

# The Diabetic Foot: Initial Experience with $^{18}\text{F}$ -FDG PET/CT

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Osteomyelitis complicates up to one third of diabetic foot infections, is often due to direct contamination from a soft-tissue lesion, and represents a clinical challenge. Early diagnosis is important since antibiotic therapy can be curative and may prevent amputation. The present study assessed the role of PET/CT using  $^{18}\text{F}$ -FDG for the diagnosis of diabetic foot osteomyelitis. **Methods:** Fourteen diabetic patients (10 men and 4 women; age range, 29–70 y) with 18 clinically suspected sites of infection underwent PET/CT after the injection of 185–370 MBq of  $^{18}\text{F}$ -FDG for suspected osteomyelitis complicating diabetic foot disease. PET, CT, and hybrid images were independently evaluated for the diagnosis and localization of an infectious process. Additional data provided by PET/CT for localization of infection in the bone or soft tissues were recorded. The final diagnosis was based on histopathologic findings and bacteriologic assays obtained at surgery or at clinical and imaging follow-up. **Results:** PET detected 14 foci of increased  $^{18}\text{F}$ -FDG uptake suspected as infection in 10 patients. PET/CT correctly localized 8 foci in 4 patients to bone, indicating osteomyelitis. PET/CT correctly excluded osteomyelitis in 5 foci in 5 patients, with the abnormal  $^{18}\text{F}$ -FDG uptake limited to infected soft tissues only. One site of mildly increased focal  $^{18}\text{F}$ -FDG uptake was localized by PET/CT to diabetic osteoarthropathy changes demonstrated on CT. Four patients showed no abnormally increased  $^{18}\text{F}$ -FDG uptake and no further evidence of an infectious process on clinical and imaging follow-up. **Conclusion:**  $^{18}\text{F}$ -FDG PET can be used for diagnosis of diabetes-related infection. The precise anatomic localization of increased  $^{18}\text{F}$ -FDG uptake provided by PET/CT enables accurate differentiation between osteomyelitis and soft-tissue infection.

**Key Words:** PET/CT; infection; diabetic foot

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**O**steomyelitis of the foot is a challenging diagnosis and affects up to 15% of diabetic patients, often as the result of direct contamination from a soft-tissue lesion (1). Early diagnosis of osteomyelitis in the diabetic foot is crucial

because antibiotic therapy can be curative and may prevent amputation. Plain radiography is usually the first imaging technique when bone infection is suspected. CT is also used routinely although not considered accurate in this clinical setting (1–3). Despite drawbacks, MRI is considered the modality of choice for the diagnosis of diabetic foot osteomyelitis and associated soft-tissue abnormalities, with a high reported sensitivity and specificity (1,4–6).

Nuclear medicine plays an important role in the evaluation of infection (7,8).  $^{18}\text{F}$ -FDG PET is a useful clinical tool for assessing malignancies.  $^{18}\text{F}$ -FDG, a nonspecific tracer of increased intracellular glucose metabolism, accumulates in sites of infection and inflammation as well (9–11). PET is highly sensitive but may be unable to define the anatomic location of a focus of increased  $^{18}\text{F}$ -FDG accumulation. The hybrid PET/CT technology, providing precise registration of metabolic and structural imaging data, obtained in the same session on a single device, may improve diagnosis and localization of infection (12).

The purpose of the present study was to assess the role of PET/CT using  $^{18}\text{F}$ -FDG in evaluating the diabetic foot for diagnosis and localization of an infectious process to the pedal skeleton or the soft tissues.

## MATERIALS AND METHODS

### Patient Population

Fourteen consecutive diabetic patients (one type 1 and 13 type 2 diabetes mellitus) with suspected foot infection were prospectively evaluated using PET/CT. The study included 10 men and 4 women, with a mean age of 54 y (range, 29–70 y). Infected diabetic foot was suspected on the basis of the presence of necrotic ulcers, nonhealing wounds, cellulites, or severe foot pain, with or without systemic fever. The 14 patients presented with 18 sites suggestive of infection, including 7 in the forefoot, 1 in the mid foot, and 10 in the hind foot. All patients underwent bone scintigraphy using  $^{99\text{m}}\text{Tc}$ -methylene diphosphonate within a week before the PET/CT study. The clinical characteristics of the patient population and reasons for referral are presented in Table 1; bone scintigraphy results are presented in Table 2. The Institutional Review Board of the hospital approved the study, and each patient gave written informed consent.

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**TABLE 1**  
Clinical Characteristics of 14 Diabetic Patients with 18 Sites of Suspected Foot Infection

Patient no.	Sex	Age	Reason for referral	Area of suspected infection	Blood glucose* (mmol/L)
1	M	50	Nonhealing wound, fever	Fourth toe, L	10.6
2	M	59	Foot pain, necrotic ulcers	First toe, R Second toe, R First toe, L	6.3
3	M	53	Necrotic ulcers, soft-tissue abscess in first toe, bacteremia, fever	First toe, L Midfoot	11.7
4	M	60	Foot pain/nonhealing wound	Ankle, R Heel, R	8.9
5	F	45	Cellulitis, edema, nonhealing wound	Ankle, R	8.5
6	M	66	Cellulitis after osteomyelitis R calcaneus	Ankle, R	18.3
7	M	67	Nonhealing wound, fever	Ankle, R	12.2
8	M	65	Nonhealing wound	First toe, R	15.9
9	F	46	Foot pain, cellulitis, edema	Ankle, R	4.8
10	F	66	Gangrene, candidiasis (sepsis)	Third toe, L	12.3
11	M	57	Foot pain, ankle swelling, fever	Ankle, L	14.9
12	M	66	Foot pain, dry necrotic wound	Heel, L	4.7
13	F	70	Nonhealing wound	Ankle, R	10.5
14	M	29	Foot pain, ankle deformation	Heel, L	13.9

\*Blood glucose levels measured before injection.

### PET/CT Acquisition and Processing

Patients were instructed to fast, except for glucose-free oral hydration, for 4–6 h before the injection of 185–370 MBq (5–10 mCi) of  $^{18}\text{F}$ -FDG and to keep their regular drug schedule. Blood glucose levels were measured before injection and at the end of the study. None of the patients were withdrawn from the study because of high blood glucose levels, and no additional glucose control drugs were used. PET and non-contrast-enhanced CT of the lower limbs were done 1 h after the injection of  $^{18}\text{F}$ -FDG using a PET/CT

system (Discovery LS; General Electric Medical Systems), combining a third-generation multislice spiral CT scanner with a dedicated full-ring PET scanner with bismuth germanate crystals. The PET and CT devices were mechanically aligned back to back and shared a table. Proper registration of the 2 images was ensured by shared positional information on the table and patient for both the CT and the PET acquisitions. Data obtained from the CT scan were used for low-noise attenuation correction of PET emission data and for fusion with attenuation-corrected PET images. PET

**TABLE 2**  
Imaging Findings and Final Diagnosis in 18 Sites in 14 Patients with Suspected Diabetic Foot Infection

Patient no.	Area of suspected infection	Bone scintigraphy	PET	Maximum SUV	CT	PET/CT localization	Final diagnosis
1	Fourth toe, L	Positive	Positive	6.5	Negative	Fourth metatarsus, L	Osteomyelitis
2	First toe, R	Positive	Positive	2	Positive	First metatarsus, R	Osteomyelitis
	Second toe, R	Positive	Positive	1.7	Positive	Second metatarsus, R	Osteomyelitis
	First toe, L	Positive	Positive	2.5	Equivocal	First metatarsus, L	Osteomyelitis
3	First toe, L	Positive	Positive	7.9	Positive	First metatarsus, L	Osteomyelitis
	Midfoot, L	Positive	Positive	7.1	Positive	Cuneiforms, L	Osteomyelitis
4	Ankle, R	Positive	Positive	9.3	Positive	Lateral malleolus, R	Osteomyelitis
	Heel, R	Positive	Positive	13	Equivocal	Calcaneus, R	Osteomyelitis
5	Ankle, R	Positive	Positive	6.2	Positive	Soft tissue	Soft-tissue infection
6	Ankle, R	Positive	Positive	2.1	Positive	Soft tissue	Soft-tissue infection
7	Ankle, R	Positive	Positive	3.3	Equivocal	Soft tissue	Soft-tissue infection
8	First toe, R	Positive	Positive	1.7	Negative	Soft tissue	Soft-tissue infection
9	Ankle, R	Positive	Positive	11.1	Equivocal	Soft tissue	Soft-tissue infection
10	Third toe, L	Positive	Positive	1.4	Equivocal	Third metatarsus, L	Osteoarthropathy
11	Ankle, L	Negative	Negative	—	Negative		No infection
12	Heel, L	Negative	Negative	—	Negative		No infection
13	Ankle, R	Positive	Negative	—	Negative		No infection
14	Heel, L	Negative	Negative	—	Equivocal		No infection

images were reconstructed iteratively using ordered-subset expectation maximization software (Xeleris; General Electric Medical Systems). PET, CT, and fused PET/CT images were available for review, displayed in axial, coronal, and sagittal planes. The PET data were displayed as noncorrected and attenuation-corrected images and also in a rotating maximum-intensity projection.

### Interpretation and Analysis of PET/CT Images

All studies were interpreted prospectively by reviewers who were aware of the patient's clinical history and the results of previous imaging studies. Initially, 2 experienced nuclear medicine physicians interpreted the stand-alone  $^{18}\text{F}$ -FDG PET images. Every focus of increased  $^{18}\text{F}$ -FDG uptake was recorded, and  $^{18}\text{F}$ -FDG uptake with an intensity higher than that of surrounding tissues was defined as an infectious process. A PET study showing at least 1 site of abnormal  $^{18}\text{F}$ -FDG uptake was considered positive for infection. A PET study showing no sites of abnormal  $^{18}\text{F}$ -FDG uptake was considered negative. Maximum standardized uptake values (SUVs) were measured for all foci of increased  $^{18}\text{F}$ -FDG activity using the software supplied by the vendor of the scanner.

An experienced skeletal radiologist reviewed the CT component of the studies without knowing the PET results. All morphologic abnormalities seen on CT were recorded. CT findings considered positive for osteomyelitis included cortical lysis, areas of bone resorption, and periosteal reaction. The diagnosis was reinforced when soft-tissue processes such as abscess, cellulitis, or skin ulcers were seen near the bony lesion. Equivocal CT findings were bone changes of diabetic osteoarthropathy such as osseous fragmentation, sclerosis, subluxation, or dislocation in the mid foot or hind foot or extensive bone resorption in the forefoot. In the presence of these findings osteomyelitis could not be definitely excluded. Negative CT findings were no areas of abnormal bone structure.

A team of nuclear medicine physicians and a radiologist interpreted the fused PET/CT images after the PET and CT reviews. Precise localization of  $^{18}\text{F}$ -FDG on the soft tissues or the skeleton, specifically to certain bones, as provided by PET/CT, was recorded. Fused images provided additional information when they allowed more precise localization of the sites of increased  $^{18}\text{F}$ -FDG uptake than was obtained by PET images alone.

A final diagnosis of osteomyelitis, soft-tissue infection, or noninfected site was confirmed by histopathologic findings and bacteriologic assays obtained at surgery or by decision of the referring clinical team after further imaging workup or clinical follow-up.

### RESULTS

Fourteen patients with 18 sites of clinically suspected infection were evaluated for diabetic foot osteomyelitis (Table 2). PET detected 14 foci of increased  $^{18}\text{F}$ -FDG uptake in 10 patients. All 14 sites were considered positive for infection, but PET alone could not precisely localize these foci to bone or soft tissue.

PET/CT localized 8 foci in 4 patients to bone, indicating a diagnosis of osteomyelitis. Five foci were localized to metatarsal bones and 1 lesion each to the medial cuneiform, lateral malleolus, and calcaneus. CT indicated bone changes consistent with osteomyelitis in 5 of these 8 sites. Two additional foci of increased  $^{18}\text{F}$ -FDG uptake demonstrated

equivocal findings on CT, and 1 focus showed no abnormalities in bone structure. All 4 patients had a final diagnosis of bone infection. One patient had osteomyelitis confirmed by histology and bone culture (isolation of *Acinetobacter* and *Proteus mirabilis*). A second patient was diagnosed with osteomyelitis on the basis of the histologic results of tissue samples obtained at surgery and sterile bone culture results (probably due to previous broad-spectrum antibiotic treatment). A third patient was diagnosed on the basis of clinical observation of the bony structures during surgical amputation and on preoperative radiography studies showing bone changes consistent with osteomyelitis. Serial radiography studies of a fourth patient showed bone changes consistent with osteomyelitis that resolved after administering intravenous antibiotic and hyperbaric oxygen therapy.

PET/CT excluded osteomyelitis in 5 sites in 5 patients by localizing the abnormal  $^{18}\text{F}$ -FDG uptake solely to soft-tissue infection. CT indicated bone changes consistent with osteomyelitis in 2 of these 5 sites. For 2 sites, CT demonstrated equivocal findings, and 1 site showed no change in bone structure. All 5 patients treated for soft-tissue infection showed good clinical response and no further evidence of osteomyelitis during a 6- to 12-mo follow-up.

One site of mildly increased focal  $^{18}\text{F}$ -FDG uptake was localized by PET/CT to diabetic osteoarthropathy changes demonstrated on CT. This patient had no evidence of osteomyelitis after further imaging workup and clinical follow-up over 14 mo.

Four patients showed no abnormal  $^{18}\text{F}$ -FDG uptake. On CT, 1 of these 4 patients had severe structural changes in the mid and hind foot, and osteomyelitis could not be excluded. CT of the other 3 patients showed no skeletal lesions. None of these 4 patients showed evidence of osteomyelitis at clinical and imaging follow-up over 9–14 mo.

PET therefore identified 14 foci of abnormal  $^{18}\text{F}$ -FDG uptake in 10 patients as consistent with infection. PET/CT confirmed the diagnosis in 13 of the 14 suggestive foci (93%) and correctly localized 8 sites to bone and 5 lesions to soft-tissue infection, whereas 1 site defined as infection on PET was localized and defined by PET/CT as diabetic osteoarthropathy. Maximum SUV in the sites of abnormal  $^{18}\text{F}$ -FDG uptake ranged from 1.4 to 11.1 (average, 5.4) (Table 2).

CT characterized 11 lesions as positive or equivocal for osteomyelitis—findings that were further confirmed at 6 sites (55%). CT findings were normal for 4 infectious foci detected on PET, with osteomyelitis confirmed in 2 of these lesions (50%).

Blood glucose levels at the time of the study ranged from 4.7 to 18.3 mmol/L (84–330 mg/dL). Glucose levels exceeded 11.1 mmol/L (200 mg/dL) in 7 of the 14 patients, including 2 patients with negative and 5 patients with positive PET findings.

## DISCUSSION

Osteomyelitis and septic arthritis complicate up to one third of diabetic foot infections that require hospitalization and often result from contaminated soft tissues. Early diagnosis is difficult to achieve through noninvasive imaging studies. Nuclear medicine and radiologic imaging techniques, although commonly used, may lack accuracy (1,13).

CT is used routinely because it is widely available, but it is of limited diagnostic value in early stages of acute osteomyelitis of the foot and in patients with diabetic osteoarthropathy. Bone structure changes are seen on radiographs 1–2 wk after the onset of an infectious process, but the time lag is somewhat shorter with CT (14–16). Diagnosing osteomyelitis using radiography or CT may be complicated by the fact that infection and neuropathic osteoarthropathy of the foot frequently coexist in diabetic patients (15).

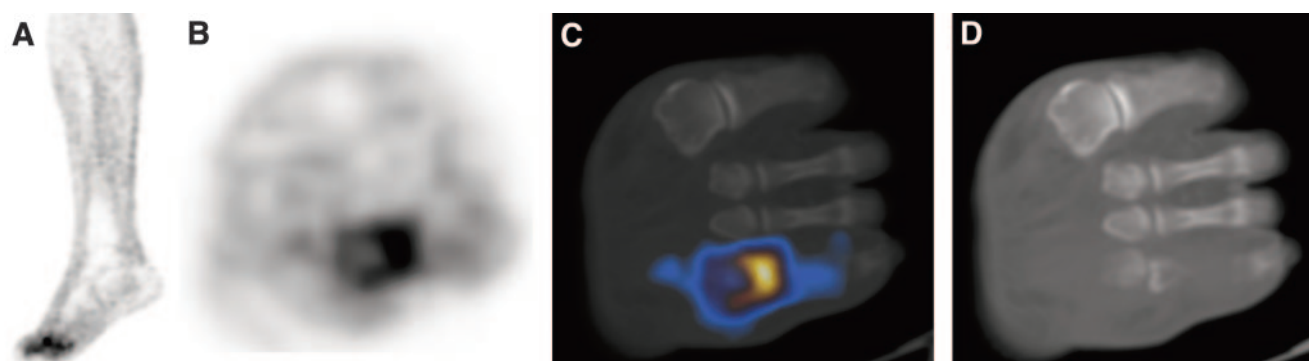
MRI, because of its high sensitivity and specificity, is considered the modality of choice for diagnosing osteomyelitis of the foot and for identifying associated soft-tissue abnormalities such as cellulitis, phlegmon, abscess, sinus tracts, and ulcers (16). However, MRI findings of acute osteomyelitis may be similar to those of acutely evolving neuropathic osteoarthropathy, biomechanical stress changes related to altered weight bearing, and bone marrow signal changes after orthopedic surgery and trauma (1,4,16). Finally, MRI of the small bones of the forefoot may be technically difficult because of coil designs and field heterogeneity at the margin of the coil (6).

Combined bone  $^{99m}\text{Tc}$ -methylene diphosphonate and  $^{111}\text{In}$ -labeled white blood cell scintigraphy are highly sensitive procedures but may be hampered by coexisting pathologic processes such as neuroarthropathy, trauma, or cellulitis (3).  $^{18}\text{F}$ -FDG, an indicator of increased intracellular glucose metabolism, accumulates in sites of infection (17,18). Recent experimental data in an animal model suggest that  $^{18}\text{F}$ -FDG accumulates specifically in osteomyelitis rather than in the bone healing process (19).  $^{18}\text{F}$ -FDG PET has the advantage of a shorter study time, higher resolution, and relatively higher target-to-background ratio than other

nuclear medicine procedures (11). As with other infection-specific scintigraphic techniques, PET, despite its high sensitivity for identifying infectious processes, may be unable to precisely locate the abnormal tracer accumulation. In the present study,  $^{18}\text{F}$ -FDG PET correctly identified 93% of all infected sites. However, PET alone could not exactly localize these infectious foci because of the proximity of bone and soft tissues in the foot. Pinpointing the focus of abnormal uptake detected by PET to bone or soft tissue is key for differentiating between osteomyelitis and soft-tissue involvement. PET/CT correctly diagnosed osteomyelitis versus soft-tissue involvement in all 13 infection sites. Eight foci of  $^{18}\text{F}$ -FDG uptake were localized by PET/CT to bone structures, consistent with the diagnosis of osteomyelitis (Fig. 1). Five sites of abnormal  $^{18}\text{F}$ -FDG uptake were localized by PET/CT only to soft tissues, thus excluding bone involvement (Fig. 2).  $^{18}\text{F}$ -FDG may accumulate in nonspecific inflammatory processes, common in diabetic patients. PET/CT correctly localized 1 focus of mildly increased  $^{18}\text{F}$ -FDG uptake to neuropathic osteoarthritic changes demonstrated on CT, with no further evidence of infection in this patient. Overall, PET/CT allowed accurate diagnosis of all sites of abnormal  $^{18}\text{F}$ -FDG uptake detected by PET.

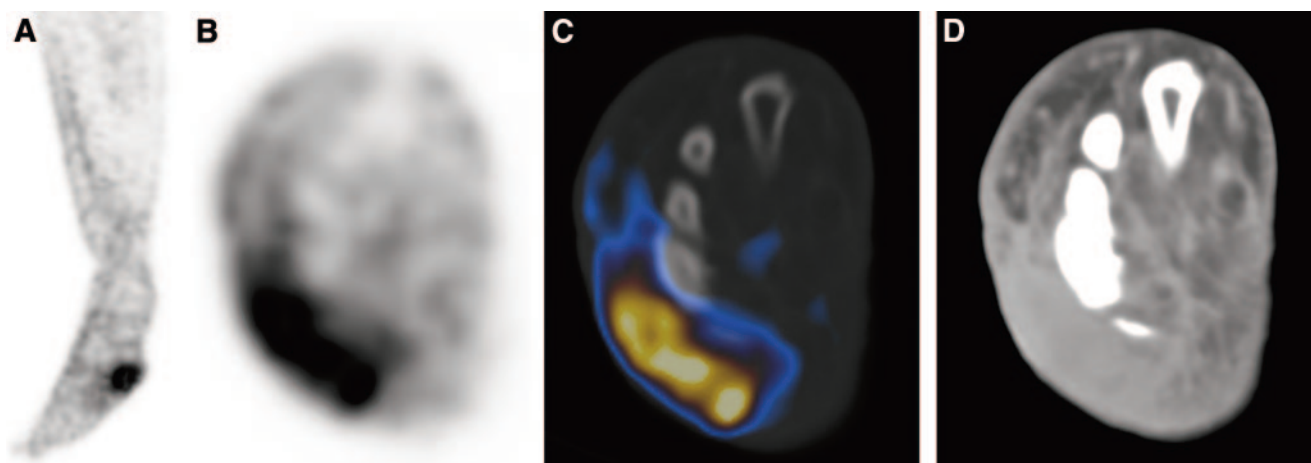
The CT component of the hybrid imaging studies showed skeletal changes consistent with or suggestive of osteomyelitis in 7 of 8 sites with confirmed bone infection, but also in 4 of 5 sites with an infectious process confined only to soft tissues (Table 2). These results confirm previous studies showing that CT is less accurate in diagnosing diabetic foot osteomyelitis because it is unable to distinguish between infection, reactive granulomatous tissue, edema, and fibrosis (15).

A limitation of the present study lies in the availability of a histopathologic diagnosis for only 2 of the 4 patients with osteomyelitis, in addition to surgical observation for a third patient. Previous publications have shown, however, that diagnosing osteomyelitis complicating foot infections is often done by observing clinical response to treatment or performing imaging follow-up studies (20).



**FIGURE 1.** PET/CT-based diagnosis of osteomyelitis complicating diabetic foot in 50-y-old man with nonhealing wound in right forefoot. (A and B)  $^{18}\text{F}$ -FDG PET coronal (A) and transaxial (B) images show area of increased  $^{18}\text{F}$ -FDG uptake in lateral aspect of forefoot. (C) PET/CT localizes abnormal  $^{18}\text{F}$ -FDG uptake to head of fourth metatarsus. (D) CT shows normal bone structure in corresponding area. Osteomyelitis was further confirmed by histopathologic examination of tissue samples obtained at surgery.





**FIGURE 2.** PET/CT-based exclusion of osteomyelitis and localization of infection to soft-tissue abscess in 43-y-old woman with nonhealing ulcer and cellulitis in lateral aspect of right foot. (A and B)  $^{18}\text{F}$ -FDG PET coronal (A) and transaxial (B) images show area of increased  $^{18}\text{F}$ -FDG uptake in lateral aspect of mid foot. (C) PET/CT localizes abnormal  $^{18}\text{F}$ -FDG uptake to soft tissues. (D) CT shows soft-tissue swelling in same area. Patient underwent local drainage and short course of antimicrobial therapy with good clinical response. No evidence of osteomyelitis was found during a clinical and imaging follow-up of 12 mo.

Software coregistration of PET with high-resolution anatomic imaging modalities may solve the clinical problem of the diabetic foot (21). Small variations in limb positioning between separate studies may lead, however, to a faulty localization of infectious foci, in particular where different structures are close to each other. Based on these initial results, hybrid PET/CT, combining  $^{18}\text{F}$ -FDG assessment of infection and CT structural data of the skeleton, is likely to be a better, more accurate, and certainly simpler procedure for diagnosing osteomyelitis in this patient population. Limited-field-of-view  $^{18}\text{F}$ -FDG PET/CT could be the single-step imaging procedure of choice in diagnosing diabetic foot disease, if further confirmed by studies including large clinical series, mandatory for defining a diagnostic algorithm.

The effect of elevated glucose serum levels on PET sensitivity is a controversial issue (22,23). Although extensively assessed in patients with malignancies, the effect of hyperglycemia on  $^{18}\text{F}$ -FDG uptake by inflammatory and infectious processes is not well documented. Scarce data suggest that elevated blood glucose levels may not impair  $^{18}\text{F}$ -FDG uptake in infection (24). Although elevated glucose serum values were found in half the present study population at the time of  $^{18}\text{F}$ -FDG injection, this did not lead to false-negative studies. There was no relationship between the glycemic state and the presence or absence of abnormal  $^{18}\text{F}$ -FDG uptake in the present study.

The degree of  $^{18}\text{F}$ -FDG uptake, as measured by maximum SUVs, was assessed for all suggestive foci showing abnormal tracer activity. The mean measured value in the infectious foci was 5.7, with variations between 1.7 and 11.1 for both osseous and soft-tissue infectious sites. Although the clinical value of SUV in oncologic diseases has been assessed (25,26), use of SUV in infectious processes needs additional investigation.

This study showed the feasibility of hybrid imaging using PET/CT in evaluating diabetic foot infection. Studies on a larger number of patients and comparing the results of concurrent combined bone and white blood cell scintigraphy are needed to validate and establish the role and diagnostic performance of PET/CT in evaluating diabetic foot infection.

## CONCLUSION

The initial experience with PET/CT demonstrates the potential value of hybrid imaging in diabetic patients with suspected foot infections. PET/CT allowed precise diagnosis of osteomyelitis versus soft-tissue infection through better anatomic localization of abnormal PET findings. This single-step, noninvasive imaging modality, combining functional and anatomic data, can facilitate diagnosing and defining diabetic foot infection, help guide further invasive tissue-sampling procedures, and improve treatment planning.

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