EDITORIAL

^{18}F-FDG PET and PET/CT for the diagnosis of diabetic foot osteomyelitis

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Diabetic foot infection is a heavily dreaded complication of diabetes, frequently leading to prolonged hospitalisation, disability and amputation[1-3]. It usually occurs in, mostly long-standing, foot ulcers and is difficult to diagnose and notoriously demanding to treat[1-5]. Diagnosis rests on meticulous clinical examination to identify local and/or systemic symptoms of inflammation[1,6,7]. However, local signs of inflammation are not entirely reliable, because their development may be prevented by both peripheral arterial disease and diabetic polyneuropathy[3,4,6,8]. If infection spreads to the bone, osteomyelitis ensues[1,9]. The latter also poses extreme difficulties for diagnosis[9]: its likelihood is particularly high in the event of exposed bone, but the accuracy of this clinical sign is far from ideal[9-12]. Finally, foot problems may occasionally present in diabetic children and adolescents: they are mostly skin and nail disorders, minor infections and neuropathic osteoarthropathy[8,13]. Such cases call for particularly meticulous monitoring and early diagnosis to avoid the development of more severe foot pathology in adulthood[8,13].

Imaging studies are of paramount importance for the timely diagnosis of diabetic foot infections, especially osteomyelitis[12,14-17]. Plain X-rays are inexpensive and readily available, but their sensitivity for osteomyelitis is rather low and they may yield false negative results in the early stages[9,16]. Technetium methyl-diphosphonate (^{99m}Tc-MDP) bone scan and radiolabelled leukocyte scans are widely used to diagnose osteomyelitis, but their precision in the anatomical localisation of bone infection is not ideal[14-16]. Conversely, Magnetic Resonance imaging (MRI) can provide more accurate information in terms of anatomical localisation (including the metaphysis), and it offers the additional advantage that it may be used for patient follow-up and treatment monitoring[16-18]. Using the aforementioned modalities, diagnosis of osteomyelitis is no longer difficult in the foot clinic. Of these, MRI, ^{99m}Tc-MDP bone scan and radiolabelled leukocyte scans are positive early enough to enable diagnosis, whereas plain radiographs may be negative in early, minor bone infection and only enable detection of severe osteomyelitis with periosteal reaction, cortical disruption, sequestra (i.e. fragments of necrotic bone) and/or abscesses[14-17]. In a comparative analysis, plain radiographs have exhibited 69% sensitivity and 80% specificity, while the corresponding values for bone scintigraphy were 83% and 75%, and for MRI 100% and 75%[19].

Fluorine-18-flurodeoxyglucose positron emission tomography (^{18}F-FDG-PET) and hybrid technique with computed tomography (PET/CT) have now emerged as alternative imaging modalities for the diagnosis of osteomyelitis in the diabetic foot[14,20]. Their advantages include the preferential ^{18}F-FDG accumulation in the infection site, facilitating the detection of osteomyelitis and the differential diagnosis from neuropathic (Charcot) osteoarthropathy; the high resolution, enabling precise tracer recognition in small bones; the option of quantitative or semi-quantitative image analysis[14,20,21]. At present, a limited number of workers have already reported their initial diagnostic experience with the new modality in diabetic foot infections[22-26].

All advantages of ^{18}F-FDG notwithstanding, results in the diabetic foot have hitherto been inconsistent and not encouraging enough[22-26], as reviewed in more detail elsewhere[21]. Specifically, sensitivity for ^{18}F-FDG PET and/or PET/CT for the differential diagnosis of osteomyelitis from soft tissue infection or Charcot osteoarthropathy has ranged from 29% to 100%[22-26]. Data on specificity and accuracy is more limited. In the largest study so far, Nawaz et al[26] have reported 93% specificity, 78% positive predictive value (PPV), 94% negative predictive value (NPV) and 90% accuracy.

More recently, two studies have re-examined the diagnostic performance of semi-quantitative ^{18}F-FDG PET/CT image analysis and yielded rather contradictory results[27,28]. In 2011, Familiari et al[27] have conducted a study on 13 patients with very high pre-test probability of osteomyelitis. These were examined with ^{99m}Tc-exametazime leukocyte scan and ^{18}F-FDG PET/CT. Importantly, both examinations were performed sequentially. Of further note, all patients had serum glucose lower than 160 mg/dl, and the reference method for diagnosis was robust (biopsy and culture)[27]. Acquisition times were 30 minutes, 3 hours and 20 hours for the former, and 10 minutes, 1 hour and 2 hours for the latter. Us-

ing a target-to-background ratio exceeding 2 at 20 hours and progressively increasing with time, leukocyte scan yielded the best combination of sensitivity (86%), specificity (100%), PPV (100%), NPV (86%), and accuracy (92%) for the diagnosis of osteomyelitis[27]. Employing the criterion of a maximal standardised uptake value (SUV) exceeding 2 at 1 hour and 2 hours and progressively increasing, ^{18}F-FDG PET/CT yielded the best of sensitivity (43%), specificity (67%), PPV (60%), NPV (50%), and accuracy (54%) for the diagnosis of osteomyelitis[27]. The authors concluded that the diagnostic performance of ^{18}F-FDG PET/CT for diabetic foot osteomyelitis was lower than that of leukocyte scan[27].

By contrast, in 2012 Kagna et al[28] have reported excellent diagnostic accuracy. They examined 39 consecutive patients with potential diabetic foot infection by ^{18}F-FDG PET/CT. Serum glucose concentration was monitored during the examination to ensure no hyperglycaemia occurred. Images were interpreted by two nuclear medicine physicians and a skeletal radiologist who were kept blind to patients' clinical status[28]. Diagnosis of osteomyelitis was based on local ^{18}F-FDG uptake localised on bone. The reference method was either histopathological and microbiological assay of surgical samples or clinical decision based on additional imaging studies and patient follow-up[28]. In a patient-based analysis, sensitivity, specificity, PPV, NPV and accuracy were very high: 100%, 92%, 87%, 100% and 95%, respectively. In a lesion-based analysis the corresponding values were 100%, 93%, 90%, 100% and 96%. No false negative results were observed[28]. Not to be ignored, there was a wide variation in serum glucose concentration (53 to 330 mg/dl), with levels exceeding 150 mg/dl in 23 patients, including 6 patients diagnosed with osteomyelitis. Nonetheless, there was no correlation between serum glucose and maximum SUV at the sites of increased FDG uptake[28].

The question, then, remains why results are still conflicting and the expectations associated with ^{18}F-FDG PET have not been fulfilled. Several, still rather unclear and not necessarily mutually exclusive, reasons may apply. Two relevant editorials have proposed that several possibilities may hold true[21,29]. The most important of these include: differences in equipment used; discrepancies in analysis, interpretation and acquisition times; patient heterogeneity; erratic serum glucose levels with undetected glucose excursions[30]; differences in the prevalence and severity of peripheral arterial disease; and, last but not least, uncertainty in the reference method for the diagnosis of osteomyelitis[21,29]. These may all be true, but it is uncertain to what extent they apply to each individual work. Moreover, we would like to add some other less appreciated potential sources of confusion, notably the presence and severity of diabetic polyneuropathy[4,8], which might interfere with bone arterial perfusion and, possibly, radiotracer uptake; chronic trauma from ill-fitting footwear[2]; impaired bone turnover and myositis associated with hypovitaminosis D[31,32]; diminished local inflammatory response[4,6,8]; and concomitant unrecognised Charcot osteoarthropathy, possibly leading to confusion in the interpretation of results[33]. Finally, it should not escape our notice that patient series were very small in some studies, calling for replication in larger series.

What, then, should be done to increase our knowledge in this area? Three issues appear to be of foremost importance. First, more experience with large patient series is needed. Such works are expected to shed more light on the diagnostic accuracy of ^{18}F-FDG PET/CT and help us towards a definitive evaluation. Indeed, as Glaudemans and colleagues[34] have emphasised, there is currently no validated ^{18}F-FDG PET protocol to diagnose diabetic foot infections, and so further data is dramatically needed to fill this gap. Secondly, better patient selection would be desirable. It may be best to refine this evaluation by separately enquiring the diagnostic performance of the new modality in each of the following situations: diabetic foot osteomyelitis vs. soft tissue foot infection, and diabetic foot osteomyelitis vs. Charcot osteoarthropathy. Improved patient selection can only be accomplished by close collaboration with the clinician. The latter will be decisive in optimising glycaemic control before the examination, as well as in deciding on patient characteristics that may be of significant value, notably severe peripheral neuropathy and/or peripheral arterial disease. Thirdly, the combination of PET with MRI has been suggested as potentially useful in improving accuracy[29,34], but this diagnostic approach is currently speculative only. Ultimately, some technical improvement and standardisation is necessary to enable higher image resolution in the small foot bones. These areas of improvement need to be fully exploited before we become familiar with new tracers such as the ^{68}Ga-Citrate for PET[35].

In conclusion, the accuracy of ^{18}F-FDG-PET and PET/CT for the diagnosis of diabetic foot osteomyelitis is, at the moment, far from encouraging. However, results should still be perhaps described as only preliminary[21,29]. Indeed, additional investigation is needed, and future works should include more patients and be more precise in the reference method for the confirmation of osteomyelitis. More caution is also required in patient selection, to avoid those with excessive hyper- or hypoglycaemia[21,29]. Indeed, such glucose fluctuations may, in theory, affect ^{18}F-FDG tissue uptake, although this remains to be quantified. Further work towards standardisation of technological details and options of interpretation is urgently awaited, as well. In Greece, these modalities are only available on a very restricted basis, emphasising the need for further experience. Moreover, their use should be reasonable and affordable, in harmony with the financial restraints due to the current economic crisis[36]. There is, certainly, still a long way to go, but improved early diagnosis of diabetic foot infections is a goal worth pursuing.

Keywords: Diabetes, diabetic foot, osteomyelitis, 18F-FDG-PET, PET/CT

Conflicts of interest

The authors declare no conflicts of interest.

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