^{18}F-FDG and Diabetic Foot Infections: The Verdict Is. . .

A diabetic foot infection is defined as an inframalleolar infection in a person with diabetes mellitus. These infections are common, complex, and costly. They cause substantial morbidity, are responsible for the largest number of diabetes-related hospital bed-days, and are the most common cause of nontraumatic lower-extremity amputations (*1*). The major predisposing factor to infection in the diabetic foot is the mal perforans ulcer, which results from trauma or excessive pressure on a foot that lacks protective sensation. Once the cutaneous integument is breached, the wound may become actively infected, and by contiguous extension, infection can involve deeper tissues, including the bone, progressing to frank osteomyelitis (*2*).

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A simple, reasonably accurate test for osteomyelitis underlying an open wound is the probe-to-bone test (*1,3,4*). Unfortunately, diabetic patients can have a significant foot infection and lack pain and not mount a systemic inflammatory response, and the diagnosis of osteomyelitis often is overlooked (*2*). Imaging studies are therefore an essential part of the diagnostic evaluation of these individuals. There are a myriad of imaging studies from which to choose. Radiographs are relatively inexpensive and readily available and should be the initial imaging procedure performed as they may provide the diagnosis and obviate additional, more costly tests. Radiographs are useful because, even when not diagnostic, they provide an anatomic overview of the area of interest and any preexisting conditions that could influence the selection and interpretation of subsequent procedures (*5*). Bone and labeled leukocyte imaging have, for many years, been the most commonly performed radionuclide studies for diagnosing pedal osteomyelitis in diabetic patients. The bone scan often is used either as a screening test or to improve the accuracy of labeled leukocyte imaging, presumably by facilitating more precise localization of labeled leukocyte accumulation. Given the low specificity of the bone scan, its value as a screening test is questionable. Published data suggest that any improvement in accuracy gained by performing the bone scan in conjunction with labeled leukocyte imaging is, at best, marginal (*2,6–9*). The availability of SPECT/CT diminishes even further the merit of the bone scan as a localizing adjunct to labeled white cell imaging.

The value of ^{18}F-FDG PET and PET/CT in a variety of infectious and inflammatory conditions is well documented. The intrinsically high resolution of PET should be a significant advantage over single-photon–emitting tracers, especially when the diagnosis depends on the ability of a technique to accurately localize radiotracer accumulation in structures as small as the distal forefoot, where most diabetic foot infections are found. The ability to perform semiquantitative analysis potentially could facilitate differentiating infectious from noninfectious conditions, that is, osteomyelitis and the neuropathic joint.

The data on the role of PET and PET/CT in the evaluation of diabetic foot infections are limited (*10–14*). Hopfner et al. (*13*) studied 16 diabetic patients with neuropathic joints to determine the role of ^{18}F-FDG PET in the preoperative identification of neuropathic joints. Blood glucose levels ranged between 92 and 254 mg/dL, but the number of patients with levels in excess of 200 mg/dL was not specified. No information was provided about the presence of ulcers or open wounds, or antibiotic treatment. ^{18}F-FDG PET identified 95% (37/39) of the lesions, including 22 of 24 bone lesions and all 15 joint or soft-tissue lesions. The mean maximum standardized uptake value (SUVmax) in these lesions was 1.8 (range, 0.5–4.1). Although image quality was superior in patients with normal blood glucose concentrations, compared with those with concentrations greater than 200 mg/dL, the sensitivity of the test was not affected by blood glucose levels. The investigators suggested that, even though none of the patients in their study had osteomyelitis, ^{18}F-FDG PET could reliably differentiate osteomyelitis from neuropathic lesions!

Basu et al. (*12*) evaluated the usefulness of ^{18}F-FDG PET for differentiating osteomyelitis and soft-tissue infection from the uninfected neuropathic joint in 63 diabetic patients. Blood glucose level was less than 200 mg/dL in 62 patients. Five patients had foot ulcers. No information about antibiotic therapy was provided. Histopathologic or microbiologic confirmation of the final diagnosis was available for 10 patients. These investigators found that the mean SUVmax in uninfected neuropathic joints was 1.3 ± 0.4, similar to what was reported by Hopfner et al. (*13*). The mean SUVmax of pedal osteomyelitis in their population was 4.38 ± 1.39, and the SUVmax in

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the one case of osteomyelitis superimposed on a neuropathic joint was 6.5. The sensitivity and accuracy of ^{18}F-FDG PET for diagnosing the osteomyelitis in this investigation were 100% and 94%, respectively. The investigators concluded that ^{18}F-FDG uptake in the neuropathic joint was distinct from that in osteomyelitis, and that ^{18}F-FDG PET had a high negative predictive value for excluding osteomyelitis in the presence of the neuropathic joint.

Nawaz et al. (*14*) prospectively investigated 110 diabetic patients. Blood glucose level was less than 200 mg/dL in all patients. No information about the presence of foot ulcers or use of antibiotics was provided. Twenty-three of 27 patients with osteomyelitis had histopathologic or microbiologic confirmation, but the total number of patients with histopathologic proof of the final diagnosis was not provided. Using visual analysis, these investigators reported that ^{18}F-FDG PET had a sensitivity, specificity, and accuracy of 81%, 93%, and 90%, respectively, for diagnosing pedal osteomyelitis.

Keidar et al. (*10*) compared ^{18}F-FDG PET and PET/CT in 18 clinically suspected sites of infection. Open wounds or ulcers were present in 12 of the 18 sites. Blood glucose levels exceeded 200 mg/dL in 7 patients. Histopathologic or microbiologic confirmation of the final diagnosis was available for 2 sites. PET/CT localized uptake to bone in 9 sites, including 8 sites of osteomyelitis. The accuracy of ^{18}F-FDG PET/CT in this investigation was about 94%. The mean SUVmax in infectious foci was 5.7 (range,1.7–11.1) for both osseous and soft-tissue sites of infection. The investigators found no relationship between the patients' glycemic state and the degree of ^{18}F-FDG uptake.

Schwegeler et al. (*11*) prospectively evaluated ^{18}F-FDG PET for diagnosing clinically unsuspected osteomyelitis in 20 diabetic patients, all of whom had pedal ulcers. Information on blood glucose levels at the time of imaging was not provided. None of the patients had received antibiotic treatment before imaging. Studies were analyzed visually; SUVs were not reported. Histopathologic or microbiologic confirmation of the final diagnosis was available for 7 patients. ^{18}F-FDG PET detected 2 of 7 cases of osteomyelitis (29% sensitivity). The authors speculated that the low sensitivity may have been related to a lower level of inflammatory response in their population or perhaps to insulin resistance, which may have impaired ^{18}F-FDG uptake by the bone. The authors also noted that their studies were hampered by motion artifacts and limited spatial resolution.

In the current issue of *The Journal of Nuclear Medicine,* Familiari et al. (*15*) report on ^{18}F-FDG PET/CT for diagnosing pedal osteomyelitis in 13 diabetic patients with a high pretest likelihood of infection, including 7 with exposed bone and 6 with a high clinical index of suspicion. All patients had a blood glucose level of less than 160 mg/dL and had not received any antibiotic therapy for at least 1 wk before imaging. Histopathologic confirmation of the final diagnosis was available for all patients. ^{18}F-FDG PET/CT was performed 10 min, 1 h, and 2 h after injection. The authors found that the highest accuracy for the test, 54%, was achieved when the SUVmax was at least 2.0 at 1 and 2 h after injection and increased over time. Accuracy improved to 62% when CT findings were considered. The accuracy of planar ^{99m}Tc-exametazime–labeled leukocyte imaging in this population was 92%. The authors concluded that ^{18}F-FDG PET/CT is not accurate, and cannot replace labeled leukocyte imaging, for diagnosing pedal osteomyelitis in diabetic patients.

The limited data on the role of ^{18}F-FDG PET and PET/CT in the evaluation of diabetic foot infections are very inconsistent. How can these very discordant results be reconciled? Are these discrepancies related to the imaging prowess of the investigators, the imaging equipment, interpretive criteria, study populations, the reference standards used? All of these investigations were performed by groups with extensive experience in radionuclide imaging, and it is not likely that the discordant results can be attributed to differences in investigator experience or skill. The advantages of PET/CT over PET are obvious. Although it is tempting to ascribe the low sensitivity reported by Schwegler et al. (*11*) to their use of PET rather than PET/CT, Familiari et al. (*15*) obtained similar results using PET/CT. Equipment alone, therefore, is not a suitable explanation. Complicating study comparisons to some degree is the variability in interpretive criteria used. In 2 investigations (*11,14*), only visual interpretation of images was performed, in 2 (*12,13*) only semiquantitative (SUV) analysis was performed, in 1 (*15*) both visual and semiquantitative analysis were used, and in 1 investigation (*13*) it is not clear exactly how images were interpreted. Imaging was performed at a single time point in all of the investigations, except that of Familiari et al. (*15*), who performed imaging at several time points.

What about study populations? Is it possible that the variable results reported could be related to differences in study populations? For example, how many patients had type 1 and how many had type 2 diabetes? How many were treated with insulin and how many with oral hypoglycemic agents? With what types of insulin and with which oral hypoglycemic agents were patients treated? What about the temporal relation between administration of insulin or oral agents and ^{18}F-FDG injection? Is it possible that the sensitivity of the test is affected by the type of medication or the interval between administration and ^{18}F-FDG injection? Unfortunately these data are incomplete. The investigation of Hopfner et al. (*13*) was limited to patients with type 2 diabetes, and the investigation of Keidar et al. (*10*) included 1 type 1 and 13 type 2 diabetic patients. Data about diabetes type or management were not provided in any of the other investigations (*11,12,14,15*).

Diabetic patients are prone to vascular (arterial) insufficiency. Perhaps the sensitivity of the test is affected by vas-

cular insufficiency and there is a possibility that the results reported by Familiari et al. (*15*) and Schwegler et al. (*11*) were related to more severe vascular insufficiency in their populations than in other populations. These important data, unfortunately, are lacking.

The importance of an appropriate reference standard, against which an investigational test is to be judged, cannot be overemphasized. The gold standard for diagnosing diabetic pedal osteomyelitis is the isolation of bacteria from a bone sample together with histologic findings of inflammatory cells and osteonecrosis (*1*). Among the various investigations of ^{18}F-FDG for diagnosing pedal osteomyelitis in diabetic patients, the percentage of individuals in whom biopsy confirmation was obtained varies from 100% to less than 20%. A precise definition of the biopsy findings deemed diagnostic of osteomyelitis was provided in only one of these investigations (*15*). Even though the gold standard for diagnosis is biopsy, there is a general aversion to it, because of perceived risks. It is important to note that bone biopsy of the foot is considered safe, with virtually no published reports of complications (*1*).

Diabetes mellitus is a complex disease; diagnosing pedal osteomyelitis may be the most difficult aspect of managing foot infections in the diabetic patient. Determining the true merit of a diagnostic test, imaging or otherwise, requires in-depth knowledge of the population being studied, together with an appropriate reference standard against which the test is measured.

What is the verdict for ^{18}F-FDG and diabetic foot infections? The jury is still out.

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