is currently considered to be the nuclear medicine imaging test of choice for the early diagnosis of osteomyelitis. Bone scintigraphy can effectively detect osteomyelitis within 24 h after the onset of symptoms (60). However, the specificity of the three-phase bone scintigraphy is not high, particularly in patients with prior traumatic injury to the osseous structures, with metal prostheses, or with neuropathic joints. Furthermore, it is frequently difficult to distinguish osteomyelitis from other pathologies such as fracture or malignancy.

Radiolabeled WBC imaging is also utilized to detect osteomyelitis, as its specificity is generally greater than that of bone scintigraphy. However, in patients who have received antibiotic therapy prior to imaging, there is low sensitivity to this test due to the poor migration of the leukocytes to sites of infection (45). In addition, radiolabeled leukocyte imaging has little value in the evaluation of osteomyelitis involving the axial skeleton, where the sensitivity is approximately 60% for acute (122) and 21% for chronic (158) osteomyelitis due to the poor contrast between the sites of infection and the surrounding red marrow. In other words, the degree of migration of labeled WBCs to these sites is not substantial enough to be distinguishable from that of normal marrow. Furthermore, in patients with low WBC counts, radiolabeled leukocyte scintigraphy is not practical because of poor harvesting of the required number of cells for labeling and the low concentrations of such preparations at sites of infection.

Laboratory tests such as determinations of the erythrocyte sedimentation rate and C-reactive protein level are also insensitive and nonspecific for the accurate diagnosis of chronic osteomyelitis.

(iii) **FDG-PET.** FDG-PET has been shown to be highly sensitive for detecting chronic osteomyelitis, even in patients who have been treated with antibiotics prior to imaging (177). This is in contrast to WBC imaging, where the sensitivity of the test is significantly affected by prior use of antibiotics. Several publications in the literature reported the superiority of FDG-PET over imaging with radiolabeled WBCs, with an accuracy exceeding 90% in this clinical setting (40, 57, 74).

Guhlmann et al. (56, 57) reported a higher accuracy for FDG-PET than antigranulocyte antibody scintigraphy for the evaluation of infection involving the central skeleton in patients with suspected chronic osteomyelitis. de Winter et al. (40) prospectively evaluated the role of FDG-PET in the diagnosis of chronic musculoskeletal infections in 60 patients with recent surgery and reported a sensitivity, specificity, and overall accuracy of 100%, 86%, and 93%, respectively. In another prospective study, Meller et al. (108) studied 30 patients with suspected chronic osteomyelitis and concluded that FDG-PET is superior to  $^{111}\text{In}$ -labeled WBC imaging in establishing a diagnosis of chronic osteomyelitis in the central skeleton. In a study by our own group (177), which utilized FDG-PET to detect chronic osteomyelitis, the authors concluded that FDG-PET holds great promise in the diagnosis of chronic osteomyelitis and that a negative FDG-PET study essentially excludes the presence of this disorder. In a study designed to evaluate the utility of FDG-PET to diagnose infections, Chacko et al. (25) noted that in contrast to conventional nuclear medicine



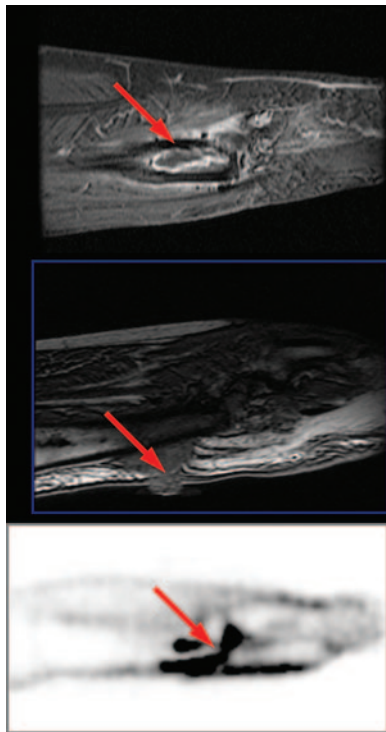


FIG. 1. Avid FDG uptake in the sinus tract (arrow) connecting soft-tissue abscess with the modularly track of the femur in a patient of proven chronic osteomyelitis. Corresponding MR abnormalities are also shown.

techniques such as gallium scintigraphy and radiolabeled WBC imaging, FDG-PET has high spatial and contrast resolution and can distinguish soft tissue infection from osteomyelitis.

Several groups also investigated FDG-PET imaging for assessments of both acute and chronic osteomyelitis. In a retrospective study, Kalicke et al. (74) evaluated the role of FDG-PET in acute osteomyelitis, chronic osteomyelitis, and inflammatory spondylitis. They examined 15 patients who underwent surgery because of suspected bone infection and therefore histopathological confirmation of the underlying diagnosis. Of these 15 patients, 7 had acute and 8 had chronic osteomyelitis or inflammatory spondylitis. FDG-PET yielded

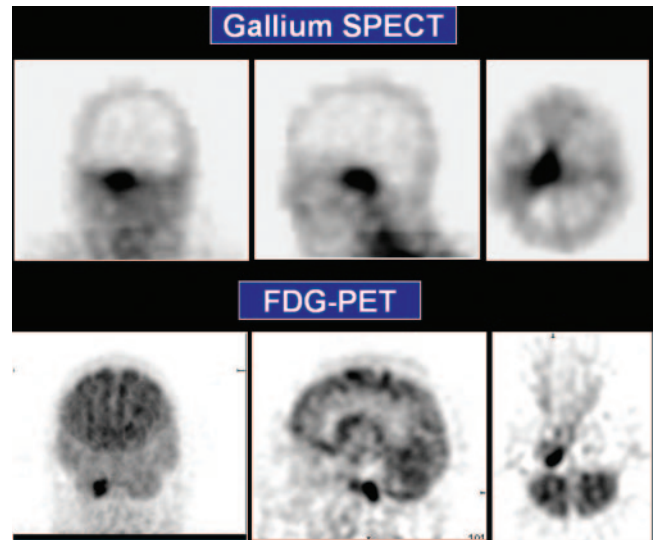


FIG. 3. Avid FDG uptake in the focus of infection in a patient of proven malignant otitis with corresponding <sup>67</sup>Ga citrate-SPECT images. Please note that PET images reveal the sites of the disease more precisely than those of SEPCT.

true-positive results for all 15 patients, while bone scintigraphy performed in 11 patients yielded 10 true-positive results and 1 false-negative result. Those authors concluded that FDG-PET is an optimal technique for the diagnosis of bone infection. Moreover, follow-up FDG-PET scans performed on two patients showed a normalization of FDG uptake, which correlated well with clinical improvement in these patients.

FDG-PET appears to be the study of choice when chronic osteomyelitis is suspected (Fig. 1, 2, and 3). This is particularly true when this type of infection is suspected in the axial skeleton (Fig. 2) or anywhere else where there is a significant concentration of red marrow. In contrast to bone scintigraphy, which remains positive for an extended period of time following fracture (103), FDG uptake generally normalizes in less than 2 to 3 months following such incidents (145, 182). As a result, this reduces the incidence of false-positive results as in the case of bone scanning when osteomyelitis is suspected in

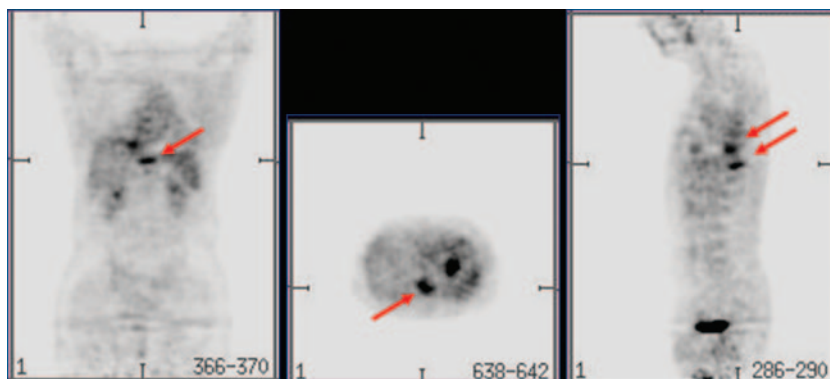


FIG. 2. Foci of FDG uptake in chronic osteomyelitis of the thoracic spine in two adjacent vertebral bodies. Radiolabeled WBC imaging in general has a low yield in this setting.

the setting of complex fractures. Therefore, FDG-PET is particularly suitable for the evaluation of suspected chronic osteomyelitis in patients with prior trauma (62). In an experimental study by Koort et al. (84), who evaluated whether FDG-PET can differentiate between normal healing bones and those with osteomyelitis, localized osteomyelitis and fracture models of the rabbit tibia were created. In the aseptic fracture group, uncomplicated bone healing was associated with an initial increase in FDG uptake at 3 weeks, which subsequently returned to normal by 6 weeks. However, in the osteomyelitis group, localized infection resulted in an intense continuous uptake of FDG. Therefore, FDG-PET has the potential for the diagnosis of osteomyelitis in the setting of prior trauma or surgery. An additional advantage of FDG-PET over conventional nuclear medicine scintigraphy is that the tomographic images provided by PET can be coregistered and compared with anatomical images provided by both CT and MRI for a more precise localization of sites of infection.

A recent meta-analysis showed that FDG-PET not only is the most sensitive imaging modality for detecting chronic osteomyelitis but also has a greater specificity than radiolabeled WBC scintigraphy, bone scintigraphy, or MRI for this purpose (158). In that meta-analysis, the pooled data demonstrated that FDG-PET has a sensitivity of 96% (95% confidence interval, 88% to 99%), compared with 82% (95% confidence interval, 70% to 89%) for bone scintigraphy, 61% (95% confidence interval, 43% to 76%) for radiolabeled WBC scintigraphy, 78% (95% confidence interval, 72% to 83%) for combined bone and radiolabeled WBC scintigraphy, and 84% (95% confidence interval, 69% to 92%) for MRI. The pooled data demonstrated that bone scintigraphy had the lowest specificity, with a value of 25% (95% confidence interval, 16% to 36%), compared with 60% (95% confidence interval, 38% to 78%) for MRI, 77% (95% confidence interval, 63% to 87%) for radiolabeled WBC scintigraphy, 84% (95% confidence interval, 75% to 90%) for combined bone and radiolabeled WBC scintigraphy, and 91% (95% confidence interval, 81% to 95%) for FDG-PET (158).

**Infected prosthesis.** With increased life expectancy in developed and developing countries around the world, a large number of patients with degenerative disease of the hip or knee joints are receiving artificial prostheses for this disabling condition. This is particularly the case for the hip joint, where more than 400,000 patients undergo hip arthroplasty in the United States every year. Although 10% of these patients suffer from significant pain, only 1% of patients are found to have periprosthetic infection following initial surgery, whereas the rest have prosthetic loosening without infection. However, the incidence of infection increases substantially following multiple surgeries, and differentiation between infection and prosthetic loosening without infection is a major challenge for orthopedic surgeons. While prosthesis revision is often successful and is not associated with major complications for aseptic loosening alone, the presence of superimposed infection requires intensive treatment before surgical revision is undertaken. Various scintigraphic techniques, including radiolabeled WBC scintigraphy, sulfur colloid bone marrow scintigraphy, and bone scintigraphy, have been employed to differentiate

between these two conditions (85, 123, 142). Unfortunately, none of the current imaging techniques can make this distinction with high accuracy.

Our own investigation (176) monitored two groups of patients who underwent total hip arthroplasty in order to assess the patterns and time course of FDG accumulation over an extended period of time. In first group, nine patients were investigated prospectively with FDG-PET at 3, 6, and 12 months after arthroplasty. The second group involved a retrospective analysis of 18 patients with a history of 21 hip arthroplasties who had undergone FDG-PET for the assessment of known malignancies but who were asymptomatic with regard to their implanted hip prostheses. We demonstrated increased FDG uptake around the femoral head or neck portions of the prostheses that extended to the soft tissues surrounding the femur in all patients of the first group. In second group of asymptomatic patients, 81% (17 of 21) showed increased FDG uptake around the femoral head or neck portions of the prostheses. The average time interval between arthroplasty and FDG-PET in these patients was 71.3 months. In the remaining four patients (19% [4 of 21]), no increased FDG uptake was seen around the prostheses or in adjacent sites. The average time interval between arthroplasty and FDG-PET in these patients was 114.8 months. We concluded that following hip arthroplasty, nonspecific increased FDG uptake around the femoral head or neck components of the prostheses persists for many years, even in patients without complications.

Increased FDG uptake can also be seen secondary to aseptic inflammation due to prior surgery. Chacko et al. (26) studied the location and intensity of FDG uptake in 41 total hip prostheses from 32 patients with complete clinical follow-up. Twelve patients had periprosthetic infection, and 11 displayed moderately increased FDG uptake along the interface between the bone and prosthesis. In contrast, FDG-PET of patients with loosening of hip prostheses but without infection revealed intense uptake around the femoral head or neck components of prostheses with SUVs as high as 7. Those authors concluded that the amount of increased FDG uptake is less important than the location of increased FDG uptake when this technique is used to diagnose periprosthetic infection in patients who have undergone prior hip arthroplasty.

Palestro et al. (121) evaluated the role of combined  $^{111}\text{In}$ -labeled WBC and  $^{99\text{m}}\text{Tc}$ -sulfur colloid imaging in suspected hip prosthesis infection and reported a reasonable accuracy for the detection of an infected prosthesis. However, this combined test is complex, requires at least 24 h to be completed, and is expensive. Furthermore, it also requires the *in vitro* labeling of WBCs with a potential for contamination by pathogens or for inadvertently mixing blood samples among patients. In a recent study, Scher et al. (142) reported a sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of  $^{111}\text{In}$ -labeled WBC imaging in the diagnosis of infected total hip and knee prostheses of 77%, 86%, 54%, 95%, and 84%, respectively. The variable results for the detection of infection reported in the literature has further diminished the enthusiasm for this procedure. Based on the experience accumulated so far, FDG-PET has great potential for examination of patients with suspected infection in hip and, to a lesser extent, in knee prostheses. The use of FDG-PET is advantageous compared to anatomic imaging

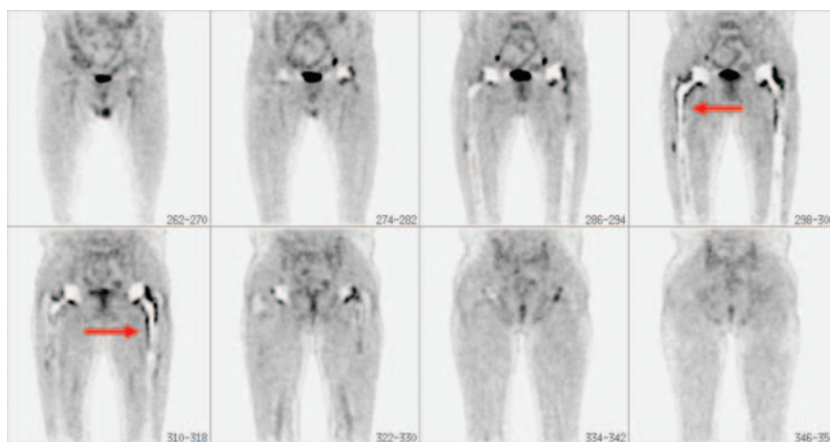


FIG. 4. Typical FDG-PET findings in a patient with infection of the hip prosthesis (bilaterally), which was subsequently proven. Significant uptake of FDG seen in the bone-prosthesis interface is characteristic of this complication.

modalities because it is not affected by artifacts from metallic implants (74, 144) and provides higher-resolution images than those provided by conventional scintigraphic techniques.

In our own study involving 36 knee prostheses and 38 hip prostheses, the sensitivity, specificity, and accuracy of FDG-PET for detecting infection were 90%, 89.3%, and 89.5% for hip prostheses (Fig. 4 and 5) and 90.9%, 72.0%, and 77.8% for knee prostheses, respectively (178). However, why FDG-PET is more accurate in the diagnosis of periprosthetic infection in hip than in knee joints is unclear. These results suggest the need for more stringent criteria to diagnose periprosthetic infection in the knee joints on the basis of FDG-PET findings to improve the specificity of the test.

Although the role of FDG-PET in the evaluation of infected prostheses is relatively well defined, some variable results have been reported in the literature (153). For example, Love et al. reported excellent sensitivity but low specificity of FDG-PET for the diagnosis of periprosthetic infections. We point out that this analysis was based on data collected from a coincident

camera and not by use of a dedicated modern instrument (99). Therefore, the conclusions reached by that group may not be applicable to results obtainable by current PET cameras.

In general, several other reports in the literature reported high sensitivity and specificity of FDG-PET (Fig. 6) for assessing such patients (113, 133, 178). Based on data from the University of Pennsylvania and other centers, a specific FDG uptake pattern for hip prosthesis infection has been defined: the presence of FDG uptake between the bone and prosthesis at the level of the midshaft portion of the prosthesis is very suggestive of an infected implant (Fig. 4). By adopting this criterion, the accuracy of FDG-PET exceeds 90%, as reported by several groups in the literature. Interestingly, some degree of inflammation around the femoral neck component, which is generally noninfectious in nature, is frequently noted (176). In summary, FDG-PET is safe and carries no risks, the entire examination can be completed in less than 2 h, and the costs are lower than those of conventional techniques. Based on the existing literature and our own experience, we believe that

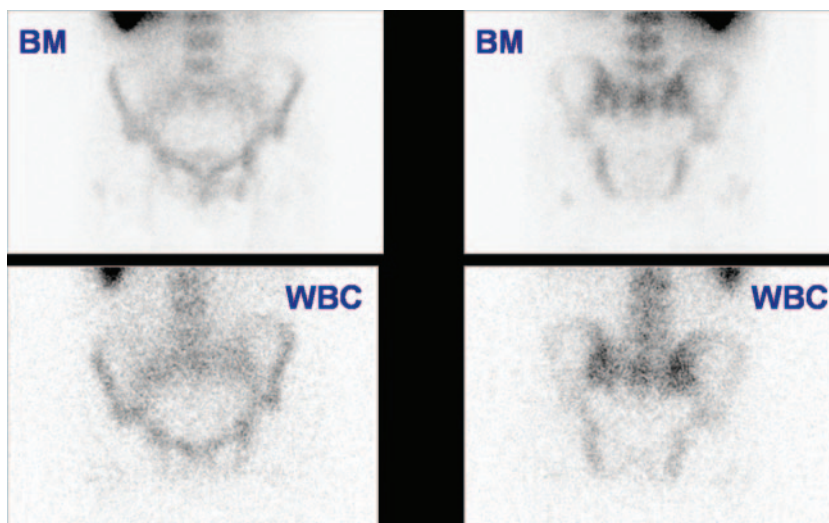


FIG. 5.  $^{111}\text{In}$ -labeled WBC/ $^{99\text{m}}\text{Tc}$ -sulfur colloid bone marrow (BM) images in the same patient are negative for infection.



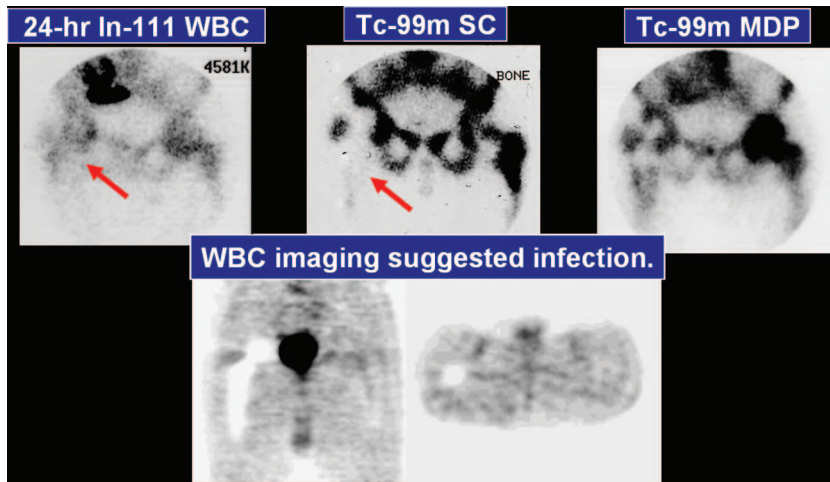


FIG. 6. Comparison of FDG-PET, WBC/sulfur colloid (SC), and bone images of a patient without infection in the implanted prosthesis: While WBC/sulfur colloid was suspicious for infection, FDG-PET was clearly negative, which was subsequently confirmed by follow-up examination of this patient. MDP, methylene diphosphonate.

FDG-PET will likely play an important role in the evaluation of complicated lower-limb prosthesis, especially after the criteria for infection and aseptic loosening are fully defined by well-designed prospective studies.

**Diabetic foot.** Peripheral neuropathy is common in patients with diabetes mellitus (DM) and can result in foot ulceration and, ultimately, the destruction of osseous structures due to Charcot osteoarthropathy and osteomyelitis. Approximately 5 to 10% of the patients with DM have foot ulcers (21), and the total annual cost of diabetic peripheral neuropathy and its complications in the United States is on the order of 10 billion dollars (52). Osteomyelitis comprises up to 33% of the diabetic foot infections and is often due to direct, contiguous contam-

ination from the soft tissue lesions (96). This is important to recognize clinically because early diagnosis and treatment with antibiotics are essential to prevent amputation. Deep infection in the diabetic foot is generally suspected in patients with a persistent ulcer, systemic symptoms or signs of infection, and persistently elevated laboratory markers for inflammation despite antibiotic therapy (Fig. 7). However, in general, systemic symptoms or signs of infection are frequently absent in patients with osteomyelitis in the setting of DM (143). Furthermore, a large proportion of diabetic patients with deep foot infection do not have leukocytosis in spite of active disease (164).

In a study that included 39 patients with Charcot osteoarthrop-

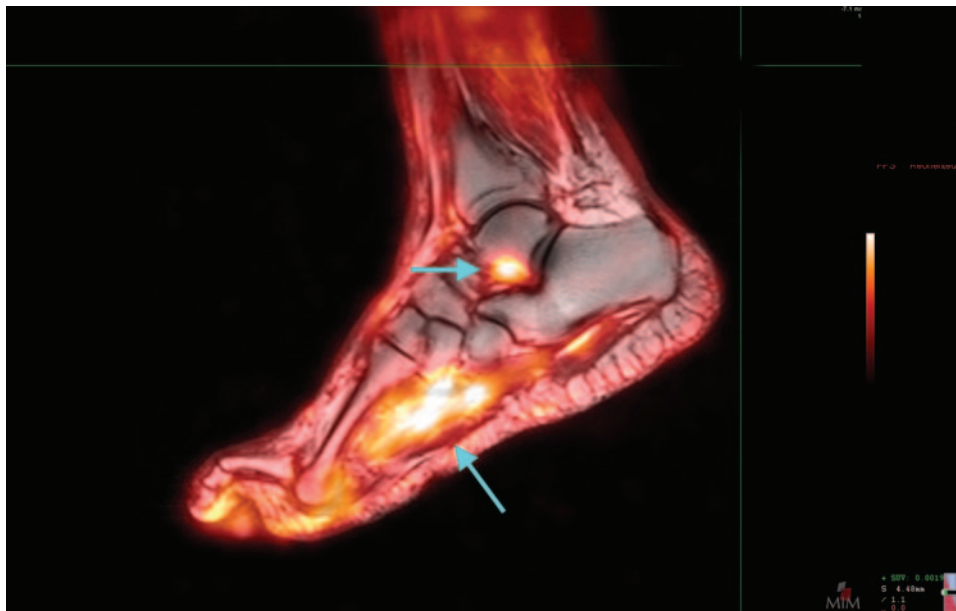


FIG. 7. Fused FDG-PET and magnetic resonance images of a patient with diabetic foot and suspected bone infection. The FDG-PET image shows significant uptake in the soft tissue in the plantar aspect of the foot (suggestive of cellulitis); in addition, it reveals a focus of abnormal activity in the talus (consistent with talar bone osteomyelitis). (Reproduced from reference 12 with permission.)



FIG. 8. Forty-four-year-old male (after heart transplant) presenting with FUO. A focus of increased FDG activity was noted in the aortopulmonary window. This was subsequently proven to represent a focus of infection, which was drained and which resulted in complete recovery and discharge from the hospital.

athy confirmed at surgery, Hopfner et al. noted that FDG-PET with a dedicated full-ring PET scanner accurately diagnosed this disorder in 37 patients, for a sensitivity of 95% (66). In contrast, the coincidence PET camera provided a sensitivity of 77% (30 of 39), and MRI had a sensitivity of 79% (31 of 39). Those authors also concluded that FDG-PET can provide an accurate assessment of patients with metal implants, which may otherwise limit evaluation by MRI, and that FDG-PET can correctly distinguish osteomyelitis from Charcot osteoarthropathy (31, 66).

In a study of 14 diabetic patients with 18 suspected infection sites, Keidar et al. (79) evaluated the role of FDG-PET in suspected osteomyelitis complicating diabetic foot disease. Those authors found that FDG-PET/CT correctly separated osteomyelitis from soft tissue involvement in all infected sites. Interestingly, the use of FDG-PET alone correctly identified osteomyelitis in eight of eight sites and soft tissue infection in

five of five sites. In contrast, CT alone correctly identified osteomyelitis in seven of eight sites and soft tissue infection in four of five sites (79).

Results from our own institution reported by Basu et al. (12) are also quite promising. A total of 63 patients in four groups were evaluated. A low degree of diffuse FDG uptake that was clearly distinguishable from that of normal joints was observed in joints of patients with Charcot osteoarthropathy. The maximum SUV ( $SUV_{max}$ ) in lesions of patients with Charcot osteoarthropathy varied from 0.7 to 2.4 (mean,  $1.3 \pm 0.4$ ), while those of midfoot of the healthy control subjects and the uncomplicated diabetic foot ranged from 0.2 to 0.7 (mean,  $0.42 \pm 0.12$ ) and from 0.2 to 0.8 (mean,  $0.5 \pm 0.16$ ), respectively. The only patient with Charcot osteoarthropathy with superimposed osteomyelitis in this series had an  $SUV_{max}$  of 6.5. The  $SUV_{max}$  of the sites of osteomyelitis as a complication of diabetic foot was 2.9 to 6.2 (mean,  $4.38 \pm 0.39$ ). A unifactorial analysis of variance test yielded a statistical significance in the  $SUV_{max}$  among the four groups ( $P < 0.01$ ). The  $SUV_{max}$  value differences between the healthy control groups and the uncomplicated diabetic foot were not statistically significant by the Student *t* test ( $P > 0.05$ ). The overall sensitivity and accuracy of FDG-PET in the diagnosis of Charcot osteoarthropathy were 100 and 93.8%, respectively, and those for MRI were 76.9 and 75%, respectively. The results indicated the valuable role of FDG-PET in the setting of Charcot neuroarthropathy by reliably differentiating it from osteomyelitis both in general and when foot ulcer is present.

Many diabetic patients tend to be hyperglycemic at the time of FDG administration in spite of appropriate and tailored therapy for DM. By now, it is well established that hyperglycemia adversely affects the uptake of FDG in many types of malignant lesions and therefore lowers the sensitivity of the test in this setting. In contrast, the effects of hyperglycemia on the accuracy of FDG-PET for detecting pedal osteomyelitis in diabetic patients appear to be minimal. In general, the quality of FDG-PET images for assessing infection is optimal when serum glucose levels are less than 250 mg/dl (184). Animal experiments have also shown that a high level of accuracy for FDG-PET in the diagnosis of osteomyelitis without fasting can be achieved (84). In a study of the diabetic foot, Keidar et al. showed that accurate interpretation was achieved in all pa-

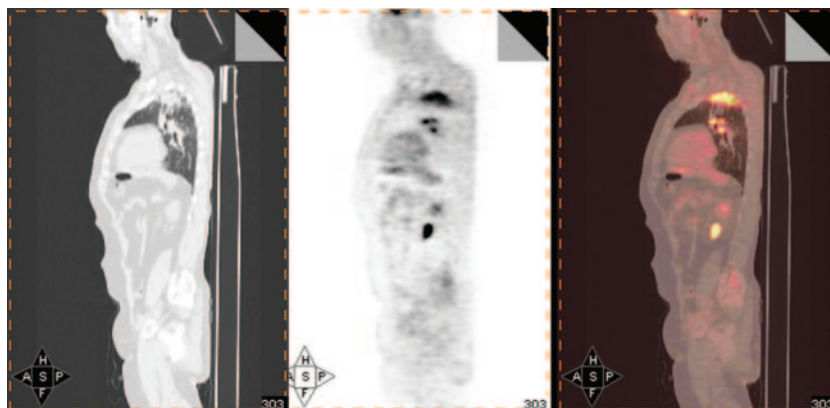


FIG. 9. Tubercular inflammatory lesion in the apex of the left lung that shows intense FDG uptake fused with the corresponding CT scan.



tients with serum glucose levels greater than 200 mg/dl (79). Therefore, a high incidence of hyperglycemia in diabetic patients does not appear to interfere with the optimal utilization of FDG-PET imaging in the setting of complicated diabetic foot. We believe that with the evolution of PET/CT fusion imaging in clinical practice, this will be the study of choice for evaluating complicated diabetic foot, especially in the setting of acute neuropathic osteoarthropathy.

### Soft Tissue Infection

**FUO.** In 1961, FUO was defined by Petersdorf and Beeson (127) as a fever of higher than 38.3°C that has been documented on several occasions with a duration of at least 3 weeks and an uncertain source after 1 week of comprehensive investigation with conventional techniques as an inpatient in the hospital setting. The definition was later modified by removing the requirement for in-hospital evaluation and redefining the latter criterion to include at least inpatient or outpatient evaluation for a minimum of 3 days or three outpatient visits along with the exclusion of immunocompromised states (126). Infections, malignancies, collagen vascular diseases, and autoimmune disorders account for the majority of cases of FUO. Among all causes, infections account for the most cases of FUO, followed by malignancy and noninfectious inflammatory diseases. Accurate localization and characterization of the underlying cause of FUO substantially improve the management of these patients who have suffered from the symptoms and signs of underlying disease for an extended period of time.

Current imaging techniques, including those provided by anatomic modalities, radiolabeled WBC imaging, and gallium 67 (<sup>67</sup>Ga) citrate scintigraphy, have a relatively low diagnostic yield in this population. Gallium 67, the most commonly used radiotracer for the evaluation of FUO, can be used to visualize malignancies as well as inflammatory and granulomatous disorders (125). In contrast, radiolabeled WBC imaging is of limited value in this setting because it is suitable only for the detection of a focal occult infection, which is the cause of FUO in a fraction of patients with this diagnosis (73). Despite these shortcomings, various studies, such as those by Knockaert et al. (81) and Syrjala et al. (157), demonstrated that either <sup>67</sup>Ga scintigraphy or <sup>111</sup>In-labeled WBC imaging has a higher yield than CT or ultrasonography in detecting sites of disease in patients with FUO. Other imaging techniques, such as radiolabeled antibody scintigraphy (42, 54, 104, 107, 119, 129) and radiolabeled antibiotic scintigraphy (22), have also been employed to detect FUO. One report compared the efficacy of <sup>99m</sup>Tc-labeled ciprofloxacin (Infecton) scintigraphy and <sup>99m</sup>Tc-hexamethylpropyleneamine oxime-labeled WBC scintigraphy and found that <sup>99m</sup>Tc-labeled ciprofloxacin scintigraphy is a superior technique for assessing spinal infection compared to radiolabeled WBC scintigraphy (149). However, the efficacy of these techniques is somewhat uncertain, and therefore, their routine use is unjustified (1).

FDG-PET allows the identification of inflammatory and cancerous disorders as the underlying cause of FUO in most patients and has been shown to detect infectious and inflammatory disease processes that were undetected when conventional scintigraphic techniques or MRI was used (20, 35, 98, 106, 166, 170). In an early prospective study involving 20 con-

secutive patients that was designed to compare the role of FDG-coincident PET imaging with that of <sup>67</sup>Ga single-photon-emission computed tomography (SPECT) in patients with FUO, Meller et al. reported a sensitivity of 81% and a specificity of 86% for FDG-PET and sensitivity and specificity of 67% and 78%, respectively, for <sup>67</sup>Ga SPECT (106). Similarly, Blockmans et al. (20) studied 58 patients with FUO prospectively, and in 64% of patients, a final diagnosis was established. The results reported for FDG-PET were comparable to those for <sup>67</sup>Ga scintigraphy, but FDG-PET was considered to be superior because the results were available within 4 h, compared to a few days for <sup>67</sup>Ga scintigraphy results. Those authors concluded that <sup>67</sup>Ga scintigraphy should be replaced by FDG-PET in the future to detect the underlying cause of disease in patients with FUO. In a retrospective study of 16 patients with FUO for whom conventional diagnostic techniques were inconclusive, a diagnosis was possible for 69% of patients by employing FDG-PET imaging (98, 106).

Sugawara et al. evaluated the role of FDG-PET in a prospective examination of 11 patients suspected of having various infections (156) and reported that FDG-PET correctly diagnosed the presence or absence of active infection in 10 of 11 subjects (Fig. 8 and 9). In another prospective study with FDG-PET involving 39 patients with suspected infection as the cause of FUO, Stumpe et al. (152) studied the results of 45 FDG-PET scans from 39 patients with suspected infectious foci and noted 40 true-positive, 4 false-positive, and 1 false-negative result. In a retrospective study of 35 patients by Bleeker-Rovers et al. (17), FDG-PET imaging was employed to assess the cause of FUO. The positive predictive value and negative predictive value of FDG-PET in these patients were 87% and 95%, respectively. In the same study, 55 FDG-PET scans were performed for 48 patients with suspected focal infection or inflammation. A final diagnosis was established for 38 patients, and the positive predictive value and negative predictive value of FDG-PET were 95% and 100%, respectively. Jaruskova and Belohlavek recently reported that FDG-PET or FDG-PET/CT contributed to establishing a final diagnosis in 84% of 51 patients with positive PET findings and in 36% of 118 patients with prolonged fever (71).

FUO frequently complicates the management of pediatric patients with terminal chronic liver failure during the pretransplantation period, which may lead to high morbidity and mortality. In a recent investigation by Sturm et al. (155), FDG-PET was utilized to evaluate 13 such patients. It was noted that while standard imaging techniques did not reveal any abnormality consistent with infection in these children, FDG-PET correctly detected intrahepatic infectious foci in five patients. Therefore, liver transplantation was carried out after continuous antibiotic treatment in these patients. In contrast, when no abnormal hepatic FDG uptake was seen, liver transplantation was successfully performed when the patients spontaneously became afebrile. Those authors therefore concluded that in children with FUO who are on the waiting list for liver transplantation, FDG-PET might be useful to guide therapeutic decisions and timing of liver transplantation.

An advantage of FDG-PET over other techniques in the evaluation of FUO is its ability to detect noninfectious inflammatory disease processes as the underlying cause of the entity. In addition to infection and malignancy, FDG-PET can also

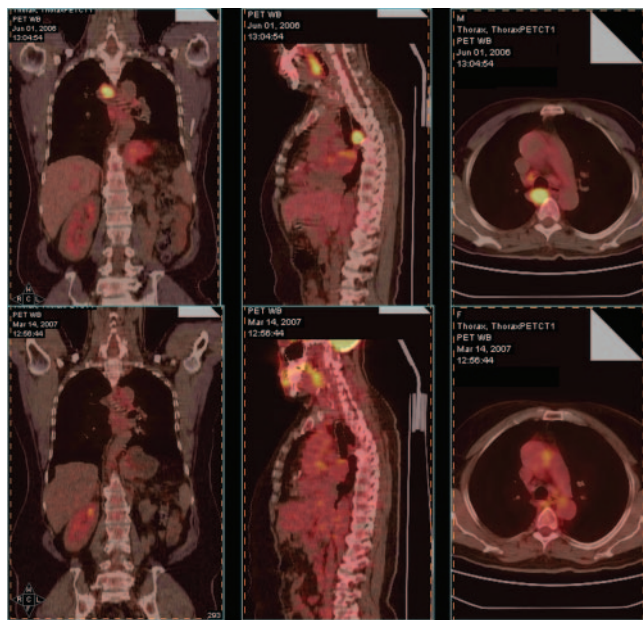


FIG. 10. Pretreatment (top) and posttreatment (bottom) FDG-PET in a proven case of tuberculosis showing treatment evidence for response to therapy.

detect aseptic inflammation. For example, FUO can be caused by sarcoidosis (29, 53, 97) and vasculitis (34, 47, 116, 138), both of which can be detected and characterized with FDG-PET at various stages of the disease (2, 10, 12, 16, 23, 39, 61, 91, 92, 109, 175, 183).

However, comparison of the performance of various other scintigraphic studies to that of FDG-PET to establish the cause

of fever in patients with FUO is difficult. This is partly due to the fact that the definition of FUO may vary among individual patients, the diagnostic workup of FUO may differ at different medical facilities, and the FDG-PET protocols are not standardized worldwide. Consequently, the percentage of patients for whom no cause can be established using these modalities can range from 10% to 36% (38). In addition, the calculation of sensitivity and specificity of FDG-PET for patients with FUO or suspected focal infection or inflammation is difficult for various reasons. Interpretation of FDG-PET images is hampered by the lack of a “gold standard,” as a final diagnosis is not established for all patients. Moreover, for patients with a negative FDG-PET result, a variety of diseases may still be found through other diagnostic testing. Additionally, FDG-PET cannot exclude cerebral disease or meningitis, as physiological uptake in the cerebral cortex in most cases obscures any pathological uptake. Similarly, normal FDG excretion through the kidneys into the collecting systems and the bladder severely limits the delineation of disease processes involving these organs.

In short, although FDG-PET is useful in the setting of FUO (Fig. 10 and 11), well-designed future prospective studies are necessary to confirm the efficacy of FDG-PET for the evaluation of FUO, as it has the potential to become a first-line routine imaging technique for assessments of patients with FUO. PET/CT fusion imaging is likely to play a major role in this clinical setting in the future.

**HIV-AIDS.** FDG-PET has a major role to play in the management of human immunodeficiency virus (HIV)-infected patients, particularly in those with central nervous system (CNS) lesions. FDG-PET is able to detect infectious foci even in patients with severe neutropenia and lymphopenia (101). In a prospective study involving 15 HIV type 1-infected patients, Scharcko et al. (141) noted an association between the clinical

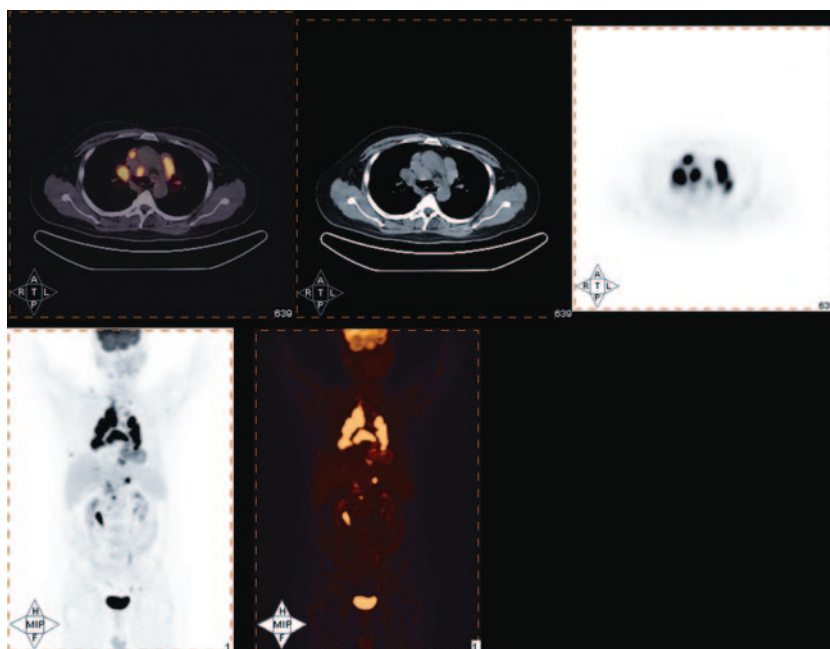


FIG. 11. FDG-PET images of a case of sarcoidosis where typical uptake is seen in the chest. In patients with active sarcoidosis, significant uptake is seen at the disease sites and can be mistaken for lymphoma or other lymphoproliferative disorders.

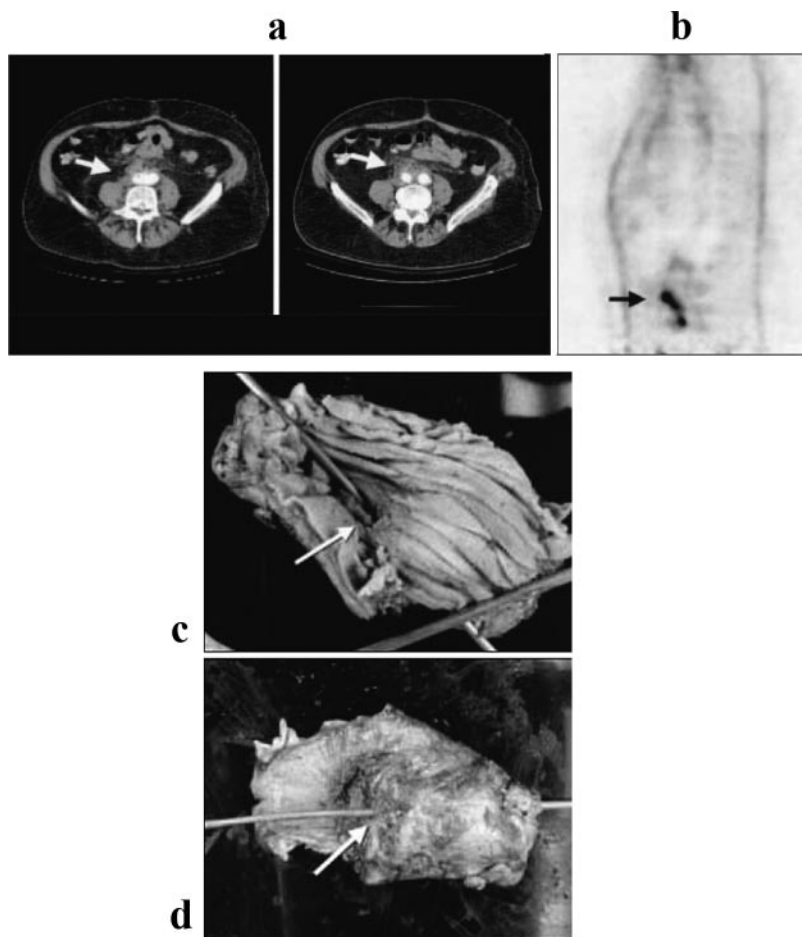


FIG. 12. (a) Patient with suspected graft infection. While the CT scan did show evidence of retroperitoneal stranding in the patient (arrows), no definite evidence of aortic graft infection such as ectopic air, perigraft abscess, or pseudoaneurysm was noted on the respective images. (b) PET scan revealing an abnormal site of FDG uptake in the area of the aorta corresponding to the graft (arrow). A fistulous connection between the jejunum and the aortic graft was evident at laparotomy. Arrows point to a probe placed through the fistula as seen from the luminal (c) and serosal (d) sides. (Reproduced from reference 86 with permission from Sage Publications.)

stage of HIV infection and the pattern of lymphoid tissue activation. FDG-PET demonstrated activated lymphoid tissue in the head and neck region during acute stages, a generalized pattern of peripheral lymph node activation at midstages, and abdominal lymph node involvement during the late stages. It has also been shown that abnormal FDG accumulation occurs in lymph nodes of subjects with detectable HIV viral loads. Healthy HIV-infected subjects with suppressed viral loads and HIV-negative individuals have no or little FDG nodal accumulation or any other hypermetabolic areas, whereas HIV-viremic subjects with early or advanced disease have increased FDG uptake in peripheral nodes (24).

In AIDS patients, toxoplasmosis is the most common opportunistic infection, and the CNS is the most common site for this infection (128). In addition, malignant lymphoma is also one of the most common malignancies encountered in HIV-infected patients (15). In a prospective study involving 11 patients with AIDS, Hoffman and Coleman (65) defined the role of FDG-PET in HIV-infected patients with CNS lesions. Those authors found FDG-PET to be more accurate than CT or MRI in differentiating between malignant CNS lymphoma

and nonmalignant CNS disease processes such as toxoplasmosis, syphilis, and progressive multifocal leukoencephalopathy. Malignant CNS lesions had greater FDG uptake than did nonmalignant lesions in this population. In another study using FDG-PET, Heald et al. (63) attempted to differentiate CNS lesions in AIDS patients by using both a qualitative visual score and a semiquantitative count ratio through comparisons of the CNS lesions with the contralateral brain. Those authors reported that CNS lesions diagnosed as lymphomas had statistically higher visual scores and count ratios than did nonmalignant CNS lesions. In a similar study, O'Doherty et al. (117) reported that FDG-PET had an overall sensitivity of 92% and a specificity of 94% in the detection and differentiation of infections and malignancies in patients with AIDS. The literature regarding the role of FDG-PET in HIV-infected patients is evolving, with the major work being done in evaluating and characterizing CNS lesions. Current data show that PET is especially valuable for differentiating lymphomas from nonmalignant CNS lesions affecting the CNS.

**Other soft tissue infections.** FDG-PET is a valuable tool for the evaluation of possible infection of vascular grafts (136).



FDG-PET is able to detect vascular graft infection even when CT results are negative (86) (Fig. 12). Fukuchi and colleagues evaluated the efficacy of FDG-PET compared to that of CT in 33 consecutive patients with suspected aortic prosthetic graft infection (48). Those authors concluded that although both imaging modalities are useful in the evaluation of patients with suspected aortic graft infection, employing the characteristic FDG uptake pattern (diffuse and intense) as a diagnostic criterion made the efficacy of FDG-PET superior to that of CT (48). When focal uptake was set as the positive criterion for FDG, the specificity and positive predictive value of PET for the diagnosis of aortic graft infection improved significantly to 95%. Furthermore, FDG-PET/CT is reported to have an even better accuracy to detect vascular graft infection (78). We believe that FDG-PET is likely to play a valuable role, especially in difficult clinical settings that are not clarified by conventional tools.

Lastly, the potential of FDG-PET for the evaluation of several other uncommon entities is great. For example, FDG-PET has been used in animal experiments to determine the various stages of malarial infection (77). FDG-PET has also been used to determine the inflammatory burden of disease in patients with cystic fibrosis (32). In patients with chronic granulomatous disease, CT usually does not discriminate between active and inactive lesions, whereas FDG-PET is very effective in this clinical setting (58, 120). Although it was initially thought that FDG accumulation in infectious or inflammatory lesions was a disadvantage in the evaluation of patients with malignancy, FDG-PET has been shown to be a valuable imaging tool for assessing possible infections in patients who are immunosuppressed (101). With time, the list of these situations is likely to grow.

#### Therapeutic Response Monitoring

FDG-PET has been shown to be useful for determining the effects of therapy on a variety of malignancies. In recent years, FDG-PET has been proposed to be an effective tool for the evaluation of therapeutic efficacy in the setting of infectious disease. In an early publication, Ozsahin et al. demonstrated that following effective therapy for invasive aspergillosis, FDG-PET findings reverted to normal (120). Animal experiments have also shown that FDG-PET is accurate for monitoring responses following antibiotic therapy in the setting of soft tissue infection (168). In a clinical study, FDG uptake returned to normal levels after successful antibiotic therapy for hepatic cyst infection (18), after antifungal therapy for a lung abscess caused by candidal infection (19), and after therapy for *Pneumocystis carinii* pneumonia (167) (Fig. 13). FDG-PET has also been reported to be reliable for assessing metabolic activity and for detecting relapses of infection in patients with alveolar echinococcosis (134). In a study to evaluate responses to antibiotic therapy in patients with *Salmonella* vertebral osteomyelitis, Win et al. found that FDG activity returned to normal following successful treatment, whereas persistent spinal abnormalities were noted on MRI (166). FDG-PET has also been proposed as a tool to evaluate the effectiveness of therapy for human alveolar echinococcosis (43, 134, 154).

Since bone scintigraphy detects reactive osteoblastic activity following the initiation of the disease process to the adjacent

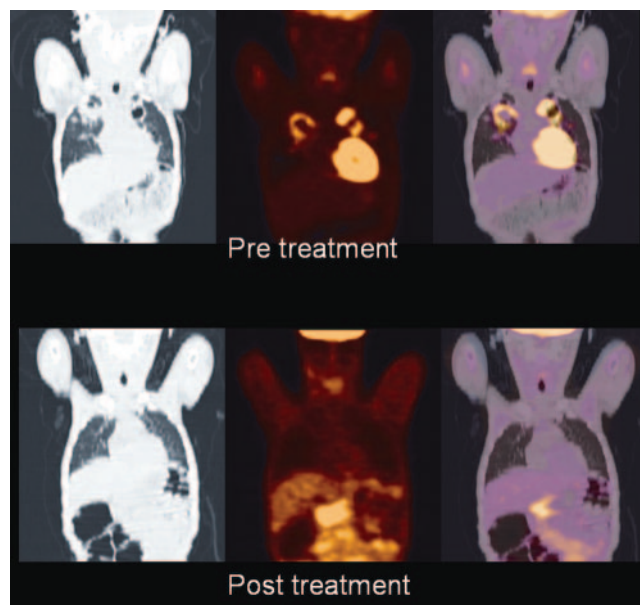


FIG. 13. Pre- and posttreatment FDG-PET in a patient with a proven case of pneumonia showing therapeutic response. Corresponding CT and fused images are shown.

marrow or other tissues whereas FDG-PET detects the disease process directly, the time intervals for images acquired by these two modalities to return to normal following successful treatment of osteomyelitis vary considerably. An interesting investigation by Hakim et al. compared the specificities of these two modalities in the evaluation of chronic osteomyelitis of the mandible following treatment of 42 patients (59). The specificity of bone scintigraphy was only 6.6%, compared to a specificity of 80% for FDG-PET (59). This suggests that during the follow-up period, bone scintigraphy should be replaced by FDG-PET (59). FDG-PET holds great promise in treatment response evaluation, akin to what it has demonstrated in the evaluation of treatment response in several malignancies. A fall of 50% in baseline FDG uptake after antibiotic treatment is considered to be a significant response.

#### CONCLUSION

The data presented in this review clearly demonstrate the critical role of modern imaging techniques in the assessment of patients with suspected infection in any organ system. FDG-PET imaging plays an important role in the management of patients with osteomyelitis, infected prostheses, FUO, and AIDS. FDG-PET imaging appears to overcome many shortcomings that are associated with either structural imaging techniques or conventional scintigraphic methodologies. FDG-PET will be increasingly employed for detecting, characterizing, and monitoring patients with suspected and proven infection in the future. This in turn will substantially improve the management of patients with serious infectious disorders.

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