



Positron Emission Tomography as a Diagnostic Tool in Infection: Present Role and Future Possibilities

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The past decade has witnessed the emergence of yet another promising application of ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in the detection and management of patients with infection and inflammatory disorders. This phenomenon is quite evident when the peer-reviewed scientific literature is searched for on this topic. Among these scientific communications, the 6 conditions in which FDG-PET has demonstrated its greatest utility include (1) chronic osteomyelitis, (2) complicated lower-limb prostheses, (3) complicated diabetic foot, (4) fever of unknown origin, (5) acquired immunodeficiency syndrome (ie, AIDS), and (6) vascular graft infection and fistula. On the basis of published literature, orthopedic infections, particularly those related to implanted prostheses and osteomyelitis (including that occurring in the setting of a complicated diabetic foot), can be detected successfully by the use of FDG-PET and, therefore, this modality has great promise for becoming the study of choice in these complex settings. Increasingly, this technique is being used to detect infection in soft tissues, including those representing the sources of fever of unknown origin. The ability of FDG-PET to diagnose vascular graft infection and fistula, even when the anatomical imaging modalities are inconclusive, is of considerable interest to practitioners of vascular surgery. Combined PET/computed tomography (CT) imaging has the potential to determine the sites of infection or inflammation with high precision. The data on the role of PET/CT imaging in the assessment of infection and inflammation is sparse, but this combined modality approach may prove to be the study of choice in foreseeable future for precise localization of involved sites. However, the role of PET/CT may be limited in the presence of metallic artifacts (such as those caused by prostheses) adjacent to the sites of infection.

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During recent years, increasing evidence for the application of ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the evaluation of several infectious and aseptic inflammatory disorders has been published.^{1,2} Because inflammatory cells, like malignant cells, preferentially metabolize glucose, the observation that FDG accumulates at the sites of inflammation and infection has been con-

sidered by many over the years as a shortcoming and a potential source of false-positive results in the assessment of cancer³⁻¹²; however, in retrospect, this phenomenon was quite serendipitous, because FDG-PET could now be extended to the very common domain of infection and inflammation.¹³ Increasingly, FDG-PET is being used to examine and manage patients with infectious and inflammatory disorders.

Assessment of this new imaging approach is often fraught with difficulty because of the lack of an apparent reference standard. Nonetheless, FDG-PET has several advantages over conventional radiological and scintigraphic techniques, including high spatial and contrast resolution and the ability to obtain results within a very short period of time. Although several molecular mechanisms have been proposed as the basis for FDG uptake in inflammatory cells, overexpression of glucose transporter 1 (GLUT1) receptors in stimulated

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Table 1 Clinical Settings in Which FDG-PET Has Been Investigated Widely as a Promising Diagnostic Tool

Chronic osteomyelitis
Complicated diabetic foot
Painful lower limb prostheses
FUO
AIDS
Vascular graft infection and fistula

macrophages, neutrophils, and lymphocytes is considered the most likely underlying biological phenomenon responsible for this observation.^{14,15} It is reasonable to conclude that activated inflammatory cells accumulate this tracer with high concentration depending on the degree of stimulation at the site.

The potential applications of FDG-PET imaging include evaluation of the complicated diabetic foot,¹⁶⁻¹⁸ painful joint prosthesis,¹⁹⁻²² fever of unknown origin (FUO),²³⁻²⁶ acquired immunodeficiency syndrome (AIDS)-related disorders,^{27,28} vascular graft infection and fistula,²⁹⁻³³ and a variety of non-infectious inflammatory diseases (Table 1).³⁴⁻³⁶ These conditions all are discussed in detail in this and the next issue of *Seminars in Nuclear Medicine*. Some of these applications have already been shown to have enough promise to be adopted in the routine day-to-day practice of medicine. Other applications are actively being tested through prospective research studies. Orthopedic infections, particularly those related to implanted prostheses and osteomyelitis, can be successfully detected with the use of FDG-PET and, soon, this technique may become the study of choice in such complicated and difficult clinical scenarios. Increasingly, this technique is also being used for detecting the sources of FUO. The increasing use of PET/computed tomography (CT) imaging in the assessment of infection and inflammation will undoubtedly prove to be even more effective than PET alone in some clinical situations for which surgical interventions are indicated. For this review, we have considered published studies with statistically valid data in the 6 promising clinical applications mentioned previously. Although the case reports and short series are not included in this scientific exchange, we have referred to important observations made by these reports.

Advantages and Limitations of FDG-PET Compared With Conventional Nuclear Medicine Techniques and Anatomic Imaging Modalities in the Evaluation of Infectious Diseases

Although FDG-PET cannot reliably distinguish infection from noninfectious inflammation, it offers several practical advantages over conventional nuclear medicine techniques (white blood cell/bone marrow/bone imaging) including (1) completion of the examination within a short period of time

(1.5 to 2 hours), (2) high-resolution tomographic images, (3) high target-to-background contrast ratios, (4) high sensitivity for chronic infections, (5) minimal labor intensity, (6) high interobserver agreement, (7) low radiation dose (2 to 3 times lower than that of most conventional nuclear medicine techniques), and (8) detection of infection in the axial skeleton (white blood cell [WBC]) scanning in particular is of limited value in this setting. The major shortcomings of this modality include (1) limited availability in most parts of the world, (2) relatively high cost, and (3) difficulty in differentiating malignant tissue from infection or inflammation, although delayed imaging and dual-time-point PET is of considerable help in this regard.³⁷⁻⁴⁰

In contrast, the conventional scintigraphic approaches suffer from substantial shortcomings. These methodologies are time consuming, labor intensive, and costly, and the results may not be available for 24 hours or longer. Together, these factors frequently delay optimal treatment for many patients. Furthermore, these approaches use planar imaging and thus cannot exactly localize the sites of disease in most anatomical regions of the body. From a technical standpoint, PET has certain inherent advantages over planar and single-photon emission computed tomography: First, it provides high-resolution tomographic images and thus enables precise localization of sites of infection, a capability that is further enhanced with PET/CT fusion. This approach is of great importance in the setting of the complicated diabetic foot for differentiating osteomyelitis from soft tissue infection. Second, semiquantitative assessment of tracer uptake provided by PET is of pivotal importance for assessing response to therapy, which will have important implications for managing patients with infection. Conventional scintigraphic techniques exhibit a relatively low sensitivity and, in particular, the detection of infection and inflammation in certain locations such as skeletal structures with significant red marrow activity is difficult. Finally, there are concerns about the safety of these preparations because of the potential for contamination with a variety of pathogens during the labeling processes.

Compared with anatomic imaging modalities, including CT and magnetic resonance imaging (MRI), the advantages offered by FDG-PET include improved ability to obtain diagnostic results in the presence of metallic implants (this will require PET alone and not PET/CT), and high specificity for assessment of cellular metabolic activity of the inflammatory process rather than assessment of perfusion or edema as indirect evidence for cellular activity. The shortcoming of PET is related to its relatively low spatial resolution compared with structural techniques; however, this can be overcome with the current generation of fusion PET/CT scanners.

Molecular Basis of FDG Uptake in Infection and Inflammation

Activated inflammatory cells, like malignant cells, predominantly metabolize glucose as a source of energy. In the stim-

ulated state, inflammatory cells, such as neutrophils and macrophages, express high concentrations of glucose transporters that facilitate the movement of FDG through the cell membrane. The following studies form the basis of this conclusions:

- Lehmann and coworkers⁴¹ demonstrated that neutrophilic granulocytes, after stimulation with substances like phorbol myristate or the chemotactic peptide *N*-formyl methionyl leucyl phenylalanine for 1 hour, exhibit significantly increased FDG uptake.
- Ishimori and coworkers⁴² showed that activated lymphocytes in concanavalin A-mediated acute inflammatory tissues demonstrate increased FDG uptake in both in vitro and in vivo models. In a study of immunologic versus oncologic uptake of FDG in a murine model, this same group demonstrated that the host immune reaction significantly contributes to the observed enhanced uptake of FDG in immunocompetent mice. The investigators concluded that since the metastatic lymph nodes contain only a relatively small number of malignant cells, the observed accumulation of FDG in these tissues represents the immune reaction of activated T-lymphocytes against cancer cells present in metastatic lymph nodes.⁴³
- Another group has demonstrated that multiple cytokines and growth factors acutely enhance the affinity of glucose transporters in inflammatory cells for deoxyglucose, and that this upregulation involves both tyrosine kinases and protein kinase C activity.^{44,45}
- Gamelli and coworkers^{46,47} performed a series of studies in murine models to examine macrophage glucose uptake and the state of GLUT1 at both the mRNA and protein levels. These investigators observed that following burn injury and infection, macrophages augment their cellular glucose uptake, which is facilitated by increased GLUT1 mRNA and protein levels. They concluded that tumor necrosis factor- α elicited by lipopolysaccharide is likely to mediate this enhanced carbohydrate metabolism at the point of glucose entry into the cell.
- Chakrabarti and coworkers⁴⁸ explored the mechanism for stimulating glucose transport during phytohemagglutinin stimulation of human peripheral blood lymphocytes enriched in T cells. They concluded that phytohemagglutinin stimulation increases glucose transport partly by inducing the expression of GLUT1 instead of GLUT3, and that GLUT1 expression is induced by signals generated by interleukin 2 binding to its high-affinity receptors.
- Heelan and coworkers⁴⁹ observed that FDG uptake was 1.5 to 2 times greater in allograft grafts than in syngeneic grafts and that the increase in uptake correlated with the histologically noted levels of T-cell infiltrate.
- Kubota and coworkers⁵⁰ showed that FDG uptake was greater in tumor-associated macrophages and young granulation tissues than in tumor cells.
- Sorbara and coworkers⁵¹ showed that GLUT3 expression increases during HIV infection. Flow cytometry

showed that GLUT3 protein expression increased specifically in the HIV-infected cells; this increase correlated with increased 2-deoxyglucose transport in the HIV-infected culture. This, they concluded, plays an important role in cellular metabolism and may provide a favorable environment for viral replication.

Potential Clinical Applications

Chronic Osteomyelitis

FDG-PET may have limited value in the diagnosis of uncomplicated cases of acute osteomyelitis compared with the combination of physical examination, evaluation of biochemical marker alteration, and 3-phase bone scanning or MRI. Although the acute condition usually does not pose a diagnostic challenge, because systemic symptoms in addition to localized signs, including reduced motion, pain, and tenderness of the involved bone, usually lead to a correct diagnosis, accurate diagnosis of chronic osteomyelitis is often difficult. Published peer-reviewed reports demonstrate that FDG-PET is highly effective in diagnosing chronic osteomyelitis (Fig. 1).⁵²⁻⁵⁵ It is not only highly sensitive but also has a greater specificity than ⁶⁷Ga-citrate scintigraphy, radiolabeled leukocyte scintigraphy, bone scintigraphy, and MRI.⁵⁶⁻⁵⁹

Several studies have documented the important role for FDG-PET in diagnosing patients with chronic osteomyelitis, and the potential appears to be particularly promising in 2 situations: (1) previously documented osteomyelitis with suspected recurrence, and (2) symptoms of osteomyelitis for more than six weeks. In contrast to other nuclear medicine methods such as ⁶⁷Ga scintigraphy and ¹¹¹In-labeled leukocyte imaging, FDG-PET has high resolution and can distinguish soft tissue infection from osteomyelitis.⁶⁰ ¹¹¹In-labeled leukocyte imaging alone is of little value in the evaluation of osteomyelitis involving the axial skeleton, where the sensitivity is approximately 66% for acute osteomyelitis⁶¹ and 21% for chronic osteomyelitis⁶² due to the poor contrast between the sites of infection and the surrounding red marrow. In addition, in patients who have previously received antibiotic therapy, poor migration of leukocytes to sites of infection leads to low sensitivity of the test.⁶³ It is expected that FDG-PET imaging will be used routinely in the near future to determine the presence or the absence of an infectious focus, to monitor response to antimicrobial treatment, and to develop certain criteria for deciding when the treatment can be safely stopped.

Guhlmann and coworkers^{56,57} reported a greater accuracy for FDG-PET than antigranulocyte antibody scintigraphy in imaging the central skeleton for infection in patients with suspected chronic osteomyelitis. de Winter and coworkers⁵⁸ investigated the role of FDG-PET in detecting chronic musculoskeletal infection in an unselected patient population. Among 60 patients who had a suspected infection, 29 had an area of increased uptake, and infection was confirmed in 25 by either histopathological studies or microbiological culture. In 35 patients, no area of increased uptake was seen, and none of these patients were shown to have infection. The

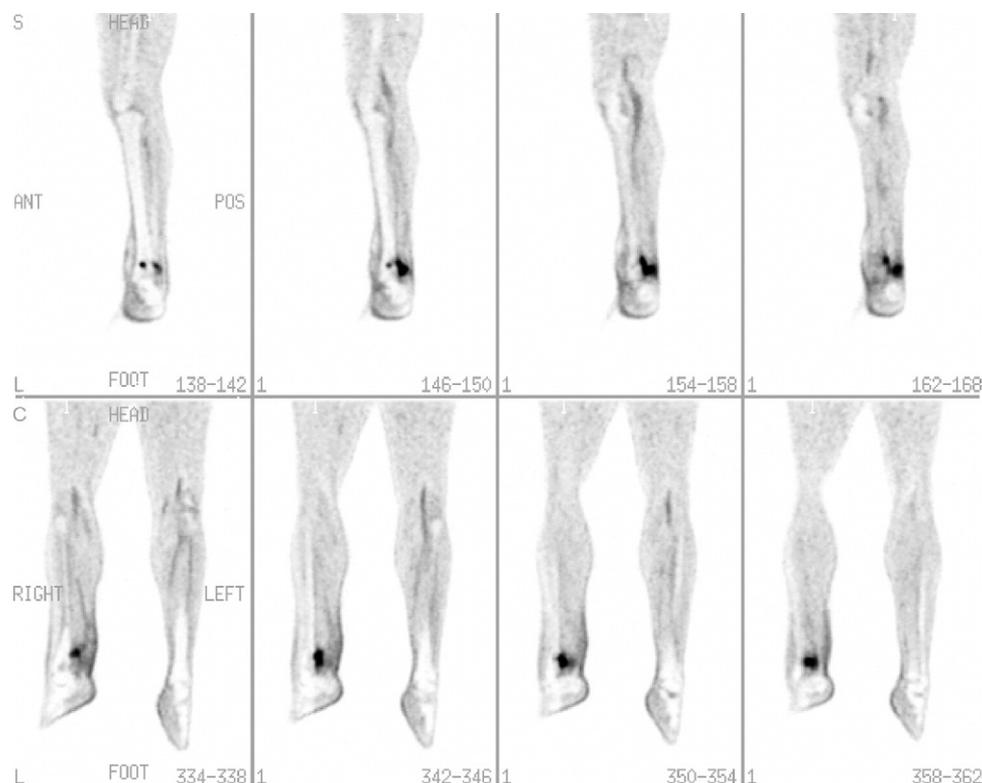


Figure 1 Shown is a 43-year-old man with a history of tibia–fibula fracture requiring external fixator. Coronal PET images demonstrate intensively increased FDG uptake in the distal tibial region that extends to the skin, representing a fistula tract. Surgical and histopathological examinations confirmed osteomyelitis.

overall sensitivity, specificity, and accuracy were 100%, 88%, and 93%, respectively. Among 4 false-positive results, the authors report that 2 were most likely related to the effects of recent surgery. Knowledge of patterns of normal postoperative FDG-PET uptake might be of value to reduce the false-positive scans in this setting. FDG-PET was especially useful in detecting uptake in the axial skeleton, an area for which WBC scanning is of limited value. The researchers concluded that FDG-PET is highly accurate as a single technique for the evaluation of chronic osteomyelitis.

Another prospective study by Meller and coworkers⁶⁴ on 30 patients with suspected active chronic osteomyelitis concluded that FDG-PET is superior to ¹¹¹In-labeled leukocyte imaging in the diagnosis of chronic osteomyelitis in the central skeleton. FDG-PET accurately detects spinal osteomyelitis and could potentially replace ⁶⁷Ga-citrate for this purpose.⁶⁵⁻⁶⁷ Increased osseous FDG activity has also been observed in inflammatory arthritis, in acute fractures, and in normally healing bone up to 4 months after surgery.^{68,69} Gulhmann and coworkers^{56,57} reported a greater accuracy for FDG-PET than antigranulocyte antibody scintigraphy in imaging the central skeleton for infection in patients with suspected chronic osteomyelitis.

A recent meta-analysis showed that FDG-PET is not only the most sensitive imaging modality for detecting chronic osteomyelitis, but it also has a greater specificity than radiolabeled WBC scintigraphy, bone scintigraphy, or MRI.⁶² In this meta-analysis, the pooled sensitivity demonstrated that

FDG-PET was the most sensitive technique, with a sensitivity of 96% (95% confidence interval [CI] 88-99%) compared with 82% (95% CI 70-89%) for bone scintigraphy, 61% (95% CI 43-76%) for radiolabeled WBC scintigraphy, 78% (95% CI 72-83%) for combined bone and radiolabeled WBC scintigraphy and 84% (95% CI 69-92%) for MRI. The pooled specificity demonstrated that bone scintigraphy had the lowest specificity, with a specificity of 25% (95% CI 16-36%) compared with 60% (95% CI 38-78%) for MRI, 77% (95% CI 63-97%) for radiolabeled WBC scintigraphy, 84% (95% CI 75-90%) for combined bone and radiolabeled WBC scintigraphy, and 91% (95% CI 81-95%) for FDG-PET.⁶²

Complicated Diabetic Foot

The detection of infection and differentiation from acute neuropathic osteoarthropathy in the setting of a complicated diabetic foot is a clinical and radiological challenge. The presence of ulceration also complicates this scenario because, in this setting, infection is strongly considered to be present until proven otherwise. Distinguishing osteomyelitis from Charcot neuroarthropathy by the use of MRI is sometimes a difficult task as signal alterations caused by edema are often nonspecific in etiology. Preliminary data provide evidence for an important role for FDG-PET imaging in assessing complicated and uncomplicated diabetic osteoarthropathy (Figs. 2 and 3). In a study that included 39 patients with Charcot osteoarthropathy that was confirmed at surgery, Höpfner and

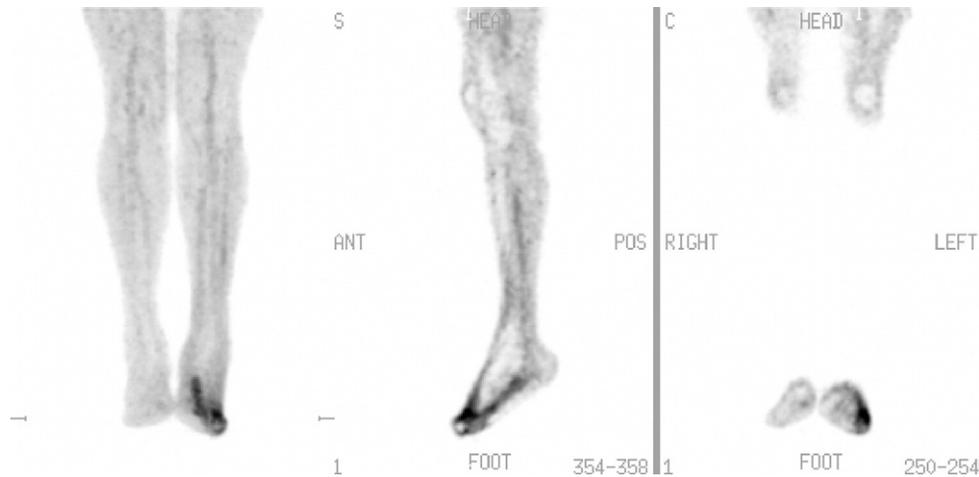


Figure 2 Shown is a 73-year-old man with insulin-dependent diabetes, hypertension, and peripheral neuropathy. PET images (maximum intensity projection [MIP], sagittal, and coronal) demonstrate abnormal FDG uptake around the dorsal and plantar aspect of the distal left fifth toe. Linear activity extends proximally from the plantar aspect of the left fifth toe into the midfoot suggestive of osteomyelitis of the left fifth metatarsal. Surgery and histopathology confirmed PET results.

coworkers⁷⁰ noted that FDG-PET with a dedicated full-ring PET scanner accurately diagnosed this disorder in 37 patients for a sensitivity of 95%. In contrast, the coincidence PET camera provided a sensitivity of 77% (30 of 39) and MRI had a sensitivity of 79% (31 of 39). The authors also concluded that FDG-PET can provide accurate assessment of patients with metal implants, which may otherwise limit evaluation by MRI, and that FDG-PET can correctly distinguish osteomyelitis from Charcot neuroarthropathy⁷¹ and septic arthritis.⁷²

Results from our own institution, reported by Basu and coworkers,¹⁶ also appear quite promising. A total of 63 patients, in 4 groups, were evaluated. A low degree of diffuse

FDG uptake was observed in the Charcot joints, which were clearly distinguishable from normal joints. The maximum standardized uptake values (SUVmax) in the Charcot lesions varied from 0.7 to 2.4 (mean 1.3 ± 0.4), whereas those of midfoot of normal control subjects and of patients with an uncomplicated diabetic foot ranged from 0.2 to 0.7 (mean 0.42 ± 0.12) and from 0.2 to 0.8 (mean 0.5 ± 0.16), respectively. The only patient with Charcot neuroarthropathy and superimposed osteomyelitis in this series had an SUVmax of 6.5. The SUVmax of the sites of osteomyelitis as a complication of diabetic foot ranged from 2.9 to 6.2 (mean 4.38 ± 1.39). Unifactorial analysis of variance testing yielded a statistically significant difference in the SUVmax between the 4

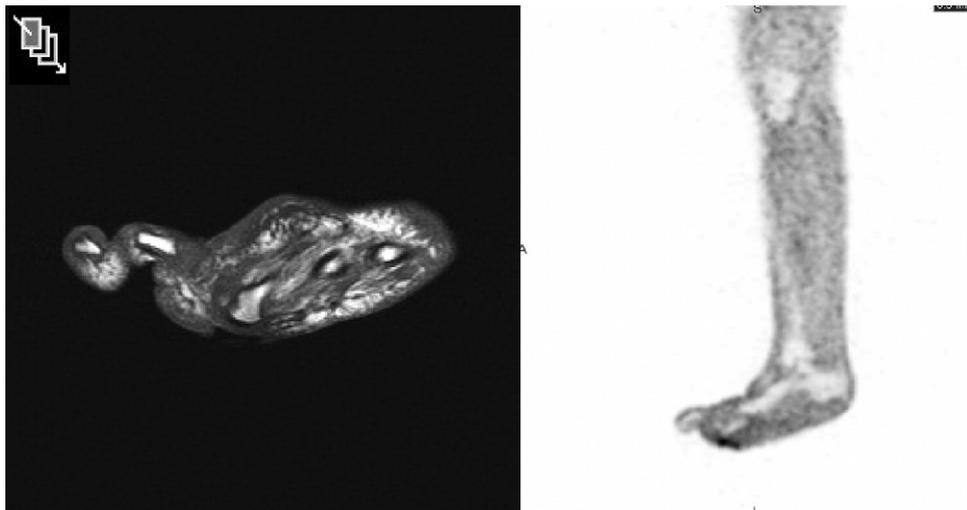


Figure 3 Shown is a 74-year-old diabetic man who presented with an ulcer on the plantar surface of midfoot. T2-weighted MRI revealed loss of signal at the site corresponding to the ulcer. No evidence of abscess or subjacent osteomyelitis is shown. FDG-PET images demonstrate superficial activity in the plantar surface of the foot with no osseous involvement consistent with cellulitis of the sole of the right foot. Long-term clinical follow-up confirmed the imaging results.

groups ($P < 0.01$). The SUVmax between the normal control groups and the uncomplicated diabetic foot was not statistically significant by the Student t -test ($P > 0.05$). Overall, the sensitivity and accuracy of FDG-PET in the diagnosis of Charcot neuroarthropathy were 100% and 93.8%, respectively, and for MRI the values were 76.9% and 75.0%, respectively. These 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 a foot ulcer is present. In summary, FDG-PET can differentiate between Charcot neuroarthropathy, osteomyelitis, and soft-tissue infection.

FDG-PET/CT was found to be highly accurate in detection of osteomyelitis by Keidar and coworkers¹⁷ The authors noted that FDG-PET/CT correctly separated osteomyelitis from soft tissue involvement in all infected sites. Interestingly, FDG-PET alone correctly identified osteomyelitis in 8 of 8 sites and soft tissue infection in 5 of 5 sites. In contrast, CT alone correctly identified osteomyelitis in 7 of 8 sites and soft tissue infection in 4 of 5 sites.

Our own group is currently conducting a long-term prospective investigation of the role of FDG-PET imaging in the detection of osteomyelitis in the diabetic foot.⁷³ In this study, we have compared the utility of FDG-PET in comparison to MRI and plain film radiographs. Among a total study population of 101 subjects (M = 68, F = 33, mean age = 59.51 years; range = 32-85 years), FDG-PET imaging correctly diagnosed the presence of osteomyelitis in 18 of 23 patients and correctly excluded the diagnosis in 70 of 75 patients, yielding values of 78%, 93%, 78%, and 93% for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), respectively. Compared with these findings, MRI correctly detected osteomyelitis in 19 of 20 patients and correctly excluded this diagnosis in 53 of 68 patients for sensitivity, specificity, PPV, and NPV of 95%, 78%, 56%, and 98%, respectively. Finally, radiographs correctly diagnosed osteomyelitis in 12 of 21 patients and correctly excluded osteomyelitis in 52 of 61 patients for sensitivity, specificity, PPV, and NPV of 57%, 85%, 57%, and 85%, respectively. In conclusion, we have found that FDG-PET is a highly specific imaging modality in excluding osteomyelitis in the diabetic foot, and proves to be a useful complimentary imaging modality with MRI, particularly in cases with positive MRI findings. Additionally, in clinical scenarios where MRI is contraindicated, the sensitivity and specificity of FDG-PET allows it to be used as the sole alternative imaging modality over other imaging techniques.

Interestingly, the effects of hyperglycemia on the accuracy of FDG-PET in 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 <250 mg/dL. Animal experiments have also shown that a high accuracy for FDG-PET can be achieved in the diagnosis of osteomyelitis without fasting.⁷⁴ In a study of the diabetic foot by Keidar and coworkers,¹⁷ it was shown that accurate interpretation was achieved in all patients with serum glucose levels >200 mg/dL.

Painful Lower-Limb Prostheses

Infection associated with hip arthroplasty is a relatively common clinical entity, with 1-4% after initial arthroplasty and approximately 25% after revision arthroplasty becoming infected. On another note, although 10% of patients with hip arthroplasty suffer from significant pain, only 1% are found to have periprosthetic infection after initial surgery, whereas the remainder have prosthetic loosening without infection. A particular challenge for orthopedic surgeons is the differentiation of mechanical loosening from superimposed infection, which has been the subject of multiple research studies during the past several years. Preliminary data suggest that FDG-PET has great potential role for detecting infection in hip prostheses, and to a lesser extent in knee prostheses (Figs. 4-8). FDG-PET imaging with standard PET (not PET/CT) is highly sensitive and is advantageous over anatomical imaging modalities because it is not affected by artifact from indwelling metal implants and provides higher resolution images than those of the conventional nuclear medicine techniques. Noninfectious reactions around the neck of the prosthesis are common months and even years after surgery, and therefore recognition of such patterns is important in this setting.⁷⁵ Increased FDG uptake around the neck and/or head of the prosthesis is very common and should not be interpreted as a finding suggestive of infection. Evidence for infection is noted at the bone-prosthesis interface, and most noninfectious inflammatory reactions are found outside the bone-prosthesis junction. At the present time, the potential for FDG-PET in the evaluation of prostheses is relatively well defined. More research may further enhance the role of FDG-PET in the evaluation of prostheses.

In a study involving 36 knee prostheses and 38 hip prostheses, our group reported that the respective sensitivity, specificity, and accuracy of FDG-PET for detecting infection were 90%, 89.3%, and 89.5%, respectively, for hip prostheses and 90.9%, 72.0%, and 77.8%, respectively, for knee prostheses.⁷⁶ Vanquickenborne and coworkers⁷⁷ reported that analysis of PET images alone resulted in 88% sensitivity and 78% specificity. The authors concluded that FDG-PET scans alone showed the same sensitivity as that of combined WBC/bone marrow (BM), whereas the specificity was slightly greater for the latter method. In an attempt to compare the accuracy of FDG-PET with combined ^{99m}Tc-sulfur colloid bone marrow imaging and ¹¹¹In-labeled white blood cell scintigraphy (TcSC-Ind WBC/BM) for the diagnosis of periprosthetic infection, Pill and coworkers²² prospectively enrolled 89 patients with 92 painful hip prostheses. These patients were given the option of undergoing either combined FDG-PET and TcSC-Ind WBC/BM or FDG-PET alone. FDG-PET correctly diagnosed 20 of 21 infected cases (sensitivity = 95.2%) and excluded infection in 66 of the 71 aseptic hips (specificity = 93%) with a PPV of 80% (20/25) and an NPV of 98.5% (66/67). TcSC-Ind WBC/BM correctly identified 5 of 10 infected cases (sensitivity = 50%) and excluded this complication in 39 of 41 aseptic cases (specificity = 95.1%) corresponding to PPV and NPV of 41.7% (5/12) and 88.6% (39/44), respectively. Based on these results, the au-

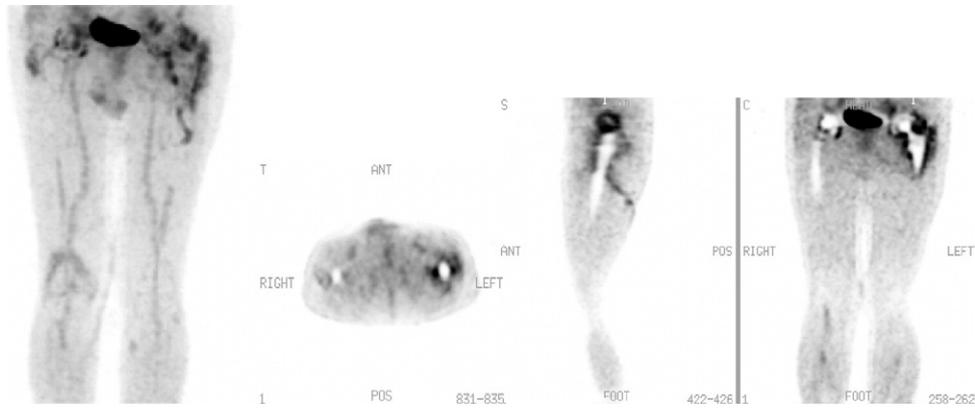


Figure 4 Shown is a 65-year-old patient with bilateral hip prostheses. PET images (MIP, transaxial, sagittal, and coronal) demonstrate abnormal FDG uptake around the neck and stem of the left hip prosthesis, extending inferiorly to the midshaft of the left prosthesis, consistent with periprosthetic infection. There is a fistula tract extending from the upper thigh region posteriorly to the skin. There is also mildly increased FDG uptake around the neck of the right hip prosthesis but no abnormal uptake is seen at the bone-prosthesis interface to suggest infection. This is a typical pattern for an uncomplicated prosthesis. Surgery and histopathology confirmed PET results.

thors concluded that FDG-PET is a promising diagnostic tool for distinguishing septic from aseptic painful hip prostheses.

In contrast, Love and coworkers^{78,79} and Stumpe and coworkers⁸⁰ reported low sensitivity and overall low accuracy for this technique, concluding that FDG-PET cannot replace WBC/BM imaging for diagnosing infection of the failed prosthetic joint. Several reasons can explain this discrepant observation about the efficacy of FDG-PET in evaluating painful hip arthroplasty. One major factor is the lack of uniform criteria for

interpreting the results generated by this technique by different investigators. It is well known that nonspecific FDG accumulation may be present around head and neck portion of the prosthesis for several months (and possibly years) after hip arthroplasty. Hence, caution should be exercised in interpreting sites of FDG uptake in these locations to minimize the number of false-positive results. In addition these investigators did not utilize a full ring dedicated PET machine (they used coincidence detection with a hybrid PET scanner). At present, the site and

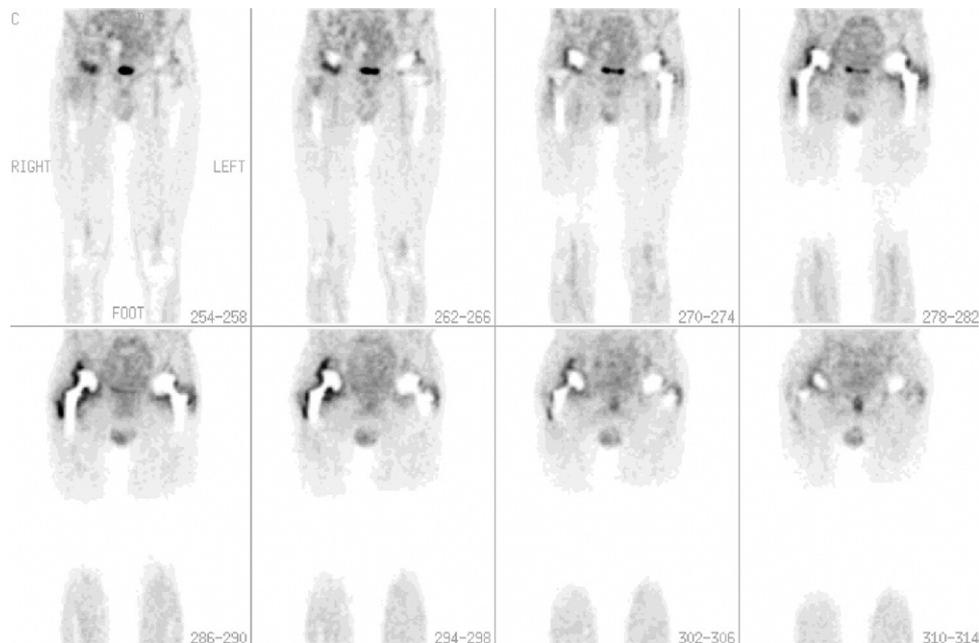


Figure 5 Shown is a 51-year-old man with bilateral hip prostheses. PET images demonstrate abnormal FDG uptake along the bone-prosthesis interface of the right hip extending from the neck to the stem, consistent with periprosthetic infection. There is also mildly increased FDG uptake in the soft tissues adjacent to right hip prosthesis, consistent with aseptic inflammation. There is mildly increased FDG uptake in the head and neck region of the left hip prosthesis without uptake along the stem. This is a typical pattern for noninfected prosthesis. Surgical findings and histopathological examination confirmed the results of FDG-PET imaging.

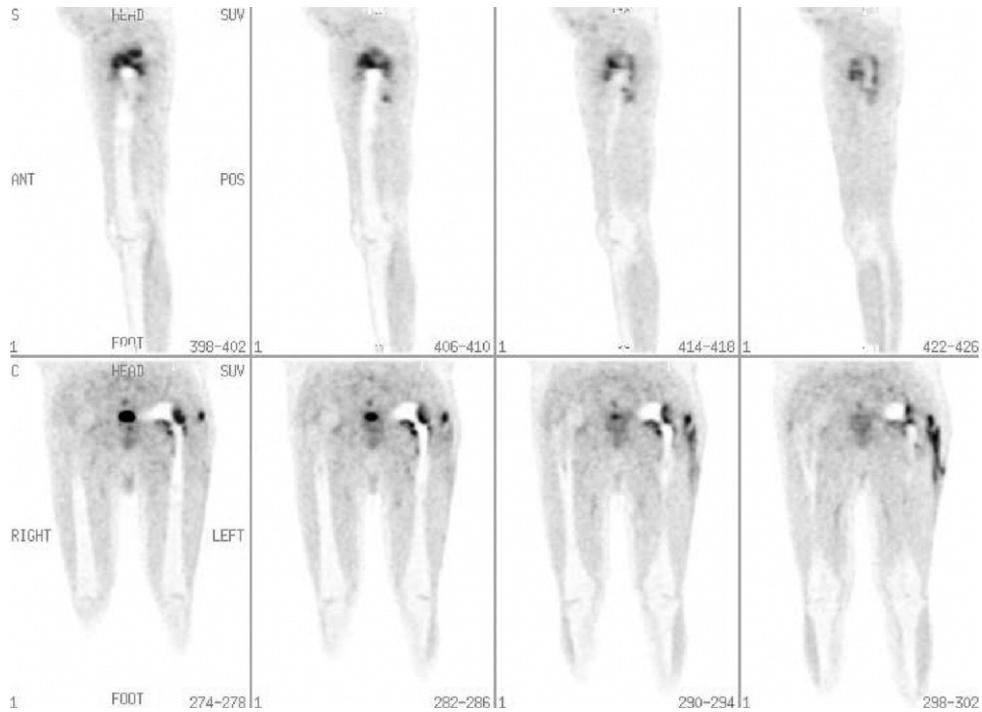


Figure 6 Shown is a 71-year-old man with painful left hip prosthesis and left lateral thigh abscess. Coronal PET images demonstrate increased FDG uptake around the neck of the hip prosthesis representing aseptic inflammation which is commonly noted with hip replacement. Increased FDG uptake in the left lateral thigh adjacent to the skin is due to abscess formation and rules out infected prosthesis. Long-term clinical follow-up confirmed the absence of infected prosthesis.

patterns of FDG accumulation appear to be more important than the intensity of uptake at these locations.

Chacko and coworkers⁸¹ studied the location and intensity of FDG uptake in 41 total hip prostheses from 32 patients with complete clinical follow-up data. 12 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 without infection revealed intense uptake around the

femoral head or neck components of prostheses with SUVs as high as 7. The 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. By adopting the standard criterion of presence of FDG uptake between the bone and prosthesis at the level of the mid shaft portion of the prosthesis, the accuracy of FDG-PET is substantially enhanced.

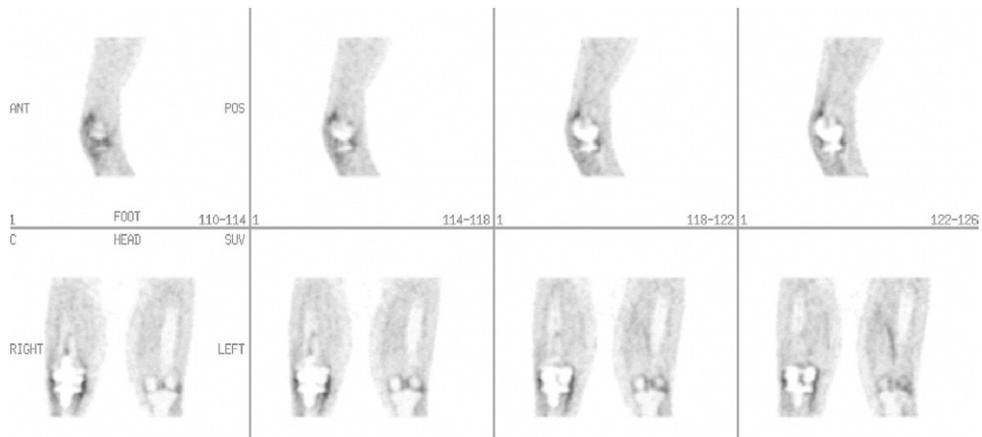


Figure 7 FDG-PET images of a 52-year-old man with painful right knee prosthesis demonstrate no abnormal uptake in the bone-prosthesis interface, which rules out superimposed infection. However, there is mild FDG uptake in the medial, lateral and anterior aspect of the knee prosthesis consistent with aseptic inflammation around the joint. Long term clinical follow up confirmed the absence of infection.

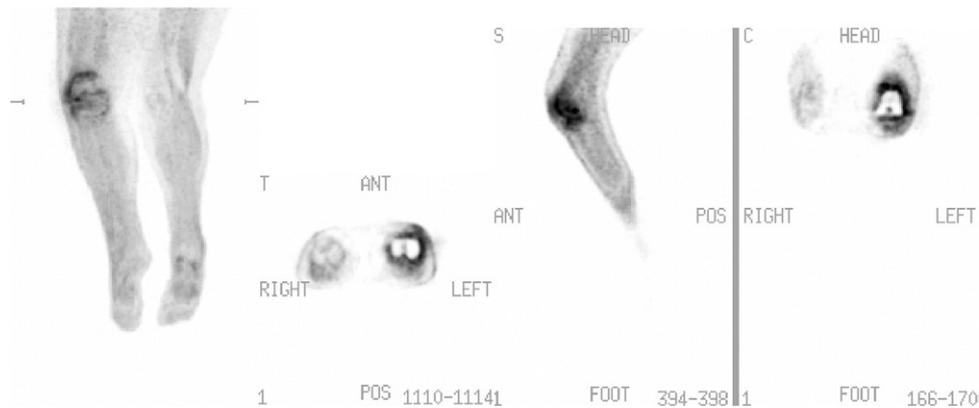


Figure 8 Shown is a 58-year-old woman with painful left knee prosthesis. PET images (MIP, axial, sagittal, and coronal) demonstrate diffusely increased FDG uptake surrounding the left knee prosthesis interface in both sides of the joint. This finding is consistent with infected knee prosthesis.

It is likely that FDG-PET will play a pivotal role in the evaluation of complicated lower-limb prostheses, especially after the criteria for infection and aseptic loosening are fully defined by well-designed prospective studies. The most recent META-analysis indicated that The FDG-PET sensitivity in identifying hip prosthesis infections was 82.8% and specificity was 87.3%. PET based on FDG could be a valid option if research is able to find an uptake pattern specific for septic and aseptic loosening.⁸²

Fever of Unknown Origin (FUO)

FUO is a clinical challenge, especially in the elderly, and is an increasingly accepted indication for FDG-PET in clinical practice (Fig. 9). Infection, malignancies, collagen vascular diseases, and autoimmune disorders account for the majority of cases of FUO. It was originally defined as a fever of greater than 38.3°C that has been documented on several occasions, with 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. Subsequently, this definition was 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 3 outpatient visits, along with exclusion of immune-compromised states.^{83,84} Conventional modalities, including structural imaging techniques, radiolabeled WBC imaging, and ⁶⁷Ga-citrate scintigraphy, have a relatively low diagnostic yield in this clinical scenario. The nonspecificity of FDG is of great value in evaluating patients with FUO because it accumulates in infections, malignancies, and inflammatory diseases, which are the 3 major causes of FUO. FDG, a “catch-all” tracer, has the potential to replace ⁶⁷Ga- and ¹¹¹In-labeled leukocyte imaging in this setting. Because of varying definitions of FUO and the lack of a structured diagnostic protocol, varying figures with regard to its efficacy have been reported in the literature. However, FDG-PET has overall provided added value to conventional techniques in 40-70% of the patients.

In a group of 40 patients who underwent both FDG-PET and ⁶⁷Ga scintigraphy, Blockmans and coworkers⁸⁵ found that FDG-PET revealed more abnormalities than the ⁶⁷Ga scintigraphy (77% vs 67%, respectively). FDG-PET was described as helpful for diagnosis in 35%, compared with ⁶⁷Ga scintigraphy in 25%. The investigators concluded that FDG-

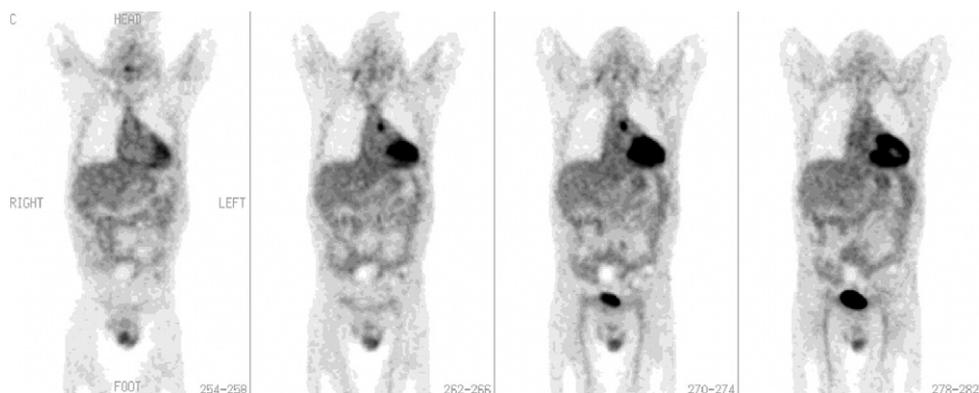


Figure 9 A 44-year-old man after heart transplant presented with fever of unknown origin and inconclusive radiologic studies, including CT. Coronal PET images demonstrate a focus of increased FDG activity in the aortopulmonary window that represents the source of infection. The patient completely recovered following drainage of the infected site in the mediastinum.

PET compares favorably with ^{67}Ga scintigraphy for evaluation of patients with FUO. Because of the quick results (within hours instead of days), PET imaging may replace ^{67}Ga scintigraphy as the procedure of choice for the evaluation of patients with FUO. Stumpe and coworkers⁸⁶ reported 98% sensitivity, 75% specificity, and 91% accuracy for FDG-PET in 39 patients with suspected infection.

In a study of 7 children with chronic granulomatous disease and signs of fever, PET was compared with CT for detecting active sites of infection. 116 lesions were detected in 22 FDG-PET scans compared with 126 lesions in 19 CT scans. PET excluded 59 lesions that appeared suspicious on CT and noted 49 suspicious lesions not shown on CT. All histopathologically confirmed active infective lesions were identified with PET, which allowed targeted biopsy and identification of the infective agent. The investigators concluded that in contrast to CT which cannot differentiate active from inactive infection, whole body FDG-PET imaging is a useful tool for screening active lesions and assisting in biopsy procedures.⁸⁷

Meller and coworkers⁸⁸ compared FDG-PET and ^{67}Ga -citrate scanning in patients referred for assessment for FUO. They reported a sensitivity of 81% and a specificity of 86% for FDG-PET in detecting the cause of fever and a sensitivity and specificity of 67% and 78%, respectively, for ^{67}Ga -citrate scanning. Bleeker-Rovers and coworkers⁸⁹ evaluated 35 patients with FUO and reported that FDG-PET was clinically helpful in 37% of cases, with a sensitivity and specificity of 93% and 90%, respectively, a PPV of 87%, and an NPV of 95%. A recent pilot study suggests that, despite the normal myocardial FDG uptake, FDG-PET accurately helps identify sites of infective endocarditis, and is a promising supplement to conventional echocardiography.⁹⁰

In a recently reported study, Federici and coworkers⁹¹ retrospectively evaluated the diagnostic contribution of FDG-PET/CT in 14 patients with FUO or unexplained prolonged inflammatory syndrome. In this series, PET/CT was helpful in 50% of the patients (7/14) for final diagnosis. FDG-PET/CT was found to be essential to establish the final diagnosis in 23% of the patients where conventional chest and abdominal CT was unable to detect the pathology.

Acquired Immunodeficiency Syndrome (AIDS)

PET has a major role to play in the management of human immunodeficiency virus (HIV)-infected patients, and is especially valuable in the assessment of diseases affecting the central nervous system (CNS). Quantitative assessment has shown that SUV of toxoplasmosis lesions are significantly lower than those of lymphoma, with virtually no overlap between the two conditions.

Hoffman and coworkers⁹² studied 11 patients with AIDS and CNS lesions; they noted that FDG-PET imaging is more accurate than CT or MRI in differentiating between malignant lymphomas and nonmalignant complications of this disease such as toxoplasmosis involving the brain. Malignant CNS lesions had significantly greater FDG uptake than that in nonmalignant abnormalities. O'Doherty and coworkers⁹³ showed that PET had an overall sensitivity and specificity of 92% and 94%, respectively, in the detection of infections or malignancies in patients with AIDS. The high specificity of FDG-PET, they concluded, can lead to initiation of an early and appropriate treatment strategy in these severely immunosuppressed patients. Heald and coworkers⁹⁴ found that CNS lesions diagnosed as lymphomas had statistically greater visual scores ($P = 0.001$) and count ratios ($P = 0.002$) than CNS lesions diagnosed as infections.

In a prospective study on HIV-1-infected patients, Scharko and coworkers⁹⁵ noted an association between the pattern of lymphoid tissue activation and the clinical stage of the disease. In a study of simian immunodeficiency virus, Scharko and coworkers⁹⁶ also showed that PET was useful in demonstrating that in acute stages there is activated lymphoid tissue in the head and neck region with some splenic involvement, a generalized pattern of peripheral lymph node activation in the mid-stage, and involvement of abdominal lymph nodes during late stage disease. Using FDG-PET in 47 AIDS patients, Santiago and coworkers⁹⁷ reported a sensitivity of 82.5% for detecting lesions with PET imaging. Specificity could not be determined as not all patients with positive PET findings had a definite diagnosis.

Vascular Graft Infection and Fistula

An important area of considerable clinical interest where this modality has had a major impact is in the evaluation of vas-

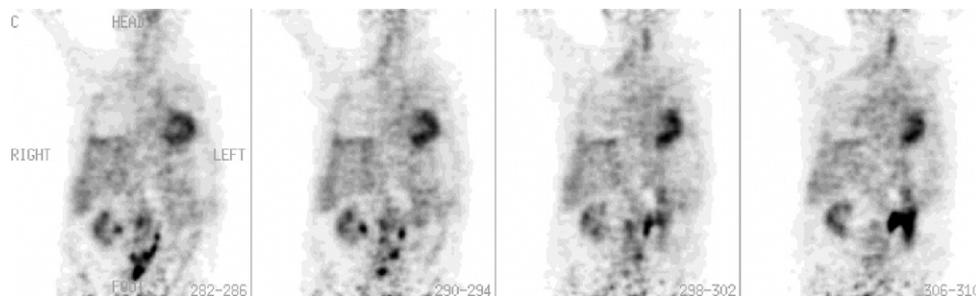


Figure 10 A 70-year-old man with a history of aortic aneurism repair was suspected of infection of prosthesis graft with inconclusive results from conventional radiologic studies. PET images show significant uptake of FDG at the site of the graft. This was confirmed by further assessment of this patient.

cular grafts. Not uncommonly, FDG-PET detects infection of vascular graft even when the CT results are negative (Fig. 10).⁹⁸ Rohde and coworkers⁹⁹ identified a rare case of a recurrent *Listeria monocytogenes* infection resulting from an infected aortic prosthesis on FDG-PET. Fukuchi and coworkers¹⁰⁰ compared the efficacy of FDG-PET to CT in patients with suspected aortic prosthetic graft infection. These authors concluded that although both imaging modalities are useful in the evaluation of patients with suspected aortic graft infection, identification of the characteristic FDG uptake pattern (diffuse and intense) as a diagnostic criterion on FDG-PET is superior to those of CT. On the basis of surgical, microbiological, and clinical follow-up findings, the aortic grafts were considered infected in 11 patients and not infected in 22 patients. Although the sensitivity of PET (91%) was greater than that of CT (64%), its specificity (64%) was lower than that of CT (86%). However, when focal uptake served as the criterion for a positive result, the specificity and PPV of PET for the diagnosis of aortic graft infection improved significantly to 95% ($P < 0.05$ for both).

Furthermore, FDG-PET/CT is reported to have an even better accuracy to detect vascular graft infection.³⁰ In a series of 39 patients (35 men and 4 women; age range 44-82 years) with suspected vascular graft infection, FDG-PET/CT was performed for the evaluation of an infectious process and its localization to the graft or soft tissues at various sites. The final diagnosis was based on histopathologic findings and microbiologic assays obtained at surgery or during clinical follow-up. PET/CT detected sites of increased FDG uptake suspected as infection in 27, and localized these findings to the graft in 16 patients. Vascular graft infection was confirmed in 14 of these patients (88%). PET/CT excluded graft involvement in 11 patients and, in 10 (91%) of these 11, long-term follow-up further confirmed that the infectious process was limited to surrounding soft tissues only. No abnormal FDG uptake was found in any of the 12 patients with no further evidence of infection. PET/CT had a sensitivity of 93%, specificity of 91%, PPV of 88%, and NPV of 96% for the diagnosis of vascular graft infection. The authors concluded that PET is a reliable noninvasive imaging modality for the diagnosis of vascular graft-related infection.

The precise anatomic localization by PET/CT enables accurate differentiation between graft and soft-tissue infection. Tegler and coworkers¹⁰¹ reported a patient with a suspected aortic graft infection that was confirmed and anatomically localized by FDG-PET/CT. An extra-anatomic bypass and extirpation of the aortic graft was performed. The perioperative location of the graft infection coincided exactly with the site of FDG uptake shown on PET/CT. The patient had an uneventful postoperative recovery and did well during 6 months of follow-up. Lauwers and coworkers²⁹ reviewed their personal experience in 5 consecutive patients with a suspected prosthetic infection (1 aortobifemoral bypass, 3 femoropopliteal bypasses, and 1 femorofemoral bypass) who underwent FDG-PET as a part of evaluation. All 3 patients with an intense FDG uptake proved to have prosthetic infection based on the result of microbiologic examination. The authors concluded from these preliminary results that FDG-

PET might be an important modality for diagnosing vascular graft infection.

Wasiková and coworkers¹⁰² reported a patient with aorto-bifemoral prosthesis infection and with an aortoduodenal fistula, where FDG-PET played a pivotal role in diagnosis. Urgent surgery was required in this patient because of massive gastrointestinal bleeding. Because of lower-limb ischemia after removal of the infected bifurcation prosthesis, implantation of a bifemoral bypass was performed as a 1-stage procedure. Eight months after surgery, the patient was in good condition without limitation in mobility. Balink and coworkers¹⁰³ described a patient who had recurrent periods

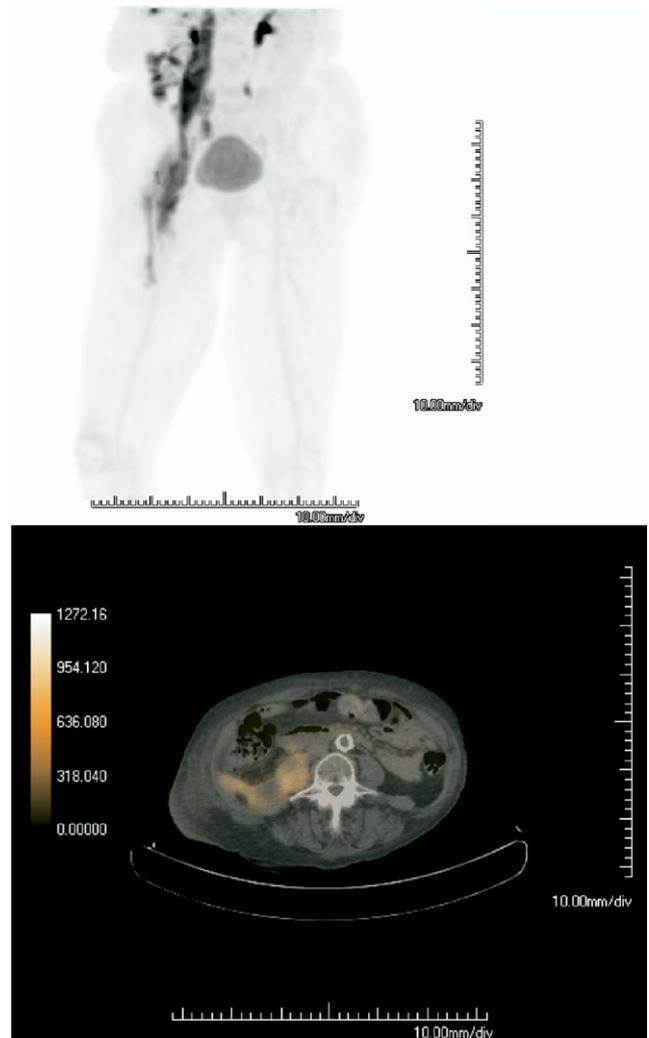


Figure 11 Shown is a 82-year-old woman who received a right hip replacement 13 years ago and who presented with hip pain. PET images (MIP) demonstrated increased FDG uptake around the proximal portion of the prosthesis, subcutaneous tissue, and muscles of the right anterior thigh and pelvis. FDG uptake is also noted in the right posterolateral abdominal wall muscles, consistent with extensive infection involving the right proximal prosthesis extending into the right flank. PET/CT images demonstrate sites of abnormal uptake in the psoas muscle which extends to the flank. On the basis of the PET/CT findings, the abscess was drained transcutaneously with successful outcome.

of fever and chills for 6 years after an aortic bifurcation graft had been implanted. A CT scan showed no signs of graft infection, although blood cultures revealed multiple enteric bacteria. PET/CT demonstrated a ring-shaped focus of abnormal uptake at the proximal anastomosis. The patient was operated on and an infected graft was found during surgery. Bacterial cultures of the explanted graft were positive, and the patient recovered well from surgery and was placed on a regimen of antimicrobial therapy. van Assen and coworkers¹⁰⁴ reported a case in which PET/CT diagnosed vascular graft infection as the cause of chronic fever.

Krupnick and coworkers⁹⁸ presented a case of aortoenteric fistula diagnosed by FDG-PET. Early diagnosis in this case led to rapid surgical intervention with graft removal and extra-anatomic bypass. Tsunekawa and coworkers¹⁰⁵ reported a case of aortoenteric fistula to the sigmoid colon that was diagnosed by the PET technique. There have also been reports of its utility in detecting other complications such as occult clotted vascular access infection.¹⁰⁶

Other Applications Based on Anecdotal Reports and Short Series

The extraordinary power of FDG-PET imaging is reflected by the continuous expansion of its domain of applications in recent years in assessing several benign disorders including infection and aseptic inflammatory processes. In addition to the aforementioned disease entities where there have been research studies either in prospective or retrospective settings, increasingly isolated case studies emphasizing the utility FDG-PET in the evaluation of infection of various etiologies are emerging (Figs 11 and 12). For example, FDG-PET has been used in animal experiments to determine the vari-

ous stages of malarial infection.⁵ In a series of 9 patients, Gugatschka and coworkers¹⁰⁷ determined the diagnostic utility of PET/CT in evaluating infection of the laryngeal cartilage and concluded that this modality is a reliable technique for diagnosing laryngeal cartilage chondritis. Furthermore, the authors also concluded that PET/CT appears to be an excellent tool for objectively monitoring the presence and grade of infection. The authors concluded that this might play a decisive role in the management of these patients.

Osteoarticular involvement is the most frequent complication of brucellosis, of which the diagnosis of brucellar spondylodiscitis is most challenging. Cobbaert and coworkers¹⁰⁸ described an uncommon case of brucellar spondylodiscitis where the diagnosis was established by PET/CT and MRI followed by a confirmation on brucella-agglutination test and positive culture of CT-guided fluid aspiration from the site.

There have been also other reports on the utility of FDG-PET in the detection of mycotic aneurysm of the thoracic aorta,¹⁰⁹ active myocarditis in chronic active Epstein-Barr virus infection,¹¹⁰ focal organizing pneumonia,¹¹¹ and acute varicella infection.¹¹²

Therapeutic Response Monitoring of Infection With PET

As in several malignant disorders, in recent years the utility of FDG-PET has been explored for determining the effects of therapy in the setting of infection. This has been tested in animal experiments where PET results have been shown to be accurate for monitoring response following antibiotic therapy in the setting of soft tissue infection.¹¹³ In the setting of osteomyelitis, time intervals required for FDG-PET and bone scan images to return to normal after successful treatment vary considerably. In a prospective study by Hakim and co-

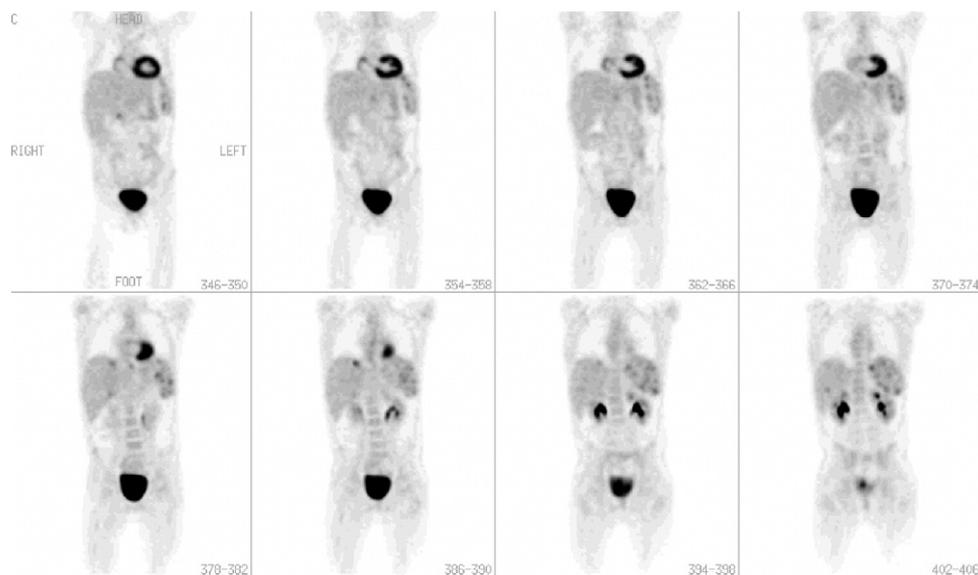


Figure 12 PET images of a patient with known fungal infection and history of T-cell lymphoblastic lymphoma reveal multiple sites of increased FDG uptake in the spleen and the liver. This demonstrates ongoing active disease at these sites.

workers,¹¹⁴ the specificity of these 2 modalities was compared in the evaluation of chronic osteomyelitis of the mandible after therapy. The specificity of bone scintigraphy was only 6.6% compared with 80% for FDG-PET. Win and coworkers¹¹⁵ observed that FDG activity returned to normal after successful treatment, whereas persistent spinal abnormalities were noted on MRI in patients with *Salmonella* vertebral osteomyelitis. In a recently published case report of an adult patient with acute infectious mononucleosis, there was marked reduction in lymphadenopathy and hypermetabolism in the liver and spleen in the 2 months of follow-up by PET/CT. Ozsahin and coworkers¹¹⁶ showed that after successful therapy for invasive aspergillosis, FDG-PET findings reverted to normal.

Several reports have documented this in various clinical settings: FDG uptake returns to normal levels after successful antibiotic therapy for hepatic cyst infection,¹¹⁷ after antifungal therapy for a lung abscess caused by candidal infection,¹¹⁸ and after therapy for *Pneumocystis jiroveci* pneumonia.¹¹⁹ FDG-PET has also been reported to be reliable for assessing disease activity and for detecting relapses of infection in patients with alveolar echinococcosis.¹²⁰⁻¹²² Chamilos and coworkers¹²³ examined the utility of this modality in the diagnosis and management of invasive mold infections. In 16 nonneutropenic patients with available FDG-PET imaging studies (11 from the authors' own institution), FDG-PET revealed an occult invasive mold infection site in 3 patients of whom 2 had unidentified CNS involvement. This was helpful in guiding the duration of treatment in most patients (n = 8). It is well-known that mycobacterial infection can result in elevated FDG activity^{124,125} and cause difficulty in interpretation when PET was utilized to evaluate oncology patient. However, on the other hand, the change of FDG activity following antibiotics is an effective way to know the efficacy of the antituberculosis therapy.¹²⁶⁻¹²⁸ Together, these data demonstrate that FDG-PET holds great promise in assessing treatment response in various infections similar to what has been observed in a wide array of malignancies.

Since the introduction of FDG-PET imaging more than 2 decades ago, the main focus of research has been devoted to assessing its application in cancer as well as in cardiac and neurological disorders. However, an increasing number of studies in the past decade have shown its great promise in the management of patients with infection and inflammation. With several groups demonstrating the usefulness of this powerful imaging methodology in the evaluation of chronic osteomyelitis, infected prostheses, diabetic foot disease, FUO, and AIDS, it is becoming quite evident that FDG-PET imaging will increasingly play a major role in the management of patients with infection and inflammation. In light of its ability to monitor disease activity and quantify the degree of abnormal metabolism, PET might prove to be an appropriate modality for assessing response to therapy.

Combined PET/CT has several advantages over existing imaging techniques for diagnosing infectious and inflammatory disorders, including high-quality images with detailed anatomic localization and fast results within 1.5 to 2 hours after the initiation of the examination. Radiolabeled WBC

imaging for infection often requires the acquisition of additional auxiliary scans (bone marrow and/or bone scanning), and therefore an extended period of time and substantial costs to obtain results. FDG has proven to be an excellent tracer for detecting inflammation in the setting of either infectious or noninfectious processes, and has the potential to become the second most common clinical application of FDG-PET imaging. Coregistration with CT is likely to further enhance the role of PET imaging in these settings. In summary, in the era of evidence-based medicine, FDG-PET imaging has shown promising results and should be used in the clinical management of a multitude of infectious disorders for optimal outcome of the affected patients.

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