FDG PET/CT in Evaluating Osteomyelitis and Diabetic Foot

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6.1 Introduction

Osteomyelitis (OM) is defined as an infection of the bone. It can involve any bone and is commonly caused by staphylococcus aureus. OM can be caused by haematogenous route, contiguous spread and iatrogenic or post- traumatic exposure of bone. OM can either be acute or chronic type. Early diagnosis is necessary in order to avoid its complications like loss of function and bone loss or fracture. Typical workup of clinically suspected OM includes leucocyte count, serological inflammatory

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Table 6.1 Advantages of FDG PET/CT over conventional radionuclide studies in infection and inflammation

High sensitivity
High resolution images
High target to background ratio
Fast technique completed in one session

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markers, X-ray, and blood culture. Histopathological examination concludes the diagnosis. However, none of the tests mentioned are very specific for OM and biopsies are invasive. Conventional radionuclide imaging tests such as bone scintigraphy, labelled white blood cell (WBC) scintigraphy, and gallium scanning all have the drawbacks of relatively low spatial resolution; they are time consuming, technically demanding, need handling of blood products (WBC labelling) and lack of sensitivity, specificity, or both. FDG PET/CT has several advantages over conventional radionuclide imaging and morphological imaging alone (Table 6.1).

Patients with diabetes mellitus (DM) are prone for developing osteomyelitis complicating the diabetic foot. Diabetic foot refers to ulceration, infection, and/or destruction of deep tissues of foot with associated neurological abnormalities and peripheral vascular disease. In the management of diabetic foot, it is very important to distinguish soft tissue infections from osteomyelitis and to know the extent of involvement. Here, FDG PET/CT scores over conventional modalities for accurate delineation of diabetic foot infections due to its superior resolution.

6.2 Osteomyelitis in Axial and Appendicular Skeleton: Performance of FDG PET/CT

The literature evidence on diagnosis of osteomyelitis using FDG PET/CT establishes this modality as one of the most promising imaging modality with sensitivity and specificity more than 90% in most of the studies [1–3]. Although, it is very sensitive for detection of infection with high negative predictive value, its specificity may be low in immediate post-operative setting. This is because post-operative inflammation persists up to 4–6 weeks after the procedure. In a meta-analysis done by Termaat et al. [4], FDG PET showed the highest accuracy in diagnosing and excluding chronic osteomyelitis, with a sensitivity of 96% and a specificity of 91%, compared to 78 and 84% with combined bone and leukocyte scintigraphy and 84% and 60% with magnetic resonance imaging (MRI).

For spinal infections, leukocyte imaging or combination of leukocyte imaging and bone marrow scan have limited sensitivity as infection may be walled off. MRI is not a preferable option in patients with metallic implants. FDG PET/CT in patients with suspected spinal infection with and without metallic implants have shown sensitivities well above 90%, and specificity and accuracy at about 90% [5, 6].

In head-to-head comparison of FDG PET/CT and MRI by Demirev et al., the investigators observed that both were accurate for diagnosis of active osteomyelitis. A SUVmax cut-off of three gave optimal results with sensitivity of 88% and

specificity of 90% for FDG PET/CT, whereas SUVmax ratio (i.e. lesion SUVmax divided by SUVmax in a reference region) gave inferior results [7]. The authors concluded that MRI can be considered the primary imaging modality for uncomplicated unifocal cases of osteomyelitis, whereas in cases of suspected multifocal disease or contraindications for MRI, FDG PET/CT should be preferred. This combined sequential strategy worked well particularly for the equivocal cases.

6.3 Infectious Spondylodiscitis

It comprises of about 2–4% of osteomyelitis cases and is mostly seen in patients with fever of unknown origin or as metastatic complication in bacteraemia [8]. CT scan or MRI imaging may be difficult to interpret because of the inability to differentiate degenerative changes and infection. Preliminary studies reported the diagnostic sensitivities of FDG PET/CT to approach 100% and specificities of 75–100%, both at 100% for discriminating degenerative changes from disc-space infection and thereby far surpassing MRI's sensitivity of only 50% [9, 10]. Thus, addition of FDG PET/CT in equivocal MRI findings may reduce the need for surgical exploration [11]. Meta-analysis done by Prodromou et al. from 12 pooled studies found the sensitivity and specificity of FDG PET/CT to be 97% and 88%, respectively, with excellent ability to rule out the diagnosis with a very low negative likelihood ratio of <0.1. Importantly, implants and other confounding factors did not affect the diagnostic efficacy when combined FDG PET/CT was employed [12].

6.4 FDG PET/CT in Diabetic Foot

Diabetic foot is a unique entity caused by diabetic neuropathy or peripheral vascular disease and frequently a combination of both. There is loss of protective sensation and development of anatomical deformities both making the feet susceptible to repetitive trauma and ulceration. These make soft tissues of feet accessible to infective organisms. Further defence and treatment is weakened because the access of protective phagocytic cells and antibiotics is reduced because of impaired circulation related to peripheral vascular disease. Another important entity in the context of DM is neuro-osteoarthropathy or Charcot arthropathy, where non-infectious soft tissue inflammation is associated with rapidly progressive destruction of joints and bone.

The estimated risk of a diabetic patient developing a foot ulcer in his or her lifetime has been proposed to be as high as 25%, and the annual incidence of foot ulcers has been estimated to be up to 2% [13, 14]. In up to one-third of diabetic foot infections, osteomyelitis can supervene and is frequently the result of direct extension of the adjacent soft tissue infection. These happen in approximately 15% of overall diabetic patients [15].

Early diagnosis of infection in diabetic foot is of paramount importance as it is treatable with appropriate antibiotics and can potentially prevent complications needing amputation in some cases. When it comes to soft tissue infection, MRI with

its excellent soft tissue delineation is the modality of choice. In a meta-analysis undertaken by Dinh and colleagues [16], they compared role of exposed bone or probe-to-bone test, plain film radiography (PFR), MRI, bone scan and leukocyte scan in detection of infection in diabetic foot. They concluded the presence of exposed bone or a positive probe-to-bone test result is moderately predictive of osteomyelitis and MR imaging is the most accurate imaging test for diagnosis of osteomyelitis. As discussed earlier FDG PET has already established as very sensitive modality in imaging bone infection. Hence, combination of PET/CT and MRI or PET-MRI has potential to become the best imaging combination for investigating suspected osteomyelitis in diabetic foot (Fig. 6.1).

The studies comparing the role of FDG PET or PET/CT in diabetic foot have shown conflicting results (Table 6.2) though the studies undertaken with highest numbers have shown utility of FDG PET in this patient group. One of the largest studies done by Nawaz and colleagues [17] reported results from 110 prospectively investigated diabetic patients. In this study, head-to-head comparison was made between FDG PET, MR imaging, and PFR of the feet. They obtained promising results with FDG PET, which correctly diagnosed osteomyelitis in 21 of 26 patients and correctly excluded it in 74 of 80, with sensitivity, specificity, PPV, NPV, and accuracy of 81%, 93%, 78%, 94%, and 90%, respectively. MR imaging had sensitivity, specificity, PPV, NPV, and accuracy of 91%, 78%, 56%, 97%, and 81%,

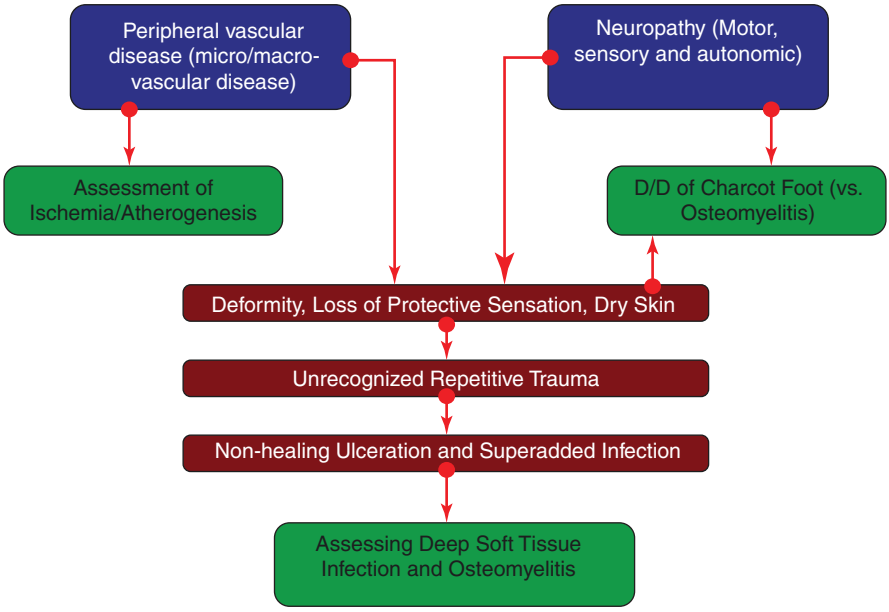

Fig. 6.1 Primary pathogenetic factors (blue); the further complicating factors (brown); in diabetic foot syndrome and diagnostic challenges where PET/CT/PET-MR imaging has a potential role (green). Reprinted from PET Clin, 2012 Apr, 7(2): 151–60, Basu et al. 'FDG PET and PET/CT imaging in complicated diabetic foot'

Table 6.2 Reported studies examining the role of FDG PET/PET/CT in diabetic foot syndrome

Study (first author, year)	No. patients	Charcot arthropathy separately analyzed	PET alone/ PET/CT	Conclusion (useful/ limited accuracy)
Hopfner et al. [14], 2004	16	Yes	PET alone	Useful
Keidar et al. [12], 2005	18	No	PET/CT	Useful
Basu et al. [18], 2007	63	Yes	PET alone	Useful
Schwegler et al. [10], 2008	20	No	PET alone	Limited accuracy
Nawaz et al. [17], 2010	110	No	PET alone	Useful
Familiari et al. [11], 2011	13	No	PET/CT	Limited accuracy

Reprinted from PET Clin, 2012 Apr, 7(2): 151–60, Basu et al. 'FDG PET and PET/CT imaging in complicated diabetic foot'

respectively, while PFR had sensitivity, specificity, PPV, NPV, and accuracy of 63%, 87%, 60%, 88%, and 81%, respectively. The investigators concluded that FDG PET is a highly specific imaging modality for the diagnosis of osteomyelitis in the diabetic foot and, therefore, should be considered to be a useful complementary imaging modality with MR imaging.

Clinically, it is very important to differentiate between osteomyelitis and Charcot arthropathy as management of these two conditions is vastly different. Another large prospective study by Basu and colleagues [18] also showed promising results in diagnosing osteomyelitis and differentiating it from Charcot foot. A low degree of diffuse FDG uptake that was clearly distinguishable from that of normal joints was observed in joints of patients with Charcot osteoarthropathy (Fig. 6.2). The SUVmax in lesions of patients with Charcot osteoarthropathy varied from 0.7 to 2.4, whereas those of the mid foot of the healthy control subjects and the uncomplicated diabetic foot ranged from 0.2 to 0.7 and from 0.2 to 0.8, respectively. The only patient with Charcot osteoarthropathy with superimposed osteomyelitis in this series had an SUVmax of 6.5. The SUVmax of the sites of osteomyelitis as a complication of diabetic foot was 2.9–6.2. The overall sensitivity and accuracy of FDG PET in the diagnosis of Charcot osteoarthropathy were100.0% and 93.8%, respectively, and those for MR imaging were 76.9% and 75.0%, respectively. The investigators concluded that these results underscored the valuable role of FDG PET in the setting of Charcot neuroarthropathy by reliably differentiating it from osteomyelitis, both in general and when foot ulcer is present.

The ischemic component in development of diabetic foot cannot be ignored. FDG PET, by its ability to assess atherosclerotic inflammation in the large vessels may be able to access this. However, this area in diabetic foot is not yet fully explored and very few studies have explored this area [19, 20]. There is need for further studies in this regard.

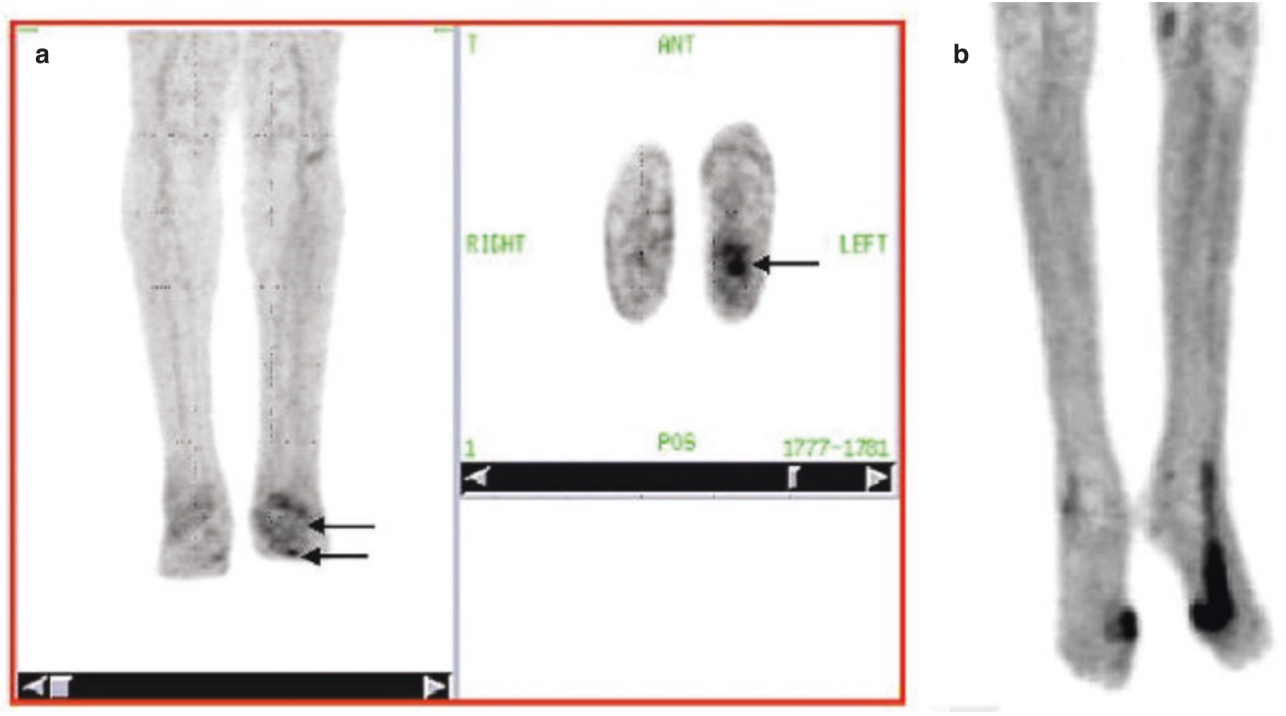

Fig. 6.2 (**a**) FDG PET in a patient with diabetes mellitus demonstrating focal uptake in the ulcer (arrows) in the transaxial images and the relatively low grade diffuse uptake in the neuropathic osteoarthropathy (arrows) are clearly distinguishable from the uptake observed on the unaffected contra lateral limb by visual inspection. (**b**) High grade FDG uptake clearly distinctive from that of Charcot's neuroarthopathy. Reprinted from Basu S, Chryssikos T, Houseni M, et al. Potential role of FDG PET in the setting of diabetic neuroosteoarthropathy: can it differentiate uncomplicated Charcot's neuropathy from osteomyelitis and soft tissue infection? Nucl Med Commun 2007;28:465–72

6.5 Response Assessment

Few studies have tried to explore potential of FDG PET/CT in assessing response to therapy in osteomyelitis. Riccio et al. [21] studied antibiotic treatment response in pyogenic spine infection in 28 patients and concluded that uptake confined to the margins of the destroyed disc should not be considered as persistent infection. However, FDG uptake in bone and/or soft tissue on follow-up was suggestive of poor clinical response. Thus, pattern of uptake along with quantification of metabolic activity was found to be important in assessing response. Treatment response in spondylodiscitis has also been explored. Nanni et al. [22] showed the feasibility and superiority of using changes in SUVmax, as compared to C-reactive protein (CRP), in establishing and monitoring response in patients with haematogenous infective spondylodiscitis. They compared scans at 2 and 4 weeks after initial therapy and found significantly lower SUVmax in responders after 4 weeks. However, further studies are warranted to establish the role of FDG PET/CT in this regard.

Conclusion

FDG PET/CT has demonstrated promising results for imaging of osteomyelitis. It is a useful adjunct to MRI in doubtful cases. It surpasses performance of MRI is spinal infections. It significantly adds to established clinical workup of the diabetic foot. Its ability to assess soft tissue, skeletal, vascular, and neurological (Charcot joints) complications in a single examination may make it an important investigational tool in conjunction with MRI, in this potentially dangerous disease. PET-MRI as a modality may evolve in this regard. However, these aspirations need strengthening with larger prospective research studies in future.

Key Points

- FDG PET/CT scores over conventional modalities for accurate delineation of diabetic foot infections due to its superior resolution.
- FDG PET/CT in osteomyelitis of axial and appendicular skeleton has a sensitivity and specificity of more than 90% in most studies.
- FDG PET/CT in patients with suspected spinal infection with and without metallic implants have shown sensitivities well above 90%, and specificity and accuracy are about 90%.
- CT scan or MRI imaging may be difficult to interpret because of the inability to differentiate degenerative changes and infectious spondylodiscitis.

- The diagnostic sensitivity of FDG PET/CT in patients suspected with infectious spondylodiscitis, approach 100% and specificity of 75–100% which surpasses sensitivity of MRIs. FDG PET/CT in equivocal MRI findings may reduce the need for surgical exploration.
- FDG PET is a highly specific imaging modality for the diagnosis of osteomyelitis in the diabetic foot and should be considered to be a useful complementary imaging modality.

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