

# Diagnostic imaging of the diabetic foot

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## Abstract

Diabetic foot syndrome is a significant complication of diabetes. Diagnostic imaging is a crucial factor determining surgical decision and extent of surgical intervention. At present the gold standard is MRI scanning, whilst the role of bone scanning is decreasing, although in some cases it brings valuable information. In particular, in early stages of osteitis and Charcot neuro-osteoarthropathy, radionuclide imaging may be superior to MRI. Additionally, a significant contribution of inflammation-targeted scintigraphy should be noted. Probably the role of PET scanning will grow, although its high cost and low availability may be a limiting factor. In every case, vascular status should be determined, at least with Doppler ultrasound, with following conventional angiography or MR angiography.

**Key words:** diabetic foot, radionuclide imaging, SPECT, PET, radiography, CT, MRI, Charcot neuro-osteoarthropathy

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## Introduction

Diabetes mellitus is a growing global epidemic of the twenty-first century. According to the WHO, the number of patients with diabetes type II will rise from 132 million in 1997 to 220 million in 2010, 250 million in 2020, and 300 million in 2025. One of the major debilitating complications of diabetes is diabetic foot, including the ulcerations and deformations of the foot with the protracted course and impaired healing. Diabetic foot ulcers and infections are common and incur substantial economic problems for society, patients,

and families. Usually the ulcerations of diabetic foot are the result of wrongly chosen shoes, small wounds caused by small objects in shoes, or thermal injury. Sometimes the patients are not aware of the wound, due to impaired feeling of pain, touch, and vibration; this may result in secondary infection of the wound, threatening foot amputation. The treatment of diabetic foot is difficult, and the history of treatment methods is rather sad and unfinished. There is no evidence that surgical debridement of the infected bone is routinely necessary. Culture and sensitivity of isolates from bone biopsy may assist in selecting properly targeted antibiotic regimens, but empirical regimens should include agents active against staphylococci, administered either intravenously or orally (with a highly bio-available agent). There are no data to support the superiority of any particular route of delivery of systemic antibiotics, or to give an indication of the optimal duration of antibiotic therapy [1].

In practice, three types of diabetic foot may be distinguished: s.c. vascular foot linked with microangiopathy and macroangiopathy, s.c neuropathic foot, and neuro-ischaemic foot mixed form.

Medical imaging of the diabetic foot entails a variety of imaging modalities. The diagnostic evaluation often includes a gamut of studies that include conventional radiography, CT, nuclear medicine scintigraphy, MRI, ultrasonography, and a newcomer, positron emission tomography combined with CT and leukocyte labelling. There is not yet "one best test" for sorting out the diagnostic dilemmas that are commonly encountered. Confirmation or exclusion of the frequent diagnosis of osteomyelitis often requires multiple studies, which are complementary to one another [2]. This paper reviews the advantages and disadvantages of particular methods with emphasis on the particular forms of diabetic foot.

## Clinical factors

One of the most important epidemiological parameters of diabetic foot is the number of lower limb amputations. Half of them are performed in diabetic patients. Most of them do not return to previous fitness, which may cause inability to work, and sometimes also to incapability of independent existence. The loss of lower limb significantly increases the risk of amputation of the other limb [3]. In patients with diabetic foot, neuropathy as a sole aetiological factor is seen in 62% of patients, microangiopathy without neuropathy in 13% of patients, and both factors in 25% of diabetic patients. In the western world the morbidity of diabetic foot is around 2%, and the frequency of amputations below the knee is 2 per 1000 cases. Risk factors are: age, sex and social status, smoking, alcohol abuse, and concomitant arterial hypertension, as well as some emotional factors, e.g. depression [4].

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## Neuroarthropathy of the foot (Charcot's neuroarthropathy)

This is a distinct form of diabetic foot, involving bone and joints. It starts with neuropathy, the loss of feeling of pain, and abnormal mechanics of the foot [3]. The autonomic nervous system neuropathy impairs the blood supply of the foot bones and joints. The clinical symptoms are foot oedema, skin rash, and foot deformation. The bones become fragmented, which may lead to the foot becoming a "skin sack" filled with bone fragments, with the threat of foot amputation [5].

### Imaging of diabetic foot

Diagnostic imaging of diabetic foot should enable the diabetologist and surgeon to determine whether osteitis is present or not, and if so — what should be the extent of planned surgery. One another important role is detecting and assessing early stages of diabetic neuroarthropathy. Lastly, radiological procedures play a significant role in assessing arteries before angioplasty. This is not an easy job. One of the most challenging tasks for the radiologist is differential diagnostics of infectious changes and non-infectious neuroarthropathy, which may be nearly impossible [6].

### Plain radiograms

Bone X-ray is widely available and inexpensive. Plain radiograms are a good initial screening tool in diabetic osteomyelitis; however, their sensitivity is poor. Sensitivity of bone X-ray in diabetic foot is estimated between 43% and 75%, and specificity between 75% and 83% [7]. Whilst interpreting bone X-rays, attention must be paid to bone deformations, osteolytic foci, and joint changes. Regrettably, plain X-ray is usually insufficiently sensitive in early osteitis, as well as in early osteoarthropathy, when bones are not deformed or fragmented, and so serial radiographs are necessary [4]. A relatively rare but characteristic finding is calcification of the foot dorsal artery in Mönckeberg's sclerosis [8].

Sometimes X-ray densitometry may be useful in Charcot's osteoarthropathy, to show regional mineral density variations. In numerous fractures mineral density is low, but at bone displacements bone calcification remains normal [9].

### Computed tomography

In dubious cases bone biopsy is indicated. MRI also has a high potential for diagnosing deep abscesses, tendon ruptures, and septic exudate in joint cavities [10].

In Charcot's osteoarthropathy, MRI shows bone and cartilage lesions (bone oedema, occult fractures, joint exudation) as early as in stage 0, when plain X-ray is normal; in the next stages: I (bone destruction), II (bone reunion), III (bone remodelling), the results are even better.

MR angiography is useful in the assessment of blood outflow, particularly in peripheral artery occlusion. Contrary to conventional X-ray, MR angiography does not show calcification in the arteries [4].

According to two meta-analyses, MRI is the best diagnostic tool in diabetic foot imaging [11, 12]. Kapoor et al. analysed 16

papers comparing different diagnostic tools and their diagnostic odds ratios (DOR) and obtained the following results: MRI sensitivity and specificity 90%, DOR compared to radionuclide studies 149.9 vs. 3.6 (7 communications), plain radiography 81.3 vs. 3.3 (9 communications), and scintigraphy of inflammation 120 vs. 3.4 (4 communications). This analysis was supported by interesting economic data. In 2006 in the USA, costs were as follows: \$288 for three-phase bone scintigraphy, \$416 for limb MRI without contrast, and \$451 for limb MRI contrast imaging. The authors postulate that due to the small difference in cost and better MRI sensitivity, MRI is more cost-effective, with the exemption of patients with initially low disease probability [11].

Similar conclusions were drawn by the American College of Radiologists Study Group in 2008 [13]. The authors agreed that in soft tissue oedema, skin ulcerations and suspicion of osteitis, MRI scanning with or without contrast is the imaging modality of choice. Also, in diabetic foot without ulceration, MRI is the preferred tool, with granulocyte-labelled scintigraphy as a second choice if contra-indications to MRI scanning exist.

Perhaps a useful compromise would be hybrid PET/MRI scanning, which has proven to be useful in many fields of pathology. CT, however, has numerous limitations, including the high dose of the ionising radiation absorbed. MRI scanning provides an excellent imaging contrast; it also enables NMR spectroscopy and functional imaging to be performed. Developing a PET/MRI device took at least 15 years. The crucial technical problem was the limitation of scintillation flash transfer through the high magnetic field [14]. This was overcome by utilising avalanche photodiodes (APDs) for gamma ray detection, as well as applying lutetium orthosilicate crystal detectors, which enabled the development of PET scanners insensitive to magnetic fields [15].

A separate issue is the utility of magnetic resonance angiography (MRA). Sometimes vascular changes invisible in conventional angiography are better seen in MRA, indicating the vessels for revascularisation [16].

### Ultrasonographic and vascular examinations

The risk of vascular changes is four-fold higher in diabetic patients than in patients without diabetes. Changes progress more aggressively in diabetic patients with a five-fold higher probability of critical ischaemia. Early diagnosis enables surgical or radiological intervention and revascularisation in 80% of patients. A non-invasive alternative is thrombolytic treatment [17].

Doppler ultrasound visualises the patency of vessels and the direction of blood flow, detecting the critically narrowed vessels without utilising conventional angiography [4]. This is important as patients with purely neuropathic forms of diabetic foot have much better prognosis than those with its ischaemic or mixed form do. Essentially, diabetic foot with and without peripheral artery disease are two distinct diseases with very different prognosis and therapy, with strong emphasis on revascularisation in the latter form [18].

Peripheral artery angioplasty (PTA) significantly decreases the number of amputations [19]. Arterial reconstruction provides excellent long-term results with regard to amputation-free survival and limb salvage. It should be considered in every diabetic patient with extensive soft tissue deficits before amputation is performed

[20]. The starting point of this management is of course clinical assessment and Doppler ultrasound, but for precise delineation of vascular changes and reconstructive surgery planning it is necessary to perform conventional angiography or MRA. The basic angiological intervention is by-pass surgery or femoral endarterectomy [21]. Angiological interventions much improve prognosis of foot healing, although angiography is not always a predictive factor [22]. Until recent times the gold standard was digital subtraction angiography (DSA); today 3D magnetic resonance angiography is preferred because in most patients with diabetic foot, arterio-venous shunts occur and 3D imaging facilitates planning of reconstructive surgery [23]. Also, it seems that ultrasonography is partially able to replace angiography as the first choice test, selecting a group of patients for angiography with simultaneous angioplasty [24]. Therefore, a thorough preoperative vascular evaluation should be performed before the initiation of any lower extremity surgical intervention, particularly in situations of diabetic foot reconstruction with compromised blood flow [25]. Additionally, on ultrasound, the atrophy of intrinsic foot muscles determined at ultrasonography is directly related to foot muscle volume determined by MRI and to various measures of diabetic neuropathy. Ultrasonography seems to be useful for the detection of foot muscle atrophy in diabetes [25].

In contrast, in diabetic foot, assessment thermography and thermometry definitely failed. Medical applications of thermography date back to the 1950s, with some progress of this method in cardiosurgery, angiology, and even ear/nose/throat (ENT) diseases and dentistry, but still its sensitivity and specificity is quite low, result dispersion is high, and in diagnosing diabetic foot it has practically no application [27], although some authors still advocate its use [28].

### Conventional radionuclide imaging

Early reports on scintigraphic imaging of diabetic foot date from about thirty years ago [29]. Today its position is diversified. The role of static and three-phase bone scan is decreasing, and the role of inflammation scintigraphy and PET increasing. Probably there is no "one-best-test" in radionuclide diabetic foot imaging, and those existing are complimentary [30]. Some authors believe that MRI is the method of choice and the others only have an auxiliary character [13]. The value of bone scintigraphy in the diabetic foot, even as a screening test, is questionable [31].

The most commonly applied method is three-phase bone scintigraphy utilising 99m-technetium phosphonates (MDP, EHDP, IDP, and others), followed by inflammation scintigraphy, and, rarely, bone marrow scintigraphy [32].

Muscle perfusion scintigraphy utilising 99m-Tc-MIBI or thallium-201 did not gain wider acceptance [33] although it may be a promising method in assessing muscle-skin graft healing in diabetic foot reconstructive surgery [34].

The main disadvantage of three-phase bone scintigraphy is unspecific bone radiotracer uptake secondary to foot degenerative changes. "Hot" spots in feet, particularly of the first digit, are a frequent artefact of bone scintigraphy in patients without diabetes. Sometimes performing a fourth phase scanning 24 hours post tracer injection may be helpful; the same concerns granulocyte-labelled scanning [35]. On the other hand, no significant difference

in the amputation rate for patients with confirmatory, indeterminate, or nonconfirmatory three-phase bone scans for osteomyelitis (36%, 37%, and 50%, respectively) ( $P > 0.5$ ) was found. Therefore, the authors conclude that the ultimate treatment decision should be based on clinical indicators of the presence of uncontrolled infection or gangrene rather than on bone scan findings [36].

Inflammation scintigraphy may be performed utilising radio-labelled granulocytes, radiolabelled polyclonal immunoglobulin, anti-granulocyte antibodies, or gallium-67. The best results are obtained utilising radiolabelled antibodies with sensitivity ranging between 72–100% and specificity between 72–98%. Some authors advocate performing dual scintigraphy: three-phase bone scintigraphy and granulocyte-radiolabelled scintigraphy, with the assumption that positive result of both scans means osteitis, and that positive granulocyte scanning only indicates soft-tissue involvement [37]. Hybrid SPECT/CT scanning does not significantly contribute to the evaluation of patients with negative scan results [38]. As the labelled leukocytes accumulate in uninfected neuropathic joints, bone marrow scintigraphy may be needed to determine whether infection is present [32]. In some cases, high-resolution scintigraphy (HRS) with mini-gamma camera and 99mTc [HMPAO]-labelled leukocyte is able to diagnose early osteitis of diabetic foot and to guide diabetic foot surgery [39]. The position of gallium-67 scintigraphy is uncertain; the sensitivity of gallium-67 SPECT scanning is estimated at 67–70% with a specificity of 92% [7]. Technetium-99m radiolabelled ciprofloxacin has a relatively high sensitivity (86%), but care must be taken in cases of fastidious organisms and ciprofloxacin-resistant bacterial flora in which false results may be obtained (86%) [40]. Theoretically good results were obtained with radiolabelled dextran, but this technique did not gain popularity [41].

### Positron emission tomography (PET)

PET/CT is also a promising technique, in the assessment of the muscular and skeletal system, in detecting inflammation sites [42]. The main target of PET is oncology and to a lesser extent cardiology and neurology; detecting inflammation currently represents around 1% of PET application. They comprise osteitis, complications of endoprostheses and bone grafting, pyrexia of unknown origin, immunodeficiency syndromes, including AIDS, infections and fistulae of vascular grafting, and diabetic foot [42, 43].

PET applications in diabetic foot date back to the beginning of the present decade [44]. PET scanning is performed today almost exclusively with hybrid PET/CT cameras, and in recent years also PET/MRI with a significant improvement of diagnostic precision. Co-registration of PET with high-resolution anatomic CT imaging modalities may solve some clinical problems of diabetic foot. Small variations in limb positioning between separate studies may lead, however, to faulty localization of infectious foci, in particular where different structures are close to each other. Based on these initial results, hybrid PET/CT, combining 18-F-FDG assessment of infection and CT structural data of the skeleton, is likely to be a better, more accurate, and certainly simpler procedure for diagnosing osteomyelitis in the diabetic foot patient population [45].

Opinions regarding the use of PET in diabetic foot are diversified. Keidar et al. underline the high usefulness of PET/CT in discriminating bone and soft tissue infection [45], whereas Schwegler

et al. in the material of 20 diabetic foot patients without suspicion of osteitis concluded that MRI was superior to 18F-FDG-PET and 99m-Tc monoclonal antibodies [46]. PET may play an important role in the diagnosis of Charcot's osteoarthropathy. PET shows the foci of bone remodelling both in visual analysis and SUV calculations. The differentiation between Charcot's neuroarthropathy and florid osteomyelitis provides the surgeon with important additional information that often is unavailable from MRI [43, 47].

There are practical problems of PET imaging related to hyperglycaemia, which is important when we analyse the diabetic foot patient population. The effect of hyperglycaemia on 18F-FDG-PET sensitivity is a controversial issue [48]. Some data suggest that elevated blood glucose levels may not impair 18F-FDG uptake in infection [49]. In a study of Keidar et al., although elevated glucose serum values were found in half the present study population at the time of 18F-FDG injection, this did not lead to false-negative studies. There was no relationship between the glycaemic state and the presence or absence of abnormal 18F-FDG uptake in the present study [45].

## Conclusions

An interesting result shows the mentioned meta-analysis by Dinh et al. which is stratifying the utility of diagnostic tests in diabetic foot [12, 13]. Bone biopsy has a sensitivity of 60%, specificity 91%, plain X-ray 54% and 68%, MRI 90% and 79%, and radiolabelled granulocytes scintigraphy 74% and 68%, respectively. The authors believe that the best tests for diagnosing osteomyelitis are bone probing, bone biopsy, and, among imaging modalities, MRI scanning. Similar results were obtained in the meta-analysis by Kapoor et al. [13]. Is it correct? Probing exposed bone or its biopsy applies to a somewhat advanced phase of foot ulceration. The meta-analysis of Dinh also does not include the role of PET.

However, other meta-analyses do exist. Butalia et al. believe that the clinical data are decisive. An area of ulceration larger than 2 cm<sup>2</sup>, blood sedimentation rate above 70 mm/h, positive bone biopsy, and positive plain X-ray result are sufficient to diagnose bone involvement. In dubious cases, MRI scanning may aid the diagnosis [50].

Other authors believe that the imaging should be started with plain X-ray, particularly if Charcot's osteoarthropathy is suspected. Three-phase bone scintigraphy is diagnostic in the toes and forefoot, but not in the hindfoot, CT is of little use, and the extent of surgical intervention is best defined by MRI; the gold standard of differentiation between osteoarthropathy and bone infection is granulocyte scanning, preferably performed at the same time as MRI [51].

Probably there is no "one best test", and the existing ones are complementary. MRI is the test of choice, but the forthcoming years will probably bring technological advances in functional modifications and hybrid imaging, redefining existing algorithms.

Therefore, at present a diagnostic imaging algorithm would look as follows:

- in uncomplicated diabetic foot, plain X-ray as a first choice, MRI scanning defining the extent of surgery, radionuclide scanning if there are doubts in MRI;
- in Charcot's osteoarthropathy: as above + three-phase bone scintigraphy or inflammation-agent scintigraphy;

— vascular assessment should always be performed: Doppler ultrasound possibly with classical angiography or MR angiography for defining the need and extent of angiological intervention.

This algorithm may be modified by the growing role of PET/CT and PET/MRI in future. Today its main limitation is the cost of PET/CT scanning and its low availability. In the authors' country the cost of diabetic foot PET scanning is not reimbursed by the national health insurance system. However, this may change along with development of conservative surgery. FDG-PET is a highly specific imaging modality for the diagnosis of osteomyelitis in diabetic foot and, therefore, should be considered as a useful complimentary imaging modality with MRI. In the setting where MRI is contraindicated, the high sensitivity and specificity of FDG-PET justifies its use after a negative or inconclusive PFR to aid an accurate diagnosis [52]. Today health care reimbursement systems prefer plain foot amputations, but if indirect costs of post operation care, pensions, and socio-economical factors of patients post-amputation are taken into consideration the development of conservative surgery with its associated imaging methods seems to be the future.

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