Eur J Nucl Med Mol Imaging (2012) 39:1525–1527
DOI 10.1007/s00259-012-2234-5

EDITORIAL COMMENTARY

Diagnosis of infection in the diabetic foot using ^{18}F-FDG PET/CT: a sweet alternative?

Gopinath Gnanasegaran · Sanjay Vijayanathan · Ignac Fogelman

Published online: 11 September 2012

Accurate diagnosis and management of skeletal infection is crucial and challenging. The goals of imaging in infection are (a) to establish an early and reliable diagnosis, as clinical and laboratory markers are often non-specific in the early stages, (b) to localize, characterize and define the extent of involvement (often influences or directs diagnostic and/or therapeutic intervention), and (c) to assess treatment response [1]. Such considerations are particularly important in several select groups of patients such as diabetics, who are relatively more prone to cutaneous ulceration and its related complications. Approximately 2 million cases of musculoskeletal infection are diagnosed each year in the USA [2] and MRI is the most commonly used imaging modality. MRI with gadolinium contrast enhancement is useful (a) in differentiating abscess from inflammatory tissue, (b) to differentiate viable from nonviable tissue, and (c) to evaluate bone involvement [1]. However, the presence of preexisting renal impairment is a potentially major limitation in the use of MRI with gadolinium contrast enhancement. Metal artefacts may obscure underlying pathology, if there has been previous intervention [1] and it may be difficult to distinguish osteomyelitis from Charcot's neuroarthropathy in the diabetic foot using MRI alone.

S. Vijayanathan
Department of Nuclear Medicine & Radiology, Guy's and St Thomas' Foundation NHS Trust,
London, UK
e-mail: sanjay.vijayanathan@gstt.nhs.uk

G. Gnanasegaran (✉) · I. Fogelman
Department of Nuclear Medicine, Guy's and St Thomas' Foundation NHS Trust,
London, UK
e-mail: gopinath.gnanasegaran@gstt.nhs.uk

I. Fogelman
e-mail: Ignac.Fogelman@kcl.ac.uk

Radionuclide imaging plays an important role in the evaluation of infection and most would agree that radiolabelled leukocyte imaging remains a key investigation in the assessment of infection and in particular fever of unknown origin (FUO), vascular graft infections, orthopaedic infections and infections complicating the diabetic foot [3, 4]. Despite advances in imaging techniques, and newer tracers, it has not been possible to achieve 100 % accuracy in diagnosis, but the goal remains.

In the current issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Kagna et al. present their results assessing the role of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT imaging in the diagnosis of osteomyelitis in the diabetic foot [5]. The authors prospectively evaluated 39 diabetic patients with 46 suspected lesions of foot infection. The final diagnosis was based on histopathology/bacteriology of surgical samples, imaging or clinical follow-up. Using ^{18}F-FDG PET/CT, they were able to confirm osteomyelitis in 18 and excluded this at 21 suspected sites of bone infection. Of the 20 sites of focal FDG uptake, 2 were reported as false-positives and 5 were reported as diabetic osteoarthropathy. On a patient-based analysis, ^{18}F-FDG PET/CT had a sensitivity, specificity and accuracy of 100, 92 and 95 %, respectively, and on a lesion-based analysis ^{18}F-FDG PET/CT had a sensitivity, specificity and accuracy of 100, 93 and 96 %, respectively [5].

Impressive results but before discussing further, we should briefly consider the wider issues relating to radionuclide infection imaging. Radiolabelled leukocyte imaging is sensitive in determining the presence of infection in most situations. However, the major limitations include (a) labelling of leukocytes, which is time-consuming and involves contact with blood, (b) dual time point imaging at 4 and 24 h with ^{111}In-labelled leukocytes, which may critically delay the diagnosis [3, 4, 6, 7], and (c) the lack of anatomical resolution to localize and characterize.

Single photon emission computed tomography (SPECT)/CT may offset the lack of spatial resolution of conventional scintigraphic investigation of infection, though evidence for this is at present limited but evolving. However, CT alone can provide useful information particularly in chronic osteomyelitis where there has been cyclic bone destruction and formation [1, 8]. CT is relatively more sensitive at demonstrating sequestra, cortical destruction and gas within sites of chronic osteomyelitis [8], whereas MRI is better at assessing bone viability within sequestered bone [1].

The role of ^{18}F-FDG PET/CT in infection imaging is evolving rapidly and its role in diagnosis is comparable with other radiolabelled tracers. This topic has been extensively reviewed in several articles over the last few years [3, 9, 10]. However, it is worthwhile briefly to summarize some of the findings. In patients with FUO, ^{18}F-FDG PET/CT is reported to be the most useful test in diagnosing/localizing the infective foci and non-infective pathologies such as malignant disease [3], where routine diagnostic modalities are often negative or equivocal.

Several studies have emphasized the role of ^{18}F-FDG PET in evaluating joint prostheses. Zhuang et al. reported a sensitivity, specificity and accuracy of 90, 89.3 and 89.5 %, respectively, for prosthetic hip infection and 90.9, 72 and 77.8 %, respectively, for prosthetic knee infection [11]. However, Stumpe et al. reported poor sensitivity of 22–33 % but reasonable specificity of 81–85 % in evaluating hip prostheses [12]. In a meta-analysis, Kwee et al. [13] reported sensitivity and specificity of 82.1 and 86.6 %, respectively, for diagnosing prosthetic joint infection, which is relatively lower than has been reported in the literature for radiolabelled leukocyte/marrow imaging [14]. Love et al. reported sensitivity in the range of 36–100 % and specificity from 9 to 97 % [15] in assessing lower extremity joint replacements (accuracy of radiolabelled leukocyte/marrow imaging, in the same population, was 95 %) [15]. Therefore, ^{18}F-FDG PET cannot be considered as a suitable replacement for radiolabelled leukocyte/marrow imaging for diagnosing prosthetic joint infections at the present time [3, 10, 14].

In patients with spinal osteomyelitis, ^{18}F-FDG PET may be particularly useful as the role of the ^{111}In-leukocyte scan is limited [9, 16, 17]. In postoperative spinal infection, ^{18}F-FDG PET is reported to have a sensitivity, specificity and accuracy of 100, 81 and 86 %, respectively [16].

However, to return to the diabetic foot, the sensitivity and specificity for diagnosing pedal osteomyelitis using planar ^{111}In-labelled leukocyte imaging is from 72 to 100 % and from 67 to 100 %, respectively [6, 7, 9]. The sensitivity and specificity of ^{99m}Tc-exametazime labelled leukocyte has ranged from 86 to 93 % and from 80 to 98 %, respectively [6, 7, 9]. Current evidence on the utility of ^{18}F-FDG PET/CT in the diabetic foot is controversial as there are several positive papers with others less conclusive [3, 9, 10, 18–21]. Basu et al. assessed the potential role of ^{18}F-FDG PET in differentiating the uninfected neuropathic joint from soft tissue infection and osteomyelitis in diabetic patients. The overall sensitivity and accuracy for ^{18}F-FDG PET in the diagnosis of Charcot's foot was 100 % (MRI 76.9 %) and 93.8 % (MRI 75 %), respectively [18]. Low-grade ^{18}F-FDG uptake was noted in patients with Charcot's arthropathy and in normal control subjects and tracer uptake was higher in patients with osteomyelitis as a complication of diabetes [18]. In general, differentiating Charcot's arthropathy from osteomyelitis superimposed with Charcot's neuropathy is often a clinical dilemma. This differentiation is important because the majority of the cases referred to radionuclide studies are the ones that are equivocal on MRI or complicated by previous interventions. However, based on the ^{18}F-FDG uptake pattern, the authors could reliably differentiate Charcot's neuroarthropathy from osteomyelitis [18]. Further, Nawaz et al., in a prospective study, using visual analysis, reported a sensitivity, specificity and accuracy of 81, 93 and 90 %, respectively, for diagnosing pedal osteomyelitis [19], and in view of its high specificity the authors deemed ^{18}F-FDG PET/CT to be useful as complementary imaging with MRI. However, several studies have reported ^{18}F-FDG PET/CT to be less useful and less sensitive in diagnosing osteomyelitis in the diabetic foot. Schwegler et al. evaluated clinically unsuspected osteomyelitis in diabetic patients with pedal ulcers and found ^{18}F-FDG PET to be positive in only 2/7 cases with biopsy-proven osteomyelitis (29 % sensitivity) [20]. Similarly Familiari et al. compared ^{18}F-FDG PET with ^{99m}Tc-exametazime-labelled leukocytes. They found accuracy and sensitivity of 54 and 43 %, respectively, for ^{18}F-FDG PET/CT, while accuracy and sensitivity of radiolabelled leukocyte imaging was 92 and 86 %, respectively [21].

Based on the current evidence with ^{18}F-FDG PET, it is not possible to unequivocally support ^{18}F-FDG as the radiotracer of choice for the diabetic foot [6, 9, 10, 14, 20, 21]. The limitations of the available data include variable methodology and differing patient populations, and more specifically (a) how images are interpreted: the use of visual image interpretation versus semi-quantitative (standardized uptake value/SUV) analysis [10, 14], (b) the presence or absence of vascular insufficiency [10, 14], (c) inconsistent correlation with MRI, (d) absence of histological confirmation, and (e) lack of crossover studies with radiolabelled leukocyte/marrow studies.

An understanding of the potential advantages and limitations of the various imaging modalities will improve diagnosis and treatment. However, we should not forget that interpretation of images is much easier with full knowledge of the patient's history, clinical examination, laboratory results and discussion with clinical colleagues and will remain the cornerstone of any diagnostic strategy [1, 10, 14].

It is apparent that radiolabelled leukocyte scans remain useful in assessing the diabetic foot and are complementary to MRI. ^{18}F-FDG PET/CT had gained realistic support due its improved sensitivity/specificity, accurate localization, absence of time-consuming/laborious blood labelling and perhaps, most important, the study is completed by 3–4 h.

Evidence appears to be evolving in a positive direction. In an excellent review of the diabetic foot by Palestro last year, it was concluded that "the jury is still out" [10]. The study by Kagna et al. [5] would appear to give the jury a little push towards supporting the use of ^{18}F-FDG PET.

Thus ^{18}F-FDG PET/CT may well emerge as the first-line radionuclide investigation for the diabetic foot. However, we may have to wait a few more years for PET to obtain the gold medal for imaging in the diabetic foot Olympics! The likeliest outcome however is that synergistic information gathered from ^{18}F-FDG PET/CT and other modalities including MRI will increase our combined diagnostic sensitivity and therefore expedite effective treatment of this complex pathology. A tantalizing final thought, however, is that with the advent of PET/MRI, ^{18}F-FDG may provide an even more sensitive and viable alternative in the future.

Conflicts of interest None.

References

1. Vijayanathan S, Butt S, Gnanasegaran G, Groves AM. Advantages and limitations of imaging the musculoskeletal system by conventional radiological, radionuclide, and hybrid modalities. Semin Nucl Med 2009;39(6):357–68.
2. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. Adv Data 2007;386:1–32.
3. Lucignani GT. The many roads to infection imaging. Eur J Nucl Med Mol Imaging 2007;34(11):1873–7.
4. Hughes DK. Nuclear medicine and infection detection: the relative effectiveness of imaging with 111In-oxine-, 99mTc-HMPAO-, and 99mTc-stannous fluoride colloid-labeled leukocytes and with 67Ga-citrate. J Nucl Med Technol 2003;31:196–201.
5. Kagna O, Srour S, Melamed E, Militianu D, Keidar Z. FDG PET/CT imaging in the diagnosis of osteomyelitis in the diabetic foot. Eur J Nucl Med Mol Imaging 2012. doi:10.1007/s00259-012-2183-z.
6. Palestro CJ, Love C, Bhargava KK. Labeled leukocyte imaging: current status and future directions. Q J Nucl Med Mol Imaging 2009;53(1):105–23.
7. Palestro CJ, Love C. Nuclear medicine and diabetic foot infections. Semin Nucl Med 2009;39(1):52–6.
8. Fayad LM, Carrino JA, Fishman EK. Musculoskeletal infection: role of CT in the emergency department. Radiographics 2007;27:1723–36.
9. Glaudemans AW, Signore A. FDG-PET/CT in infections: the imaging method of choice? Eur J Nucl Med Mol Imaging 2010;37(10):1986–91.
10. Palestro CJ. 18F-FDG and diabetic foot infections: the verdict is…. J Nucl Med 2011;52(7):1009–11.
11. Zhuang H, Duarte PS, Pourdehnad M, Maes A, Van Acker F, Shnier D, et al. The promising role of 18F-FDG PET in detecting infected lower limb prosthesis implants. J Nucl Med 2001;42:44–8.
12. Stumpe KD, Nötzli HP, Zanetti M, Kamel EM, Hany TF, Görres GW, et al. FDG PET for differentiation of infection and aseptic loosening in total hip replacements: comparison with conventional radiography and three-phase bone scintigraphy. Radiology 2004;231:333–41.
13. Kwee TC, Kwee RM, Alavi A. FDG-PET for diagnosing prosthetic joint infection: systematic review and metaanalysis. Eur J Nucl Med Mol Imaging 2008;35:2122–32.
14. Palestro CJ, Love C. Decreased sensitivity of (18)F-fluorodeoxyglucose imaging in infection and inflammation. Semin Nucl Med 2012;42(4):261–6.
15. Love C, Marwin SE, Tomas MB, Krauss ES, Tronco GG, Bhargava KK, et al. Diagnosing infection in the failed joint replacement: a comparison of coincidence detection 18F-FDG and 111In-labeled leukocyte/99mTc-sulfur colloid marrow imaging. J Nucl Med 2004;45:1864–71.
16. De Winter F, Gemmel F, Van De Wiele C, Poffijn B, Uyttendaele D, Dierckx R. 18-Fluorine fluorodeoxyglucose positron emission tomography for the diagnosis of infection in the postoperative spine. Spine 2003;28:1314–9.
17. Strobel K, Stumpe KD. PET/CT in musculoskeletal infection. Semin Musculoskelet Radiol 2007;11(4):353–64.
18. Basu S, Chryssikos T, Houseni M, Scot Malay D, Shah J, Zhuang H, et al. Potential role of FDG PET in the setting of diabetic neuro-osteoarthropathy: can it differentiate uncomplicated Charcot's neuroarthropathy from osteomyelitis and soft-tissue infection? Nucl Med Commun 2007;28:465–72.
19. Nawaz A, Torigian DA, Siegelman ES, Basu S, Chryssikos T, Alavi A. Diagnostic performance of FDG-PET, MRI, and plain film radiography (PFR) for the diagnosis of osteomyelitis in the diabetic foot. Mol Imaging Biol 2010;12(3):335–42.
20. Schwegler B, Stumpe KD, Weishaupt D, Strobel K, Spinas GA, von Schulthess GK, et al. Unsuspected osteomyelitis is frequent in persistent diabetic foot ulcer and better diagnosed by MRI than by 18F-FDG PET or 99mTc-MOAB. J Intern Med 2008;263:99–106.
21. Familiari D, Glaudemans AW, Vitale V, Prosperi D, Bagni O, Lenza A, et al. Can sequential 18F-FDG PET/CT replace WBC imaging in the diabetic foot? J Nucl Med 2011;52(7):1012–9.