

# DISCUSSIONS IN

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PET



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I M A G I N G

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## LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

1. Describe uptake mechanisms of FDG in infection and inflammation.
2. Name at least two indications for infection/inflammation imaging in which FDG may replace current agents.
3. Explain why it may be difficult, using FDG-PET, to distinguish the infected from the aseptically loosened joint replacement.
4. Describe the potential role of FDG-PET in the patient with vasculitis.

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## Imaging Infection and Inflammation with F-18 FDG-PET

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**N**uclear medicine plays an important role in the evaluation of inflammation and infection. Radionuclide imaging is complementary to CT in the postoperative patient and is used to help differentiate postoperative changes from infection. In the case of painful joint replacement, radionuclide studies are the primary diagnostic imaging modality for differentiating infection from other causes of prosthetic failure. Several tracers are available for imaging infection: technetium-99m diphosphonates, gallium-67 citrate, indium-111- and technetium-99m-labeled leukocytes, and the recently approved antigranulocyte antibody Tc-99m fanolesomab.

Although useful, each of these tracers has disadvantages, and investigators continue to seek alternative agents. Fluorine-18 FDG is readily available, exquisitely sensitive, and relatively inexpensive. PET imaging using F-18 FDG is rapidly completed, and the high-resolution tomographic images are superior to those provided by most SPECT agents. Thus, it is not surprising that the use of FDG-PET for detecting infection and inflammation has attracted interest.

### UPTAKE MECHANISMS

Glucose is transported into cells via transporters located in the cell membrane. F-18-fluorodeoxyglucose, a radiolabeled glucose analog, is transported into cells via the same glucose transporters. Intracellular FDG is then phosphorylated by hexokinase enzyme

to F-18-2'-FDG-6 phosphate, which does not easily pass through the cell membrane. Compared with glucose, this fluorinated deoxyglucose is not metabolized.<sup>1</sup>

Increased uptake of FDG in inflammation, as in tumors, is related in part to an increased number of glucose transporters. The affinity of glucose transporters for deoxyglucose is presumably increased in inflammation by various cytokines and growth factors.<sup>2</sup>

The normal distribution of FDG includes the brain, myocardium, and genitourinary tract. Activity in the bone marrow, stomach, and bowel is variable. Thymic uptake, especially in children, can be seen. Liver and spleen uptake is generally low-grade and



Figure 1. Increased periprosthetic FDG activity at the bone-prosthesis interface along the lateral aspect of the femoral component of an infected left hip prosthesis (left). Similar uptake is present along the lateral margin of an aseptically loosened right hip prosthesis (right). Bone-prosthesis interface activity on FDG imaging, once thought to be specific for infection, is probably related to osteolysis, which is present in both infection and aseptic loosening. (Reproduced with permission<sup>10</sup>)

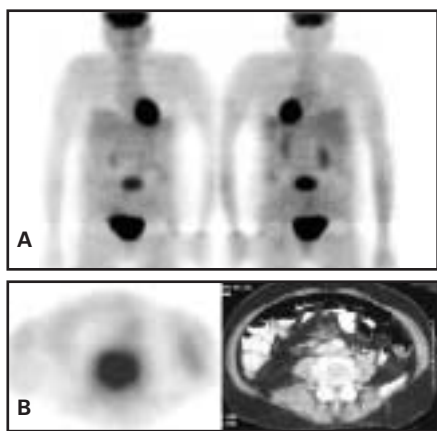


Figure 2. Intense FDG accumulation is present in a case of lower lumbar spine osteomyelitis. Maximum intensity projection (A), transaxial FDG-PET and CT images (B).

diffuse, although splenic uptake may be intense in infection, as the spleen is an integral part of the body's immune system. Increased splenic activity in infection likely reflects increased glucose utilization by this organ, and it is important to recognize that this increased activity cannot automatically be attributed to infection or tumor of the organ itself.<sup>1</sup>

To minimize FDG uptake in normal tissues, patients fast for at least several hours before imaging to reduce competition for glucose transporters. Limiting physical activity before injection reduces uptake in FDG-avid striated muscle. Muscle and brown adipose tissue accumulation of FDG can be significantly reduced by administration of benzodiazepines orally, 30 to 60 minutes before tracer FDG injection.<sup>3</sup> When evaluating the lower extremities, it useful to have patients remain at bed rest for at least one hour before injection, to further reduce undesirable soft-tissue tracer uptake.

FDG uptake is related to tissue metabolism in general; there is nothing specific about its uptake in inflammation. If the value of this tracer as an imaging agent for infection and inflammation is to be maximized, appropriate indications for its use must be developed.

### MUSCULOSKELETAL INFECTION

In otherwise normal bone, three-phase bone scintigraphy is both sensitive and specific for osteomyelitis. Bone scintigraphy is less useful in patients with previously traumatized bone and in the presence of orthopedic hardware or the neuropathic joint, however, because of diminished specificity. Sequential bone/gallium and combined leukocyte/marrow imaging are often used in these situations.<sup>4</sup> The use of multiple tracers and the need to image at multiple times increase the expense and complexity of the tests and impose additional burdens on patients, who are often elderly and/or debilitated. FDG has

generated considerable interest as an alternative to these tests, and recent reports suggest that it may be useful for diagnosing osteomyelitis.<sup>5,8</sup> FDG uptake by normal cortical bone is quite low, while bone marrow uptake is variable.

In osteomyelitis, activated inflammatory cells, such as neutrophils, lymphocytes, and macrophages, are metabolically active and consume large quantities of glucose and, hence, FDG. Unfortunately, increased uptake of FDG is also associated with inflammatory arthritis, acute fractures, and normally healing bone.<sup>19</sup> Since FDG accumulates in the bone marrow, increased osseous uptake also may be related to localized hypercellular marrow.<sup>10</sup>

While reports about the value of FDG-PET for diagnosing osteomyelitis in general are encouraging, extensive investigations focused on specific indications are needed to define its role in musculoskeletal infection.

- *Prosthetic joint infection.* Nearly 500,000 lower extremity joint replacements are performed annually in the U.S. While many complications of joint replacement surgery can be easily and accurately diagnosed and promptly remedied, differentiating infection from the most common cause of joint arthroplasty failure—aseptic loosening—is a more challenging task. These entities are remarkably similar, both clinically and histopathologically. Aseptic loosening is often caused by an immune reaction to the prosthesis. Histiocytes, giant cells, lymphocytes, and plasma cells accompany the inflammation. The secretion of proinflammatory cytokines and proteolytic enzymes leads to osteolysis and loosening. These same events are present in infection, with one important difference: Neutrophils, usually absent in aseptic loosening, are invariably present in infection.<sup>11</sup>

Differentiating infection from aseptic loosening is crucial because the management of these two conditions differs markedly. The diagnosis of infection has significant implications, clinically and economically, in terms of prolonged antibiotic treatment, longer hospital stay, and a second operation. The failure to diagnose infection has serious ramifications. Persistence of infection will almost assuredly lead to failure of a revision arthroplasty and the need for additional surgery. In-111-labeled leukocyte/Tc-99m sulfur colloid marrow imaging, with an accuracy of about 90%, is the radionuclide gold standard for diagnosing prosthetic joint infection.<sup>11</sup>

The role of FDG-PET in the evaluation of painful lower extremity joint prostheses has been investigated extensively. Although initial reports suggested that FDG-PET could accurately identify the infected joint prosthesis, more recent studies are less encouraging. They suggest

that the test cannot accurately differentiate aseptic loosening from infection (Figure 1).<sup>10,12-14</sup> The ability to detect inflammatory conditions with FDG depends on glucose utilization by leukocytes during their metabolic burst; i.e., when they are activated. But aseptic loosening and infection of a prosthetic joint are both accompanied by an inflammatory response in which leukocytes participate, and the inability of FDG to accurately differentiate the two conditions is, therefore, not surprising.

The success of labeled leukocyte imaging is related to the difference in the body's cellular response to aseptic loosening and infection. In the usual clinical environment, most of the leukocytes labeled are neutrophils, and labeled leukocyte imaging is most sensitive for detecting neutrophil-mediated inflammatory processes. Neutrophils, invariably present in the infected prosthesis, are rarely present in the aseptically loosened device. Thus leukocyte imaging is both sensitive and specific for diagnosing prosthetic joint infection.<sup>10,11</sup> Because the PET and CT data sets are acquired sequentially instead of simultaneously, registration of the two can be a challenge, particularly near large metallic arthroplasty components, which can cause CT artifacts. Reading the images side by side as well as in a synthesized, attenuation-corrected format can help minimize errors.

- *Diabetic foot.* The radionuclide study of choice for diagnosing diabetic pedal osteomyelitis in the forefoot is the labeled leukocyte, although some data suggest the recently approved antigranulocyte antibody, Tc-99m fanolesomab, may be a suitable replacement. In the mid- and hindfoot, the most commonly encountered complication is neuropathic arthropathy, or Charcot's joint. Determining if superimposed infection is present, or differentiating the rapidly progressive neuropathic joint from osteomyelitis, is difficult. Combined leukocyte/marrow scintigraphy is the radionuclide procedure of choice for determining whether the neuropathic joint is infected.<sup>15</sup>

FDG imaging is affected by circulating glu-

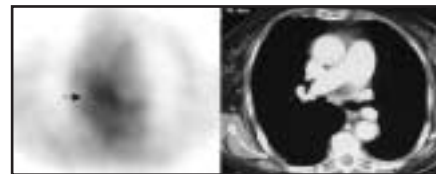


Figure 3. FDG-PET imaging performed on 81-year-old woman with history of renal cell carcinoma, persistent fevers, and no localizing signs demonstrates a hypermetabolic focus in mediastinum (arrow), corresponding to CT-identified lymphadenopathy. Biopsy confirmed mediastinal lymph node involvement by metastatic renal cell carcinoma.

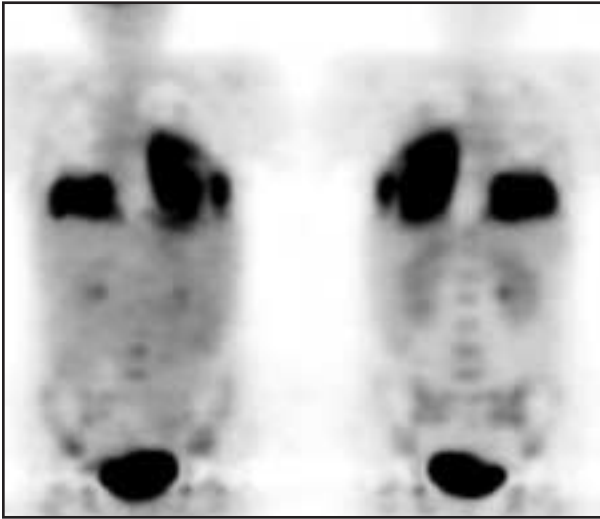


Figure 4. 52-year-old woman with history of hairy cell leukemia presented with spiking fevers but no localizing signs. Chest x-ray was reported as showing only small pleural effusions. MIP image demonstrates intense bilateral lower lung FDG accumulation. Bronchoscopy confirmed presence of acute pulmonary inflammation.

cose and insulin levels, as FDG and glucose compete for transporters. Elevated glucose levels, therefore, decrease FDG uptake by cells. While insulin decreases blood glucose levels, it also increases skeletal muscle uptake of glucose and FDG, and it may also result in decreased uptake of FDG by the target cells, which in the setting of infection would be activated leukocytes. Successful FDG imaging of infection in diabetic patients is likely to be more complicated than in the general population. At the present time, scant, if any, data are available about the role of FDG-PET in the evaluation of foot complications in diabetes.

- *Spinal osteomyelitis.* MR is the imaging modality of choice for diagnosing spinal osteomyelitis. It is sensitive to motion degradation, however, and patients with movement disorders may not be suitable candidates for imaging. Certain metallic implants are contraindications to the study, and MRI cannot always distinguish osteomyelitis from severe degenerative arthritis. Nuclear medicine provides important information in these patients. The radionuclide study of choice for diagnosing spinal osteomyelitis is gallium imaging, with or without bone scintigraphy.<sup>16</sup> Regardless of whether gallium imaging is used alone or in combination with bone scintigraphy, the image quality is less than desirable, the study is time-consuming, and the patient must make multiple visits to the nuclear medicine department. Although most of the series reported to date are small, FDG-PET appears to be useful for diagnosing spinal osteomyelitis, with accuracy comparable to that of gallium imaging (Figure 2).<sup>1,17,18</sup>

## NONOSSEOUS INFECTION AND INFLAMMATION

FDG-PET shows promise in several nonosseous conditions.

- *Acquired immunodeficiency syndrome.* Patients with AIDS are subject to a variety of opportunistic infections and tumors, and gallium imaging is often performed to evaluate these patients. FDG-PET also accurately localizes foci of infection, as well as tumor, in this population. It is important to recognize that, outside of the central nervous system, it is not possible to distinguish infection from tumor with FDG. In the CNS, however, FDG-PET reliably differentiates lymphoma from toxoplasmosis. CNS lymphoma is highly active metabolically, while toxoplasmosis is not.

The standardized uptake values of toxoplasmosis are significantly lower than those of lymphoma, with virtually no overlap of the uptake values between these two groups.<sup>1</sup>

- *Fever of undetermined origin.* FUO is an illness of at least three weeks' duration, with several episodes of fever exceeding 38.3°C, and no diagnosis after an appropriate inpatient or outpatient evaluation. There are numerous causes of FUO, and infection accounts for only about 25% of them. Neoplasms are responsible for about 15% to 25%. Other etiologies include collagen vascular disease, granulomatous diseases, pulmonary emboli, cerebrovascular accidents, and drug fever.<sup>15</sup>

There is no uniform radionuclide approach to FUO. Labeled leukocyte imaging is more sensitive early in the course of an illness, while gallium is more sensitive later in the illness. The selection of procedure may thus be governed by the duration of the illness. The etiologies of FUO are diverse, and some individuals prefer the sensitive, but nonspecific, gallium as the initial radionuclide study. Regardless of which study is performed first, it takes several days to perform both procedures. FDG poses no such problems. It is sensitive, ideally suited to the evaluation of an entity with numerous etiologies (Figures 3, 4). The short half-life of F-18, furthermore, does not delay the performance of any additional radionuclide studies that might be contemplated. Recent studies support the use of FDG-PET in the patient with FUO.<sup>19-21</sup>

Blockmans et al<sup>19</sup> studied FDG-PET in 58 cases of FUO and found that the test provided useful information in 41% of the patients. In a

subgroup of 40 patients who also underwent gallium imaging, FDG-PET was helpful in 35% of the cases, while gallium was helpful in 25%. These investigators concluded that FDG-PET could replace gallium scintigraphy as a test for the evaluation of patients with FUO. Meller et al<sup>20</sup> reported that FDG-PET was 84% sensitive and 86% specific for identifying the source of the FUO and was superior to gallium imaging. Bleeker-Rovers et al<sup>21</sup> evaluated 35 patients with FUO and reported that FDG-PET studies were clinically helpful in 37% of the cases. The test was 93% sensitive and 90% specific and had a negative predictive of 95%.

Only about half of all FUOs are caused by infection or tumor. Vasculitis, thromboembolic disease, sarcoidosis, and chronic granulomatous disease, all of which can be the source of an FUO, are associated with increased FDG uptake.<sup>1,2</sup>

In the patient with FUO, FDG-PET identifies the organ or tissue likely to be the source of the fever, thereby guiding additional testing. Its high negative predictive value is equally important. A negative FDG-PET makes it very unlikely that a morphologic origin of the fever will be found.

- *Focal infection.* Patients with suspected focal infection often present with a discrete abnormality detected, but not characterized, with morphologic tests. This population includes patients suspected of having a postoperative infection or those who have a history of tumor. The radionuclide study is used to help differentiate infection from postoperative changes and tumor.<sup>22</sup> The limitations of FDG in differentiating infection from tumor are obvious. Persistent uptake of FDG in uninfected surgical incisions has been reported. Investigations have found that, in patients suspected of having focal infection, FDG-PET demonstrates sensitivity comparable to that of In-111-labeled autologous leukocytes, but it is considerably less specific. False-positive results were associated with tumor and postoperative changes.<sup>1,23</sup>

- *Inflammatory conditions.* Sarcoidosis is a chronic inflammatory condition of unknown etiology. Assessment of disease activity deter-



Figure 5. Focally increased intracardiac activity can be seen on axial (left) and coronal (right) FDG-PET images performed on patient with prosthetic mitral valve and persistent bacteremia. Echocardiography confirmed presence of valvular vegetations and mitral annular abscess. (Reproduced with permission)



Figure 6. Six months after insertion of spinal hardware, 80-year-old woman underwent PET/CT for increasing back pain. Axial CT image (left) demonstrates osteopenia and destruction of L4 vertebral body. Axial FDG-PET image (center) demonstrates increased activity in lower lumbar spine. Axial coregistered PET/CT image (right) confirms that abnormal FDG accumulation involves bone. (Courtesy of Dr. K. Stumpe)

mines, to a great degree, the type of therapy to be administered, and the degree of FDG uptake in sarcoidosis correlates with disease activity. Though not useful for initial diagnosis, because of nonspecific uptake patterns, FDG-PET will probably be useful in the patient with known sarcoidosis for evaluating the extent of active disease and for monitoring response to therapy.<sup>24</sup>

Vasculitis is characterized by inflammation and necrosis of blood vessel walls. FDG-PET may eventually play a significant role in the diagnosis and treatment of patients with this condition. Uptake of FDG in giant cell arteritis, Takayasu's arteritis, aortitis, and unspecified large vessel vasculitis has been described. Blockmans et al<sup>25</sup> observed abnormal vascular

FDG uptake in 76% of 25 patients with proven temporal arteritis or polymyalgia rheumatica. Thoracic artery uptake had a positive predictive value of 93% and a negative predictive value of 80%. Meller et al<sup>26</sup> compared FDG-

PET with MRI in 15 patients with vasculitis and found that the radionuclide study detected more sites of involvement than MRI and was effective in the diagnosis and follow-up of patients with aortitis.

- **Endocarditis.** The clinical value of the radionuclide diagnosis of infective endocarditis has never been established. A recent pilot study suggests, however, that FDG-PET accurately identifies foci of infective endocarditis and may become a useful adjunct to echocardiography (Figure 5).<sup>27</sup>

**CONCLUSION**

Despite the fact that few data are available on its role in infection and inflammation imaging, PET/CT will undoubtedly be useful, especially

for evaluating the musculoskeletal system when it is not always possible to use radionuclide imaging alone, to determine whether infection involves bone, soft tissue, or both (Figure 6). PET/CT is likely to have a major impact on the workup of patients with fever of unknown origin. These patients undergo numerous anatomic and functional imaging tests, and PET/CT has the potential to greatly reduce the number of tests performed. While a negative study makes it unlikely that a morphologic cause of the fever will be identified, a focal FDG-PET abnormality can be precisely localized, a specimen obtained, and intervention undertaken, conceivably during the same imaging session.

Although its role is still evolving, FDG-PET is a promising modality in the diagnosis of infection and inflammation. While this technique will probably be of limited utility for differentiating infection from tumor and normal postoperative changes, and aseptic loosening from infection of a prosthetic joint, it is likely that for FUO, spinal osteomyelitis, and inflammatory conditions such as vasculitis and sarcoidosis, FDG-PET will assume increasing importance, perhaps even becoming the radionuclide procedure of choice in some or all of these entities. ■

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