The role of nuclear medicine in the diagnosis of common and specific diabetic infections

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Abstract

Infections are usually detected in diabetes mellitus. They may be divided into: common infections such as fungal infections, pulmonary tuberculosis, pneumonia, bacteraemia, urinary tract infections, and diabetic foot infections and specific infections. The latter occur almost exclusively in diabetes and include rhinocerebral mucormycosis, malignant external otitis, emphysematous pyelonephritis, perirenal abscess, emphysematous cystitis and emphysematous cholecystitis. Radionuclide tests are decisive in the diagnosis and localisation of foot osteomyelitis, as well as the distinction of osteomyelitis from other conditions, notably Charcot osteoarthropathy. Technetium-99m methylene disphosphonate and labelled leukocyte bone scans are the main imaging techniques employed, while emerging techniques include single-photon emission tomography/computed tomography (CT) and positron emission tomography/CT. Nuclear medicine is also useful in the diagnosis and follow-up of specific infections in diabetes like, malignant external otitis, rhinocerebral mucormycosis, acute pyelonephritis, renal papillary necrosis and cholecystitis. The main indications of nuclear medicine tests are diabetic foot osteomyelitis, malignant external otitis, rhinocerebral mucormycosis and renal infections.

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Introduction

Diabetes mellitus (DM) is steadily increasing in frequency [1]. Especially type 2 diabetes has nowadays reached epidemic proportions, becoming a major health problem for the 21st century [1, 2]. Traditionally, the risk of infection is increased in diabetic patients, and the same holds true for the severity of infections [3-6]. Poor glycaemic control has been linked with both susceptibility to infections and sinister outcomes [3-6]. Indeed, some of the so-called special infections encountered in DM usually occur during extreme metabolic decompensation, typically ketoacidosis [6]. By contrast, the risk of infections is not significantly increased in patients with normoglycaemia [6]. Several lines of evidence point to reduced humoral and cellular immune responses in poorly controlled DM [4-7]. Such perturbations of the immune system include diminished chemotaxis, impaired bacteriocidic function, low phagocytic activity of macrophages, reduced CD4/CD8 lymphocyte ratio and impaired delayed type, sensitivity reactions [7-12]. All these perturbations appear to be dependent on the level of hyperglycaemia [3, 5, 6]. Vice versa, severe infections lead to increased secretion of stress hormones such as cortisol, catecholamines, glucagon and growth hormone and to insulin resistance, thereby aggravating glycaemic control [3, 5, 6]. Finally, a vicious circle ensues, in which infections aggravate hyperglycaemia, which, in turn, perpetuates the susceptibility to infections [3, 5, 6].

Imaging modalities are valuable for the diagnosis of infections in DM. The present review aims to briefly outline the role of nuclear medicine in the diagnosis of common and specific diabetic injections.

Infections in diabetes

Infections in diabetic patients may be classified into common and specific infections [5, 6, 12]. The former are not specific to DM, but are characterised by increased severity. The latter occur almost exclusively in DM [5, 6, 12].

Common infections in DM include fungal infections, pulmonary tuberculosis, pneumonia, bacteraemia, urinary tract infections, infections associated with renal replacement treatment (haemodialysis or continuous ambulatory peritoneal dialysis, CAPD), skin and bone infections, as well as diabetic foot infections [5, 6, 12-15]. Fungal infections comprise skin and nail infections, oral and vulvovaginal candidiasis, and fungal urinary tract infections [6, 12]. Pulmonary tuberculosis and recurrent pneumonia are more common among diabetic subjects [6, 16-18]. Bacteraemia ensues by haematogenous dissemination of Gram-positive or Gram-negative bacteria [6, 12]. Urinary tract infections (cystitis and pyelonephritis) are frequent among diabetic patients [3, 6, 12, 19]. An ominous complication is renal papillary ne-

cronsis due to ischaemia in the renal medulla [20, 21].

Patients undergoing haemodialysis may develop infections of the vascular access (arteriovenous fistula, synthetic graft or double-lumen catheter), while those on CAPD may suffer from catheter and surrounding soft tissue infections or peritonitis [22, 23].

Skin infections include cellulitis, necrotising fasciitis and Fournier's gangrene [3, 24-26]. Cellulitis represents infection of the epidermis and subcutaneous tissue [3, 25, 26]. The affected area is characterised by erythema, increased temperature and tenderness on palpation [3, 25, 26]. A more severe condition is necrotising fasciitis [3, 25, 26]. This is characterised by increased tension, haemorrhagic bullae and dark red colour with a "peau d' orange" picture [3, 25, 26]. Eventually, subcutaneous emphysema and gangrenous skin ulcerations may occur. In the worst cases, the patient develops septic shock with hypotension and multi-organ failure [3, 25, 26]. Fournier's gangrene is a life-threatening necrotising fasciitis of the perineum and external genitalia [27, 28]. Diabetic patients, predominantly those with end-stage renal failure, may also develop severe hand infections [29, 30]. Finally, haematogenous dissemination of bacteria may lead to osteomyelitis, especially of the thoracic and lumbar vertebrae [31].

Diabetic foot infections constitute a major cause of morbidity [13-15]. Infection usually develops in a pre-existing ulceration [13, 15]. Indeed, the longer the duration of a foot ulcer, the more likely it becomes to develop infection [13, 15, 32-34]. Acute ulcers may become infected by Gram-positive cocci, most commonly staphylococcus aureus [13, 15, 33]. By contrast, more severe infections, as well as those complicating a chronic ulceration, are frequently polymicrobial, with a combination of Gram-positive cocci, Gram-negative bacteria and anaerobes [13, 15, 33, 35]. Methicillin-resistant staphylococcus aureus (MRSA) is being increasingly isolated and represents a serious threat for foot clinics [14, 36].

Infection is usually added to peripheral arterial disease and to diabetic neuropathy, forming the ominous triad of the diabetic foot [37, 38-40]. Prompt diagnosis of infection is often difficult, because clinical signs are very poor [33, 35, 39]. The clinician should not overlook even minor signs, such as erythema, modest increase in temperature, new onset of pain etc. It is also crucial to assess the severity of infection [13, 15, 33, 35, 39]. Detailed evaluation systems like the Wagner classification, the University of Texas classification and the classification of the International Working Group on the Diabetic Foot, evaluate the depth of a foot lesion, the presence and extent of infection, the evidence of bony involvement and the presence of arterial disease [13, 15, 33, 41]. A more practical distinction between limb-threatening and not limb-threatening infections has also been proposed [35]. Limb-threatening infections may exhibit one or more of the following signs and symptoms: cellulitis > 2cm; oedema, pain or lymphangitis; gangrenous necrosis; infection extending to the bone or joint; nausea, malaise, high fever, lethargy, hypotension, tachycardia, metabolic derangement and severe ischaemia of the infected area [35].

The complication of osteomyelitis needs to be ascertained. Clinical manifestations (probing to exposed bone or sausage-like oedema of the toes) are strongly suggestive of infection. The diagnosis is confirmed by imaging modalities, and nuclear medicine has a pivotal role in the diagnosis. In the event of osteomyelitis, long-term antibiotic treatment and, possibly, orthopaedic surgery will be required [13, 15, 33, 35].

Specific infections in diabetic patients include rhinocerebral mucormycosis, malignant external otitis, emphysematous pyelonephritis, perirenal abscess, emphysematous cystitis and emphysematous cholecystitis [42-53].

Malignant external otitis is a severe invasive necrotic infection that may even be life-threatening [44-46]. The diagnostic hallmark is spread of infection to the mastoid process and the base of skull. It may be complicated by osteomyelitis of the temporal bone [44-46].

Emphysematous pyelonephritis is a severe form of pyelonephritis, almost exclusively encountered in DM [47-49]. The high concentration of glucose in the kidney is a suitable substrate for the production of gas. The patient complains of fever, nausea, vomiting, abdominal pain, while physical examination reveals local tenderness [47-49]. The extensive tissue destruction may lead to pus formation in the form of a perirenal abscess [50]. Emphysematous cystitis is a less severe infection, which affects the bladder [47-49].

Similarly, emphysematous cholecystitis is a severe form of cholecystitis encountered in diabetic patients [51-53]. Again, it is characterised by gas formation. The initial clinical presentation is that of common cholecystitis, but the patient's condition soon deteriorates, and gallbladder gangrene may ensue [51-53].

The role of nuclear medicine in the diagnosis of diabetic foot infections

Diabetic foot infections may be classified into uncomplicated soft tissue infections and those complicated by osteomyelitis [33, 35]. It is imperative to detect the presence of osteomyelitis early, as it necessitates a different treatment approach with longer administration of antibiotics [33, 35, 40, 54]. If there is inadequate improvement after antibiotic treatment, adjuvant surgery must be considered [33, 35, 54-56]. Both diagnosis and management of diabetic foot osteomyelitis are so challenging for the everyday practitioner that the ideal approach is sill being discussed by the experts [55-57].

Magnetic resonance imaging (MRI) has been established as the imaging modality of choice for the diagnosis of osteomyelitis in the diabetic foot for diagnosis and treatment [58-60]. Radionuclide scintigraphy is becoming increasingly reliable in the diagnosis of DM infections [61, 62]. Essentially, all judgements about the sensitivity, specificity and accuracy of imaging modalities need to be viewed with caution, given that legitimate comparisons need a true gold standard. Ideally, the latter should be bone culture and/or biopsy, which is rarely, if ever, performed in practice [55, 57].

The classical radionuclide test is a 740MBq 3-phase technetium methyl-diphosphonate (^{99m}Tc-MDP) bone scan [63]. The triad of localised hyperperfusion, hyperaemia and increased bony uptake offer a strong clue in favour of osteomyelitis [61, 63]. However, this picture alone is not reliable in the differential diagnosis from neuropathic osteoarthropathy (Charcot osteoarthropathy) or fracture [64]. This test is more sensitive than specific and cannot adequately distinguish active from cured infection [65]. Looking at published data, sensitivity of the 3-phase technetium (^{99m}Tc) bone scan ranges between 75% and 100% (mostly 91%-

100%) and its specificity ranges between 10% and 67% (mostly around 40%) [63, 66-73] (Fig. 1, 2).

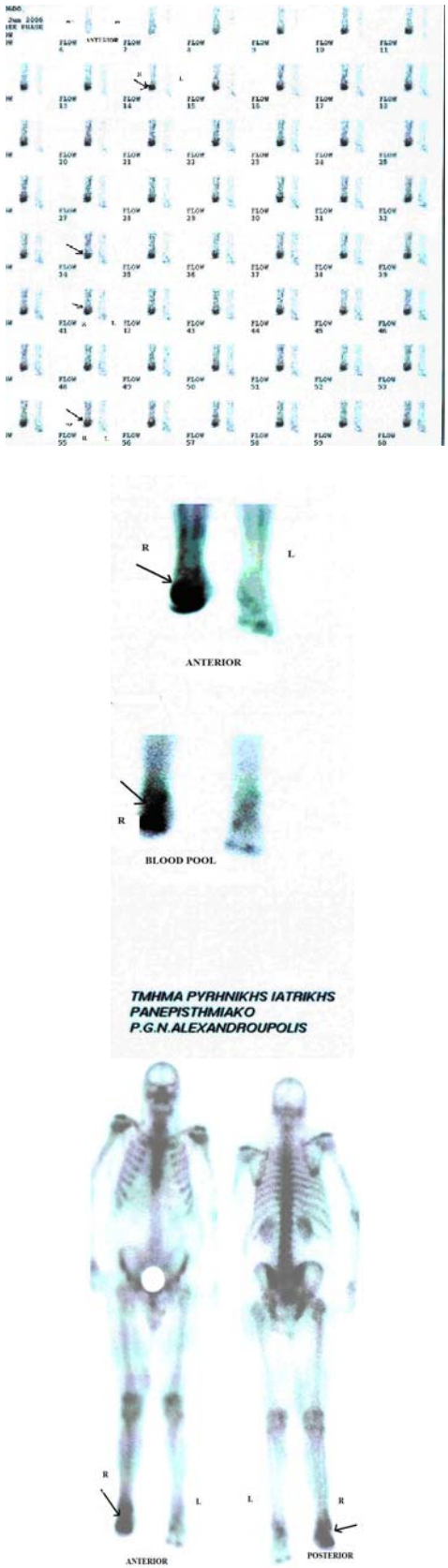

Figure 1. Three-phase bone scan with 740MBq ^{99m}Tc -MDP in a 65 years old male. Osteomyelitis of the right tarsal bones.

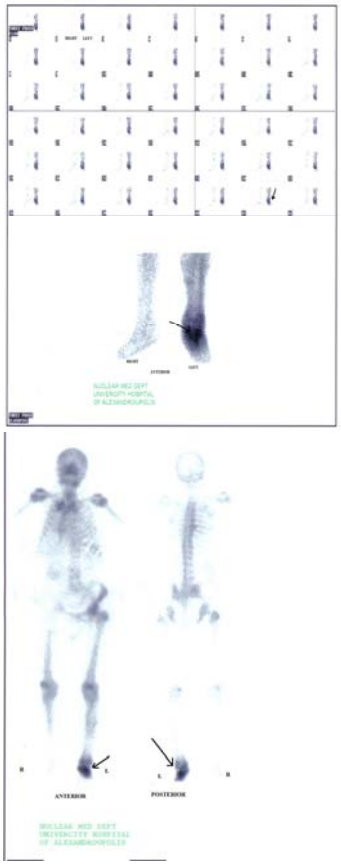

Figure 2. Three-phase bone scan with 740MBq ^{99m}Tc -MDP in a 50 years old female.

The low specificity of the 3-phase bone scan has led to interesting variations of the method, in an attempt to improve results [61, 74]. One idea has been to add a fourth phase in the bone scan [75-77]. This is based on the notion that accumulation of radioactive tracer in osteomyelitic bone persists for several hours, whereas it terminates after approximately four hours in unaffected bone [75-77]. Obtaining a fourth phase after 24 hours creates a delayed static image [75]. If the ratio of lesion to background activity progressively increases, the 4-phase scan is deemed positive for osteomyelitis [75] (Fig. 3). In comparison to the conventional 3-phase bone scan, this modality showed slightly better overall accuracy (85% vs. 80%), higher specificity (87% vs. 40%), but lower sensitivity (80% vs. 100%) [75]. The 24/4 hours ratio of lesion-to-normal ^{99m}Tc-MDP uptake has been reported to be of value in the confirmation of osteomyelitis [76]. In subjects with osteomyelitis, this ratio was significantly ($P<0.001$) higher than in those with increased uptake due to adjacent soft-tissue infection (1.18±0.18 vs. 0.98±0.05) [76]. Using a cut-off value of 1.06, sensitivity and specificity were 82% and 92%, respectively [76].

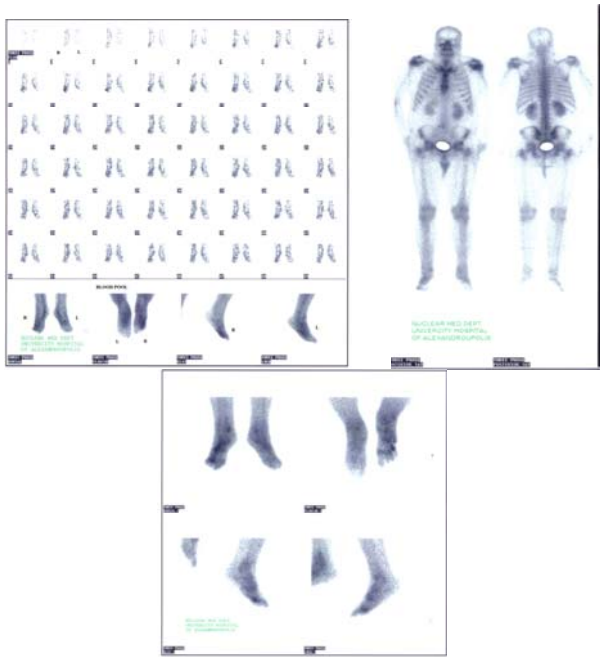

Figure 3. Four-phase bone scan with 740MBq ^{99m}Tc -MDP in a 45 years old male.Negative bone scan for osteomyelitis.

A further variation would be to base diagnosis on one particular rather than on all three scintigraphic phases [78]. Defining osteomyelitis as arterial hyperperfusion by contrast to venous hyperperfusion, which was taken to denote soft tissue infection, sensitivity and specificity values of 94% and 79%, respectively, were obtained [78]. Moreover, several workers have suggested combining a ^{99m}Tc bone scan with a gallium-67 citrate (^{67}Ga) scan to facilitate the differential diagnosis between osteomyelitis and cellulitis [79-81] (Fig.4). This interesting approach, however, has, to the best of our knowledge, not been studied in the diabetic foot, and needs further evaluation. Of note, none of the abovementioned radiolabeled agents is entirely reliable in differentiating between infection and inflammation [78-81]. At the moment, the same holds true for the combination of ^{99m}Tc and ^{67}Ga, as well as for the study of arterial hyperperfusion [78, 79]. Progress in the differential diagnosis between inflammation and infection with the use of these modalities is eagerly awaited.

Considerable improvement in the diagnosis of osteomyelitis has been accomplished with the use of radiolabelled leukocytes. This is based on the principle that leukocytes gather in the area of infected bone. Labelling may be performed either *in vitro* or *in vivo* [61, 74]. *In vitro*

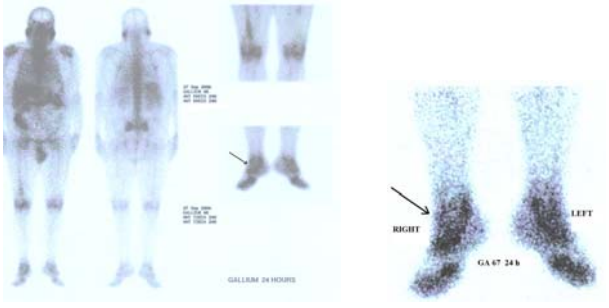

Figure 4. Imaging with 148MBq ^{67}Ga in a 56 years old male. Osteomyelitis of the right tarsal bones.

labelling is a more demanding procedure, and so research has recently focused on *in vivo* labelling with the use of peptides and special antibodies [61, 74]. Two tracers may be used for labelling i*n vitro*: Indium-111 (^{111}In) and technetium hexamethylpropylenamine oxime (^{99m}Tc-HMPAO) [61, 74]. Advantages of the former include stability of labelling and appropriately long half-life of the label, while advantages of the latter include more suitable photon energy, superior image quality and the ability for quick diagnosis [61, 74]. Disadvantages include poor image quality and the long time period between injection and diagnosis with the former, and instability as well as short half-life of the label with the latter [61, 74]. Both ^{111}In and ^{99m}Tc-HMPAO may easily be combined with conventional 3-phase bone scans to enhance diagnostic accuracy, mainly by increasing the relatively low specificity of the 3-phase bone scans (Fig. 5) [61, 74].

Sensitivity and specificity of ^{111}In for diabetic foot osteomyelitis have been found to lie between 72%-100% and between 67%-100%, respectively [63, 66, 68, 69, 73, 78, 82, 83]. Sensitivity of ^{99m}Tc-HMPAO has been reported at 90% [71] and 93% [85] with a specificity of 86% [71] and 100% [85] . Interestingly, the combination of ^{99m}Tc-HMPAO leukocyte scan with ^{99m}Tc 3-phase bone scan has yielded both high sensitivity and high specificity (92.6% and 97.6%, respectively) [84]. An important

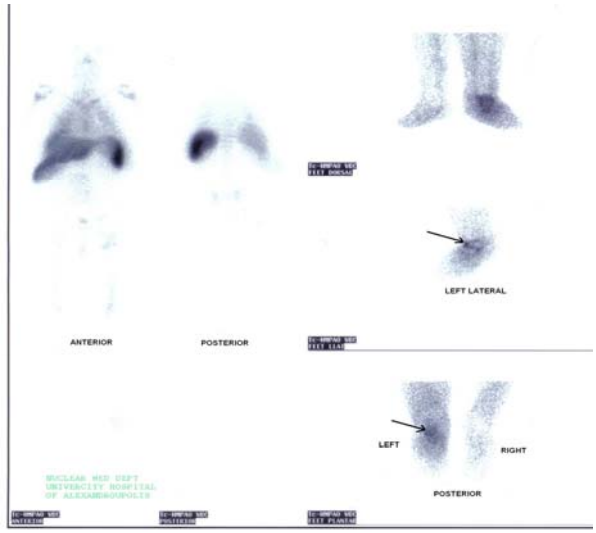

Figure 5. Whole body imaging with 222MBq ^{99m}Tc-HMPAO-leukocytes scan in a 65 years old male. Osteomyelitis of the left tarsal bones.

advantage of this combination was that Charcot osteoarthropathy did not affect diagnostic accuracy [84].

In vivo techniques are continuously evolving. Labelling options are numerous, as reviewed elsewhere [61], and include murine monoclonal G1 immunoglobulin, fane-losomab (a monoclonal murine M class immunoglobulin), sulesomab (a murine monoclonal antibody fragment), ^{99m}Tc-labelled antigranulocyte monoclonal antibody fragment Fab (leukoscan), non-specific polyclonal IgG, as well as labelled antibiotics. (Fig. 6) Most of these techniques are very rarely used in Greece. While a comparison between diverse techniques is not absolutely justified, reported sensitivities lie between 67% and 93%, while specificities lie between 56% and 85% [61]. Arguably, leukoscan is the most promising for widespread use of the new agents. Researchers have shown that its sensitivity and specificity for the diagnosis of infections amount to 86% and 72%, resepectively [85]. Others reported that leukoscan is less accurate than ^{99m}Tc-HMPAO leukocyte

scan in the differential diagnosis of diabetic foot osteomyelitis from soft tissue infection, especially in the event of deep plantar ulcers [85]. More recently, two leukoscan protocols have been developed [86]. The first adopts evaluation of early 4-hour images and the second the evaluation of both early and delayed 24-hour images. Both protocols yielded the same sensitivity (91.9%), but specificity was higher with the second protocol (87.5% vs. 75%) [86]. Obviously, leukoscan shows considerable diagnostic potential, but more familiarisation with the technique is necessary.

Scintigraphy with ^{99m}Tc-nanocolloid also appears useful [87]. In a very small study of diabetic foot osteomyelitis confirmed with bone biopsy or surgical excision, sensitivity of ^{99m}Tc-nanocolloid scintigraphy was 100% and specificity 60% [87]. Another work evaluated the role of combined leukocytes plus ^{99m}Tc-sulfur colloid (^{99m}Tc-SC) marrow scintigraphy in the differential diagnosis of uncomplicated Charcot osteoarthropathy from that complicated by osteomyelitis. It was demonstrated that the combination of leukocytes plus ^{99m}Tc-SC marrow scintigraphy was a reliable way to differentiate between marrow oedema and osteomyelitis [88]. For this purpose, this test was superior to both 3-phase bone scintigraphy and combined leukocytes/bone scintigraphy (Fig.7).

While the aforementioned scintigraphic techniques still constitute the mainstay of diagnosis, emerging techniques, namely single-photon emission tomography/computed tomography (SPET/CT), fluorine-18-flurodeoxyglucose positron emission tomography

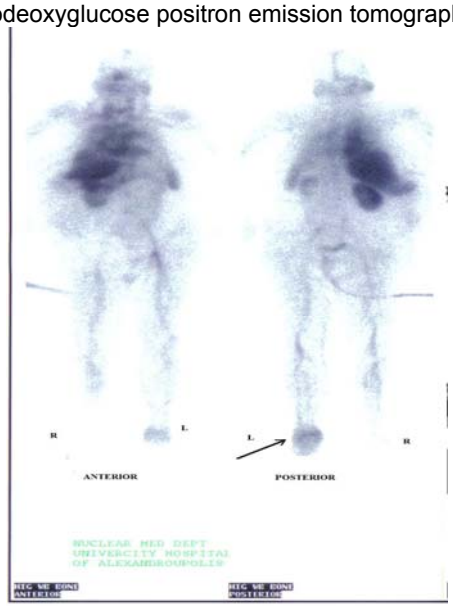

Figure 6. Whole body imaging with 555MBq ^{99m}Tc-labelled human immunoglobulin in a 58 years old female. Osteomyelitis of the left talus area.

(^{18}F-FDG-PET) and positron emission tomogram-phy/computed tomography (PET/CT) now come into play [61, 62, 89, 90]. There is accumulating evidence that SPET/CT may be combined with classical scintigraphy to improve diagnostic accuracy for osteomyelitis [61]. However, research has mainly focused on larger bones, and there is scepticism as to whether this

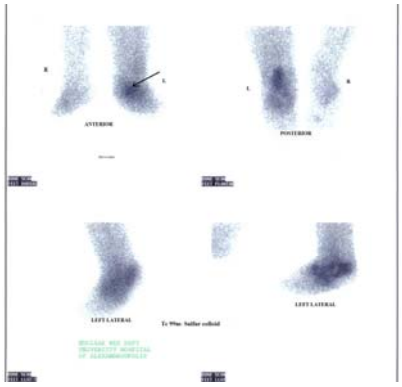

Figure 7. Imaging with 185MBq ^{99m}Tc-sulfur colloid in a 62 years old male. Charcot osteoarthropathy of the left talus area.

technique is well-applicable to the diabetic foot [61]. Others have recently reported that the combination of SPET/CT and ^{99m}Tc-HMPAO-labelled leukocytes imaging can substantially support a more precise diagnosis or exclusion of diabetic foot osteomyelitis [90]. While this study was rather small (17 patients with 19 clinically suspected sites of infection) [90], the findings hold promise and additional investigation is warranted.

During the last five years, ^{18}F-FDG-PET and PET/CT are gaining importance as adjunctive diagnostic tools for bone infection in the diabetic foot [61, 62, 89]. Because ^{18}F-FDG appears to accumulate in areas of infection, it facilitates the anatomic localisation of osteomyelitis, as well as the distinction from Charcot osteoarthropathy [61, 62]. In an ongoing prospective study of 110 consecutive patients, researchers have compared ^{18}F-FDG-PET with MRI and plain radiographs [89]. By ^{18}F-FDG-PET sensitivity, specificity and accuracy of 81%, 93% and 90%, respectively were reported, while the corresponding values for MRI were 91%, 78% and 81% [89]. The authors concluded that ^{18}F-FDG-PET is a highly specific complimentary imaging modality for the diagnosis of diabetic foot osteomyelitis [89]. Nonetheless, such positive results have not yet been replicated, and so results obtained with ^{18}F-FDG-PET and PET/CT are interesting but, for the time being, not conclusive [61, 62, 65].

The role of nuclear medicine in the diagnosis of other specific or common infections in diabetes mellitus

Nuclear medicine is also very useful in the diagnosis and follow-up of other specific or common infections in DM. Its main applications include malignant external otitis, rhinocerebral mucormycosis, acute pyelonephritis, renal papillary necrosis and cholecystitis, as will be described below.

In malignant external otitis, ^{99m}Tc-MDP bone scan is valuable for the differential diagnosis from simple external otitis by the identification of osteomyelitis affecting the temporal bone and/or base of skull [91-95]. The complication of osteomyelitis is demonstrated by increased radionuclide uptake in the affected bones [91-95]. For this purpose, ^{99m}Tc bone scan has been shown as more sensitive than plain radiographs and CT scans [93]. Equally important, bone scintigraphy permits earlier diagnosis of malignant external otitis [91-93]. Gallium-67 scintigraphy is also very sensitive in the diagnosis [92,

93], and has been described as more specific for patients follow-up, evaluating response to treatment [92, 93, 96]. Alternatively, the ^{111}In-labelled leukocyte scan is reliable for early diagnosis of bone infection, but less so for patients follow-up [97, 98]. A further improvement in the diagnosis of malignant external otitis is the development of 24-hour bone scintigraphy by obtaining delayed images that may more accurately depict increased local bone uptake [99]. Finally, SPET-imaging is very helpful in the anatomic localisation and follow-up of malignant external otitis [99-101]. Others have suggested that routine diagnosis should be based on CT and/or MRI combined with SPET imaging, and the latter should be the investigation of choice for patients' follow-up [97].

In rhinocerebral mucormycosis, ^{99m}Tc bone may show a homogenous, frequently triangular, region of increased radionuclide uptake in the naso-orbital-calvarian region [102, 103]. An identical picture may be seen in the ^{99m}Tc-diaethyleno tramino pentaacetic acid (DTPA) brain scan, as well, attributable to increased vascularisation of the affected oedematous, granulomatous tissue [102, 103]. Scintigraphic re-evaluation of the patient in the course of the disease and following antifungal treatment are useful documenting the regression of radioactive uptake [102, 103].

Nuclear medicine aids in the diagnosis of acute pyelonephritis and renal papillary necrosis, although findings are not specific for DM [104-106]. The tracer of choice for the detection of renal infection is ^{99m}Tc dimercaptosuccinic acid (^{99m}Tc-DMSA) enabling clear delineation of the renal cortex [104-106]. In acute pyelonephritis, three patterns of abnormal scintigraphic findings have been described: unifocal, multifocal and diffuse [106]. In the affected areas, there is reduced tracer uptake without renal cortical or volume loss [105, 106]. This radio pharmaceutical, ^{99m}Tc-DMSA has the potential to depict gradual changes resulting from acute infections, notably cortical scarring [107-109]. In children, ^{99m}Tc-DMSA is the gold standard and is superior to ultrasound for early diagnosis [110]. Alternatively, ^{99m}Tc-mercaptoacetyltrigycline (^{99}Tc-MAG3) and ^{99m}Tc ethylene dicysteine (^{99m}Tc-EC) may be used, but these agents have so far yielded lower diagnostic accuracy [107, 111]. The ^{18}F-FDG-PET [112], ^{67}Ga-C scintigraphy and the leukocyte scans [113, 114] have been employed for the diagnosis of acute renal infection, but experience remains extremely limited. In acute renal papillary necrosis ^{99m}Tc-DMSA may also visualise necrotic papillae (Fig.8) [115].

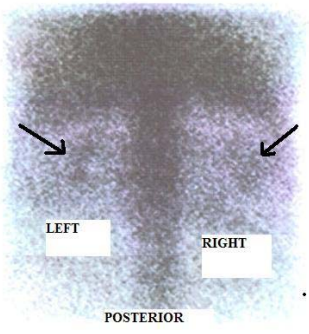

Figure 8. Four days post injection imaging with 148MBq ^{67}Ga in a 46 years old female with acute pyelonephritis.

Finally, cholecystoscintigraphy with ^{99m}Tc-iminodiacetic acid (^{99m}Tc-IDA) may be used to diagnose acute cholecystitis, even in the emergency setting [116, 117]. This modality has been reported to yield higher sensitivity than ultrasound (86% vs. 48%), while combination of both modities was most sensitive (90%) [117].The diagnostic hallmark is the presence or absence of gallbladder visualisation, suggesting cystic duct patency or obstruction, respectively. Secondary findings include degree and rate of liver uptake, visualisation and calibre of the bile ducts, and the rapidity of ^{99m}Tc-IDA transit from the biliary tract to the small bowel [118, 119]. Morphine-augmented cholescintigraphy is an important variation [120, 121]. Morphine sulphate is administered intravenously and delayed images are obtained [120, 121]. Thus, sensitivity for acute cholecystitis increases to 93% and specificity to 78% [120].

In conclusion, infections are common in DM, and nuclear medicine has a pivotal role to play in their diagnosis. Radionuclide tests are decisive in the localisation and diagnosis of foot osteomyelitis as well as in its diaphoric diagnosis. Technetium bisphosphonate and labelled leukocytes bone scans are the main imaging modalities employed, while emerging techniques include SPET/CT and, ^{18}F-FDG-PET/CT.

Nuclear medicine is also very useful in the diagnosis and follow-up of other infections in DM. Its main applications include malignant external otitis rhinocerebral mucormycosis, acute pyelonephritis [105, 106, 110] and renal papillary necrosis.

In all these areas, there is continuous progress, and collaboration between nuclear medicine, the clinician and the pathologist is needed, in order to maximise the diagnostic effect.

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