The Diabetic Foot—Imaging Options and Considerations

a report by

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Patients with diabetes may present with an array of foot disorders that include, but are not limited to, neuropathy, ulceration, and osteomyelitis. Ischemia and infection are common clinical concerns as either, or both, may be involved in the pathogenesis of these disorders. Management choices can be difficult to make and diagnostic imaging is often sought to help clarify the clinical picture. The imaging options available all have strengths and weaknesses in terms of their clinical relevance. A common problem encountered with imaging is distinguishing inflammation that is due to trauma—e.g. surgical, mechanical or Charcot arthropathy—from soft-tissue or osseous infection. This article reviews the most common imaging options available to clinicians and summarizes the benefits and drawbacks of each. No single imaging modality can answer all the clinical questions that arise in the setting of the diabetic foot, but knowing the features of the imaging choices available to you may help answer the most pressing questions.

Pathogenesis of Ischemia and Infection

While foot ulcers are the most common complication in the diabetic foot, infections rank a close second.[1] Sensory neuropathy in the distal regions of the extremities predisposes many diabetics to traumatic insults that can lead to skin breakdown, ulceration, and infection. Impaired perfusion due to peripheral vascular disease and microvascular abnormalities reduces the patient's capacity to heal wounds and recover from infection.[2] In the diabetic foot, infected skin ulcers, the development of cellulitis, osteomyelitis, and abscess are major sources of morbidity.

The management of patients with diabetic foot disorders can vary substantially depending on the presence and extent of infection, necrosis, and osteomyelitis.[3] Imaging of the diabetic foot may provide information that can aid the clinician in making patient management decisions. Diagnostic imaging procedures may also provide information that helps guide surgical planning.

Radiographs

This basic modality may be indicated when bone involvement is suspected. Radiographs can detect cortical fragmentation, osteomyelitis, fractures, arterial calcifications, and soft-tissue gas and articular deformities, including Charcot osteoarthropathy (see *Figure 1*).[1,4] While radiography is often used initially, an early diagnosis of osteomyelitis may be difficult to make as changes on radiographs are often subtle, or absent, in the early stages of the disease process.[5] Thus, this imaging modality is useful for detecting changes associated with the later stages of osseous infection (typically two or more weeks from onset) (see *Figure 2*).[6] This limitation is partly responsible for the modality having low sensitivity in the detection of osteomyelitis. While studies show radiographs typically have a higher specificity than sensitivity, periosteal reaction and post-traumatic changes can be non-specific. For example, the appearance of Charcot osteoarthropathy can be mistakenly identified as osteomyelitis on radiographs.[6]

Radionucleotide Scans

Four radionucleotide studies are discussed here:

- technetium Tc-99m (^{99m}Tc)-labeled diphosphonate bone scanning;
- indium In-111 white blood cell (WBC);
- non-specific human immunoglobulin (HIG) labeled with Tc-99; and
- 18-flourodeoxyglucose positron emission tomography (18-FDG-PET).

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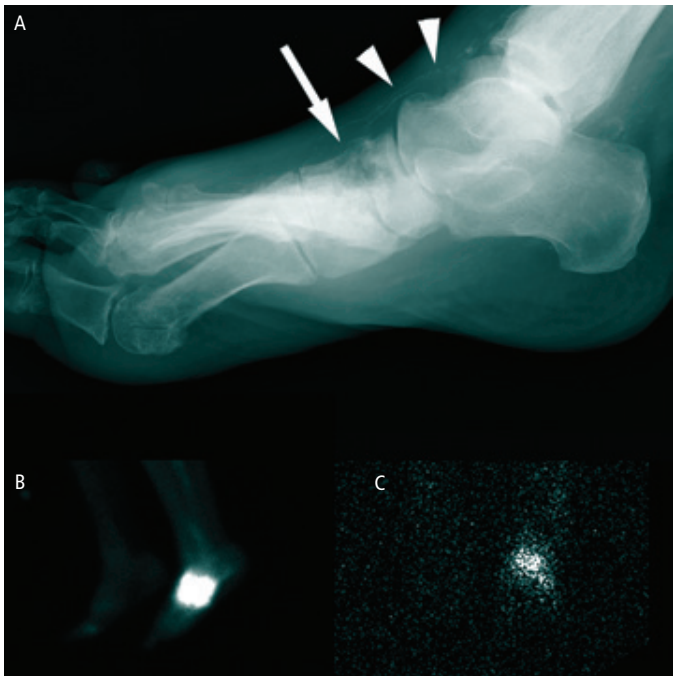
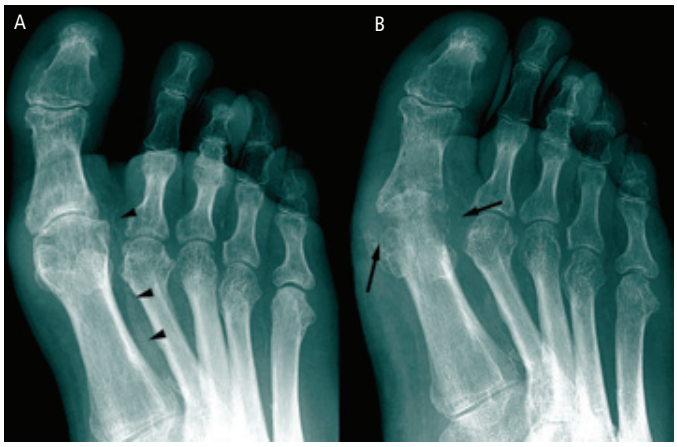
Figure 1: Radionucleotide Studies



A: Lateral radiograph of the foot shows mid-foot osseous disorganization and destruction (white arrow), typical of Charcot arthropathy. Arrow heads point out atherosclerotic arterial calcifications.
B: ^{99m}Tc bone scan reveals corresponding abnormal uptake of radiotracer. This appearance can be seen with either osseous fracture or osteomyelitis
C: In-111 white blood cell scan depicts corresponding abnormal uptake of radiotracer, confirming the diagnosis of osteomyelitis.

Figure 2: Foot Radiographs



Compared with image A, image B shows interval cortical destruction of the first metatarsal head (black arrows) in this patient with osteomyelitis and septic arthritis of the first metatarsal–phalangeal joint. The arrow heads in image A identify atherosclerotic arterial calcifications, a common finding in patients with diabetes.

Nuclear medicine techniques, such as ^{99m}Tc-labeled diphosphonate bone scanning and indium In-111 WBC scanning, are capable of detecting changes of osteomyelitis earlier than plain radiographs.

^{99m}Tc-labeled Diphosphonate Bone Scanning

Multiphase bone scintigraphy has very high sensitivity for diagnosing osteomyelitis, but suffers from low specificity.[7] Any condition that causes an increase in bone turnover—such as neuropathic osteoarthropathy, fracture, or surgery—may produce abnormal uptake, making these entities difficult to distinguish from osteomyelitus (see *Figure 2*).[8,9] However, its high sensitivity contributes to a high negative predictive value, and a negative bone scan typically provides convincing evidence for ruling out infection.[1]

Indium In-111 White Blood Cell

In-111-labeled WBC scintigraphy combined with bone scintigraphy can improve the specificity for osteomyelitus beyond that of bone scintigraphy alone.[10] Drawbacks associated with this option are that the In-111-labeled WBC scintigraphy is expensive, is not readily available, and involves time-consuming preparation of labeled WBCs,[11] which may take up to 48 hours.[8,12,13]

^{99}Tc Human Immunoglobulin

This technique has the potential to differentiate cellulitis from osteomyelitis.[17] The disadvantage of HIG is its non-specific uptake in both infection and non-infectious inflammation;[14,18,19] also, recent trauma may interfere with a diagnosis of infection in the diabetic foot.[20] Similar to ^{99}Tc WBC scans, ^{99}Tc HIG scans are associated with false-positive results in conditions such as rheumatoid arthritis (RA), osteoarthropathy, and healing fracture.[17]

Flourodeoxyglucose Positron Emission Tomography

FDG-PET imaging has the advantage of relatively short preparation and duration, and higher target-to-background contrast ratio than other techniques of nuclear medicine.[21] Despite having high sensitivity for imaging areas of active infection, PET may not be as specific in identifying areas of abnormal tracer accumulation, which may be partly attributed to low spatial resolution. This limitation can be mitigated by combining PET with computed tomography (PET/CT), which improves diagnostic accuracy by allowing the co-registration of abnormal 18F-FDG uptake with specific anatomical structures.[22]

Studies using the combined modalities of PET and CT have demonstrated the ability to accurately differentiate between soft-tissue infection and osteomyelitis.[22] The hybrid PET/CT technique provides accurate registration of metabolic and structural data in a single examination, resulting in improved diagnosis and localization of infection. The PET component uses 18F-FDG as a tracer, which accumulates at the sites of both infection and inflammation.[21,23,24]

Radionucleotide Scans—General Limitations

There are several general limitations of radionucleotide techniques. Poor spatial resolution may make it difficult to identify osetomyelitis when it is adjacent to sites of soft-tissue infection.[8,13,25] False-negative results, in the setting of peripheral vascular disease, are attributable to diminished regional delivery of isotope. The negative predictive value may thus be limited in the setting of local ischemia. Finally, these examinations are expensive.[4,25,26]

Computed Tomography

Much like radiographs, CT uses X-rays to generate an image. CT, while more sensitive than radiographs for detecting osteomyelitis, may still fail to detect osteomyelitis in the early stage of disease. Additionally, CT may

not be able to distinguish neuropathic osteoarthropathy from the sequelae of chronic infection.

Contrast-enhanced CT can detect soft-tissue and osseous abscess formation. The discovery of an abscess may alter clinical management, as treatment for abscess is typically surgical debridement. CT lacks sensitivity for differentiating changes associated with infection, edema, fibrosis, and granulation tissue.[27] The risk of use of iodinated contrast in diabetic patients may not be a trivial one as chronic renal insufficiency is commonly a comorbidity in patients with diabetes.

Magnetic Resonance Imaging

The wide range of tissue contrast that is integral to magnetic resonance imaging (MRI) makes it well suited for visualizing the extent of soft-tissue infection as well as bone infection (*see Figure 3*). MRI is used, with increasing frequency, to assess the complications associated with the diabetic foot.[1,28] Due to the high spatial resolution that is achievable and its ability to accurately evaluate the extent of inflammation, it is usually preferred over CT to investigate the presence of osteomyelitis.[1] The ability of MRI to visualize the extent of osseous and soft-tissue infection also facilitates its use in pre-operative planning.[28]

Gadolinium (Gd)-based contrast agents improve the detection of soft-tissue infection and help to determine its extent. It is also used to improve the delineation of necrotic tissues and sinus tracts and the detection of abscesses. The excellent contrast characteristics of MRI and the ability to visualize infection in multiple planes with good anatomical detail using contrast enhancement makes MRI the preferred modality for evaluating for the presence of abscess. Recently, a serious adverse reaction called nephrogenic systemic fibrosis (NSF) has been observed. NSF has been associated with the administration of MRI contrast agents and patients with renal dysfunction.[29] NSF is characterized by widespread tissue fibrosis. Since renal dysfunction is a common complication of diabetes, this relative contraindication for Gd-enhanced MRI may disqualify a number of patients. At the time of this publication, decision paradigms addressing who is and who is not a good candidate for Gd-enhanced MRI are institution-specific and evolving.

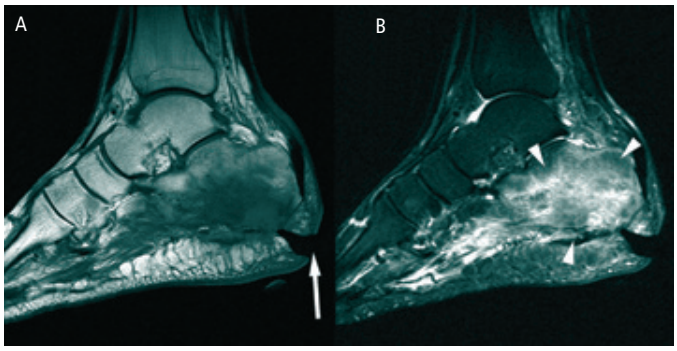
While MRI has high sensitivity for identifying inflammation, it too can lack specificity. For example, a patient may present with an ulcer that is in close proximity to a broken bone associated with Charcot osteoarthropathy. In this hypothetical—yet commonly seen—case, the inflammation associated with the skin ulcer may overlap with the inflammation that surrounds the Charcot-related osseous fracture. In such a case, it can be difficult to identify the boundaries of the inflammation associated with infection from the inflammation associated with trauma.

While MRI has high diagnostic accuracy for delineating both bone and soft-tissue infections, the Infectious Disease Society of America (IDSA) and the Clinical Practice Guideline Diabetes Panel[4] of the American College of Foot and Ankle Surgeons (ACFAS)[1] recommends radiographs as the initial imaging study when infection is suspected.

Angiography

Diabetic patients are at significantly higher risk of developing peripheral vascular disease than the general population.[1,30] Angiography may help to quantify the burden of occlusive disease and can identify targets for vascular bypass.

Figure 3: Magnetic Resonance Imaging of the Foot



A: Sagital T1-weighted magnetic resonance image of the foot shows a skin ulcer overlying the posterior calcaneous (white arrow).
B: Sagital fluid-sensitive image reveals high signal edema (white arrow heads) throughout the calcaneous, representing the inflammatory changes seen with osteomyelitis.

When prescribing imaging studies that involve iodinated contrast materials for patients with diabetes, the risk of contrast-induced nephropathy (CIN) should be considered. Of all causes of acute renal failure (ARF) among all hospitalized patients, CIN ranks third.[31,32]

Digital Subtraction Angiography

As its name implies, digital subtraction angiography (DSA) is performed by subtracting a pre-injection image from a contrast-enhanced post-injection image. This process removes distracting background anatomical structures. The resulting angiograph has high contrast resolution compared with standard non-subtracted angiography, and allows for the use of lower concentrations of contrast materials relative to other vascular imaging methods. DSA allows for the visualization of patent vessels beyond a proximal occlusion better than non-subtracted angiography, which may make DSA better suited for evaluating diabetic patients with chronic severe resting ischemia.[32]

DSA is still considered to be the gold standard imaging study for assessing peripheral artery disease.[32,33] DSA is an invasive technique that requires the insertion and direction of an intra-vascular catheter to the site that is to be assessed, where injection of a radio-opaque contrast agent is made. The procedure therefore involves some risk to the patient, including hemorrhage at the site of vascular puncture, distal embolization, and mural dissection.[30,32] One limitation of aniography occurs when multiple stenoses are present, as is common in diabetes. In such cases, small peripheral vessels of the foot may not be seen in DSA.[33]

Duplex Ultrasound

Duplex ultrasound (DSU) can depict vascular flow with directional and velocity-related information. This information can be superimposed on the standard grayscale ultrasound image using color and is sometimes referred to as 'color Doppler.' Longitudinal and cross-sectional depiction of medium and large arteries and veins is possible. DSU is a non-invasive method of documenting artery morphology and vascular flow.[30] DSU is not as sensitive as DSA in depicting small vessels with slow flow.

Computed Tomography Angiography

CT angiography (CTA) is beginning to be used more frequently to assess peripheral vascular disease as it is less invasive than DSA and can provide 3D images. Multidetector CT (MDCT) is a recent technological advance in CTA that can decrease acquisition time and increase spatial resolution. This method can produce high-spatial-resolution images of the entire extremity in several seconds.[33] MDCT does use iodine-based contrast agents and, as with the use of all such contrast agents, there is a risk of CIN.

Magnetic Resonance Angiography

MRI scanners can be used to perform MR angiography (MRA). While MRI provides anatomical detail of the soft tissue and bones, MRA also allows the visualization of flowing blood within the vessels.[30] Both 2D and 3D MRA techniques are available. One method, known as time-of-flight, allows for visualization of blood flow without the use of an injected contrast agent. Gd-enhanced MRA is a more sensitive method of demonstrating blood flow that is not perpendicular to the plane of imaging. As previously mentioned in the section on MRI, it has become important to screen patients for renal insufficiency, which may disqualify them for Gd-enhanced MRA studies.

MRA has been recognized as a useful non-invasive tool for analyzing the peripheral arteries in the diabetic foot, particularly for the non-healing ulcer.[34] MRA may be better suited for evaluating peripheral vascular disease (PVD) in chronic resting ischemia than conventional angiography, since it has been shown to visualize distal vessels in the presence of numerous stenoses and occlusions.[33] Thus, MRA may identify suitable target vessels for pedal bypass surgery.[33]

Summary and Conclusions

Many studies describing imaging of the diabetic foot provide assessments of the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) for investigating specific foot disorders. The published values of these measures vary substantially among studies. These measures are highly dependent on the circumstances that are related to the individual studies. The patient population, whether or not patients have peripheral vascular disease, the stage of the specific disorder, and other factors all affect the cited quantified results of these imaging studies. In particular, prevalence of disease in a given study population can widely skew reported values for PPV and NPV.

The imaging modalities described in this article vary substantially in cost. As indicated, none of the imaging modalities that have been discussed here is 100% sensitive or specific for diagnosing or ruling out infection. However, of all of the techniques MRI typically has the best sensitivity, PPV, and NPV compared with other modalities in the detection of osteomyelitis. It may be able to differentiate bone infection from soft-tissue infection and has the potential to detect both osseous and soft-tissue abscess.[35] ■

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