

Nuclear Medicine and Diabetic Foot Infections

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Up to 25% of the diabetic population is at risk for developing a pedal ulcer. These ulcers serve as a portal of entry for osteomyelitis and overlie more than 90% of diabetic pedal osteomyelitis cases. The diagnosis of osteomyelitis often is overlooked, and imaging studies are an essential part of the evaluation. The most commonly performed radionuclide tests are bone and labeled leukocyte imaging. Focal hyperperfusion, focal hyperemia, and focal bony uptake on the 3-phase bone scan comprise the usual presentation of osteomyelitis. Many conditions to which the diabetic population with foot problems is prone, however, mimic osteomyelitis, and the test is sensitive but not specific. Consequently, the bone scan often is used as a screening test or to facilitate localization of activity on labeled leukocyte images. Because of its high sensitivity and prevalence of positive results, its value as a screening test is questionable. Investigations comparing labeled leukocyte imaging alone to labeled leukocyte plus bone imaging, demonstrate only marginal improvement for the combined study. Thus, it is time to reevaluate the role of the bone scan in diabetic foot infections. Labeled leukocyte imaging is the radionuclide procedure of choice for evaluating diabetic pedal osteomyelitis. Sensitivity and specificity range between 72% and 100%, and 67% and 98%, respectively. Although intraindividual comparisons are few, the accuracy of the test is similar, whether the leukocytes are labeled with ^{99m}Tc or ¹¹¹In. Labeled leukocytes accumulate in uninfected neuropathic joints, and marrow scintigraphy may be needed to determine whether infection is present. Alternatives to labeled leukocyte imaging include in vivo methods of labeling leukocytes, radiolabeled polyclonal IgG, and radiolabeled antibiotics. The results obtained have been variable and none of these agents is available in the United States. There are few data available on single-photon emission computed tomography/computed tomography. It probably will be useful in the mid and hind foot; in the distal forefoot, given the small size of the structures, its value is less certain. Data on ¹⁸F-fluorodeoxyglucose positron emission tomography and positron emission tomography/computed tomography are limited and inconclusive, and further investigation is needed.

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The worldwide prevalence of diabetes now exceeds 200 million and is expected to exceed 300 million in the next 20 years. Approximately 7% of the American population has diabetes. With increasing life expectancy, the incidence of diabetic-related complications also is increasing. It is estimated that up to 25% of the diabetic population is at risk of developing a pedal ulcer, the most common risk factor for subsequent amputation. More than 1 million amputations are performed annually for diabetes-related foot problems,

and diabetes is the most common cause of amputations in the United States.¹

The most important underlying condition leading to diabetic foot problems is a neuropathy that involves sensory, motor, and autonomic nerves. Sensory neuropathy results in a loss of protective sensation. With loss of protective sensation, foot trauma is not recognized and leads to ulcer formation. The ulcer often is the portal of entry for bacteria, leading to cellulitis and/or abscess formation. Motor neuropathy results in muscle atrophy, foot deformity, and altered biomechanics. This leads to areas of high pressure during standing or walking and repeated trauma that may go unrecognized because of sensory deficits. Autonomic neuropathy results in dry skin, leading to cracks and fissures, which serve as sites of entry for bacteria. Autonomic neuropathy also leads to an alteration of the neurogenic regulation of cutaneous blood supply that can contribute to ulcer formation and altered response to infection.¹

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Figure 1 Osteomyelitis right fifth toe. There is soft-tissue swelling and cortical destruction of the phalanges (arrows), characteristic of osteomyelitis. Radiographs, readily available and relatively inexpensive, should be the initial imaging procedure performed because they may provide the diagnosis and avoid the ordering of additional, more costly tests.

Any breach in the cutaneous integument of the foot in a person with diabetes can lead to severe soft-tissue and/or osseous infection. Osteomyelitis should be considered in any patient with a chronic non-healing wound, especially if it is deeper than the dermis layer. A simple, reasonably accurate bedside clinical test for osteomyelitis underlying an open wound is the “probe to bone test.”^{2,3} 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.¹ Imaging studies are therefore, an essential part of the diagnostic evaluation of these individuals.

There are a myriad of imaging studies, both morphological and functional, from which to choose. Relatively inexpensive

and readily available, radiographs should be the initial imaging procedure performed because they may provide the diagnosis and obviate the need for additional, more costly tests (Fig. 1). Even when they are not diagnostic, radiographs are useful. They provide an anatomic overview of the region of interest and any pre-existing conditions that could potentially influence both the selection and interpretation of subsequent procedures.⁴ The most commonly performed radionuclide, or functional, studies for the evaluation of diabetic foot infections, are bone scintigraphy and labeled leukocyte imaging.

Bone Scintigraphy

The presence of focal hyperperfusion, focal hyperemia, and focal bony uptake on the 3-phase bone scan once was thought to be virtually diagnostic of osteomyelitis (Fig. 2). Many of the conditions to which the diabetic patient with foot problems is prone, however, mimic osteomyelitis. Fracture, the neuropathic joint, and even the pedal ulcer, all can yield positive 3-phase bone scans (Fig. 3).⁵ In a review of 77 diabetic patients with suspected pedal osteomyelitis, Keenan and coworkers⁶ reported a sensitivity of 100% and a specificity of 38% for the 3-phase bone scan. Larcos and coworkers⁷ studied 51 diabetic patients with suspected pedal osteomyelitis and reported a sensitivity of 93% and a specificity of 43% for the test. Maurer and coworkers⁸ reported a sensitivity and specificity of 75% and 59% for 3-phase bone imaging. More recent investigations have yielded similar results. Johnson and coworkers,⁹ in a prospective investigation of 22 diabetic patients, reported a sensitivity of 100% and a specificity of 10% for the 3-phase bone scan. Devillers and coworkers¹⁰ prospectively evaluated 3-phase bone scintigraphy in 42 diabetic patients with 56 foot ulcers and found the test to be 100% sensitive and 30% specific. Harvey and coworkers,¹¹ in a study of 31 diabetic patients with pedal ulcers, reported that the 3-phase bone scan was 91% sensitive but only 40% specific for diagnosing pedal osteomyelitis in their population. In a prospective investigation of 27 patients with suspected pedal osteomyelitis, Blume and coworkers¹² reported that the sensitivity and specificity of 3-phase bone scintigraphy were 75% and 29%, respectively. In a recent multicenter study, Palestro and coworkers¹³ reported similar results.



Figure 2 Osteomyelitis right great toe. There is focal hyperperfusion, focal hyperemia, and focally increased bone activity on the three phase bone scan.



Figure 3 Reactive bone right great toe. There is focal hyperperfusion, focal hyperemia, and focally increased bone activity on the three phase bone scan. The appearance is indistinguishable from that of osteomyelitis (see Fig. 2).

Attempts at improving the specificity of the bone scan have had mixed results. Seldin and coworkers¹⁴ evaluated the first, or angiographic, phase of the study. Hyperperfusion, which was present at the same time as, or before, the appearance of activity in surrounding tissues, was defined as arterial. Hyperperfusion that developed only after activity appeared in surrounding tissues was defined as venous. These investigators found that arterial hyperperfusion was associated with osteomyelitis, while venous hyperperfusion was associated with soft tissue infection. Classifying the study as positive for osteomyelitis only when arterial hyperperfusion was present, the sensitivity and specificity of the 3-phase bone scan were 94% and 79%, respectively. Newman and coworkers,¹⁵ however, were not able to duplicate these results. These investigators found that, using arterial hyperperfusion as a criterion for a positive study, the bone scan was neither sensitive (69%) nor specific (39%).

Another attempt at enhancing the specificity of bone imaging is the 4-phase bone scan. In contrast to normal bone, in which tracer accumulation ceases about 3 to 4 hours after injection, tracer accumulation in woven, or immature bone, which is present in osteomyelitis, continues for several hours more, resulting in greater lesion-to-background ratios on the fourth-phase than on the third-phase images. Alazraki and coworkers,¹⁶ using visual image interpretation, reported an

accuracy of 80% for the 3-phase bone scan and an accuracy of 85% for the 4-phase study. The 4-phase procedure was more specific (87% versus 73%) but less sensitive (80% versus 100%) than the 3-phase study. Israel and coworkers,¹⁷ using semiquantitative image analysis, also reported an accuracy of about 85% for the 4-phase study. Woven bone is not unique to osteomyelitis; it also is present in fractures, degenerative changes, and other conditions present in the foot of the diabetic patient; in these circumstances, 4-phase bone scintigraphy is less useful.

In Vitro Labeled Leukocyte Imaging

The role of in vitro labeled leukocyte scintigraphy in the diagnosis of diabetic pedal osteomyelitis has been extensively investigated. The sensitivity of the test, when ¹¹¹In-labeled leukocytes are used, has ranged from 72% to 100% and the specificity from 67% to 100% (Fig. 4).^{6-9,13,15} In one of the earliest investigations of the technique, Maurer and coworkers⁸ reported that the sensitivity and specificity of labeled leukocyte imaging for diagnosing osteomyelitis in 13 patients with diabetic osteoarthropathy were 75% and 89%, respectively. These investigators reported that the study was most useful for excluding infection. Poor

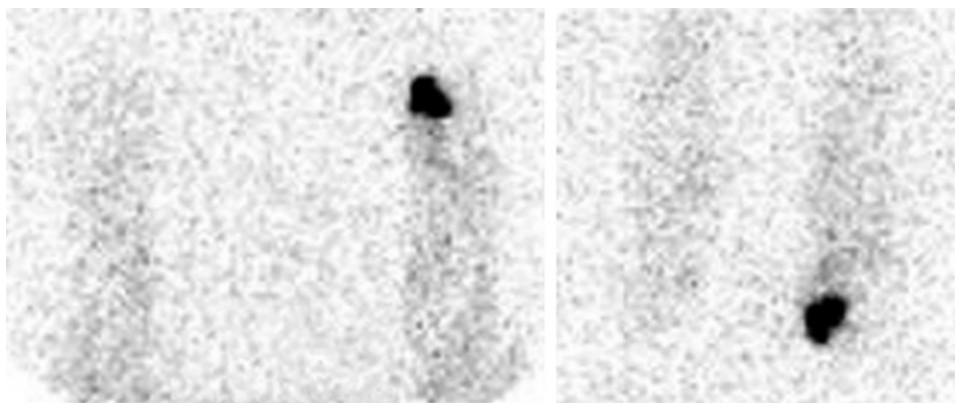


Figure 4 Osteomyelitis left great toe. There is focally increased accumulation of ¹¹¹In-labeled leukocytes on the plantar (left) and dorsal (right) images which were obtained about 24 hours after injection of labeled leukocytes.

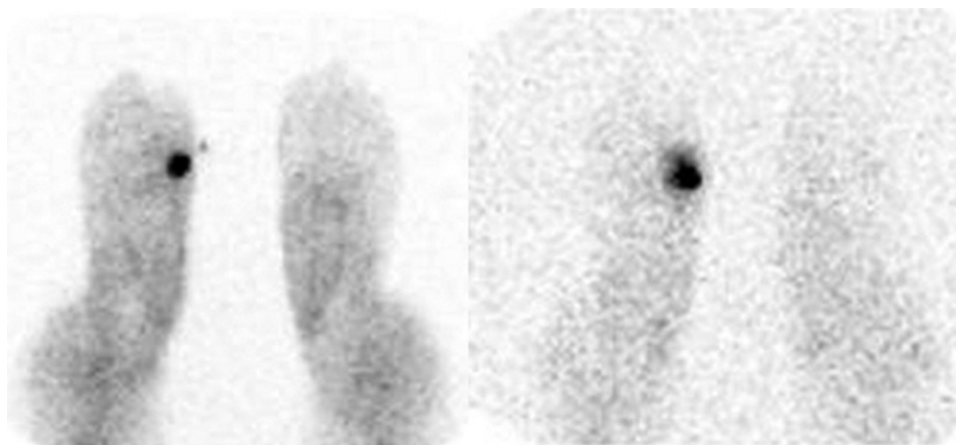


Figure 5 Osteomyelitis right first metatarsal. Plantar images were obtained about four (left) and 24 (right) hours after injection of ^{99m}Tc -labeled leukocytes. Compare the quality and detail of these images to those in Fig. 4.

spatial resolution and lack of bony landmarks made differentiation of soft tissue from bone infection difficult. Schauwecker and coworkers,¹⁸ by using the bone scan as an anatomic reference, reported a sensitivity of 100% and a specificity of 83% for labeled leukocyte imaging in 35 patients, including 25 with diabetes. False-positive results included 3 cases of extraosseous white cell accumulation mistakenly attributed to bone. Keenan and coworkers⁶ retrospectively analyzed ^{111}In -labeled leukocyte scintigraphy in 77 diabetic patients with suspected osteomyelitis of the foot and reported a sensitivity and specificity of 100% and 78%, respectively. Larcos and coworkers⁷ retrospectively reviewed labeled leukocyte imaging in 51 diabetic patients with suspected pedal osteomyelitis and found a sensitivity of 79% and a specificity of 78% for the test. Among the 35 patients with soft tissue ulcers, the sensitivity and specificity of the test were 85% and 77% respectively. The accuracy was not affected by the presence of neuropathy, coexistent soft tissue infection, or prior administration of antibiotics.

Newman and coworkers,¹⁵ in perhaps the largest prospective investigation reported to date, evaluated 41 foot ulcers in 35 diabetic patients. No patient was on antibiotic therapy for more than 7 days before entry into the study, and bone specimens for histological analysis and culture were obtained from all 41 sites. Patients underwent both 4- and 24-hour labeled leukocyte imaging. Osteomyelitis was present in 28 (68%) of 41 diabetic foot ulcers. Focally increased activity of approximately the same intensity on the dorsal and plantar views was the criterion for osteomyelitis (Fig. 4). The sensitivity and specificity of four hour leukocyte imaging both were 77%; the sensitivity of 24-hour leukocyte imaging was 89% and the specificity was 69%. The 24-hour labeled leukocyte scan was the most accurate test for diagnosing pedal osteomyelitis in this population (82%). It was more sensitive (89% versus 69%) and more specific (69% versus 39%) than bone scintigraphy.

Johnson and coworkers⁹ studied 22 diabetic patients and found that labeled leukocyte imaging was 100% sensitive and 70% specific for diagnosing pedal osteomyelitis. In a recent prospective investigation of 25 diabetic patients with pedal ulcers, when the criteria of Newman and coworkers¹⁵ were

used, the sensitivity and specificity of the test were 80%, and 67%, respectively.¹³

The reported sensitivities and specificities of ^{99m}Tc -exametazime-labeled leukocyte imaging for diagnosing diabetic pedal osteomyelitis have ranged from 86% to 93% and from 80% to 98%, respectively (Fig. 5).^{10-12,19} Devillers and coworkers¹⁰ prospectively evaluated 4-hour ^{99m}Tc -labeled leukocyte imaging in 42 diabetic patients with 56 foot ulcers. Labeled leukocyte images were interpreted in conjunction with bone scans and studies in which the distribution of abnormal uptake was spatially congruent on both studies were considered positive for osteomyelitis. When these criteria were used, the sensitivity and specificity of labeled leukocyte imaging were 88% and 97%, respectively. Blume and coworkers¹² prospectively evaluated the utility of ^{99m}Tc -exametazime-labeled leukocytes for diagnosing pedal osteomyelitis in 27 patients, including 20 with diabetes. Fifteen patients had frank ulcers at the time of imaging. Images, acquired 3 to 4 hours after injection, were classified as positive for osteomyelitis when focally increased bony uptake at the site of suspected infection was greater than surrounding soft tissue uptake. The sensitivity and specificity of the test were 90% and 80%, respectively. Poirer and coworkers¹⁹ evaluated ^{99m}Tc -labeled leukocytes in 83 sites of suspected diabetic pedal osteomyelitis. Images were acquired 4 to 5 hours after injection and interpreted together with the bone scan by using criteria similar to those of Devillers and coworkers.¹⁰ These investigators reported a sensitivity and specificity of 92.6% and 97.6%. Harvey and coworkers¹¹ investigated 52 diabetic patients, with non healing ulcers, who were suspected of having pedal osteomyelitis and reported a sensitivity of 86% and a specificity of 90%. Neither the criteria for image interpretation, nor the time interval between injection and imaging, however, were specified.

The Neuropathic Joint

Most diabetic patients who undergo radionuclide imaging for pedal osteomyelitis present with an ulcer in the distal forefoot (metatarsal/toe) region. A less-frequent complication that

usually develops in the diabetic mid- or hind-foot is the neuropathic, or Charcot, joint. At least 35% of all diabetic patients develop a neuropathy and approximately 5% of them, after long-standing diabetes, eventually develop a neuropathic joint, usually in the fifth to seventh decades of life. The tarsal and tarsometatarsal or Lisfranc joints are affected in 60%, the metatarsophalangeal joint in 30% and the tibiotalar joint in about 10% of cases. Repetitive stress on an insensitive foot leads to bone and joint disruption, deformity, and instability, which lead to degeneration, subluxation, and eventually destruction of the joint. The endless cycle of injury, destruction, incomplete healing, and partial repair results in a grossly deformed foot. The longitudinal arch of the foot collapses, producing the “rocker bottom” appearance. Clinically, the neuropathic joint usually presents with swelling that can be massive, crepitus (due to destruction of bone and cartilage), instability (due to loss of the longitudinal arch), palpable loose bodies, and large osteophytes. Pain often is absent, but when present it is typically not proportional to the gross appearance of the foot. Synovial effusions usually

are noninflammatory or hemorrhagic and are composed predominantly of mononuclear cells.²⁰

Although infection is a relatively uncommon complication of the neuropathic joint, differentiating between the 2 or diagnosing infection superimposed on the neuropathic joint is challenging. Not surprisingly, with such extensive bony changes, 3-phase bone scintigraphy usually is positive, whether or not infection is present (Fig. 6).²¹⁻²³ It also is important to be cognizant of the fact that labeled leukocytes accumulate in both the infected and the uninfected neuropathic joint. In the past, such uptake was attributed to the inflammation, fractures, and reparative process that are part of the disease. It is now known, however, that labeled leukocyte accumulation in the uninfected neuropathic joint is caused, at least in part, by hematopoietically active marrow.²¹ The explanation for the presence of hematopoietically active marrow in the neuropathic joint is uncertain. It may be attributable to the arthropathy itself. The conversion of fatty into hematopoietically active marrow in induced arthritis of the lower extremities is well documented in animal models

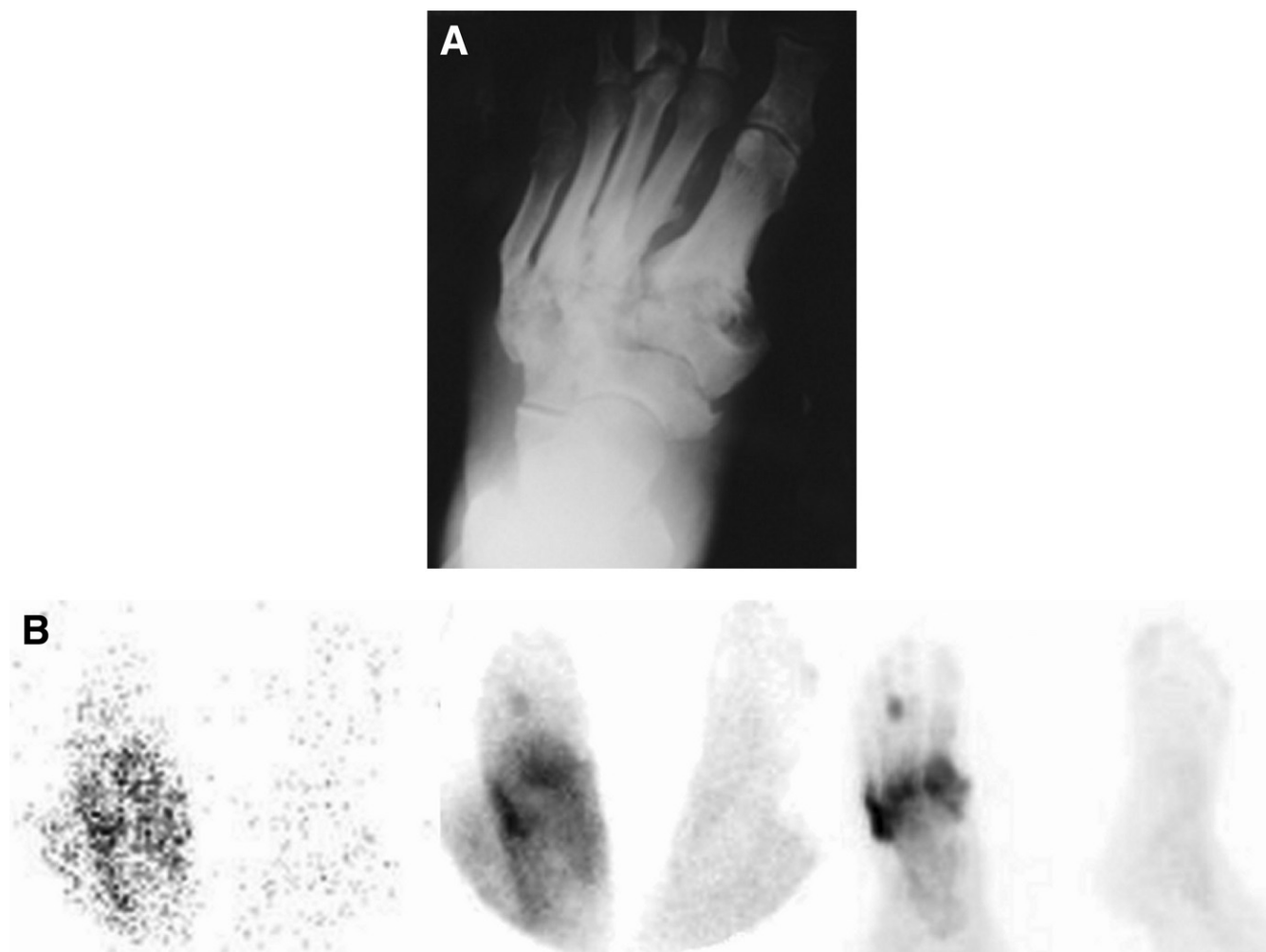


Figure 6 (A) Neuropathic joint. Radiograph demonstrates extensive tarsal metatarsal (Lisfranc) joint destruction and marked soft-tissue swelling. The fifth toe and distal metatarsal were amputated previously. (B) 3-phase bone scan is strikingly positive.

and a similar process may take place in the neuropathic joint. Fractures are an integral part of the neuropathic joint, and bone marrow is intimately involved in fracture repair.^{20,21} This too may account for the presence of bone marrow in the neuropathic joint. Regardless of the explanation, labeled leukocyte accumulation in the uninfected neuropathic joint does occur. As with other sites in the skeleton, performing complementary marrow imaging facilitates the differentiation of labeled leukocyte uptake due to bone marrow from that due to infection (Fig. 7).²¹

Other Tracers

In Vivo Leukocyte Labeling Agents

There are significant limitations to the in vitro labeled leukocyte procedure and considerable effort has been devoted to developing in vivo methods of labeling leukocytes, including

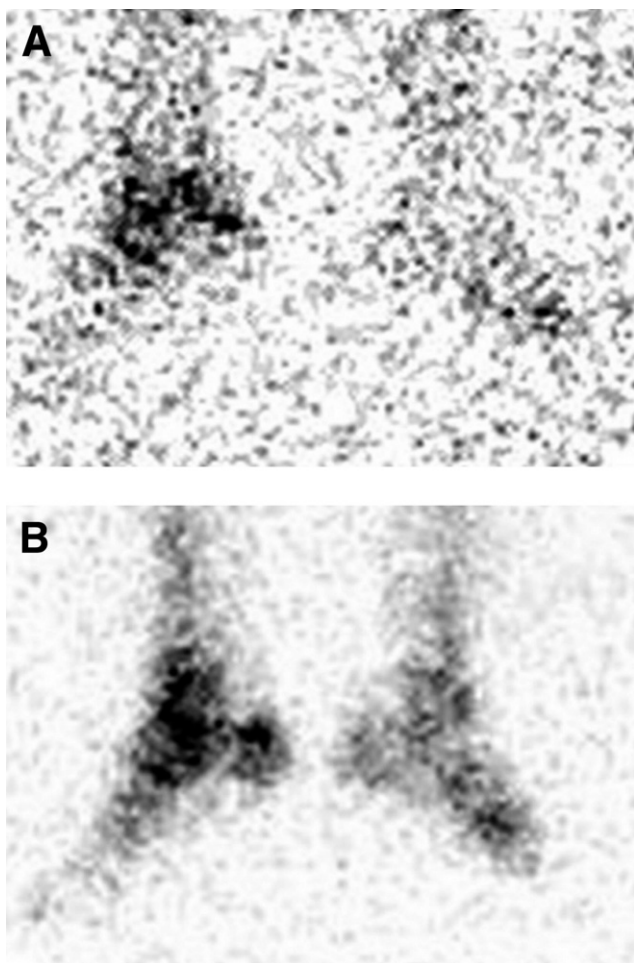


Figure 7 (A) Neuropathic joint. ¹¹¹In-labeled leukocyte images demonstrate activity in the neuropathic joint of the right foot. (B) ^{99m}Tc sulfur colloid bone marrow image also demonstrates activity in the neuropathic joint, in a distribution similar to that on the labeled leukocyte study, which confirms that the labeled leukocyte activity is due to marrow, not to infection. Combined leukocyte/marrow imaging accurately differentiates the neuropathic joint from infection.

peptides and antigranulocyte antibodies/antibody fragments. One such agent is a murine monoclonal G1 immunoglobulin, BW 250/183, which binds to Nonspecific Cross-reactive Antigen-95 present on neutrophils. Studies generally become positive by 6 hours after injection; delayed imaging at 24 hours may increase lesion detection.²⁴ In an investigation of 25 diabetic patients Dominguez-Gadea and coworkers²⁵ reported that this agent was 93% sensitive, 78% specific, and 84% accurate for diagnosing pedal osteomyelitis. Imaging was performed at 4 to 6, and again at 24 hours after injection, but these investigators found that the delayed imaging did not improve the accuracy of the test.

Fanolesomab is a monoclonal murine M class immunoglobulin binds to CD15 receptors present on leukocytes. This agent presumably binds both to circulating neutrophils that eventually migrate to the focus of infection, as well as to neutrophils, or neutrophil debris containing CD15 receptors, already sequestered in the area of infection.²⁶ Palestro and coworkers¹³ prospectively investigated 25 diabetic patients with pedal ulcers, with ^{99m}Tc-fanolesomab, ¹¹¹In-labeled leukocytes, and 3-phase bone imaging. The sensitivity, specificity, and accuracy of the antibody were 90%, 67%, and 76%, respectively, not significantly different from those obtained with labeled leukocyte imaging: 80%, 67%, and 72%. The antibody was as sensitive as, and significantly more specific ($P = 0.004$) than, 3-phase bone imaging (67% versus 27%; Fig. 8).

Antibody fragments are appealing because, unlike the whole antibody, they do not induce a HAMA response. Sulesomab is a murine monoclonal antibody fragment of the IgG1 class that binds to normal cross-reactive antigen-90 present on leukocytes. The mechanisms of uptake include binding to circulating neutrophils and crossing permeable capillary membranes and binding of the fragment to leukocytes already present at the site of infection.²⁴ Harwood and coworkers²⁷ performed sulesomab imaging on 122 diabetic patients with foot ulcers. Imaging was performed 1 to 2 hours after injection. Sulesomab had 91% sensitivity, 56% specificity, and an accuracy of 80%, which was comparable with that of in vitro-labeled leukocyte imaging (81% versus 75%). It was significantly more sensitive (92% versus 79%; $P < 0.05$), and slightly less specific (58% versus 67%) than labeled leukocyte imaging and was significantly more specific than bone scintigraphy (50% versus 21%; $P < 0.05$; Fig. 9). Delcourt and coworkers²⁸ prospectively compared combined sulesomab/bone to combined bone/gallium imaging in 25 diabetic patients with 31 sites of suspected pedal osteomyelitis. The sensitivity, specificity, and accuracy of sulesomab/bone were 67%, 85%, and 74%. The sensitivity, specificity, and accuracy of bone/gallium were 44%, 77%, and 58%, respectively.

Radiolabeled Antibiotics

The concept of using radiolabeled antibiotics for diagnosing infection was introduced about 15 years ago. The presumption was that the labeled antibiotic would be incorporated and me-

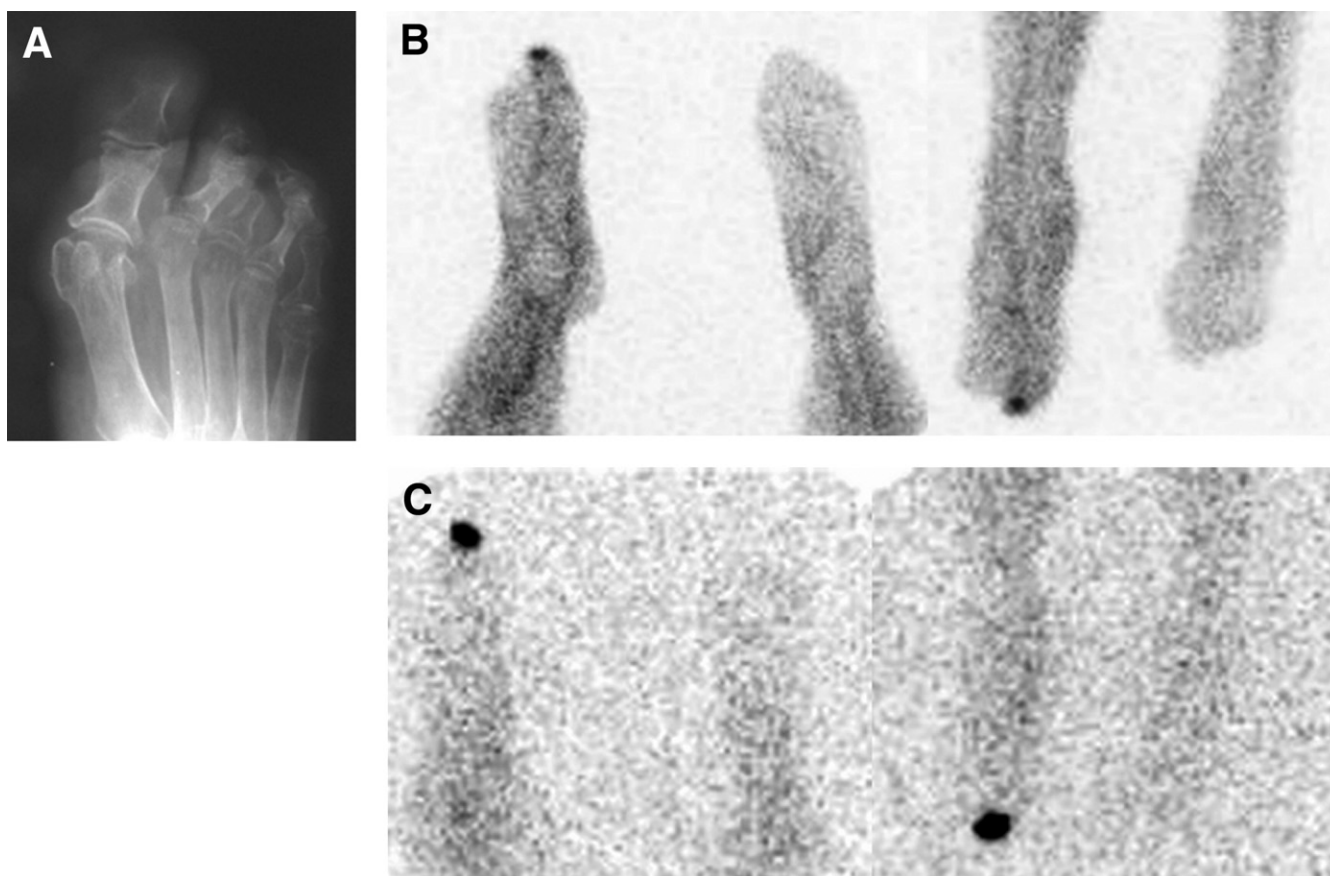


Figure 8 (A) Osteomyelitis right great toe. Radiograph was interpreted as suspicious for right great toe osteomyelitis. (B) Plantar and dorsal images obtained approximately 1 hour after injection of the murine antigranulocyte antibody, ^{99m}Tc -fanolesomab, demonstrate focally increased uptake in the distal right great toe. (C) 24-hour ^{111}In -labeled leukocyte images also demonstrate focally intense uptake in the distal right great toe.

tabolized by bacteria present in the infectious focus and, assuming that the uptake was proportional to the number of microorganism present, the measured radioactivity would accurately and specifically localize infection. One of the first, and certainly the most extensively investigated, of these compounds is the

4-fluoroquinolone antibiotic, ciprofloxacin, labeled with ^{99m}Tc .⁴ Published results, however, have been variable.²⁹⁻³² Palestro and coworkers³³ found that radiolabeled ciprofloxacin was less accurate than labeled leukocyte imaging for diagnosing diabetic pedal osteomyelitis (Fig. 10).

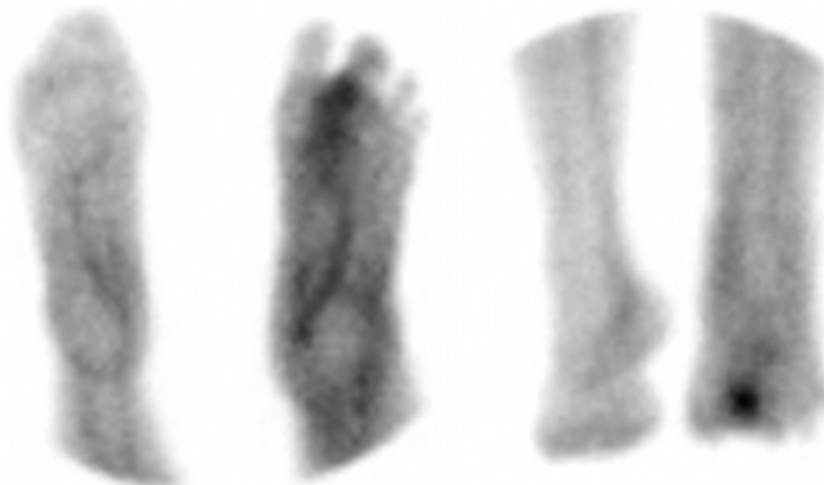


Figure 9 Osteomyelitis distal left second metatarsal. Plantar and dorsal images obtained about 2 hours after injection of the antigranulocyte antibody fragment, ^{99m}Tc -sulesomab.

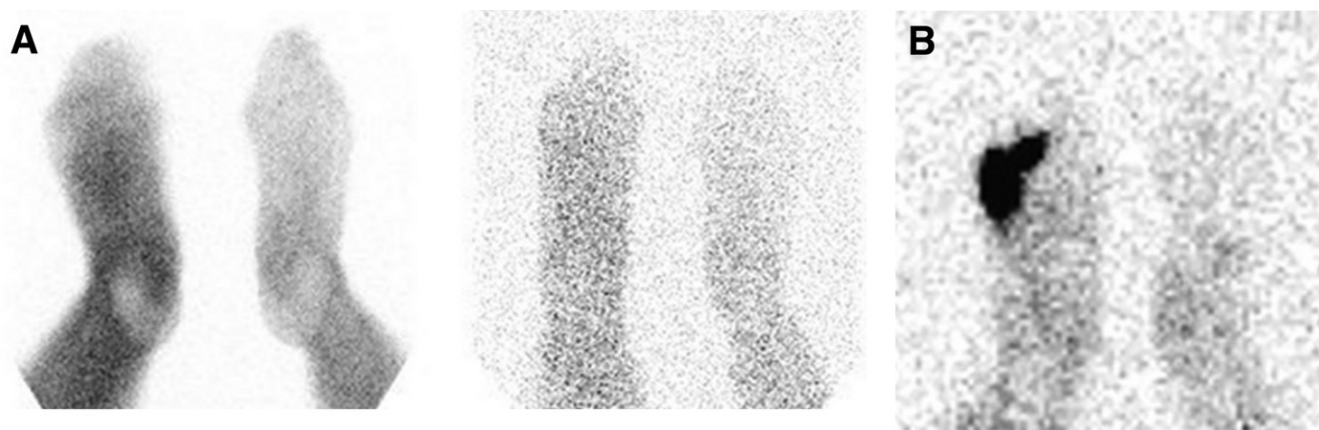


Figure 10 (A) Osteomyelitis right fourth and fifth toes. Two- (left) and 24-hour (right) ^{99m}Tc -ciprofloxacin images are normal. (B) 24-hour ^{111}In -labeled leukocyte image shows intense uptake of labeled leukocytes in the distal lateral aspect of the right foot. Interestingly the organisms cultured (*Staphylococcus aureus* and *Citrobacter diversus*) were sensitive to ciprofloxacin.

Polyclonal IgG

Radiolabeled human nonspecific IgG has been used to image infection and inflammation. Accumulation of this tracer is primarily related to increased capillary permeability, locally increased extracellular space, and macromolecular entrapment in the area of inflammation.²⁰ Oyen and coworkers³⁴ reported on the results of ^{111}In -labeled IgG scintigraphy in 16 diabetic patients. Images were obtained at 4, 24, and 48 hours after injection and were interpreted in conjunction with bone scans for localization purposes. The sensitivity of the test was 86% and the specificity 84%. Advantages of IgG include elimination of in vitro leukocyte labeling and an absence of side effects. Disadvantages include the need to perform 2 radionuclide studies, multiple imaging sessions over 2 days, and accumulation in the uninfected neuropathic joint.

Nanocolloid

^{99m}Tc nanocolloid, a bone marrow imaging agent, has been used for diagnosing bone and joint infection. Uptake of the tracer is presumably caused by extravasation through the capillary basement membrane, followed by phagocytosis or adsorption of the particles by granulocytes and macrophages. In a series of 9 patients, the sensitivity and specificity of this agent for diagnosing osteomyelitis in diabetic patients with neuropathic foot disease were 100% and 60% respectively.³⁵ None of these agents, at the present time, are available in the United States; fanolesomab is not available anywhere.

Single-Photon Emission Computed Tomography/Computed Tomography (SPECT/CT)

Establishing the diagnosis of pedal osteomyelitis in the setting of contiguous soft-tissue infection or altered bony anatomy, situations frequently encountered in the diabetic patient, is a challenge. The current radionuclide gold standard

for this purpose is labeled leukocyte imaging. Labeled leukocyte images, however, are relatively count poor, especially when ^{111}In is the radiolabel, with few or no anatomic landmarks, making it difficult, even in the larger bones of the mid and hind foot, to differentiate soft tissue from bone infection.

Recent publications confirm the incremental value of SPECT/CT in patients being evaluated for musculoskeletal infection.³⁶⁻³⁹ Bar-Shalom and coworkers,³⁶ as part of a larger investigation, reviewed the results of ^{111}In -labeled leukocyte SPECT/CT in 11 patients with suspected osteomyelitis. They found that SPECT/CT was contributory in 6 (55%) of the 11 patients. Filippi and coworkers³⁷ evaluated ^{99m}Tc -exametazime labeled leukocyte scintigraphy with, and without, SPECT/CT in 28 patients suspected of having musculoskeletal infection. They reported an accuracy of 64% for planar plus SPECT imaging and an accuracy of 100% for SPECT/CT. SPECT/CT significantly changed the interpretation of the study in 10 (36%) patients. As a result of improved labeled leukocyte localization provided by the CT component, osteomyelitis was excluded in seven patients and was more precisely delineated in three patients. Horger and coworkers,³⁸ by using a ^{99m}Tc -labeled antigranulocyte antibody, evaluated SPECT/CT in 27 patients with a history of trauma and superimposed bone infection. The accuracy of planar plus SPECT imaging was 59%; the accuracy of SPECT/CT was 97%. These investigators found that SPECT/CT was particularly useful for distinguishing soft tissue infection from osteomyelitis in the appendicular skeleton. Interobserver agreement was stronger for SPECT/CT ($k = 1.0$) than for scintigraphy alone ($k = 0.68$).

Although these data indicate that SPECT/CT improves the accuracy of the radionuclide diagnosis of osteomyelitis, the majority of the investigations conducted to date have focused on relatively large structures. Whether or not these results can be duplicated in the diabetic foot remains a matter of conjecture. The osseous structures of the mid and hind foot are relatively large, with a fair amount of adjacent soft tissue, so it is likely that SPECT/CT will be useful in this region (Fig. 11). Unfortunately, in the majority of diabetics referred to

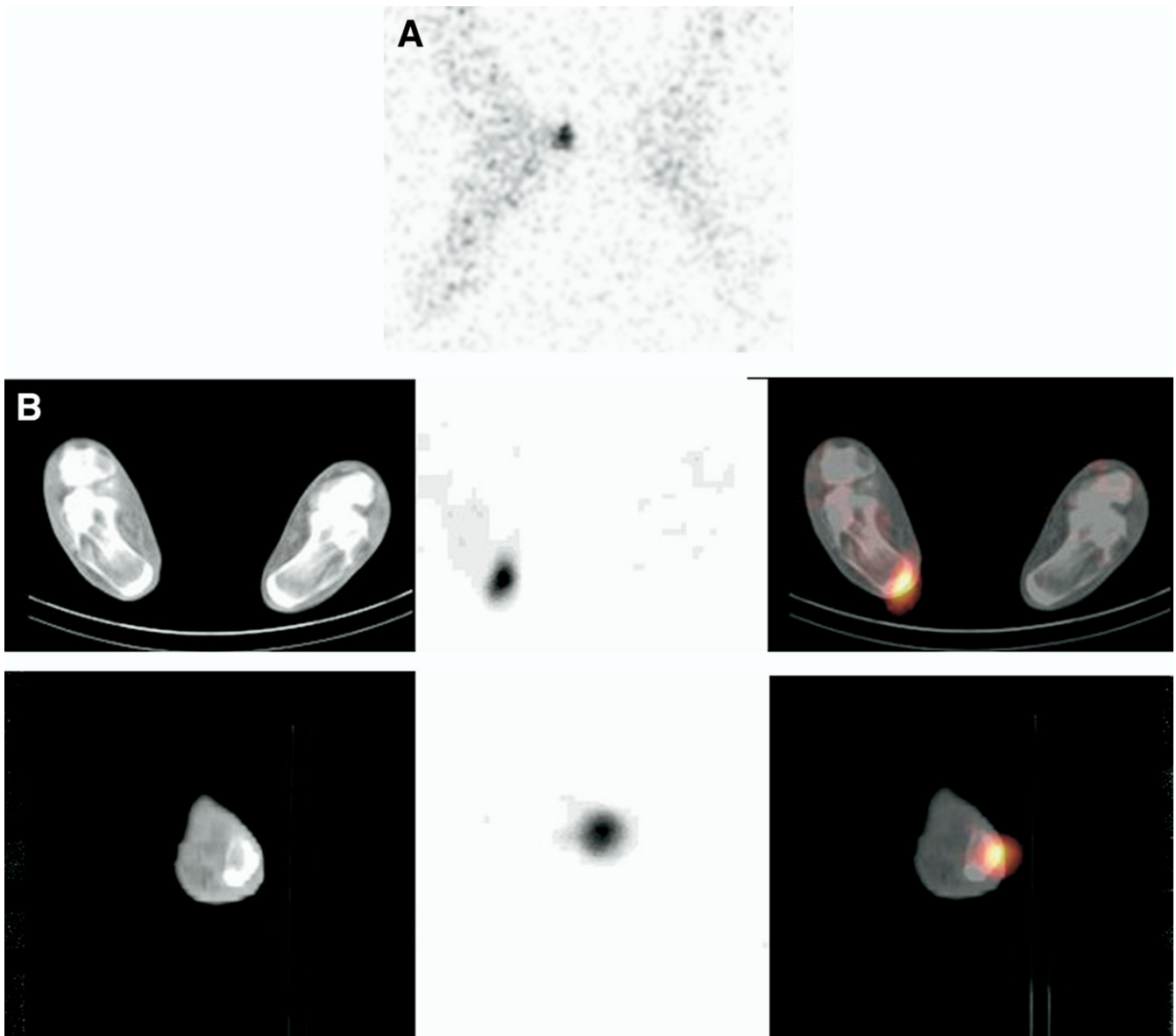


Figure 11 (A) Osteomyelitis right calcaneus. 24-hour planar ¹¹¹In-labeled leukocyte image shows focally increased activity along the posterior aspect of the right heel. It is not possible to determine whether this focus extends into bone or is confined to the soft tissues. (B) On the axial and sagittal SPECT/CT images, the labeled leukocyte activity clearly extends into the bone.

nuclear medicine, the area of concern involves the distal metatarsal or toe. These structures are so small that differentiating soft tissue infection from that of bone is likely to remain a challenge, even with SPECT/CT (Fig. 12).

Positron Emission Tomography (PET) and PET/CT

Data on the role of PET and PET/CT in the evaluation of diabetic foot infections are just emerging and are, as of yet, inconclusive. Keidar and coworkers⁴⁰ evaluated ¹⁸F-fluorodeoxyglucose (FDG)-PET/CT in 14 patients with 18 clinically suspected sites of infection. They reported increased FDG uptake in 14 of the 18 sites, but found that PET alone could not differentiate soft tissue from

bone uptake. PET/CT localized uptake to bone in nine of the 14 sites, including eight sites of osteomyelitis. One site of mildly increased FDG uptake occurred at a focus of diabetic osteoarthropathy. PET/CT correctly localized FDG uptake to the soft tissues in five cases. The overall accuracy of FDG-PET/CT in this investigation was about 94% (17 of 18; Fig. 13). The mean SUVmax in infectious foci was 5.7, and ranged from 1.7 to 11.1, for both osseous and soft tissue sites of infection. In the study population, blood glucose levels exceeded 200 mg/dL in 7 of the 14 patients, including 5 with positive PET findings. The investigators found no relationship between the patients' glycemic state and the presence or absence of FDG uptake. Though encouraging, these results need to be placed in proper perspective. Eleven of the 18 sites were located in the mid/hind foot or ankle,

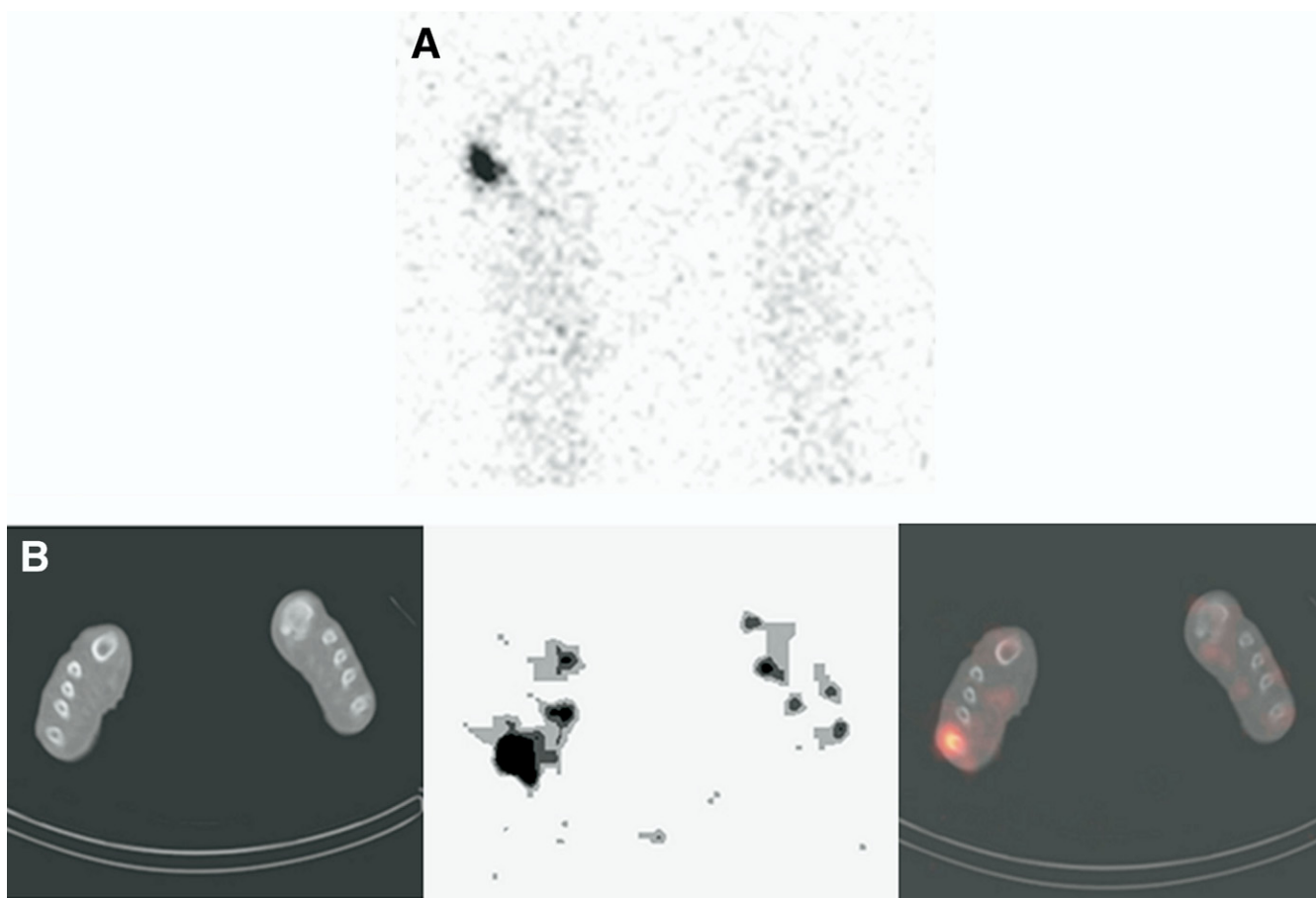


Figure 12 (A) Reactive bone right fifth metatarsal. There is intense activity in the right fifth metatarsal and toe on the 24-hour planar ^{111}In -labeled leukocyte image. (B) On coronal SPECT/CT images, the labeled leukocyte activity appears to involve bone. The patient underwent left fifth metatarsal and toe amputation. Histopathology revealed only reactive bone and bone cultures revealed no growth. The small size of the structures, together with the limited resolution of the radionuclide component of the study, limit the utility of SPECT/CT in the forefoot.

and open wounds or ulcers were present in only 12 of the 18 sites. The usual diabetic patient referred for radionuclide imaging of suspected osteomyelitis presents with a pedal ulcer located in the distal metatarsal and or toe region where the very small size of the structures tests even the highest resolution PET systems. Histopathological confirmation was available for only two of the 18 sites. While biopsy proof of the final diagnosis may not be the norm for clinical care, it still is the standard of reference for diagnosis.¹

Schwegeler and coworkers⁴¹ prospectively compared FDG-PET and a $^{99\text{m}}\text{Tc}$ -labeled antigranulocyte antibody to magnetic resonance imaging (MRI) for diagnosing clinically unsuspected osteomyelitis in 20 diabetic patients with persistent pedal ulcers. Ulcers were present for at least 8 weeks in all patients, and none had received antibiotic treatment before imaging. Eighteen of the 20 ulcers were in the distal forefoot, and 2 were in the hind foot. Biopsy was performed when at least one of the imaging studies was positive for osteomyelitis. Studies were analyzed visually, SUVs were not reported. Blood glucose levels at the time of FDG-PET studies were not reported. Seven patients in this series had osteomyelitis. MRI was positive in 6 of 7, whereas FDG-PET and the antigranulocyte antibody were positive in 2 of

7. The accuracies of FDG-PET, antibody, and MRI were 70%, 65%, and 90%, respectively. The poor sensitivities of the radionuclide studies are somewhat surprising, given the generally high sensitivities for diabetic pedal osteomyelitis that have been reported previously for both in vitro and in vivo labeled leukocyte imaging and the high sensitivity for osteomyelitis in general that has been reported previously for FDG-PET. The authors suggested that the low sensitivities may have been the result of a lower level of inflammatory response in their population. There are some data that suggest that bone uptake of glucose is at least partly dependent on insulin, and the authors speculated that perhaps insulin resistance in their population may have limited FDG uptake in infected bone. The authors also noted that their FDG-PET studies were hampered by motion artifacts and limited spatial resolution.

Basu and coworkers⁴² evaluated the usefulness of FDG-PET for differentiating osteomyelitis and soft tissue infection from the uncomplicated neuropathic joint in diabetics. The 63 patients in their study population were divided into 4 groups: 20 nondiabetic control patients, 21 diabetic patients with uncomplicated feet, 17 diabetic patients with a neuropathic joint, and 5 diabetic patients with pedal osteomyelitis.

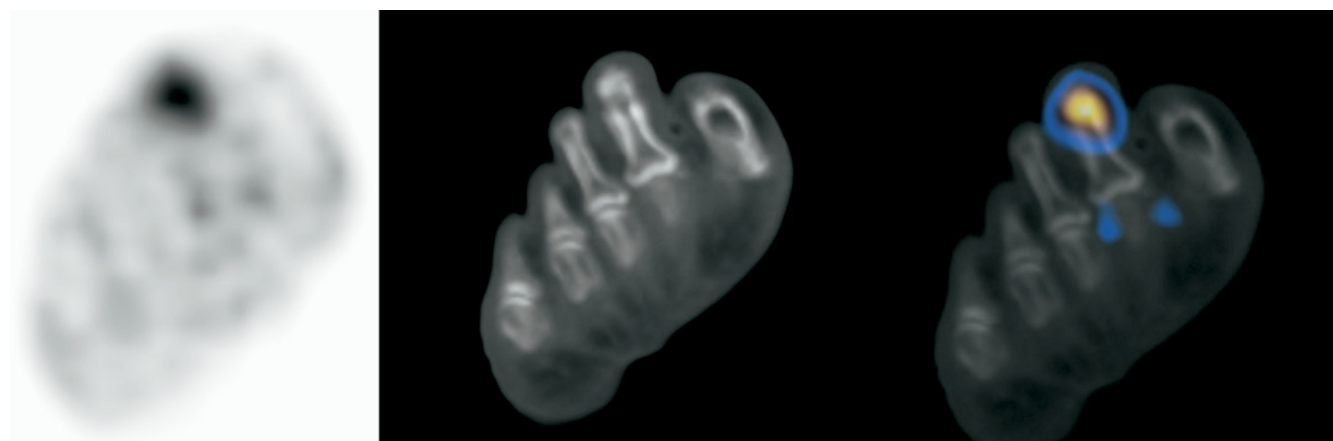


Figure 13 Osteomyelitis left second toe. FDG-PET image (left) demonstrates focally increased activity in the second digit. CT component (middle) shows cortical destruction of the bone. Fused PET/CT image (right) confirms that the abnormal FDG accumulation involves bone. The SUV max was 3.6. The patient's blood glucose level at the time of imaging was 138 mg/dL. (Courtesy of Z. Kedar.)

At the time of imaging, the blood glucose level was less than 200 mg/dL in 62 patients; it was 233 mg/dL in 1 patient. All patients also underwent MRI. Five patients had foot ulcers. Histopathological proof of final diagnoses was available in 10 patients. These investigators found that the mean SUVmax in the mid-foot of control patients, 0.42 ± 0.12 , was similar to that in the uncomplicated diabetic mid foot, 0.5 ± 0.16 , whereas the mean SUVmax in uninfected neuropathic joints was 1.3 ± 0.4 . The mean SUVmax for diabetic pedal osteomyelitis was 4.38 ± 1.39 ; the SUVmax in the one case of osteomyelitis superimposed on a neuropathic joint was 6.5. These investigators reported that the sensitivity and accuracy of FDG-PET for diagnosing the neuropathic foot were 100% and 94% compared with 77% and 75% for MRI. They concluded that the uptake pattern of FDG in the neuropathic joint was distinct from that in osteomyelitis and that FDG-PET had a high negative predictive value for excluding osteomyelitis in the setting of the neuropathic joint, although only 1 patient in this series had osteomyelitis superimposed on the neuropathic joint.

Hopfner and coworkers⁴³ performed preoperative FDG-PET imaging in 16 diabetic patients with neuropathic joints. This investigation was performed, not to diagnose osteomyelitis, but to determine the value of the test in the preoperative evaluation of these patients and to compare FDG-PET to MRI for this purpose. All patients subsequently went to surgery. Blood glucose levels ranged from 92 to 254 mg/dL. Thirty-nine lesions consistent with Charcot neuropathy were identified at surgery; 24 were osseous and 15 involved joints or soft tissues. FDG-PET identified 95% (37/39) of the lesions, including 22/24 bone lesions and all 15 joint/soft tissue lesions. Mean SUV max 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 >200 mg/dL, the sensitivity of the test was not affected by blood glucose levels. MRI correctly identified 79% (31/39) of the neuropathic lesions. When 3 patients with metallic implants were excluded from analysis

the sensitivity of MRI, 94% (31/33), was comparable to that of FDG-PET, 97% (32/33). These investigators concluded that FDG-PET is comparable, and should be considered as an adjunct, to MRI for the preoperative evaluation of Charcot neuropathy, being especially useful in the setting of metallic implants. The investigators also suggested that, even though none of the patients in the investigation had osteomyelitis, because of the relatively low uptake in the uninfected neuropathic joint, FDG-PET can reliably differentiate osteomyelitis from neuropathic lesions.

Radionuclide Diagnosis of Diabetic Foot Infections

At the present time, the standard radionuclide approach to the diabetic patient with a foot infection is bone scintigraphy and/or labeled leukocyte imaging. There is, however, no consensus on the optimum approach to these patients. An important issue concerns the role of the bone scan in the evaluation of diabetic foot infections. It can be argued that, because of its exquisite sensitivity, the bone scan is useful as a screening test to identify those individuals who should undergo labeled leukocyte imaging. Given the very high prevalence of positive results, and low specificity of the test, however, its value as a screening test is questionable. In a prospective investigation of 25 diabetic patients, for example, the 3-phase bone scan was positive in 20 patients, including 9 of 10 with, and 11 of 15 without, osteomyelitis.¹³ Using the bone scan as a screening test in this investigation, 20 of the 25 patients would still have had to undergo labeled leukocyte imaging.

Labeled leukocyte images lack anatomic detail, and it has been suggested that the addition of bone scintigraphy facilitates the differentiation of soft tissue and bone infection. Published data, however, suggest that any improvement is marginal. Keenan and coworkers⁶ reported that for diagnosing pedal osteomyelitis, the accuracies of labeled leukocyte im-

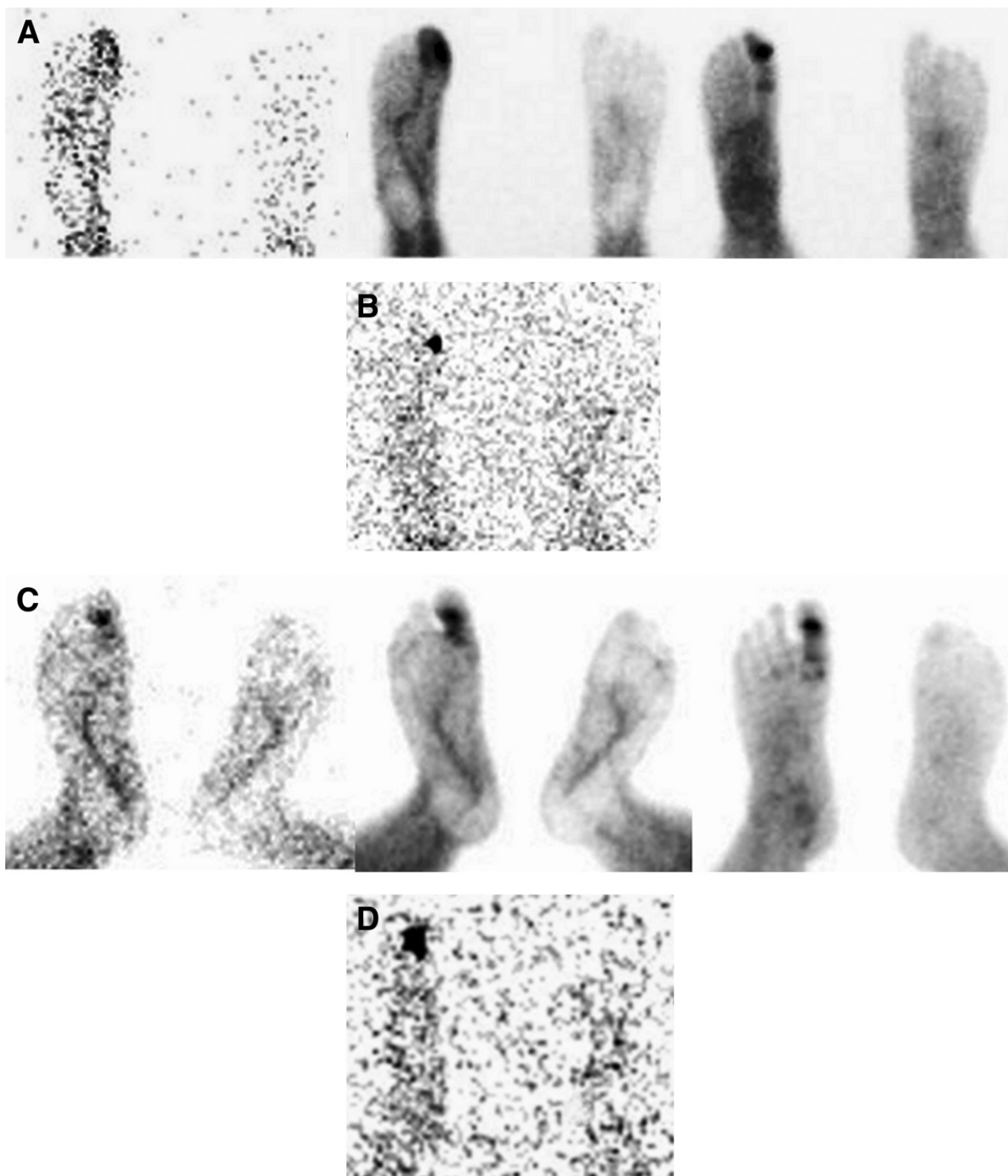


Figure 14 (A) Osteomyelitis of the right great toe is shown. Three-phase bone scan is true positive. (B) Labeled leukocyte study is true positive. (C) Reactive bone (same patient illustrated in Fig. 3). Three-phase bone scan is false positive. (D) Labeled leukocyte study is false positive. In these 2 cases, the bone scan did not alter the interpretation of the labeled leukocyte scan.

aging alone or in combination with bone scintigraphy were identical: 87%. Johnson and coworkers⁹ reported that the accuracy of labeled leukocyte imaging rose from 86% (19/22), when interpreted alone, to 91% (20/22) when interpreted together with the bone scan. In a prospective investi-

gation of 25 diabetic patients, Palestro and coworkers¹³ reported that labeled leukocyte imaging alone was correct in 18 (72% accuracy). When combined with bone imaging the test was correct in 20 (80% accuracy). In 2 patients with gangrene, leukocyte imaging was false positive when inter-

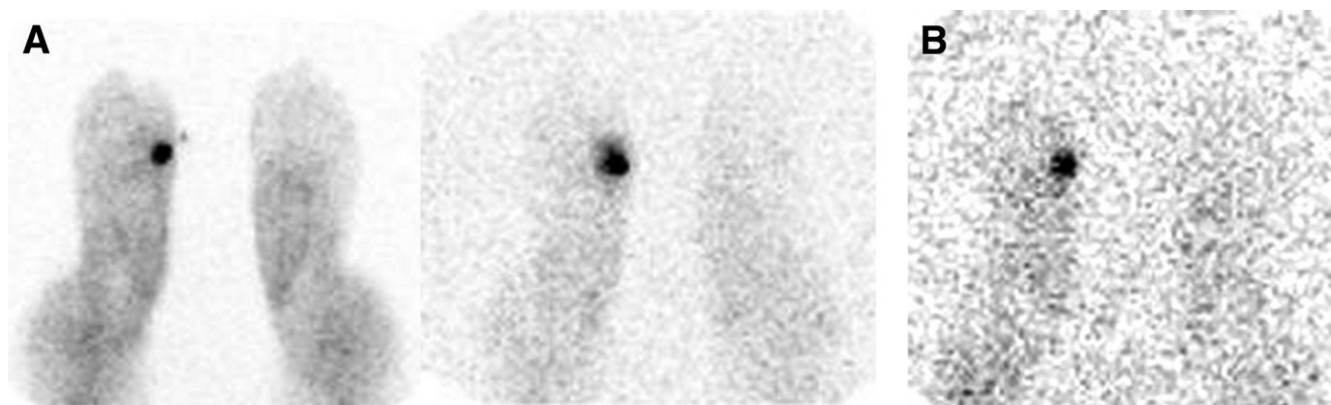


Figure 15 (A) Osteomyelitis right first metatarsal (same patient illustrated in Fig. 5). Four-hour (left) and 24-hour (right) ^{99m}Tc -labeled leukocyte images. (B) 24-hour ^{111}In -labeled leukocyte image. The quality of the 4-hour ^{99m}Tc leukocyte image is clearly superior to that of the 24-hour image and the ^{111}In -labeled leukocyte image.

preted alone and true negative when interpreted with the bone scan. In the remaining 23 patients, the addition of bone imaging did not change the study interpretation (Fig. 14).

Jay and coworkers⁴⁴ retrospectively evaluated the role of the 3-phase bone scan in the management of the diabetic foot ulcer. They found that management (amputation versus local wound care) of these ulcers was based on clinical, radiographic, and laboratory findings of infection and/or gangrene, not on bone scan findings. They concluded that since the bone scan did not influence patient management, its use could not be justified. We have not found the bone scan to be useful in the evaluation of diabetic foot infections, and we stopped performing this test some years ago.

Another concern often raised is whether ^{99m}Tc - or ^{111}In -labeled leukocytes are the preferred agent. Advantages of ^{99m}Tc -labeled leukocytes include a photon energy ideally suited for imaging using current instrumentation, superior image quality, and the ability to detect abnormalities within a few hours after injection. Disadvantages include instability of the label and the short half-life of ^{99m}Tc which limits delayed imaging. When marrow scintigraphy is necessary, as in the case of the neuropathic joint, an interval of at least 48, and preferably 72, hours is required between the white cell and marrow scans.⁵

Advantages of ^{111}In -labeled leukocytes include stability of the label, and the physical half-life of ^{111}In , which is long enough for delayed imaging. Marrow scintigraphy can be performed while the patient's cells are being labeled, or as simultaneous dual isotope acquisitions, or immediately after completion of the labeled leukocyte study. Disadvantages include less than ideal photon energies, poor image quality and the 24-hour interval between injection and imaging.⁵

There are few intraindividual comparisons of ^{99m}Tc - and ^{111}In -labeled leukocytes for imaging diabetic foot infections. In an investigation of 14 patients, all with histopathologically and microbiologically proved diagnoses, Love and coworkers⁴⁵ found that 4- and 24-hour ^{99m}Tc imaging both were correct in 13 of 14 patients, whereas ^{111}In -labeled leukocyte imaging was correct in 12 of 14 (Fig. 15). A review of the

published literature, even allowing for differences in study populations, image interpretations, etc, also suggests that the accuracies of the two tests are similar. Thus, the choice of the radiolabel is a matter of personal preference and availability.

At the present time, labeled leukocyte imaging is the nuclear medicine procedure of choice for investigation of diabetic foot infections. The overall accuracy of the test is about 80-85%, and either ^{99m}Tc - or ^{111}In -labeled leukocytes can be used. In the presence of the neuropathic joint it may be necessary to perform complementary marrow imaging. The value of the conventional bone scan, either as a screening test, or as anatomical reference is questionable, and its use in most cases probably is not warranted. It is likely that SPECT/CT will improve diagnostic accuracy, especially in the mid and hind foot; its incremental value in the forefoot, where the structures are considerably smaller, will likely be less. Data on FDG-PET and PET/CT are limited and inconclusive, and await further investigation.

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