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REVIEW ARTICLE

Neuropathic osteoarthropathy with and without superimposed osteomyelitis in patients with a diabetic foot

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Abstract Soft tissue and bone infection involving the foot is one of the most common long-term complications of diabetes mellitus, implying a serious impairment in quality of life for patients in the advanced stages of the disease. Neuropathic osteoarthropathy often coexists and differentiating between these two entities is commonly challenging, but crucial, as the management may differ substantially. The importance of correct diagnosis cannot be understated and effective management requires a multidisciplinary approach owing to the complicated nature of therapy in such patients. A missed diagnosis has a high likelihood of major morbidity for the patient, including limb amputation, and over-diagnosis results in a great socioeconomic challenge for healthcare systems, the over-utilization of healthcare resources, and the unwise use of antibiotics. Diagnosis is largely based on clinical signs supplemented by various imaging modalities such as radiography, MR imaging, and hybrid imaging techniques such as F-18 fluorodeoxyglucose-positron emission tomography. In the interests of the management of diabetic foot complications, this review article is aimed on the one hand at providing radiologists with important clinical knowledge, and on the other hand to equip clinicians with relevant radiological semiotics.

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Introduction

Diabetes mellitus is a large and increasing health problem that is common throughout the world; it is likely to continue to grow substantially over the next few decades, with clinical practice and public health policy implications. In 2013, a total of 382 million people were afflicted with diabetes worldwide; this number is expected to rise to 592 million by 2035 [1]. Diabetes is a multi-systemic disease that can involve any musculoskeletal site, but the foot, in particular. Microvascular and macrovascular disease, in addition to peripheral sensorimotor and autonomic neuropathy, are the major pathological processes that lead to the development of diabetes-related foot complications such as deformity and altered weight bearing with subsequent neuropathic osteoarthropathy, callus, ulcerations, infections, and often amputation [2]. Diabetes confers a dramatically increased risk of foot ulceration; the lifetime risk for the development of foot ulcers is approximately 25 % [3, 4]. As many as 50 % of patients develop infections [4], and limb amputation is preceded by foot ulceration in 85 % of cases [5]. The most common route of infection is spread from contiguous infected tissue with skin ulceration, altered biomechanics and trauma as particular risk factors. Direct implantation of infectious material into the bone, following surgery or penetrating injuries, is another important route of infection [5, 6]. In these patients, neuropathic osteoarthropathy, occurring as a result of chronic, repetitive trauma to the joints and supporting ligaments of the foot, often coexists. Distinguishing neuropathic osteoarthropathy from soft-tissue and bone infection is often clinically and radiologically

challenging, but crucial as they require quite different treatments [5]. Imaging plays a central role in detecting neuropathic osteoarthropathy and/or infections, in evaluating the extent of infections, and in defining when infection has resolved with treatment. The non-invasive diagnostic work-up usually begins with radiography, but magnetic resonance (MR) imaging is currently the modality of choice for the evaluation of diabetes-related foot complications. Hybrid imaging modalities such as positron emission tomography (PET)/CT play an increasing role. Even though prompt diagnosis of neuropathic osteoarthropathy is essential for the minimization of the eventual damage, this condition can be very difficult to manage since its pathogenesis is not definitively understood and, apart from offloading, there is currently no treatment of proven efficacy [7]. Therefore, correlation between imaging findings and clinical manifestations is crucial, and a multidisciplinary team in a specialized center is required to ensure effective care. The aim of this review article was to provide the clinical knowledge that radiologists need to know and the relevant imaging knowledge that clinicians require in diagnosing diabetic foot complications.

Neuropathic osteoarthropathy

Neuropathic osteoarthropathy, commonly referred to as Charcot foot, represents a spectrum of bone and joint destructive processes that occur secondary to neurosensory loss. It was first described in 1868 by Jean-Martin Charcot related to syphilis [8]. Diabetes mellitus is currently the leading cause, and in this setting, the foot and the ankle are most often affected [9]. Both acute and chronic forms are clinically recognized. Acute forms are characterized by active localized inflammation; in chronic forms, there is typically an absence of the local inflammation, and a progression of bony and joint changes that leads to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity [10].

Etiological hypotheses

The exact mechanism for developing neuropathic osteoarthropathy still remains to be elucidated, but two main theories have been proposed. The neurotraumatic theory states that in the absence of normal protective sensory feedback, neuropathic osteoarthropathy occurs as a result of repetitive, unperceived trauma to the joints and supporting ligaments of the foot. The neurovascular theory maintains that the underlying condition leads to the development of an autonomically stimulated vascular reflex that causes vasodilation, hyperemia, and arteriovenous shunting with subsequent osteopenia, bone resorption, and fracture [11]. Neuropathic osteoarthropathy most likely results from a combination of the effects involved in the above theories [12, 13]. The sensory neuropathy renders the patient unaware of the progressive bone and joint destruction, and enhances a local inflammation that is triggered by a minor injury, a local surgical procedure or infection [14]. In a neuropathic patient, the insensitive foot does not exhibit pain appropriately. Without the protective behavior ensured by the pain, the lack of required immobilization and repetitive trauma flare up the inflammatory cycle. As a result of associated autonomic neuropathy, blood flow to the foot increases, resulting in osteopenia and attendant weakness of the bone. Cartilage damage is also a feature, resulting in a progressive arthropathy with erosions and subchondral cysts [6]. Inflammation and increased osteoclastic activity are well-recognized key factors of the rapid bone destruction that occurs in acute forms of neuropathic osteoarthropathy, although the link between them is not fully understood [15]. Bone loss is limited to the inflamed affected foot [15, 16] and it is possible that local inflammatory factors released after initial trauma may act as osteoclastogenic mediators [17]. The key abnormality may lie in an enhanced inflammatory response to injury, which is itself linked to increased bone lysis. An injury, which may or may not be detected, is sufficient to initiate an uncontrolled inflammatory process with the release of pro-inflammatory cytokines including tumor necrosis factor-α and interleukin-1β, which, in turn, would trigger increased expression of the osteoclastogenic polypeptide receptor activator of nuclear factor-κB ligand (RANKL), leading to osteoclastogenesis and subsequent local osteolysis [7]. Furthermore, repetitive trauma owing to the loss of pain sensation, may result in the continual production of pro-inflammatory cytokines, RANKL, and osteoclasts, which in turn leads to continual local osteolysis with progressive bone and joint destruction [17–19].

Classification

Traditionally, the natural history of the clinical and radiographic changes seen in this condition has been divided, according to the Eichenholtz classification system [20], into three different stages: stage 1, the stage of fragmentation\dissolution; stage 2, the stage of coalescence; and stage 3, the stage of remodeling. This staging system does not include the clinically important stage 0, an addition by Shibata et al. [21], which describes warmth, dull pain, swelling, and joint instability, with normal appearing bone and joints on radiography. Furthermore, Chantelau and Grützner [22] have considered this radiography-based system obsolete, because of advances in medical imaging technology, and have proposed an MR imaging-based classification system comprising two severity grades (0 and 1, according to the absence/presence of cortical fractures) and two stages (active/inactive, according to the presence/absence of skeletal inflammation). Sanders and Frykberg [23] classified neuropathic

osteoarthropathy anatomically into five patterns of joint involvement. Pattern I involves the forefoot (metatarsophalangeal and interphalangeal joints); pattern II involves the tarsometatarsal (Lisfranc) joints; pattern III involves the talonavicular, calcaneocuboid (Chopart's) and cuneonavicular joints; pattern IV involves the ankle and subtalar joints; and pattern V involves the posterior calcaneus. Patterns II and III are the most common, and associated with the highest complication rates; they are often associated with plantar ulceration at the apex of the deformity. Another anatomical classification system is the Brodsky system [24]. This system is based on the location of the neuropathic osteoarthropathy. Type 1 involves the Lisfranc joint; type 2 involves Chopart's joint and/or the subtalar joint; type 3A involves the ankle joint and type 3B is a pathological fracture of the calcaneus that leads to Achilles tendon dysfunction. Anatomical classifications could be clinically important as they have been reported to predict outcomes. Forefoot involvement seems to have a better prognosis than hindfoot arthropathy owing to the effects on weight distribution during walking [25]. In 2008, Rogers and Bevilacqua [26] proposed a classification system based on the clinical examination and on imaging. This system considers deformity, ulceration, and osteomyelitis, and may be helpful in predicting amputation.

Clinical features

Neuropathic osteoarthropathy is considered a rare disease, but its true prevalence and incidence remain unknown and probably greatly underestimated because of the limited number of prospective studies and subtle clinical presentation of acute forms that are often confused with cellulitis, deep vein thrombosis, or acute gout by nonspecialists [26, 27]. However, it is estimated to affect 0.8 –8 % of the diabetic population [25], with incidence rates ranging from 3 to 11.7 out of 1,000 patients per year [28]. Patients are usually in their fifth and sixth decades of life, and 80 % of them have had diabetes for over 10 years [29]. There is no particular sex preponderance, but differences exist between patients with type 1 diabetes mellitus and type 2 diabetes mellitus. In patients with type 1 diabetes, the most frequent decade for the presentation of neuropathic osteoarthropathy is the fifth decade, while for patients with type 2 diabetes, it is the sixth decade. Furthermore, in type 1 diabetes, the highest rate of presentation is among those with diabetes of 20–24 years' duration, whereas for type 2 diabetes, the highest rate of presentation is in patients who had had diabetes for 5–9 years [30]. Neuropathic osteoarthropathy can present as an acute or chronic condition and clinical features depend on the nature of the presentation. The acute condition is typically characterized by the presence of acute local inflammation, with a warm, tender, edematous, and erythematous foot with only mild to modest pain or discomfort [18, 30]. There is most often a temperature differential between the two feet of several degrees [18]. Furthermore, there is always evidence of a dense peripheral neuropathy, but the vascularity of the limb is usually preserved and the peripheral pulses are characteristically bounding, although swelling or edema may make their palpation difficult [18]. The natural course of the disease is usually self-limiting; neuropathic osteoarthropathy practically never re-activates, but may later affect the contralateral foot [13]. The progression from the acute to the chronic phase can be rapid, occurring within 6 months or less [31]. However, immediate offloading and immobilization generally resolves the inflammation and stops the acute bone and joint damage [32].

Chronic neuropathic osteoarthropathy is characterized by a decrease in the local inflammatory changes, but progression of bony changes that lead to permanent deformities. Although any part of the foot and ankle may be involved, bone and joint destructive processes typically begin in the midfoot or tarsometatarsal joints [33], and subluxation usually starts at the second tarsometatarsal joint and proceeds laterally (Fig. 1) [10]. This leads to a collapse of the longitudinal arch and increased load-bearing on the cuboid, resulting in a "rocker-bottom" deformity (Fig. 2). The architectural support for the foot crumbles. Atrophic osseous degeneration may be present in the forefoot. It is characterized by gradual osteolysis at the ends of the phalanges and metatarsals, which produces a tapered, "penciled" appearance of the bones resembling "sucked candy" (Fig. 3) [34]. Neuropathy-induced dorsiflexion and shortening of the toes combined with plantar subluxation of the metatarsal heads (Fig. 2) predispose to neuropathic ulceration of the soft tissues. Unperceived chronic trauma may lead to exuberant periosteal new bone along the shaft of a bone (Fig. 4) and may evolve into sclerosis of the entire shaft. The ankle and hindfoot may also show neuropathic changes. Neuropathic fractures such as avulsion fractures of the calcaneus and subchondral fracture of the head of the second metatarsal (similar to Freiberg infraction) can occur in the diabetic foot (Fig. 3) [35]. The calcaneal insufficiency avulsion fracture is an extra-articular fracture confined to the posterior calcaneus that is seen almost exclusively in diabetic patients. The avulsed fragment is eventually displaced superiorly owing to the pull of the Achilles tendon, a finding that is not encountered in typical stress fractures (Fig. 5). Factors that can be implicated in these fractures include osteoporosis, peripheral neuropathy, altered vascularity, and gait abnormalities [6, 36]. All these deformities lead to altered loading on standing and walking with a high pressure area at the base of the foot that in turn predisposes to the formation of callus tissue, ulceration, and subsequent infection [31]. The presence of plantar callus, a consequence of peripheral sympathetic dysfunction in the neuropathic foot, is highly predictive of subsequent foot ulceration [37]. Foot ulcers occur most frequently beneath the first and fifth metatarsophalangeal joints, the tip of the great toe, and the

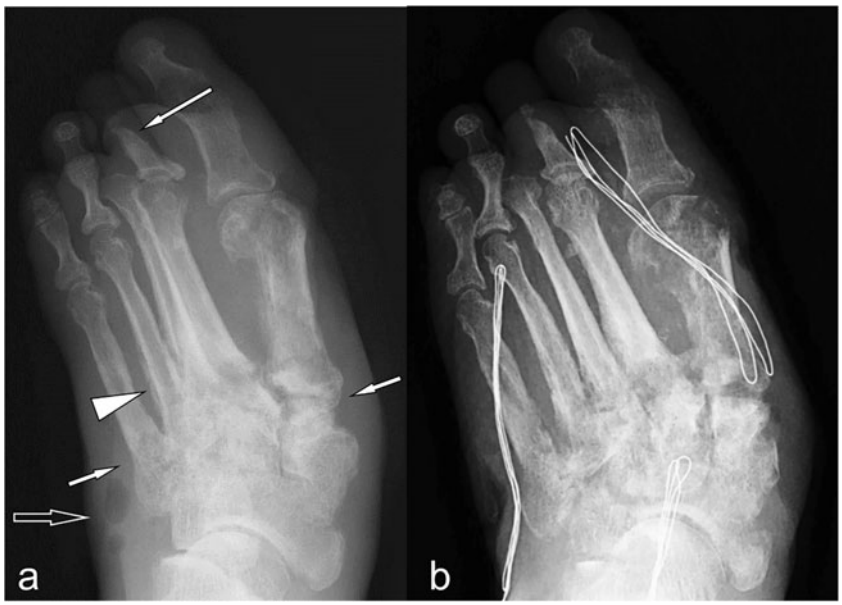

Fig. 1 Neuropathic osteoarthropathy in a 67-year-old diabetic woman who had undergone amputation of the third phalanges. **a** Frontal radiograph clearly depicts resorptive changes at the tarsometatarsal joints with a Lisfranc pattern of fracture dislocation (*small arrows*). Note also the typical "sucked candy stick" tapering of the second proximal phalanx (*arrow*), periosteal reaction in the fourth metatarsal bone (*arrowhead*), and soft tissue gas (*open arrow*). **b** Corresponding radiograph obtained 2 years later shows complete disorganization of the tarsometatarsal joints with bony debris present

heel (Fig. 5) [38]. Once ulceration develops, the risk of infection and amputation rises dramatically. The amputation risk has been reported to be 12 times higher in patients with foot ulcers compared with patients without foot ulcers [27, 39].

Imaging features

Both hypertrophic and atrophic patterns of neuropathic osteoarthropathy can be depicted radiologically. Hypertrophic neuropathic osteoarthropathy classically implicates joint destruction and fragmentation, sclerosis of bone ends, and osteophyte formation. Osteophytes that form may differ from those of osteoarthritis on the basis of the early production of ill-defined and rounded margins and the later attainment of an enormous size. In many cases, however, it is difficult to distinguish neuropathic osteoarthropathy from severe osteoarthritis. Periosteal new bone formation is also characteristic (Fig. 4) [9]. The atrophic form is characterized by the dominance of bone resorption, may appear similar to septic arthritis, and is most commonly seen in nonweight-bearing joints of the upper extremity. Joint disorganization and persistent bloody joint effusion, however, are features of both the atrophic and the hypertrophic forms of neuropathic osteoarthropathy. Frequently, patients present with features of both hypertrophic and atrophic patterns (Fig. 4), and in some cases, an affected joint may exhibit the atrophic pattern early and evolve into the hypertrophic form later [9]. Fractures are another important feature of neuropathic osteoarthropathy (Fig. 4), with the potential development of exuberant and bizarre callus formation because of their frequent misdiagnosis in the acute condition and consequent delayed treatment. In the absence of acute trauma, a Lisfranc joint fracture dislocation strongly indicates diabetic neuropathic osteoarthropathy [9].

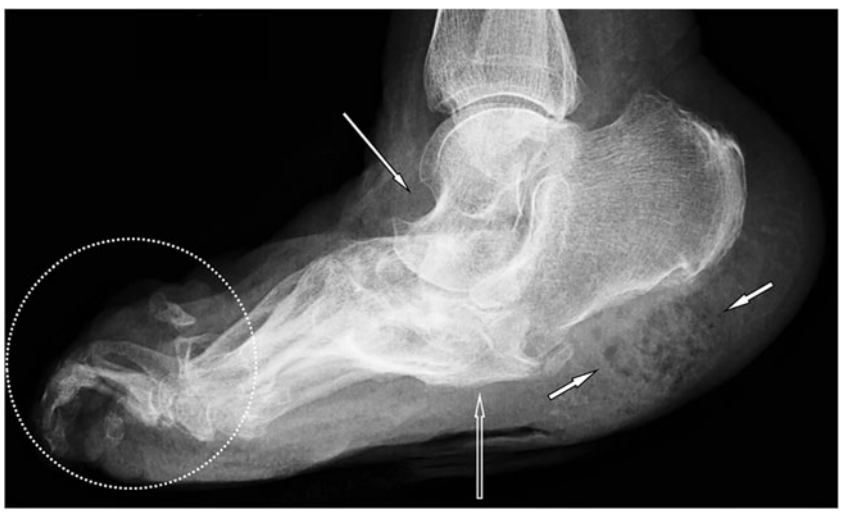

Fig. 2 Lateral radiograph of the right foot shows "rocker-bottom" deformity with talar plantarflexion (*arrow*), osseous and articular disorganization with midfoot collapse (*open arrow*). Note soft tissue gas beneath the calcaneus (*small arrows*), and dorsiflexion and luxation of the tapered toes combined with plantar subluxation of the metatarsal heads (*circle*)

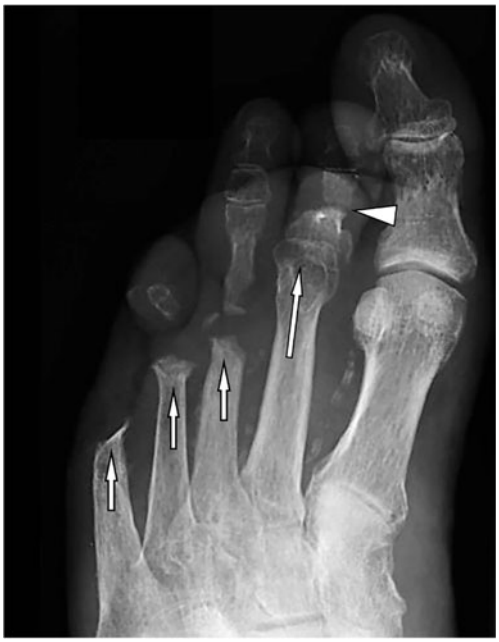

Fig. 3 Neuropathic osteoarthropathy in a 61-year-old diabetic man. Frontal radiograph shows forefoot osteolysis with typical "sucked candy stick" tapering of the third, fourth, and fifth metatarsal bones (*small arrows*). Osseous resorption and/or absence of the phalanges is also evident. Note the fracture of the second proximal phalange (*arrowhead*), and flattening of the second metatarsal head, which is often the first radiographic sign of diabetic neuropathic osteoarthropathy (*arrow*)

Radiography

Radiography is used as the first-line imaging modality in the diagnosis of neuropathic osteoarthropathy of a diabetic foot. The sensitivity of radiography, however, is very low for the acute condition (<50 %) [25, 40]; therefore, radiographic examinations of affected areas are often normal at the time of presentation. If radiographic changes are present, there may be focal demineralization, minimal soft-tissue swelling, subchondral fracture of the head of the second metatarsal, and slight resorption of bone around the affected joint [9, 10]. Radiographic findings in the chronic condition are more prominent and include bony fragmentation, debris formation, fractures, subluxation/dislocation, and then fusion of large fragments to adjacent bones, sclerosis of bone ends, osteophyte formation, and deformity (Figs. 1–4).

Weight-bearing radiography, which usually consists of anteroposterior and lateral radiographs of the foot and ankle, may provide information about abnormal alignment of bones due to peripheral neuropathy that may be missed by more advanced imaging. Furthermore, it is valuable in predicting foot ulcer and in the preoperative evaluation of deformity [41, 42]. Authors of several biomechanical and clinical studies [41–47] have reported the association of foot ulcer with several radiographic measures, assessed on lateral radiograph (Fig. 6). These measures include the talar–first metatarsal angle, the calcaneal–fifth metatarsal angle, the calcaneal pitch, the cuboid height, the talar declination angle, and the lateral tibiotalar angle. The talar–first metatarsal angle (Fig. 6) is measured by drawing a line bisecting the body and neck of the talus and a line bisecting the first metatarsal. The normal measurement ranges from 0 to 20°. When midfoot collapse exists, the talus rotates inferiorly to the axis of the first metatarsal, and the talar–first metatarsal angle is less than 0°. The calcaneal–fifth metatarsal angle (Fig. 6) is measured by drawing a line

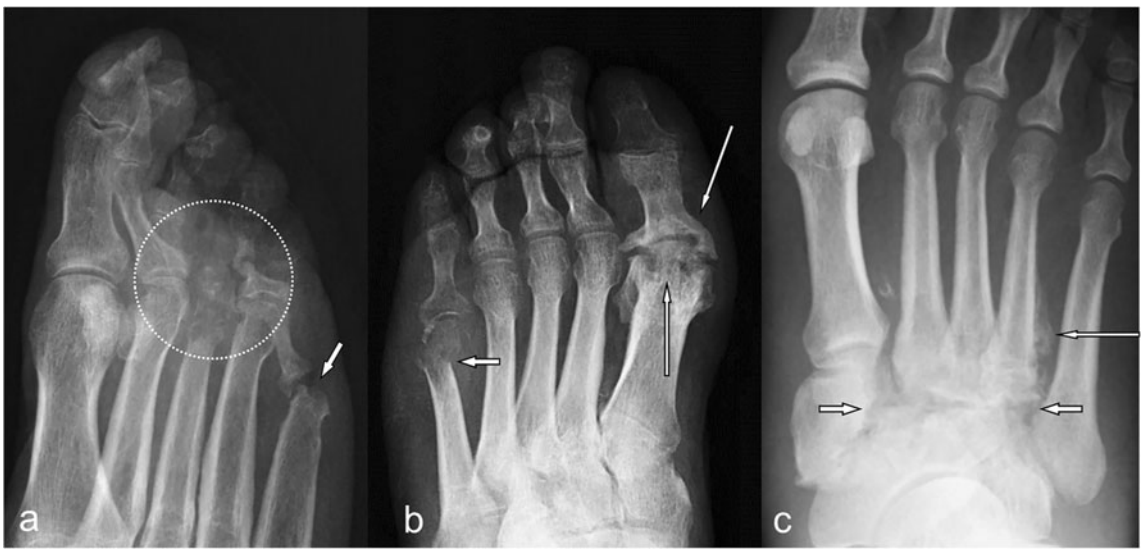

Fig. 4 Neuropathic osteoarthropathy in three diabetic patients. **a** Oblique view shows destruction, bone fragmentation, and dislocation of the third metatarsal–phalangeal joint (*circle*) and the typical "sucked candy stick" tapering of the fifth metatarsal bone (*arrow*). **b** Anteroposterior radiograph showing bone resorption, similar to septic arthritis, of the first metatarsal–phalangeal joint (*arrows*), and fracture of the fifth metatarsal bone (*small arrow*). **c** Anteroposterior radiograph shows resorptive changes at the tarsometatarsal joints with a Lisfranc pattern of fracture/dislocation (*small arrows*). Note also the periosteal new bone along the shaft of the fourth metatarsal bone (*arrow*)

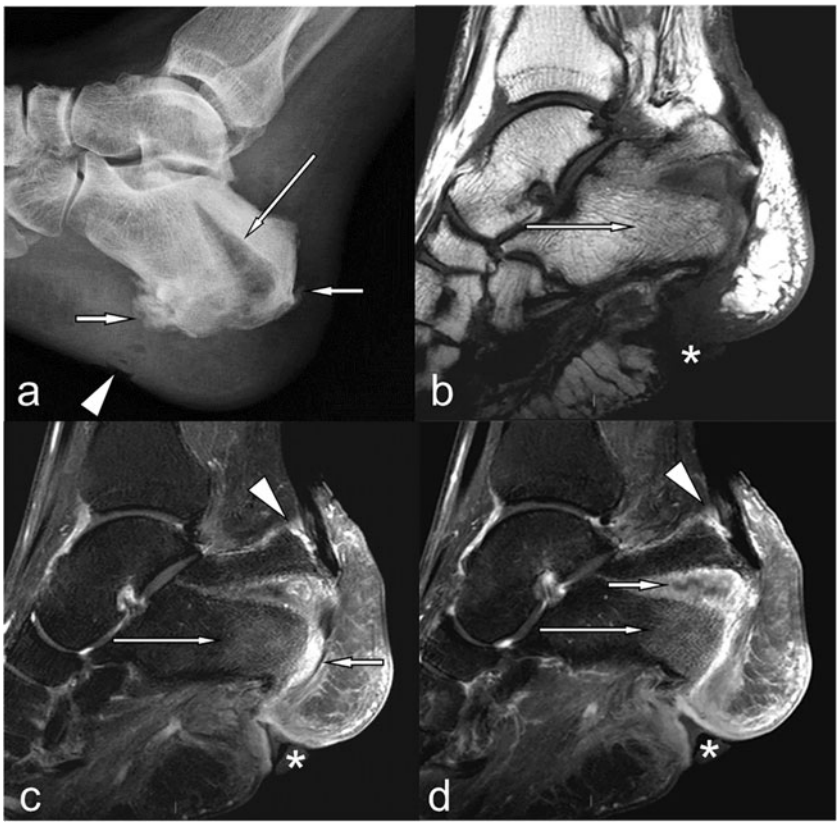

Fig. 5 Calcaneal insufficiency avulsion fracture extending to the plantar surface associated with osteomyelitis, heel ulcer, and sinus tract in a 66-year-old woman with an 18-year history of insulin-dependent diabetes. **a** Lateral radiograph clearly shows the calcaneal avulsion fracture (*arrow*) and the heel ulcer (*arrowhead*). Large calcaneal enthesophytes are also evident (*small arrows*). **b** Sagittal T1-weighted and **c**, **d** post-contrast T1-weighted fat-suppressed MR images show an enhancing deep sinus tract with "tram track" pattern extending down from the calcaneal fracture to the heel ulcer (*small arrow* in **c**), and better define the open heel ulcer, which is hypointense on the T1-weighted image, and enhances after the administration of contrast material (*asterisk* in **b**–**d**). Hypointensity (*arrow* in **b**) and post-contrast enhancement (*arrow* in **c**, **d**) in the calcaneus are indicative of osteomyelitis. Cranial displacement of the calcaneal avulsed fragment, Achilles tendinopathy with mild distention of the retrocalcaneal bursa (*arrowhead* in **c**, **d**), and soft-tissue inflammation deep to the sinus tract are also evident

bisecting the fifth metatarsal and a line extending from the most plantar aspect of the calcaneal tuberosity to the most plantar aspect of the anterior process of the calcaneus. Cuboid height (Fig. 6) is measured as the perpendicular distance from the plantar aspect of the cuboid to a line drawn from the plantar aspect of the calcaneal tuberosity to the plantar

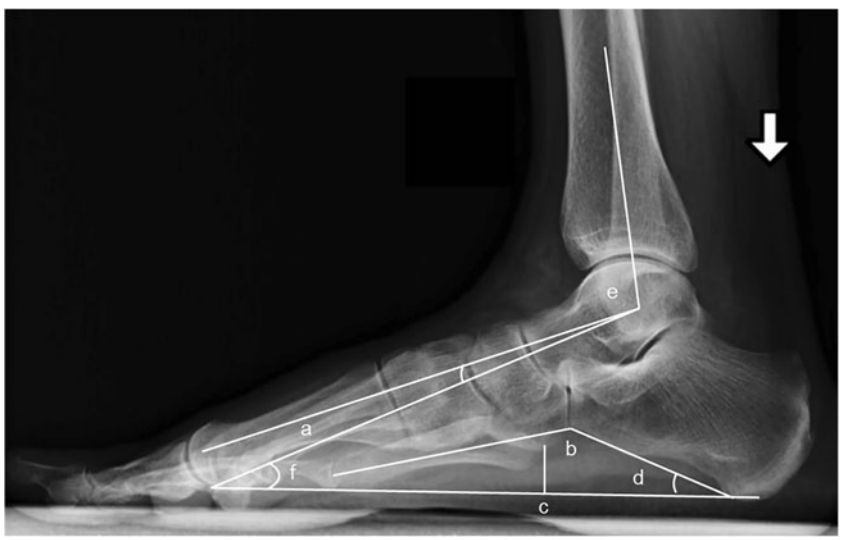

Fig. 6 Lateral weight-bearing radiograph of the foot showing the following radiographic measures that may be associated with foot ulcer: *a* the talar–first metatarsal angle, *b* the calcaneal–fifth metatarsal angle, *c* cuboid height, *d* calcaneal pitch *e* the tibiotalar angle, *f* the talar declination angle

aspect of the fifth metatarsal head. This distance is positive if the plantar cuboid remains dorsal to the reference line and negative if the plantar cuboid is plantar to this line. A decrease in the calcaneal–fifth metatarsal angle and a negative cuboid height manifest as lateral column involvement. Calcaneal pitch (Fig. 6) is defined as the angle between the line drawn from the plantar aspect of the calcaneal tuberosity to the plantar aspect of the fifth metatarsal head and a line extending from the plantar-most aspect of the calcaneal tuberosity to the plantar-most aspect of the anterior process of the calcaneus. Calcaneal pitch less than 10° is associated with calcaneocuboid subluxation/dislocation and lateral column malalignment. The tibiotalar angle (Fig. 6) is defined as the angle between the longitudinal axis of the tibia and a line bisecting the talar body and neck. This angle is normally close to 105°; a larger angle corresponds to the talar equinus because of an excessively plantar-flexed talus. The talar declination angle (Fig. 6) is measured by drawing a line bisecting the body and neck of the talus and a line extending from the plantar aspect of the calcaneal tuberosity to the plantar aspect of the fifth metatarsal head. Talar declination angles greater than 30° are typically associated with talonavicular joint subluxation/dislocation and the resultant medial column deformity.

The talocalcaneal angle (Fig. 7) is assessed on a weight-bearing anteroposterior radiograph and may be valuable in the preoperative evaluation of deformity, assessing the presence of hindfoot varus or valgus. This angle is formed by two lines bisecting the calcaneus and the body and neck of the talus respectively. The normal measurement ranges from 15° to 40°. If the angle decreases, the ankle is in hindfoot varus, and the calcaneus appears to be rotated medially. If the angle is increased to more than 40°, the ankle is in hindfoot valgus, and the calcaneus appears to be rotated laterally [40].

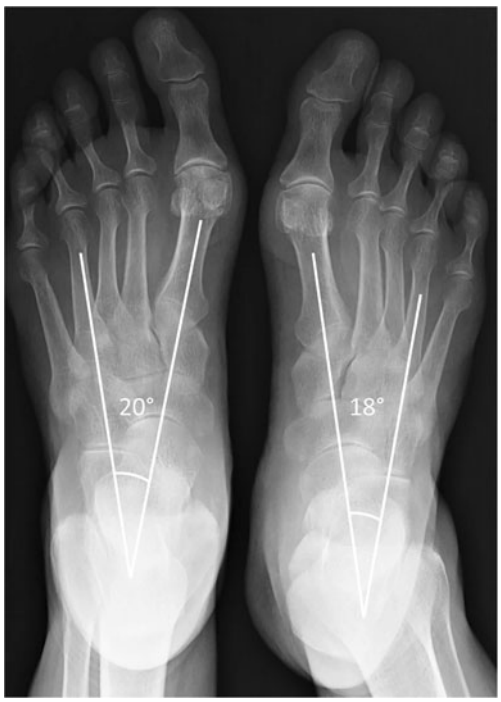

Fig. 7 Normal talocalcaneal angle on the anteroposterior weight-bearing radiograph of the foot in a 58-year-old diabetic man

CT

Early features of neuropathic osteoarthropathy, such as bone marrow edema and occult fractures, cannot be distinguished in a CT examination; therefore, there is no potential role for this imaging modality in the acute condition [48, 49]. Occasionally, and in the chronic condition, CT may be acquired for a preoperative detailed bone assessment [26].

MR imaging

Magnetic resonance imaging with fluid-sensitive, fat-suppressed sequences (i.e., short-tau inversion recovery [STIR] or fat-saturated T2-weighted images), is the most sensitive imaging modality in the detection of early changes of neuropathic osteoarthropathy, such as joint effusions, bone marrow, and soft-tissue edema [50]. Bone marrow edema is typically present, predominantly in the subchondral region, and is characterized by either focally or diffusely decreased signal intensity on T1-weighted images, and high signal intensity on both T2-weighted and fluid-sensitive images. Post-contrast MR imaging reveals enhancement of the bone marrow and periarticular soft tissue, on fat-suppressed T1-weighted images (Fig. 8) [2]. Bone bruise, without a history of trauma, may contribute to bone marrow signal changes that can lead to misinterpretation [51]. Bone bruise is the manifestation of trabecular microfractures associated with increased water in the extravascular compartment, resulting in edema. In the early stages of Lisfranc joint disease, MR imaging may depict disruption of the Lisfranc ligament that results in the malalignment and collapse of the longitudinal arch.

In chronic neuropathic osteoarthropathy, the altered bone marrow signal is represented by low signal in the subchondral bone on both T1-weighted and fluid-sensitive fat-suppressed images, a finding that correlates with osteosclerosis radiographically [49, 51]. Subchondral cysts are common and appear as well-marginated foci of low signal intensity on T1-weighted MR images and of high signal intensity on both T2-weighted and fluid-sensitive images [51]. Bone marrow and soft-tissue edema is less prominent or absent in the chronic form of neuropathic osteoarthropathy [52], whereas many articular MR signs, including effusion, subluxation, destruction, and bone proliferation are present, with debris or intra-articular bodies [49, 51].

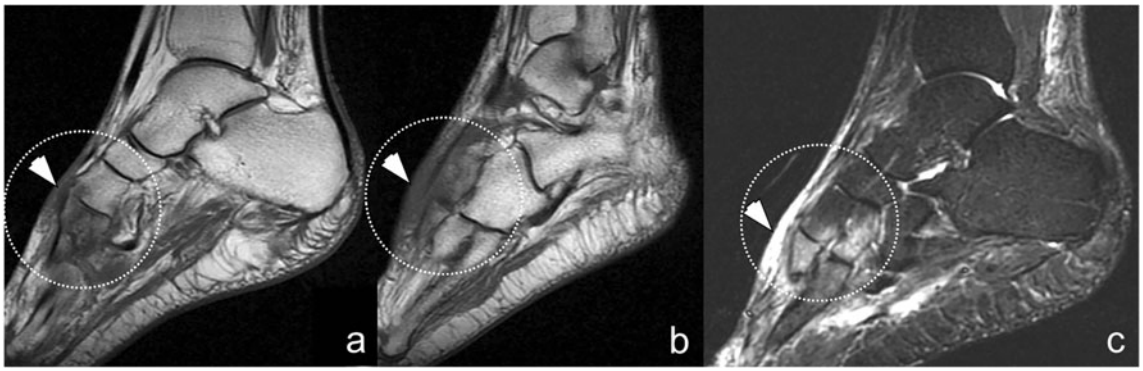

Fig. 8 Bone marrow edema in a 60-year-old diabetic woman with neuropathic osteoarthropathy. **a**, **b** Sagittal T1-weighted, and **c** short-tau inversion recovery (STIR) MR images show that the marrow in the tarsometatarsal region has a low signal intensity on the T1-weighted images, and a high signal intensity on the STIR image (*circle* in **a–c**). Adjacent cellulitis of the midfoot with loss of the normal subcutaneous fat signal is also evident (*arrowhead* in **a–c**)

Treatment

Offloading

Offloading of the affected foot is the cornerstone of therapy for acute neuropathic osteoarthropathy to relieve pain, prevent foot deformity, and reduce disease activity, which can be monitored by pain scores and by radiological and clinical assessment (skin temperature, erythema, and swelling) [25, 53, 54]. Offloading can consist of the use of a removable or non-removable device. Several offloading devices are available, such as walkers, half shoes, orthoses, removable cast walkers, and the total contact cast (TCC), which appears to be the most effective [28, 55–57]. The aim of the TCC is to reduce plantar pressures by increasing the weight-bearing surface of the foot. In addition to pressure reduction in acute neuropathic osteoarthropathy, the TCC has been proven to be an effective tool for healing plantar foot ulcerations [58–60]. Use of a TCC is usually continued for 8–12 weeks; however, the duration of casting is dependent upon ulcer healing and/or the resolution of swelling and the warmth of the affected foot. To avoid cast complications, such as dermal abrasions, frequent cast changing is recommended. Cast changing allows for inspection and proper care of the foot, and for adjustment for changes in foot size, according to the resolution of edema [61]. Pinzur et al. [62] recommended weight-bearing with biweekly cast changing for acute neuropathic osteoarthropathy. The location of the arthropathy also determines how long the TCC is indicated, as forefoot arthropathy heals faster than that of the ankle, midfoot, and hindfoot [63]. Although randomized clinical trials [58–60] have shown that a TCC can be an effective offloading modality in the treatment of neuropathic, noninfected ulcers, the combination of peripheral arterial disease and infection renders a poor prognosis, and alternative strategies should be sought. Nabuurs-Franssen et al. [64] found that only 36 % of patients with both peripheral arterial disease and infection healed with TCC. It is likely that the peripheral perfusion deficit resulted in impaired penetration of the antibiotics [65]. Furthermore, Wu et al. [66] found that CTT is actively used by less than 2 % of specialized centers. Most of the centers (73.4 %) used TCC in less than 25 % of their patients intermittently, and a further 45.5 % of centers reported not using TCC at all. This discrepancy between randomized controlled trials, and clinical reality may be secondary to several TCC disadvantages: fitting and preparing a TCC requires considerable time and expertise, new ulcers may occur, mobility is impaired, and daily wound care is not possible; therefore, TCC is often contraindicated in cases of soft-tissue infections or osteomyelitis. Furthermore, a prolonged casting has its related risks such as joint rigidity and muscular atrophy, and it is often very difficult for the patients to accept prolonged use of a cast, as they can be relatively asymptomatic.

Alternatively, removable cast walkers can be used. Several studies have shown that removable cast walkers are as effective as the TCC for offloading the plantar neuropathic ulcer, but the TCC heals a higher proportion of wounds in a shorter amount of time compared with the removable cast walker [67–69]. This is because of the difficulty of removing the TCC; therefore, the patient has little choice other than to adhere to the prescribed regimen.

When the acute phase of neuropathic osteoarthropathy has ended, the patient can be fitted with an ankle–foot orthosis or a custom-made shoe.

Pharmacological therapy

Intravenous bisphosphonates, including pamidronate and zoledronic acid, and intranasal calcitonin have been used in the treatment of neuropathic osteoarthropathy, because of the firm evidence that neuropathic osteoarthropathy is associated with increased osteoclastic activity [70, 71]. Bisphosphonates act by suppressing osteoclastic bone resorption and turnover [72]. Short-term results are promising, but these agents are not yet

recommended for routine use. TNF-α antagonists (infliximab, etanercept) and RANK-L antagonists (denosumab) have also been proposed [73], but further research is needed.

Surgery

Historically, surgery was considered in chronic conditions with nonplantigrade foot, severe dislocations, manifest or impending ulcers, instability, infection, or deformity that precluded the use of therapeutic footwear. Surgery during acute neuropathic osteoarthropathy has been a relative contraindication because of the increased risk of mechanical failure of fixation or wound infection when operating on an edematous limb. However, some centers advocate early surgical correction of deformity combined with arthrodesis, based on the assumption that early surgical intervention in high-risk patients may allow shorter periods of treatment at lower costs with an improved patient-perceived quality of life [74–76]. Other factors that should be considered when surgical intervention is indicated include: the patient's comorbidities, the vascular supply to the affected limb, the compliance, the patient's life expectancy, the location and severity of the deformity, and the ability of the contralateral foot to be the primary weight-bearing limb [77, 78].

The surgical procedures used are: excision of bony prominences to allow the use of appropriate footwear and reduce the chance of further foot ulceration [79]; realignment and arthrodesis, with internal or external fixation, of the destroyed joints to provide a functional foot and ankle [80, 81]; and amputation, which is a last resort in cases of failed previous surgery due to recurrent ulceration/infection or unstable arthrodesis. Achilles tendon lengthening combined with a TCC has been recommended in cases of recurrent plantar ulcerations and severe equinus deformity [82]. Lengthening of the Achilles tendon decreases the deforming forces at the midfoot and improves the alignment of the ankle and hindfoot to the midfoot and forefoot. Potential risks of surgery include long-term worsening of the condition, nonunion, infection, in addition to the general risks of surgery and anesthesia [25].

Osteomyelitis

Evaluation of the diabetic foot for osteomyelitis is frequently requested by clinicians concerned with initiating appropriate therapy such as antibiotics and surgical debridement, thereby avoiding future complications. The severity of the treatment makes the consequences of a false-positive diagnosis as lamentable for the patient as a missed diagnosis.

Nearly all diabetes-related foot infections originate from an infected foot ulcer. Thus, patients with a history or the presence of a local ulcer are at a high risk for osteomyelitis. The reference standard for diagnosis is histopathological and microbiological examination of bone specimens. Bone biopsy is valuable for establishing the diagnosis of osteomyelitis, for defining the pathogenic organism(s), and for determining the antibiotic susceptibilities of such organisms, but many clinicians consider bone biopsy an invasive procedure that puts patients at risk, and often rely on imaging studies to make the correct diagnosis. Inflammatory signs and symptoms may be blunted because of diabetes-related vascular insufficiency, and peripheral neuropathy. The following three clinical findings have been shown to increase the probability of osteomyelitis:

1. An ulcer with a cross-sectional area > 2 cm^2 (sensitivity of 56–88 % and specificity of 77–92 % in diagnosing osteomyelitis) [83, 84]
2. An ulcer with a depth > 3 mm [84]
3. An erythrocyte sedimentation rate > 70 mm/h [85]

In addition, a positive "probe-to-bone" test is of great diagnostic value, and efficient at detecting osteomyelitis in the diabetic foot [86–90]. "Probe-to-bone" test consists in exploring the wound for palpable bone with a sterile blunt metal probe. Contacting a bony surface or joint space (perceived as a hard, gritty surface) constitutes a positive "probe-to-bone" test. Some authors [86, 90] suggested that after a positive "probe-to-bone" test, the evaluation might proceed directly to microbiological and histological confirmation of osteomyelitis, and thereafter to treatment. In these patients, MR imaging may be performed to evaluate the extent of the disease rather than to make a diagnosis [5, 91]. However, it should be kept in mind that:

1. The presence of a skin ulcer has a relatively low positive predictive value for osteomyelitis
2. An erythrocyte sedimentation rate of more than 70 mm/h is highly specific for osteomyelitis, but has sensitivity of only 28 % [85]
3. A "probe-to-bone" test with a negative predictive value of 56 % [86] indicates that failure to contact bone during probing is inadequate for excluding osteomyelitis

Given this uncertainty, imaging is an essential part of the diagnostic evaluation of these individuals. A positive diagnostic imaging result increases the likelihood of osteomyelitis and vice versa, a negative diagnostic imaging result makes osteomyelitis much less likely [86]. Radiography and MR imaging are the most commonly used radiological modalities for evaluating the diabetic foot, although ultrasound and CT may provide additional information. F-18 fluorodeoxyglucose (F-18 FDG)-PET)/CT plays an increasing role and may redefine the noninvasive diagnostic work-up of diabetic foot complications.

Imaging features

Radiography

It is generally accepted that radiography has poor sensitivity to the early stages of osteomyelitis [85]. The radiographic findings of osteomyelitis, such as demineralization, bone resorption, cortical destruction, and periosteal reaction, do not generally become visible until the second or third week following bone infection. Furthermore, when radiographic changes are seen, they may be difficult to interpret, because similar abnormalities may occur with neuropathic osteoarthropathy or gout [25]. Thus, in patients with normal or indeterminate radiographic results, advanced imaging modalities may be needed. Nevertheless, radiography is useful, because, even when not diagnostic, it provides an anatomical overview of the area of interest and any preexisting conditions that might influence the selection and interpretation of subsequent procedures.

Ultrasound

Ultrasound can be used in providing guidance for periarticular aspirations or the removal of foreign bodies [92]; however, it is not currently recommended by the diabetic foot guidelines of the American College of Radiology [93, 94].

CT

Although CT is more sensitive than radiography and MR imaging in detecting cortical erosions, periosteal reaction, small sequestra, soft-tissue gas, and calcifications within sites of chronic osteomyelitis, its role in the imaging of diabetes-related foot complications is very limited.

MR imaging

Magnetic resonance imaging, which provides excellent spatial resolution and precise anatomical details is a powerful, non-invasive tool for determining the presence or absence of pedal osteomyelitis and soft-tissue infection [6], with sensitivity of 90 % and specificity of 83 % [93, 95]. MR imaging is widely accepted as the modality of choice for the assessment of osteomyelitis and associated soft-tissue complications. It also allows the preoperative mapping of the extent of infection and thus may help to minimize the area of resection. MR imaging protocols of the foot vary widely, as they should be tailored to the patient and the specific clinical concern. The field of view includes the area of concern and is usually limited to the forefoot, midfoot or hindfoot. Plane selection depends in part on the site of infection; however, a minimum of two planes should be obtained. The standard MR imaging protocol usually includes T1-weighted and fluid-sensitive fat-suppressed sequences obtained in the sagittal and coronal planes. The T1-weighted sequences allow excellent depiction of both normal and abnormal anatomy, whereas the fluid-sensitive, fat-suppressed sequences are better at demonstrating bone marrow and soft-tissue edema [6]. Midfoot neuropathic osteoarthropathy and hindfoot calcaneal ulcers are best depicted in the sagittal plane (Fig. 5). Medial or lateral ulceration in the hindfoot is best depicted in the coronal or axial planes (Fig. 9) [5]. Although the routine use of gadolinium has been debatable, post-contrast imaging improves the evaluation of soft-tissue complications such as sinus tracts, abscesses, and necrosis (Figs. 5, 10) [5, 6]. These findings are useful for augmenting diagnostic confidence when primary signs of osteomyelitis are equivocal [96]. Furthermore, the use of gadolinium provides invaluable information for the preoperative planning of limited limb resection, and for differentiating enhancing regions of viable bone and soft tissue from nonenhancing and nonviable regions [5]. Post-contrast examination often requires one sequence in each plane and an additional delayed sequence in the key plane. Obtaining this delayed sequence may be important because the slow blood flow may lead to false-negative features due to a lack of enhancement [5]. Obviously, contrast medium is contraindicated in diabetic patients with renal impairment because of the risk

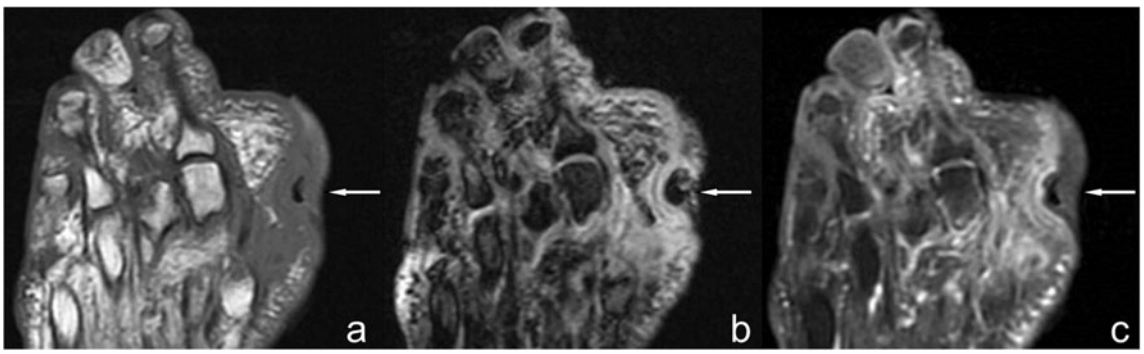

Fig. 9 Skin ulcer in a 66-year-old diabetic woman. **a**) Axial T1-weighted, **b**) T2-weighted fat-suppressed, and **c**) post-contrast, T1-weighted, fat-suppressed MR images show a plantar ulcer (*arrow* in **a–c**) along the medial aspect of the first metatarsophalangeal joint. The ulcer is hypointense on the T1-weighted image, hyperintense on the T2-weighted, fat-suppressed image, and enhances after the administration of contrast medium

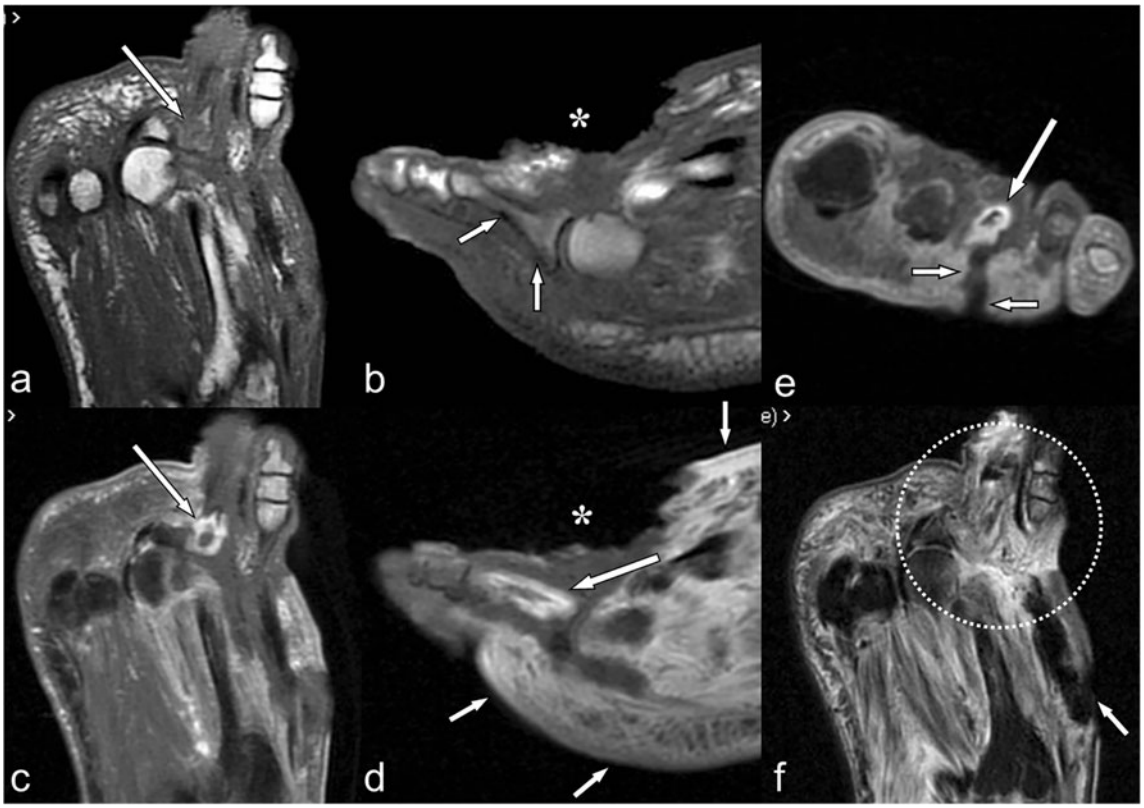

Fig. 10 Abscess and osteomyelitis in a 73-year-old diabetic woman who had undergone aggressive sharp debridement of her ulcers 2 days earlier. **a** Axial and **b** sagittal T1-weighted MR images, obtained at the level of the forefoot, show an extensive region of hypointensity in the marrow of the third proximal phalanx suggesting osteomyelitis (*arrow* in **a**, *small arrows* in **b**). **c** Axial, **d** sagittal, and **e** coronal, post-contrast, T1-weighted, fat-suppressed MR images show a thick rim enhancement of an intraosseous fluid collection (*arrow* in **c**–**e**) extending to the deeper aspect of a plantar ulcer (*small arrows* in **e**). The plantar aspect of the ulcer does not enhance because of recent debridement. Note diffuse swelling and post-contrast enhancement at the dorsal and plantar soft-tissue planes indicating cellulitis (*small arrows* in **d**), and a wide dorsal wound (*asterisk* in **b**, **d**). **f** Coronal T2-weighted fat-suppressed MR image shows soft-tissue and third proximal phalanx edema (*circle*), which is consistent with soft-tissue and bone infection, and better defines the extent of the ulcer, which interrupts the skin adjacent to the fifth metatarsal (*small arrow*). MR imaging helped to evaluate the residual extent of the foot infection. The patient ultimately underwent phalangeal amputation

of systemic fibrosis. On MR imaging, bone marrow with normal signal intensity excludes the diagnosis of osteomyelitis in diabetic patients with soft-tissue infection. Osteomyelitis is characterized by decreased marrow signal intensity on T1-weighted images, increased marrow signal intensity on fluid-sensitive, fat-suppressed sequences, and post-contrast enhancement (Fig. 10). However, these signal intensity abnormalities may mimic those of other conditions such as biomechanical stress changes related to altered weight-bearing, recent post-operative surgery, inflammatory arthritis, and neuropathic osteoarthropathy. In addition, these conditions may coexist with osteomyelitis, further complicating the ability to make an accurate diagnosis. As a result, marrow signal intensity changes in the foot with a noninfectious cause may simulate those seen in osteomyelitis or may be equivocal for the diagnosis of osteomyelitis. Articular MR findings such as joint effusion and enhancement, subluxation and dislocation, bone fragmentation and proliferation, erosion and destruction, and intra-articular bodies may be seen in septic arthritis and neuropathic osteoarthropathy [2]. However, several secondary signs, including periosteal reaction, subtending skin ulcer, sinus tract, abscess, tenosynovitis, or septic arthritis may help to confirm the diagnosis of osteomyelitis (Table 1).

Periosteal reaction is usually seen in the metatarsal bones and malleoli and appears as a thin, linear pattern of edema with post-contrast enhancement surrounding the outer cortical margin [6].

Foot ulcer typically appears as a focal skin interruption with peripheral post-contrast enhancement, a finding indicative of granulation tissue at the base of the ulcer (Fig. 9). In diabetic patients, ulcers are usually surrounded by a skin callus, which appears as a mass within subcutaneous fat, with low signal intensity on T1-weighted images and low to intermediate signal intensity on fluid-sensitive, fat-suppressed images [5, 6].

Sinus tracts are common in osteomyelitis with adjacent skin ulceration [96]. On MR imaging, they appear as linear fluid signal intensity on fluid-sensitive fat-suppressed images

Table 1 Relative utility of various clinical and MR imaging findings for establishing the diagnosis of osteomyelitis (Reflecting the authors' opinions based on the overall evidence of the exiting literature)

Finding	Relative utility
Low marrow signal intensity on T1-w images. High on fluid-sensitive sequences. Post-contrast enhancement	Equivocal[a]
Joint effusion and enhancement, subluxation and dislocation, bone fragmentation and proliferation, erosion and destruction, intraarticular bodies	Equivocal[b]
Periosteal reaction	*
Subtending skin ulcer	*
Ulcer cross-sectional area > 2 mm	**
Ulcer depth > 3 mm	**
Tenosynovitis	*
Focal involvement	*
Septic arthritis	***
The "ghost sign"	***
Sinus tract	***
Abscess	***
Positive "probe-to-bone" test	****
Erythrocyte sedimentation rate > 70 mm/h	**

[a] May be related to other conditions such as biomechanical stress changes, post-operative surgery, inflammatory arthritis, and acute neuropathic osteoarthropathy

[b] May be seen in septic arthritis and neuropathic ostheoarthropathy

*Minimum value

**Intermediate value

***High value

****Maximum value

or parallel lines of enhancement in a "tram-track" pattern on post-contrast, fat-suppressed images (Fig. 5). In a study by Morrison et al. [96], identification of a sinus tract in the soft tissues showed high specificity (average, 85 %) for the diagnosis of osteomyelitis in the adjacent bone. The simplest method of determining whether osteomyelitis is present is to track the ulcer or sinus tract down to the bone on MR imaging and evaluate the signal intensity of the marrow (Figs. 5, 10) [5].

Abscesses appear as localized, relatively well-marginated fluid collections within bone and/or soft tissues (Figs. 10, 11), usually, in close vicinity to the area of skin ulceration or along adjacent fascial planes. Signal intensity in such collections approximates fluid on fluid-sensitive, fat-suppressed images with thick rim post-contrast enhancement. The presence of rim enhancement, and mass effect allows abscesses to be distinguished from cellulitis or phlegmon, which present diffuse post-contrast enhancement (Figs. 8, 12). Abscesses often

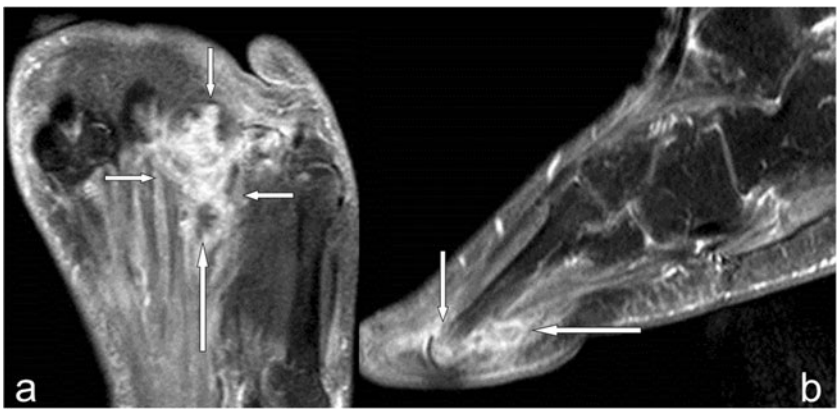

Fig. 11 Abscess and osteomyelitis in a 72-year-old man who had undergone phalangeal amputation. **a** Axial and **b** sagittal gadolinium-enhanced, T1-weighted, fat-suppressed MR images show diffuse contrast enhancement in the third metatarsal region due to soft-tissue infection (*small arrows* in **a**), contrast enhancement in the third metatarsal head indicative of osteomyelitis (*arrow* in **b**), and a plantar rim-enhancing abscess adjacent to the third metatarsal head (*long arrow* in **a**, **b**)

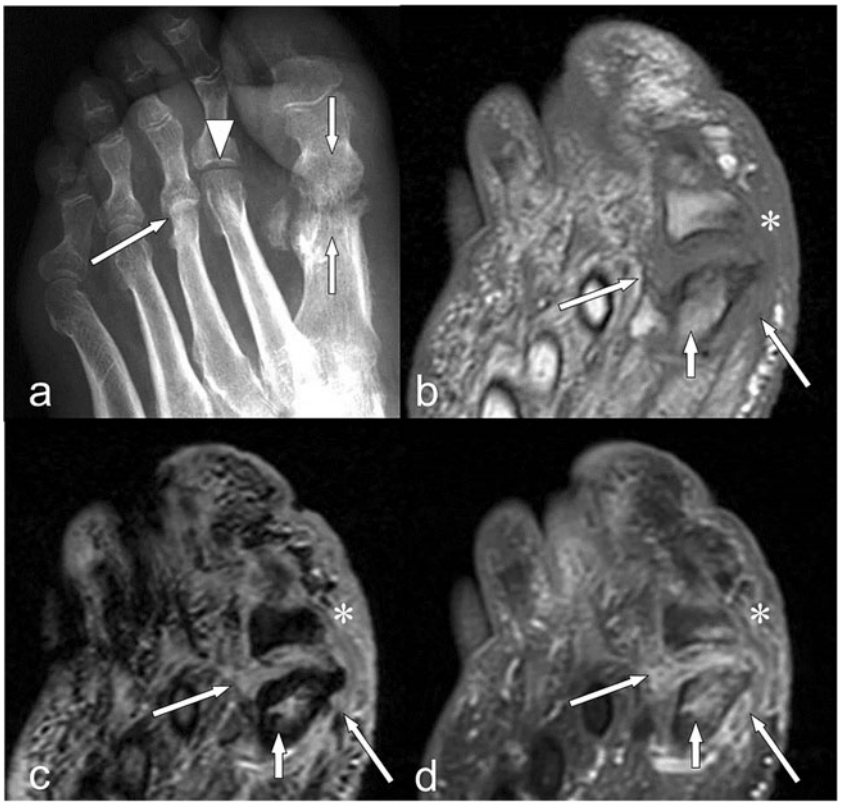

Fig. 12 Neuropathic osteoarthropathy and septic arthritis of the foot in the same patient as in Fig. 9. **a** Medial oblique radiograph shows destruction of the first metatarsophalangeal joint (*small arrows*), flattening of the head of the second metatarsal (*arrowhead*), and the "sucked candy stick" tapering of the third metatarsal bone (*arrow*). **b** Axial T1-weighted, **c** T2-weighted, fat-suppressed, and **d** post-contrast, T1-weighted, fat-suppressed MR images show plantar cellulitis (*asterisk* in **b–d**), effusion with an area of enhancement (*arrows* in **b–d**), and erosion in the first metatarsophalangeal joint, findings indicative of septic arthritis. The marrow abnormality is localized to the subarticular bone (*small arrow* in **b–d**). There is no associated osteomyelitis

communicate with sinus tracts that extend to bones, joints, tendon sheaths or skin ulceration [6].

Tenosynovitis typically occurs as a result of the contiguous spread of subcutaneous infection into the tendon sheaths. The presence of a small amount of fluid in the major tendon sheaths of the foot is common and may be seen in mechanical and traumatic disorders. An important and abnormal increase in fluid within the tendon sheath results in the thickening of the tendon and increased signal intensity on fluid-sensitive, fat-suppressed images, compared with the constant low signal intensity of the normal tendon. Post-contrast images may show a thick rim enhancement around the tendon, representing the proliferative, inflamed synovium.

Septic arthritis is a well-known complication of advanced diabetic foot infection and usually results from the contiguous spread from an ulcer or skin defect. It usually occurs in the metatarsophalangeal and interphalangeal; however, the ankle and subtalar joints may also be involved when malleolar or calcaneal ulceration is present. Diagnostic imaging plays an important role in both the diagnosis and the management of septic arthritis. However, radiography is of limited usefulness in the early diagnosis of this disease, and MR imaging changes such as increased joint fluid and synovial thickening with contrast enhancement appear to be nonspecific, overlapping with findings seen in other forms of inflammatory arthritis. At the same time, up to one third of patients who have septic arthritis may lack a joint effusion [97]. Although no single MR imaging feature can differentiate septic from nonseptic arthritis, concomitant bony erosions and marrow edema are highly suggestive of septic arthritis, and the added presence of soft-tissue edema, or bone marrow enhancement is even more suggestive of infection (Fig. 12) [98, 99]. In pedal infections, however, the diagnosis of septic arthritis with the use of MR imaging may be more specific, since ulceration and adjacent soft-tissue infection directly abut the joint, or, sinus tracts extend into the joint with obvious destruction of the joint itself.

It is important to distinguish reactive bone marrow changes that are secondary to septic arthritis from those associated with superimposed osteomyelitis. In cases in which bone marrow hyperintensity on fluid-sensitive, fat-suppressed images is not associated with hypointensity on corresponding T1-weighted images, bone marrow edema is more likely than osteomyelitis, even when bone marrow enhancement is present [100]. Furthermore, the greater the signal from the marrow on T2-weighted images, the more likely the bone is to be infected (Fig. 12).

Regarding the differentiation of osteomyelitis from neuropathic osteoarthropathy, the MR imaging features are useful in helping to differentiate these entities (Table 2):

1. The "ghost sign": bones that "disappear" on T1-weighted images and then "reappear" on contrast-enhanced or T2-weighted images (the ghost sign) likely have superimposed osteomyelitis (Fig. 13). In the

Table 2 Clinical and radiological features in neuropathic osteoarthropathy with or without superimposed osteomyelitis

Feature	Neuropathic osteoarthropathy	Infected neuropathic osteoarthropathy
Acute local inflammation	*(Acute)	*
Distribution	Intertarsal, tarso-metatarsal joints	Metatarsal heads, toes or calcaneus
Bony fragmentation, debris, fractures, subluxation/dislocation, sclerosis of bone ends, and osteophytes on radiography	*	
Deformity	*	*
Low marrow MR signal intensity on T1-weighted images, high on fluid-sensitive sequences, post-contrast enhancement	*(Acute)	*
Low marrow MR signal on both T1-weighted and fluid-sensitive images	*(Chronic)	
Subchondral cysts and intra-articular bodies on MR imaging	*	
Focal periarticular bone marrow involvement	*	
Diffuse bone marrow involvement		*
"Ghost sign"		*
Sinus tract formation, replacement of soft-tissue fat, diffuse marrow abnormality, thick rim enhancement or diffuse joint fluid enhancement, and joint erosion on MR imaging		*
Progression of bone erosions, disappearance of subchondral cysts or intra-articular bodies, increased bone marrow changes, and contrast enhancement of the articular surface on follow-up MR imaging of neuropathic osteoarthropathy		*

*Presence of the corresponding feature in neuropathic osteoarthropathy or infected neuropathic osteoarhropathy respectively

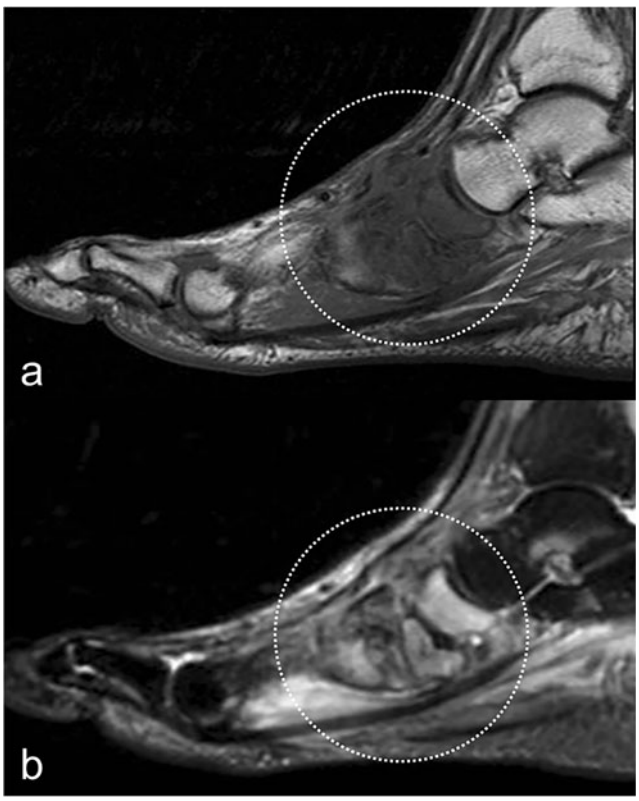

Fig. 13 Neuroarthropathy with superimposed osteomyelitis. **a** Sagittal T1-weighted MR image shows fragmentation and subluxation at the midfoot (*circle*). The osseous structures of the midfoot appear to be absent, and an extensive, diffuse area of hypointensity is seen. **b** Sagittal T2-weighted, fat-suppressed MR image shows the osseous structures of the midfoot, which appear more regular and better defined than in **a**. This appearance, which is known as the "ghost sign," is indicative of neuroarthropathy with superimposed osteomyelitis

neuroarthropathic foot, the ghost sign is absent because the bones are destroyed, not just edematous.

2. Bone marrow signal change: neuropathic osteoarthropathy is primarily an articular disease; thus, bone marrow involvement is limited to periarticular locations (Fig. 12), whereas the bone marrow changes associated with osteomyelitis tend to be more diffuse and are generally greater on one side of the joint.
3. Distribution: osteomyelitis is usually confined to a solitary site in the metatarsal heads, toes or calcaneus [6, 91]. In contrast, neuropathic osteoarthropathy occurs most frequently in the intertarsal and tarsometatarsal joints (60 % of cases), followed by the metatarsophalangeal joints of the forefoot (30 % of cases) [101].
4. Deformity: in osteomyelitis, there is usually no deformity unless there is an underlying neuropathic joint.

The differentiation of infected from non-infected neuropathic osteoarthropathy is extremely problematic; however, certain MR imaging findings may be useful for distinguishing between these two conditions (Table 2). Sinus tract formation, replacement of soft-tissue fat, diffuse marrow abnormality, thick rim enhancement or diffuse joint fluid enhancement, and joint erosion support superimposed infection [2]. Progression of bone erosions, disappearance of subchondral cysts or intra-articular bodies, increased bone marrow changes, and contrast enhancement of the articular surface should be suggestive of osteomyelitis on follow-up MR imaging of neuropathic osteoarthropathy [2, 6]. Regarding subchondral cysts and intra-articular bodies, Ahmadi et al. [2] investigated the

MR imaging of 128 neuropathic joints in 63 patients (43 with superimposed osteomyelitis) and found that intra-articular bodies were more common in noninfected joints (53 % vs 12 %), and subchondral cysts were seen almost exclusively in noninfected joints (76 % vs 2 %). The lower frequency of intra-articular bodies in infected neuropathic joints is unclear. It may be due to dissolution of the bodies after superinfection of the joint. The low incidence of subchondral cysts in the group with infection (and disappearance on follow-up images of neuropathic joints that became superinfected) is also unclear. The cysts may be obscured by the surrounding subchondral signal intensity in infection, or they could possibly have been destroyed by articular erosion. However, the presence of subchondral cysts and intra-articular bodies supports neuropathic osteoarthropathy alone, without infection. Bone marrow signal abnormalities without adjacent soft-tissue change are unlikely to represent infection. However, Ahmadi et al. [2] suggest that soft-tissue enhancement or the lack thereof might not be a good discriminator for distinguishing between infected and noninfected neuropathic joints, as it may be influenced by the degree of soft-tissue ischemia (false-negative finding in the setting of infection) or by hyperemia (false-positive finding in the setting of acute neuropathic osteoarthropathy).

Radionuclide imaging

Radionuclide imaging plays an important role in the evaluation of infection. Nevertheless, bone scintigraphy, the most frequently performed radionuclide modality (mainly to support a clinically suspected diagnosis, not as definitive as a noninvasive imaging modality), is highly sensitive, but quite nonspecific [102–104]. The sensitivity of a 3- (or 4-) phase bisphosphonate-linked technetium bone scan has been reported to range from 50 % [103] to 83 % [104]. Specificity, however, is poor (averaging 50 %) because of the uptake of the radiopharmaceutical at all sites of increased bone metabolism irrespective of the underlying cause [89, 101–103]. Given the low specificity of the bone scintigraphy, positive technetium bone scans do not increase the probability of disease very much and negative ones do not decrease it very much; therefore, its value as a diagnostic test is questionable [95].

The fusion of scintigraphic and morphological images, using hybrid single-photon emission computed tomography (SPECT)/CT, may offset the lack of spatial resolution of planar scintigraphy alone [105, 106], although evidence for this is at present limited. According to the current literature, the radiolabeled leukocyte imaging remains a key investigation in the assessment of infections complicating the diabetic foot [107–109]. The sensitivity and specificity of ^{99m}Tc-exametazime-labeled leukocyte planar imaging for diagnosing diabetic pedal osteomyelitis have ranged from 86 % to 93 % and from 80 % to 98 % respectively [107]. Hybrid imaging modalities, such as ^{99m}Tc-hexamethylpropylene amine oxime-labelled leukocyte SPECT/CT, are highly effective and improve the accuracy of radiolabeled leucocyte scintigraphy in diagnosing diabetic foot osteomyelitis and defining when infection has resolved with treatment [110]. However, the small size of the structures being evaluated, the intrinsically low resolution of these imaging modalities, and the limitations inherent in the in vitro labeling process (a time-consuming procedure requiring blood handling) have led to much interest being generated in evaluating F-18 fluorodeoxyglucose (F-18 FDG)-PET, alone, or as the functional component of F-18 FDG-PET/CT.

Positive emission tomography (PET) delivers high-resolution images using biologically active compounds labelled with positron emitters. F-18 FDG, a radiolabeled glycogen analog, is accumulated via glucose transporters in neutrophils, macrophages, and activated lymphocytes that present with increased intracellular glucose metabolism. The enhanced uptake of FDG in activated inflammatory cells is related to significantly increased levels of glycolysis as a result of increased numbers of cell surface glucose transporters, particularly after cellular stimulation by multiple cytokines [109, 111]. F-18 FDG is injected intravenously, and then the PET camera can identify hypermetabolic foci by detecting the positron emission of this radiolabeled tracer. A semi-quantitative analysis is performed by determining the standardized uptake value, which is related to the concentration of F-18 FDG in the hypermetabolic foci detected. Semiquantitative analysis could potentially be used to differentiate infectious from noninfectious conditions and to monitor response to treatment. Hyperglycemia has been long viewed as a main cause of false-negative F-18FDG-PET studies. Nevertheless, the quality of PET/CT images for assessing infection in diabetic patients is optimal when glycemic levels are lower than 200–250 mg/dL [109, 111–114], and the results of a recent study have found that the false-negative rates are not significantly different in patients with high versus normal serum glucose levels at the time of the study [114, 115]. F-18 FDG-PET combines many advantages when associated with CT: rapid diagnostic results, whole-body analysis, lack of metallic hardware artifacts, and the intrinsically high resolution. The latter allows the precise anatomical localization of radiotracer accumulation in structures as small as the distal forefoot, where the majority of diabetic foot infections occur [109]. F-18FDG-PET/CT may well emerge as the radionuclide investigation of choice for the complicating diabetic foot. However, it has the disadvantage of using ionizing radiation, is among the most expensive of the diagnostic modalities, and availability, although rapidly increasing, is still limited. Radiation-free assessment is becoming particularly important in the young population, and when repeated follow-up imaging is likely to be necessary. Whether the information derived from F-18FDG-PET/CT justifies the radiation exposure related to

the radiopharmaceutical administration requires additional investigation.

Gnanasegaran et al. [108] in 2012, Treglia et al. [116] in 2013, and Israel et al. [115] in 2014, in their reviews and/or meta-analyses of published data, demonstrated that current evidence on the utility of F-18FDG-PET/CT in the diabetic foot is controversial, as there are several positive papers but also others that are less conclusive. Kagna et al. [117] assessed the role of F-18FDG-PET/CT in the diagnosis of osteomyelitis in 39 patients with 46 suspected lesions of foot infection. The final diagnosis was based on histopathological and microbiological examination of bone specimens, imaging or clinical follow-up. The sensitivity, specificity, and accuracy, using lesion analysis, were 100 %, 93 %, and 96 % respectively. In a patient-based analysis, the sensitivity, specificity, and accuracy were 100 %, 92 %, and 95 % respectively. Basu et al. [118], using visual and semi-quantitative analysis, reported a superiority of F-18FDG-PET/CT compared with MR imaging in the setting of neuropathic osteoarthropathy by differentiating the uninfected neuropathic joint from soft-tissue infection and osteomyelitis in diabetic patients. The overall sensitivity and accuracy for F-18FDG-PET/CT in the diagnosis of neuropathic osteoarthropathy were 100 % (MR imaging 76.9 %) and 93.8 % (MR imaging 75 %) respectively. The same group [119] in a further prospective study on 110 patients, using visual analysis, reported a sensitivity, specificity, and accuracy of 81 %, 93 %, and 90 % respectively for the diagnosis of osteomyelitis related to diabetic foot. In view of its high specificity, the authors deemed F-18FDG-PET/CT to be a useful complementary imaging modality for use with MR imaging. Nevertheless, several studies have reported F-18FDG-PET/CT to be less useful and less sensitive in diagnosing pedal osteomyelitis in diabetes. Schwegler et al. [120] assessed the prevalence of clinically unsuspected osteomyelitis and compared the value of MR imaging, F-18FDG-PET, and ^{99m}Tc-labelled monoclonal anti-granulocyte antibody scintigraphy. They found MR imaging to be superior to F-18FDG-PET in detecting foot ulcer-associated osteomyelitis. F-18FDG-PET was positive in only 2 out of 7 cases with biopsy-proven osteomyelitis (29 % sensitivity), and its accuracy in detecting osteomyelitis was similar to that of ^{99m}Tc-labelled monoclonal antigranulocyte antibody scintigraphy. Although it is tempting to ascribe the low sensitivity reported by Schwegler et al. [120] to their use of PET rather than PET/CT, Familiari et al. [121], using visual and semi-quantitative analysis, found F-18FDG-PET/CT, even with sequential imaging at different times after tracer injection, to have a lower diagnostic accuracy for osteomyelitis compared with ^{99m}Tc-exametazime-labeled leucocyte scintigraphy. In this study, the accuracy and sensitivity were 54 % (^{99m}Tc-exametazime-labeled leucocyte scintigraphy 92 %) and 43 % (^{99m}Tc-exametazime-labeled leucocyte scintigraphy 86 %) respectively. Histopathological confirmation of the final diagnosis was available for all patients.

Thus, the current data on the role of F-18FDG-PET/CT in the evaluation of diabetic foot infections are very discordant. These discrepancies may be related to differences in study populations and variability in the methodology, interpretive criteria, and reference standards used; specifically, the presence or absence of vascular insufficiency, the lack of data on diabetes type or management in most series, the use of visual and/or semi-quantitative analysis, and inconsistent correlation with MR imaging. Therefore, more studies comparing 18F-FDG-PET/CT with other imaging modalities in patients with osteomyelitis complicating diabetic foot are warranted, in particular using bone biopsy as a reference standard [108, 116, 122].

In conclusion, MR imaging is now the noninvasive imaging tool of choice with high spatial resolution and the highest soft-tissue contrast for the assessment of osteomyelitis and associated soft-tissue complications. In the setting in which MR imaging is contraindicated or not conclusive, the high sensitivity and specificity of F-18FDG-PET/CT justifies its use to aid an accurate diagnosis. If clinical and imaging evaluation is not conclusive, or if the confidence that a patient has osteomyelitis is high, bone biopsy is recommended. Bone specimens can be obtained either percutaneously, under imaging guidance or by open surgery. Limitations of percutaneous and surgical bone biopsy include sampling error, difficulties in distinguishing other osteopathy from osteomyelitis histopathologically, and false-negative results, because of either patchy infectious involvement or previous antibiotic therapy [6].

Treatment

The choice of treatment for diabetic foot-related osteomyelitis is based on the site of infection, the local vascular supply, the extent of soft-tissue and bone involvement, the presence of necrosis, systemic signs of infection, and the clinician's and patient's preferences; however, the question of surgical versus nonsurgical treatment remains subject to debate [123]. Surgical resection of all necrotic and infected bone was traditionally considered the only definitive treatment of osteomyelitis and antibiotic therapy was largely considered adjunctive

Table 3 Situations in which the nonsurgical management of osteomyelitis may be considered (from the 2012 Infectious Diseases Society of America guidelines)

There is no acceptable surgical target (i.e., radical cure of the infection would cause unacceptable loss of function)
The patient has irreparable vascular disease and, therefore, ischemia, but wishes to avoid amputation
Infection is confined to the forefoot, and there is minimal soft-tissue loss
The patient and health care professionals agree that surgical management carries excessive risk

to surgery [124]. This belief has been challenged by several retrospective reports of treatment with prolonged (3–6 months) antibiotic therapy alone and a clinical success rate of 65–80 % [125–127]. Unfortunately, no controlled studies, whether randomized or not, directly compared outcomes of the two approaches.

Surgical procedures range from debridement and conservative surgery to amputation. Debridement consists of the removal of infected, devitalized, and/or necrotized soft tissue. Conservative surgery consists of procedures in which only infected bone and nonviable soft tissue are removed, but no amputation of any part of the foot is undertaken. Minor amputations consist of a partial amputation of the foot, not involving the ankle joint. Major amputations are those performed proximal to the ankle. The main argument used to justify the solely antibiotic treatment of osteomyelitis is the postsurgical changes of foot biomechanics that may result in new high-pressure areas and expose patients to the risk of re-ulceration [128, 129]. However, the Infectious Diseases Society of America guidelines [130] state that there are four situations in which the nonsurgical management of osteomyelitis may be considered (Table 3). Conservative surgery combined with antibiotics is an attractive option in treating diabetic foot osteomyelitis, but further research and well-designed clinical trials in particular are required to establish the relative importance of each approach [131]. At the clinical extremes (i.e., minimal or massive bone involvement), it is easy to decide whether the patient requires surgical debridement of the infected bone or amputation, but in most cases an individualized approach, in consultation with a multidisciplinary team, is recommended.

Conclusion

Neuropathic osteoarthropathy and osteomyelitis are processes that frequently overlap. Diagnosis is largely based on clinical signs supplemented by various imaging modalities. Familiarity with the advantages and disadvantages of each currently available imaging modality allows rapid initial diagnosis and prompt institution of treatment. With its increased general availability, MR imaging has shown utility in the evaluation and surgical planning of diabetes-related foot complications. However, speedy and effective care of the patients with these conditions requires regular screening, patient education, and a multidisciplinary team approach to management.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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