9 Other Complications of Diabetes

44 Foot Problems in Patients With Diabetes

Andrew J.M. Boulton

Department of Medicine, University of Manchester and Manchester Royal Infirmary, Manchester, UK and Miller School of Medicine, University of Miami, Miami, FL, USA

Keypoints

- Diabetic foot problems remain the most common cause of hospital admissions amongst patients with diabetes in Western countries.
- Up to 50% of older patients with type 2 diabetes have risk factors for foot problems.
- Up to 85% of lower limb amputations are preceded by foot ulcers.
- All patients with diabetes should be screened for risk of foot problems on an annual basis: those with risk factors require regular podiatry, patient education and instruction in self-foot care.
- Most foot ulcers should heal if pressure is removed from the ulcer site, the arterial circulation is sufficient and infection is managed and treated aggressively.
- Any patient with a warm unilateral swollen foot without ulceration should be presumed to have an acute Charcot neuroarthropathy until proven otherwise.

Introduction

"*Superior doctors prevent the disease. Mediocre doctors treat the disease before evident. Inferior doctors treat the full-blown disease.*" [Huang Dee, China, 2600 BC]

The Chinese proverb suggests that inferior doctors treat the full-blown disease, and until recent years, this was sadly the case with diabetic foot disease. Realizing the global importance of diabetic foot disease, the International Diabetes Federation (IDF) focused on the diabetic foot throughout the year 2005, during which there was a worldwide campaign to "put feet first" and highlight the all too common problem of amputation amongst patients with diabetes throughout the world. To coincide with World Diabetes Day in 2005, *The Lancet* launched an issue almost exclusively dedicated to the diabetic foot: this was the first time that any major non-specialist journal had focused on this worldwide problem; however, major challenges remain in getting across important messages relating to the diabetic foot:

1 Foot ulceration is common, affecting up to 25% of patients with diabetes during their lifetime [1].

2 Over 85% of lower limb amputations are preceded by foot ulcers and diabetes remains the most common cause of non-traumatic amputation in western countries [2].

3 Prevention is the first step towards solving diabetic foot problems. Although it was estimated that a leg is lost to diabetes somewhere in the world every 30 seconds, a more important fact is that up to 85% of all amputations in diabetes should be preventable [2].

4 Reductions in amputations will only be achieved if health care professionals from all specialties realize that, as Brand once stated, "pain is God's greatest gift to mankind": it is the loss of pain that permits patients with neuropathy to develop ulcers and continue walking on them despite the presence of often overwhelming infection [3].

5 Strategies aimed at preventing foot ulcers are cost-effective and can even be cost-saving if increased education and effort are focused on those patients with recognized risk factors for the development of foot problems [4].

6 Diabetes is now the most common cause of Charcot neuroarthropathy in Western countries, another condition that should be generally preventable [3].

Much progress in our understanding of the pathogenesis and management of the diabetic foot has been made over the last quarter century. This has been matched by an increasing number of publications in peer-reviewed journals. Taken as a percentage of all PubMed listed articles on diabetes, those on the diabetic foot have increased from 0.7% in the 1980–1988 period to more than 2.7% in the years 1998–2004 [3]. Prior to 1980, little progress had been made in the previous 100 years despite the fact that the association between gangrene and diabetes was recognized in the mid-19th century [5]. For the first 100 years following these descriptions, diabetic foot problems were considered to be predominantly vascular and complicated by infection. It was not until during the Second World War, for example, that McKeown performed the first ray excision on a patient with diabetes and osteomyelitis but good blood supply: this was performed under

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 44.1 Epidemiology of foot ulceration and amputation.

Authors [Ref]	Country	Year	N	Prevalence (%)		Incidence (%)		Risk factors for foot ulcers (%)
				Ulcers	Amputation			
Samann *et al.* [9]	Germany	2008	4778	0.8†	1.6	–	–	>40
Al-Mahroos & Al-Roomi [10]	Bahrain	2007	1477	5.9	–	–	–	45
Abbott *et al.* [11]	UK	2002	9710	1.7	1.3	2.2	–	>50
Manes *et al.* [12]	Greece	2002	821	4.8	–	–	–	>50
Muller *et al.* [13]	Netherlands	2002	665	–	–	2.1	0.6	–
Ramsay *et al.* [14]	USA	1999	8965			5.8*	0.9*	–
Vozar *et al.* [15]	Slovakia	1997	1205	2.5	0.9	0.6	0.6	–
Kumar *et al.* [16]	UK	1994	821	1.4†	–	–	–	42
Moss *et al.* [17]	USA	1992	2900	–	–	10.1‡	2.1‡	–

* Incidence figures over 3 years.
† Active ulcers: 5.4% past or current ulcer.
‡ Incidence figures over 4 years.

the encouragement of Lawrence, who had diabetes himself and was co-founder of the British Diabetic Association, now Diabetes UK [6].

In the last two decades many major national and international societies were formed including diabetic foot study groups and the international working group on the diabetic foot was established in 1991. New editions of two leading international textbooks on the diabetic foot have been published in recent years [7,8], and a number of collaborative research groups are now tackling many of the outstanding problems regarding the pathogenesis and management of diabetic foot disease.

In this chapter, the global term "diabetic foot" will be used to refer to a variety of pathologic conditions that might affect the feet of people with diabetes. Initially, the epidemiology and economic impact of diabetic foot disease are discussed, followed by the contributory factors that result in diabetic foot ulceration. The potential for prevention of these late sequelae of neuropathy and vascular disease are discussed, followed by a section on the management of foot ulcers. The chapter closes with a brief description of the pathogenesis and management of Charcot neuroarthropathy, an end-stage complication of diabetic neuropathy. Throughout, cross-referencing will be provided to other chapters that also cover aspects of diabetic foot disease, particularly those on diabetic neuropathy (see Chapter 38), peripheral vascular disease (see Chapter 43), bone and rheumatic disorders in diabetes (see Chapter 48) and infection (see Chapter 50).

Epidemiology and economic aspects of diabetic foot disease

As foot ulceration and amputation are closely inter-related in diabetes [2], they will be considered together in this section. A selection of epidemiologic data for foot ulceration and amputation, originating from studies from a number of different countries [9–17], is provided in Table 44.1. Globally, diabetic foot complications remain major medical, social and economic problems that are seen in all types of diabetes and in every country [18]; however, the reported frequencies of amputation and ulceration vary considerably as a consequence of different diagnostic criteria used as well as regional differences [19]. Diabetes remains a major cause of non-traumatic amputation across the world with rates being as much as 15 times higher than in the non-diabetic population.

Although many of the studies referred to and listed in Table 44.1 were well conducted, methodologic issues remain which make it difficult to perform direct comparisons between studies and/or countries. First, definitions as to what constitutes a foot ulcer vary and, secondly, surveys invariably include only patients with previously diagnosed diabetes, whereas in type 2 diabetes, foot problems may be the presenting feature. In one study from the UK, for example, 15% of patients undergoing amputation were first diagnosed with diabetes on that hospital admission [20]. Third, reported foot ulcers are not always confirmed by direct examination by the investigators involved in the study. Finally, as can be seen from the table, in those studies that assess the percentage of the population that had risk factors for foot ulceration, 40–70% of patients fell into that category. Such observations clearly indicate the need for all diabetes services to have a regular screening program to identify such high risk individuals.

Health economics of diabetic foot disease

In addition to causing substantial morbidity and even mortality, foot lesions in patients with diabetes additionally have substantial economic consequences.

Diabetic foot ulceration and amputations were estimated to cost US health care payers $10.9 billion in 2001 [21,22].

Corresponding estimates from the UK based upon similar methodology suggested that the total annual costs of diabetes-related foot complications was £252 million [23]; however, similar problems to those noted with epidemiology exist when comparing data on the costs of diabetic foot lesions relating to methodology but also as to whether direct and indirect costs were included. Moreover, few studies have estimated costs of the long-term follow-up of patients with foot ulcers or amputations [2].

The most recent data from the USA suggest that in 2007 $18.9 billion was spent on the care of diabetic foot ulcers, and $11.7 billion on lower extremity amputations [24]. Having estimated the total cost of diabetic foot disease to be $30.6 billion in 2007, the authors went on to estimate the potential savings based upon realistic reductions in ulceration and amputation, to be as high as $21.8 billion. Such strong economic arguments may help to drive improvements in preventative foot care which could potentially lead to significant savings for health care systems.

Etiopathogenesis of diabetic foot lesions

"Coming events cast their shadow before." [Thomas Campbell]

If we are to be successful in reducing the high incidence of foot ulcers and ultimately amputation, a thorough understanding of the pathways that result in the development of an ulcer is increasingly important. The words of the Scottish poet, Thomas Campbell, can usefully be applied to the breakdown of the diabetic foot. Ulceration does not occur spontaneously: rather it is the combination of causative factors that result in the development of a lesion. There are many warning signs or "shadows" that can identify those at risk before the occurrence of an ulcer. It is not an inevitable consequence of having diabetes that ulcers occur: ulcers invariably result from an interaction between specific pathologies in the lower limb and environment hazards. The breakdown of the diabetic foot traditionally has been considered to result from an interaction of peripheral vascular disease (PVD), peripheral neuropathy and some form of trauma. Other causes are also briefly described.

Peripheral vascular disease

Although described in detail in Chapter 43, brief mention of the role of PVD in the genesis of foot ulcers must be made here. PVD tends to occur at a younger age in patients with diabetes and is more likely to involve distal vessels. Reports from the USA and Finland have confirmed that PVD is a major contributory factor in the pathogenesis of foot ulceration and subsequent major amputations [25,26]. In the pathogenesis of ulceration, PVD itself in isolation rarely causes ulceration: as will be discussed for neuropathy, it is the combination of risk factors with minor trauma that inevitably leads to ulceration (Figure 44.1). Thus, minor injury and subsequent infection increase the demand for blood supply beyond the circulatory capacity and ischemic ulceration and the risk of amputation ensues. In recent years, neuroischemic ulcers in which the combination of neuropathy and PVD exists in the same patient, together with some form of trauma, are becoming increasingly common in diabetic foot clinics.

Diabetic neuropathy

As discussed in Chapter 38, the diabetic neuropathies represent the most common form of the long-term complications of diabetes, affect different parts of the nervous system and may present with diverse clinical manifestations [27]. Most common amongst the neuropathies are chronic sensorimotor distal symmetrical

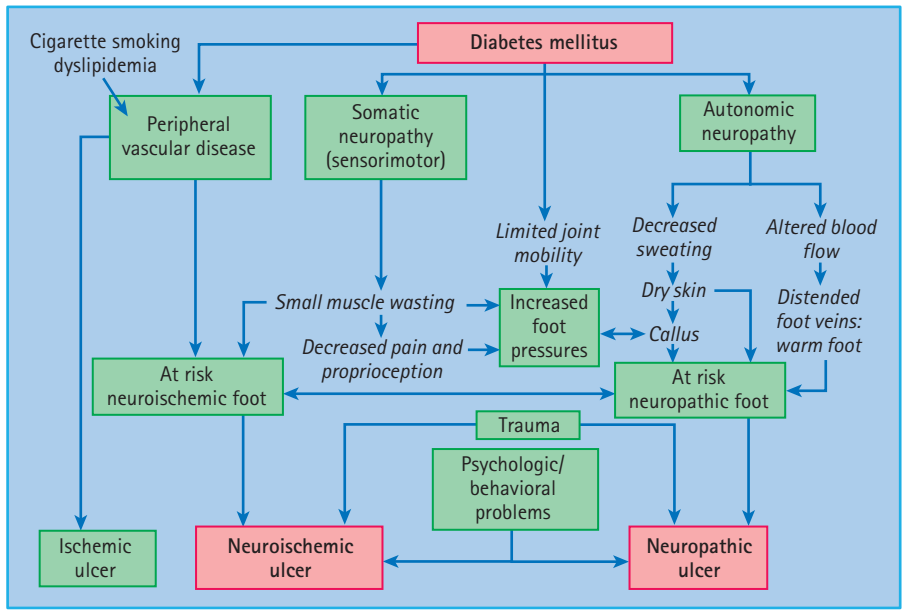

Figure 44.1 Pathways to foot ulceration in diabetes. Reproduced from Boulton *et al.* [7], with permission.

polyneuropathy and the autonomic neuropathies. It is the common sensorimotor neuropathy together with peripheral autonomic sympathetic neuropathy that together have an important role in the pathogenesis of ulceration.

Sensorimotor neuropathy

As noted in Chapter 38, this type of neuropathy is very common and it has been estimated that up to 50% of older patients with type 2 diabetes have evidence of sensory loss on clinical examination and therefore must be considered at risk of insensitive foot injury [27]. This type of neuropathy commonly results in a sensory loss confirmed on examination by a deficit in the stocking distribution to all sensory modalities: evidence of motor dysfunction in the form of small muscle wasting is also often present. While some patients may give a history (past or present) of typical neuropathic symptoms such as burning pain, stabbing pain, paresthesia with nocturnal exacerbation, others may develop sensory loss with no history of any symptoms. Other patients may have the "painful-painless" leg with spontaneous discomfort secondary to neuropathic symptoms but who on examination have both small and large fiber sensory deficits: such patients are at great risk of painless injury to their feet.

From the above it should be clear that a spectrum of symptomatic severity may be present with some patients experiencing severe pain and at the other end of the spectrum, patients who have no spontaneous symptoms but both groups may have significant sensory loss. The most challenging patients are those who develop sensory loss with no symptoms because it is often difficult to convince them that they are at risk of foot ulceration as they feel no discomfort, and motivation to perform regular foot self-care is difficult. The important message is that neuropathic symptoms correlate poorly with sensory loss, and their absence must *never* be equated with lack of foot ulcer risk. Thus, assessment of foot ulcer risk must *always* include a careful foot examination after removal of shoes and socks, whatever the neuropathic history [27].

The patient with sensory loss

A reduction in neuropathic foot problems will only be achieved if we remember that those patients with insensitive feet have lost their warning signal – pain – that ordinarily brings patients to their doctors. Thus, the care of a patient with sensory loss is a new challenge for which we have no training. It is difficult for us to understand, for example, that an intelligent patient would buy and wear a pair of shoes three sizes too small and come to the clinic with extensive shoe-induced ulceration. The explanation is simple: with reduced sensation, a very tight fit stimulates the remaining pressure nerve endings and is thus interpreted as a normal fit – hence the common complaint when we provide patients with custom-designed shoes that "these shoes are too loose". We can learn much about the management of such patients from the treatment of patients with leprosy [28]. Although the cause of sensory loss is very different from that in diabetes, the end result is the same, thus work in leprosy has been very relevant to our understanding of the pathogenesis of diabetic foot lesions. It was Brand (1914–2003) who worked as a surgeon and a missionary in South India, who described pain as "God's greatest gift to mankind" [29]. He emphasized the power of clinical observation to his students and one remark of his that was very relevant to diabetic foot ulceration was that any patient with a plantar ulcer who walks into the clinic without a limp must have neuropathy. Brand also taught us that if we are to succeed, we must realize that with loss of pain there is also diminished motivation in the healing of, and prevention of, injury.

Peripheral sympathetic autonomic neuropathy

Sympathetic autonomic dysfunction of the lower limbs leads to reduced sweating and results in both dry skin that is prone to crack and fissure, and to increased blood flow (in the absence of large vessel obstructive PVD) with arteriovenous shunting leading to the warm foot. The complex interactions of the neuropathies and other contributory factors in the causation of foot ulcers are summarized in Figure 44.1.

Other risk factors

Of all the other risk factors for ulceration (Table 44.2) one of the most important is a past history of similar problems. In many series this has been associated with an annual risk of re-ulceration of up to 50%.

Other long-term complications

Patients with other late complications, particularly nephropathy, have been reported to have an increased foot ulcer risk. Those most at risk are patients who have recently started dialysis as treatment of their end-stage renal disease [30]. It must also be remembered that those patients with renal transplants and more recently combined pancreas–renal transplants are usually at high risk of ulceration even if normoglycemic as a result of the pancreas transplant.

Table 44.2 Factors increasing risk of diabetic foot ulceration. More common contributory factors shown in bold.

Peripheral neuropathy
• **Somatic**
• **Autonomic**
Peripheral vascular disease
Past history of foot ulcers
Other long-term complication
• **End-stage renal disease**
• Visual loss
Plantar callus
Foot deformity
Edema
Ethnic background
Poor social background

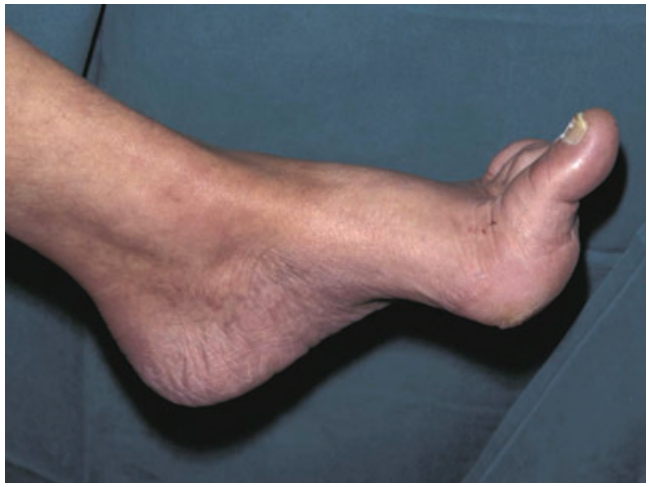

Figure 44.2 The high risk neuropathic diabetic foot demonstrating high arch, prominent metatarsal heads, clawing of toes and callus under first metatarsal head.

Plantar callus

Callus forms under weight-bearing areas as a consequence of dry skin (autonomic dysfunction), insensitivity and repetitive moderate stress from high foot pressure. It acts as a foreign body and causes ulceration [31]. The presence of callus in an insensate foot should alert the physician that this patient is at high risk of ulceration, and callus should be removed by the podiatrist or other trained health care professional.

Elevated foot pressures

Numerous studies have confirmed the contributory role that abnormal plantar pressures play in the pathogenesis of foot ulcers [3,32].

Foot deformity

A combination of motor neuropathy, cheiroarthropathy and altered gait patterns are thought to result in the "high risk" neuropathic foot with clawing of the toes, prominent metatarsal heads, high arch and small muscle wasting (Figure 44.2).

Ethnicity and gender

The male sex has been associated with a 1.6-fold increase of ulcers [11]. With respect to ethnic origin, data from cross-sectional studies in Europe suggests that foot ulceration is more common in Europid subjects than other racial groups: for example, the North-West Diabetes Foot Care Study in the UK showed that the age-adjusted prevalence of diabetic foot ulcers (past or present) for Europeans, South Asians and African-Caribbeans was 5.5%, 1.8% and 2.7%, respectively [33]. Reasons for these ethnic differences certainly warrant further investigation. In contrast, in the southern USA, ulceration was much more common in Latino Americans and Native Americans than in White people of Northern European ancestry [34]; however, more recent data confirmed this increased risk in Latinos, despite the foot pressures being actually lower in this group [35].

Pathway to ulceration

It is the combination of two or more risk factors that ultimately results in diabetic foot ulceration (Figure 44.1). Both Pecoraro *et al.* [25] and later Reiber *et al.* [36] have taken the Rothman model for causation and applied this to amputation and foot ulceration in diabetes. This model is based upon the concept that a component cause (e.g. neuropathy) is not sufficient in itself to lead to ulceration, but when the component causes act together, they result in a sufficient cause which will inevitably result in ulceration. Applying this model to foot ulceration, a small number of causal pathways were identified: the most common triad of component causes, present in nearly two out of three incident foot ulcer cases, was neuropathy, deformity and trauma. Edema and ischemia were also common component causes. Other simple examples of two component causeways to ulceration are loss of sensation and mechanical trauma such as standing on a nail, wearing shoes that are too small; or neuropathy and thermal trauma (e.g. walking on hot surfaces or burning feet in the bath); finally, neuropathy and chemical trauma may result in ulceration from the inappropriate use for example of chemical "corn cures." Similarly, this model can be applied to neuroischemic ulcers where the three component causes comprising ischemia, trauma and neuropathy are often seen.

Prevention of diabetic foot ulcers

Screening

It has been estimated that the vast majority of foot ulcers are potentially preventable, and the first step in prevention is the identification of the "at risk" population. Many countries have now adopted the principle of the "annual review" for patients with diabetes, whereby every patient is screened at least annually for evidence of diabetic complications. Such a review can be carried out either in the primary care center or in a hospital clinic.

A taskforce of the American Diabetes Association recently addressed the question of what should be included for the annual review in the "comprehensive diabetic foot examination (CDFE)" [37]. The taskforce addressed and concisely summarized the recent literature in this area and recommended, where possible using evidence-based medicine, what should be included in the CDFE for adult patients with diabetes. Whereas a brief history was regarded as important, a careful examination of the foot including assessing its neurologic and vascular status was regarded as essential. There is a strong evidence base to support the use of simple clinical tests as predictors of risk of foot ulcers [11,37]. A summary of the key components of the CDFE is provided in Table 44.3. Whereas each potential simple neurologic clinical test has advantages and disadvantages, it was felt that the 10-g monofilament had much evidence to support its use hence the recommendation that assessment of neuropathy should comprise the

Table 44.3 Key components of the diabetic foot examination.

Inspection

Evidence of past/present ulcers?

Foot shape?

- Prominent metatarsal heads/claw toes
- Hallux valgus
- Muscle wasting
- Charcot deformity

Dermatologic?

- Callus
- Erythema
- Sweating

Neurologic

10-g monofilament at four sites on each foot + 1 of the following:

- Vibration using 128 Hz tuning fork
- Pinprick sensation
- Ankle reflexes
- Vibration perception threshold

Vascular

Foot pulses

Ankle brachial index, if indicated

use of a 10 g monofilament plus one other test. In addition to those simple tests listed in Table 44.3, one possible test for neuropathy was assessment of vibration perception threshold. Although this is a semi-quantitative test of sensation, it was included as many centers in both Europe and North America have such equipment. As can be seen from Table 44.3, this is not regarded as essential, but strong evidence does support the use of vibration perception threshold as an excellent predictor of foot ulceration [38,39].

With respect to the vasculature, the ankle brachial index was recommended although it was realized that many centers in primary care may not be able to perform this in day-to-day clinical practice.

Intervention for high-risk patients

Any abnormality of the above screening test would put the patient into a group at higher risk of foot ulceration. Potential interventions are discussed under a number of headings, the most important of which is education.

Education

Previous studies have suggested that patients with foot ulcer risk lack knowledge and skills and consequently are unable to provide appropriate foot self-care [40]. Patients need to be informed of the risk of having insensate feet, the need for regular self-inspection, foot hygiene and chiropody/podiatry treatment as required, and they must be told what action to take in the event of an injury or the discovery of a foot ulcer. Recent studies summarized by Vileikyte *et al.* [41,42] suggests that patients often have distorted beliefs about neuropathy, thinking that this is a circulatory problem and link neuropathy directly to amputation. Thus, an education program that focuses on reducing foot ulcers will be doomed to failure if patients do not believe that foot ulcers precede amputations. It is clear that much work is required in this area if appropriate education is to succeed in reducing foot ulcers and subsequently amputations. The potential for education and self-care at various points on the pathway to neuropathic ulceration is shown in Figure 44.3.

There have been a small number of reports that assess educational interventions, but these have mostly been small single-center studies. In the most recently published study, even though the foot care education program was followed by improved foot care behavior, there is no evidence that such targeted education was associated with a reduced incidence of recurrent foot ulcers [43]. It has been suggested that patients find the concept of neuropathy difficult to understand: they are reassured because they have no discomfort or pain in their feet. It may be that using visual aids (which can also be used for diagnosis of the at risk foot) may help patients to understand that there is something different about their feet compared with their partner's, for example. This might include the use of the administered indicator plaster (Neuropad): when applied to the foot this changes color from blue to pink if there is normal sweating [44]. The absence of sweating such as in a high risk foot, results in no color change enabling patients to see that there is something different about their feet. A similar visual aid is the PressureStat (Podotrack) (Figure 44.4) [45]. This is a simple inexpensive semi-quantitative footprint mat that is able to identify high plantar pressures. The higher the pressure, the darker the color of the footprint. Similarly, this can be used as an educational aid and might help the patient realize that specific areas under their feet are at particular risk of ulceration.

In summary, foot care education is believed to be crucial in the prevention of ulceration, although there is little support for this from randomized controlled trials. Further studies in this area are therefore urgently required.

Podiatry/chiropody

Although not available in every country, regular nail and skin care from a podiatrist/chiropodist is essential in the high-risk neuropathic foot. Attempted self-care has been reported in several cases to cause ulceration and similarly self-care of calluses should be discouraged. Chiropodists and podiatrists should be attached to the foot care team if available and can also educate the patient while treating the feet.

Footwear/othoses/hosiery

Inappropriate footwear is a common cause of foot ulceration in insensitive feet, whereas good footwear can reduce ulcer occurrence [40]. This statement is supported by randomized controlled trials [46]. There is evidence from the literature also to support the use of specialist hosiery which might reduce foot pressures and give all round protection to high risk neuropathic feet [47,48].

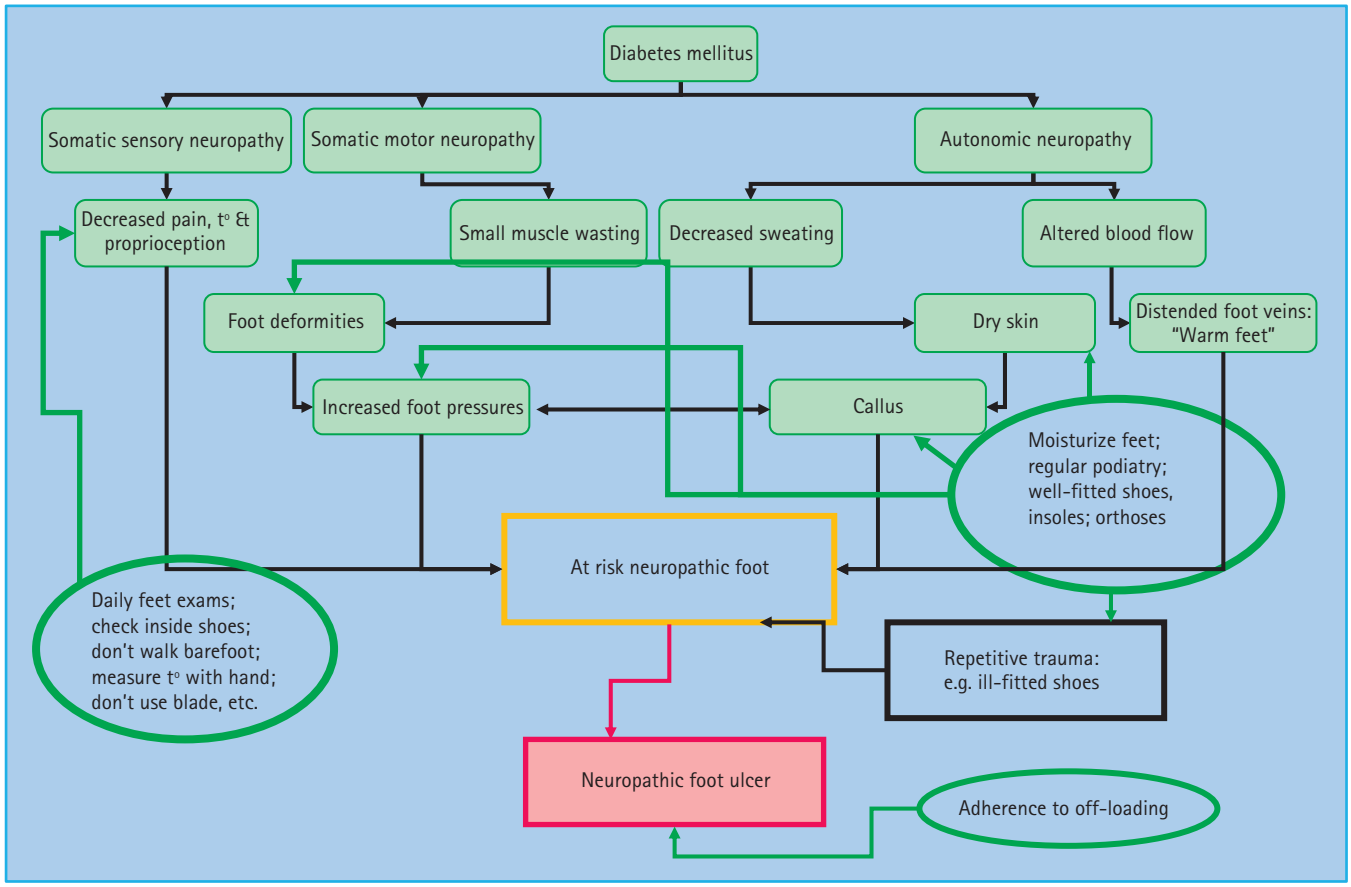

Figure 44.3 The potential for education and self-care in prevention of neuropathic foot ulcers. t°, temperature. Courtesy of L. Vileikyte MD, PhD.

Self-monitoring of skin temperature

It has been known for some time that prior to skin breakdown and ulceration, the involved area of the foot tends to warm up as a consequence of local inflammation. In an appropriately designed, randomized controlled trial, Lavery *et al.* [49] randomized patients with a history of neuropathic foot ulceration to one of three groups, the main intervention being self-monitoring of skin temperature of both feet: those patients who received this skin temperature thermometer were advised to rest or contact their foot clinic should there be a maintained difference in temperature between the two feet. This study clearly showed that those patients who monitored their skin temperatures and followed the advice had a markedly reduced incidence of recurrent ulceration (8% vs 30%). Thus, infrared temperature home monitoring might help to identify the "pre-ulcerative" foot and permit intervention prior to actual skin breakdown. A more recent study has provided further support for this notion [50].

Injected liquid silicone

Injected liquid silicone under high pressure areas of the diabetic foot has been used for some years in the USA and is supported by a randomized controlled trial [51] which confirmed that those patients receiving active agent had reduced foot pressures and increased subcutaneous tissue under the high pressure areas of the forefoot. This therapy is now available in certain European countries, and a follow-up study [52] confirmed that the effect of this "injectable orthosis" lasts for up to 2 years, although booster injections may be required from time to time.

Foot ulcers: diagnosis and management

Foot ulcer classification

Despite increasing efforts in the early identification and preventative foot care education of high risk patients, foot ulcers continue to be a major issue in diabetes management and may indeed be the presenting feature of type 2 diabetes. The principles of management depend up a careful assessment of the causative factors, the presence or absence of infection, the degree of neuropathy and/or ischemia in the foot. Before discussing the management of specific types of ulcers, it is important to consider how to classify foot lesions. Numerous classification systems for diabetic foot ulcers have been proposed [53] but only a few are described here.

The most widely used foot ulcer classification system worldwide at the time of writing is the Meggitt–Wagner grading, as shown in Table 44.4. Despite its wide use, this system does lack

specificity and it does not refer to the neuropathic, ischemic or infective status of the ulcers.

The newer University of Texas (UT) wound classification system is currently widely used (Table 44.5) [54]. This is based upon the Meggitt–Wagner system but with the addition of grades of ulcers and stages each grade for the presence or absence of infection and ischemia. In a comparative study of these two systems, the UT system was shown to be a useful predictor of outcome although the Meggitt–Wagner system was still confirmed to be useful [55]. A high risk foot with pre-ulcerative lesions (Wagner 0, UT1A) is shown in Figure 44.5. The two more recently described classification systems, S(AD) SAD system, (size (area, depth), sepsis, arteriopathy and denervation) and the PEDIS (perfusion, extent, depth, infection, sensation) systems appear to have some advantages over the earlier systems, but are not in widespread use [53]. Thus, the UT system will be used to describe ulcer classification here.

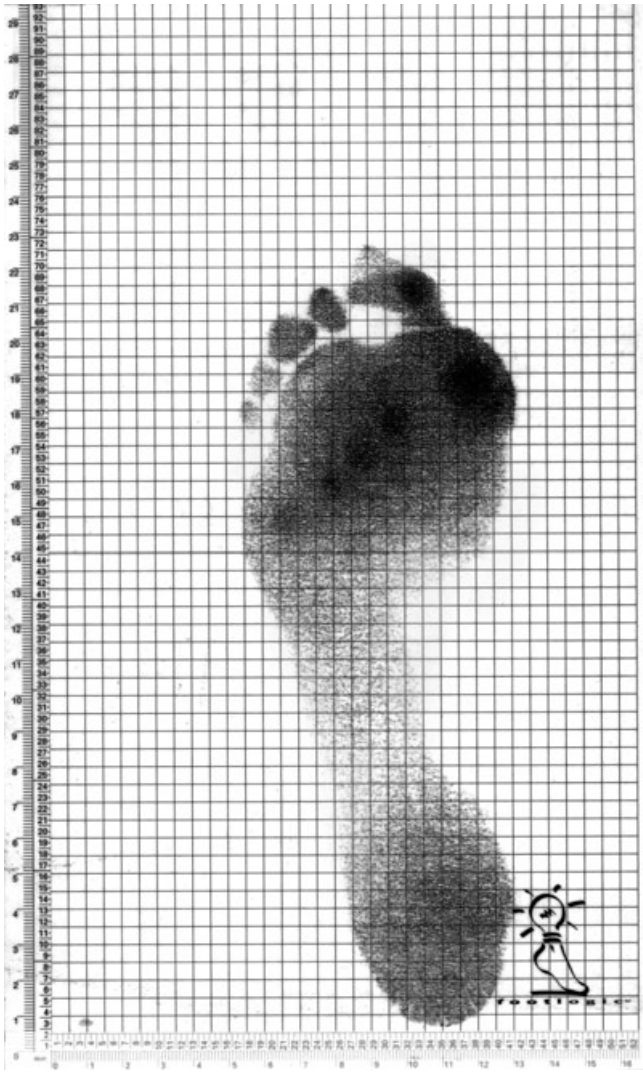

Figure 44.4 A black and white pressure distribution of one footstep using PressureStat: the darkest areas represent highest pressures, in this case under metatarsal heads 1 and 3 and the hallux.

Wound healing in the diabetic foot

Wound healing is a tissue response to injury and passes through the phases of inflammation, chemotaxis, cellular proliferation, extracellular matrix deposition and finally wound remodeling and scarring. Diabetes may influence foot wound healing in a number of different ways including an impairment of the peripheral circulation, altered leukocyte function, disturbed balance of cytokines and proteases and even chronic hyperglycemia itself [3,56]. Thus, foot ulcers in patients with diabetes are recalcitrant to healing because of many cellular and molecular aberrations. When compared with normal acute wound healing, chronic foot ulcers are often stalled in the chronic inflammatory phase with impaired granulation tissue formation. A key question is therefore: is there a fundamental impairment of wound healing in diabetes, and if so, what are the molecular/cellular impairments and are they specific to chronic wounds? A number of studies have reported abnormalities in cytokines and growth factors in tissue from chronic diabetic foot ulcers [57–59]. Most recently, it has been suggested that levels of matrix metallopro-

Table 44.4 Meggitt–Wagner classification. Modified from Oyibo *et al.* [55].

Grade 0	No ulcer, but high risk foot (deformity, callus, etc)
Grade 1	Superficial ulcer
Grade 2	Deep ulcer, may involve tendons but not bone
Grade 3	Deep ulcer with bone involvement, osteomyelitis
Grade 4	Localized gangrene (e.g. toes)
Grade 5	Gangrene of whole foot

Table 44.5 The University of Texas ulcer classification system.

Stage	Grade			
	0	1	2	3
A	High risk foot: no ulcer	Superficial ulcer	Deep ulcer to tendon/capsule	Wound penetrating bone/joint
B	+Infection	+Infection	+Infection	+Infection
C	+Ischemia	+Ischemia	+Ischemia	+Ischemia
D	+Infection and ischemia	+Infection and ischemia	+Infection and ischemia	+Infection and ischemia

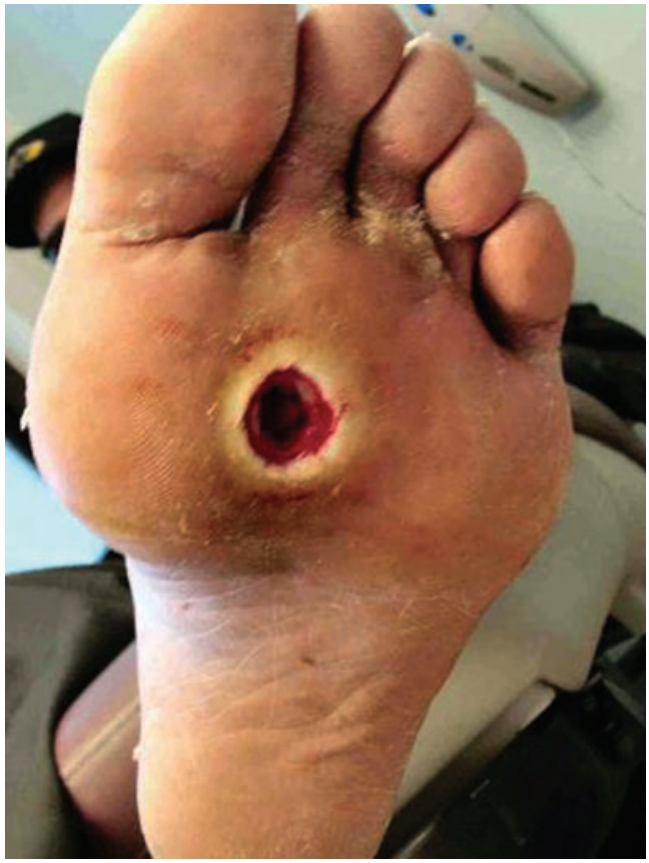

Figure 44.5 Wagner grade I ulcer, UT1A foot ulcer, showing a rim of callus and a punched out neuropathic ulcer in the metatarsal head region with no evidence of infection.

teinases (MMP) are important in predicting the likelihood of wound healing and a high level of MMP-1 seems essential to wound healing [59].

Another contributory factor to impaired wound healing in diabetes appears to be repetitive pressure on the wound. The pivotal role of offloading is therefore considered in the next section.

Offloading

A normal individual with a foot wound will limp: it has been known for some time that neuropathic plantar foot wounds will heal satisfactorily when offloaded in a Total Contact Cast (TCC) [3]. The principle of TCC management is that pressure is mitigated but, in addition, the device is irremovable thus enforcing compliance with therapy. A number of randomized controlled trials have compared the TCC with other removable offloading devices in plantar diabetic foot ulcers and invariably, healing is most rapid in those randomized to TCC treatment [3,60]. As it is known that the Removable Cast Walkers (RCW) redistribute pressure in a similar manner to the TCC, however, the question remained as to why the TCC usually demonstrated superiority in terms of speed of wound closure. The most likely explanation which is that of patient non-compliance, was confirmed in a study of 20 subjects with plantar neuropathic diabetic foot ulcers who were provided with RCWs and their total activity was recorded both from the waist, and from an activity monitor hidden in the RCW. It transpired that patients only wore the RCW for 28% of all footsteps [61]. Subsequent to this observation, it was proposed that an RCW might be rendered irremovable by wrapping it with one or two bands of plaster of Paris, therefore addressing most of the disadvantages of the TCC but preserving irremovability. A subsequent randomized controlled trial of this modified, irremovable RCW versus the TCC showed that healing times were identical [62].

The impact of appropriate offloading on the histopathologic features of neuropathic diabetic foot ulcers was reported by Piaggesi *et al.* [63]. These authors confirm that appropriate offloading resulted in the foot wound appearing more like an acute wound with reparative patterns, angiogenesis and fibroblast proliferation and the presence of granulation tissue. In contrast, biopsies from wounds that had not previously been offloaded confirmed the presence of hyperkeratosis, fibrosis and chronic inflammation. These observations certainly suggest that appropriate offloading is associated with change in the histology of neuropathic foot ulcers including the reduction of inflammatory and reactive components and the acceleration of wound healing.

Another important consideration is the importance of emotional distress (e.g. depression and anxiety) on wound healing in patients with diabetes [64]. Such effects may have direct and indirect effect on wound healing. The direct effects include altered catecholamine and steroid secretion in addition to an imbalance of cytokines which might directly impair wound healing. Indirectly, those patients who are depressed, for example, are less likely to adhere to treatment advice such as wearing an RCW at all times when walking. These important observations have previously been neglected by clinicians and if any patient with a plantar foot ulcer treated by an RCW shows no sign of healing, consideration should be given to compliance and the possibility of rendering the RCW irremovable as noted above.

As might be deduced from the above discussion, offloading is an essential component to the management of predominantly neuropathic plantar foot ulcers. This would include most UT 1A and 2A ulcers. Casts may also be used in the presence of localized infection in neuropathic foot ulcers (Figure 44.6). There is also evidence to support the use of offloading devices in the management of neuroischaemic ulcers but only if they are not clinically infected (UT 1C, 2C) [65].

For those patients treated with irremovable cast walkers, it is recommended that the cast be removed initially on a weekly basis for wound assessment, débridement and cleansing. Healing can generally be a achieved in a period of 6–12 weeks in a cast: it is strongly recommended that after the plantar wound has healed, that the cast be worn for a further 4 weeks to permit the scar tissue to firm up. Thereafter, the patient may be gradually transferred to appropriate footwear which may need extra depth or in the case of severe deformity, custom moulded.

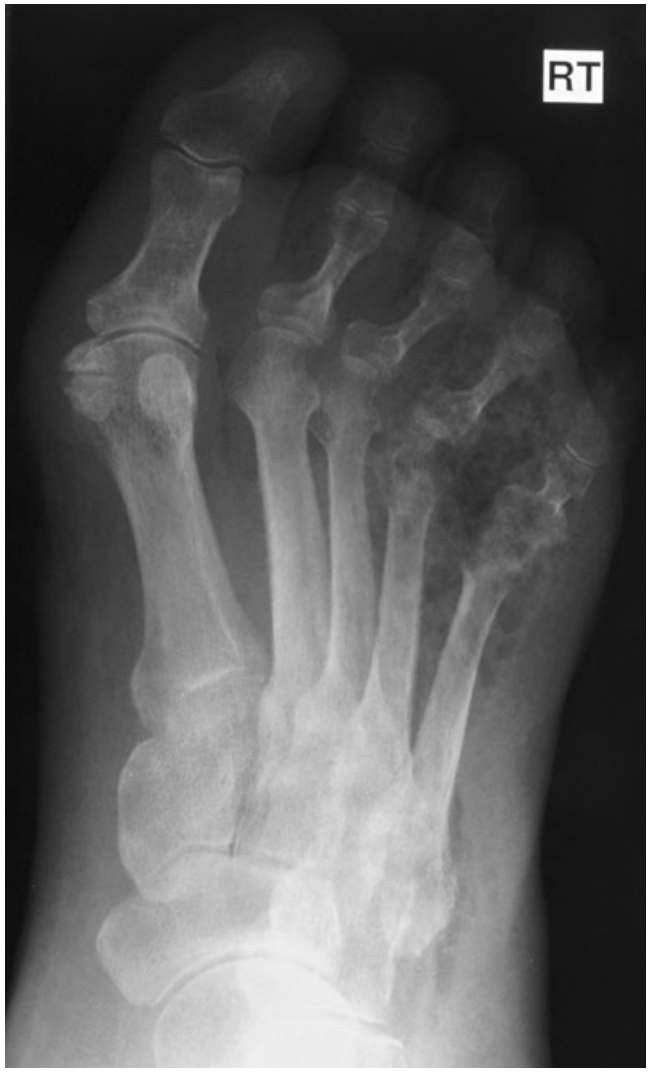

Figure 44.6 Radiograph from a patient with a deep neuropathic ulcer under the right fifth metatarsal head. Gas in the tissues is not uncommon in radiographs of neuropathic foot ulcers as patients lacking pain sensation are able to walk despite the ulcer, "pumping" gas into the tissue. In this example, however, the gas makes it difficult to assess whether osteomyelitis is present.

Dressings

The danger of dressings and bandages is that some health care professionals may draw from them a false sense of security, believing that by dressing an ulcer they are curing it. Nothing could be further from the truth for a neuropathic ulcer. The three most important factors in the healing of a diabetic foot ulcer are: freedom from pressure, freedom from infection and good vascularity. The purpose of dressings is to protect the wound from local trauma, minimize the risk of infection and optimize the wound environment which should be moist in most cases. The evidence base to support the choice of any particular dressing is woefully inadequate with few trials generally hampered by small numbers, inappropriate comparators and poor study design [66,67]. There is little evidence that any specific dressing will have a major impact on the rate of wound healing.

Management of infection

One of the first steps in the management of a foot ulcer is to determine whether infection is present or not: remember that all foot ulcers are colonized with potentially pathogenic organisms and it is generally accepted by the international working group on the diabetic foot that the diagnosis of infection in the diabetic foot ulcer remains a clinical one [68]. Thus, the presence of signs such as purulent discharge, erythema, local warmth and swelling which suggests infection requiring appropriate treatment.

Clinically non-infected ulcers

Where ulcers are not infected and predominantly neuropathic (UT grades 1A, 2A), the use of antibiotics may be withheld as Chantelau *et al.* [69] have shown that with appropriate wound management, patients do equally well with or without systemic antibiotics in a randomized controlled trial. Nevertheless, frequent review, débridement and callus removal together with offloading are essential parts of management of neuropathic foot ulcers and should signs of infection develop, antibiotics may be needed. For those ulcers with an ischemic component which do not have gross signs of infection (UT 1C, 2C) antibiotics should probably be given in most cases as the combination of infection and ischemia in the diabetic foot are a common cause of ultimate lower extremity amputation.

Clinically infected ulcers

Non-limb-threatening infected ulcers (UT 1B, 1D, 2B, 2D) can generally be treated on an outpatient basis, and oral broad-spectrum antibiotics should be used initially until results of sensitivities are obtained. As reviewed by Lipsky, two sets of international guidelines have been published in recent years [68,70,71]. One important aspect of these recent guidelines has been the development of criteria by which to classify the severity of a diabetic foot infection. Generally, mild infections are relatively superficial and limited, moderate infections involve deeper tissues and severe infections are accompanied by systematic signs or symptoms of infection or metabolic disturbances [68]. Any ulcer with clinical evidence of infection should have tissue taken and sent for culture and sensitivity in the microbiology department. Although superficial swabs are commonly taken, deep (preferably tissue) specimens are preferable in terms of accuracy of diagnosis [68]. Most infective ulcers are polymicrobial, often with a mixture of anaerobes and aerobes. Unfortunately, a systematic review of antimicrobial treatments for diabetic foot ulcers revealed that few appropriately designed randomized controlled studies have been conducted and it was difficult to give specific guidelines as to antibiotic regimens for specific infective organisms [72]; however, if there is any suspicion of osteomyelitis (signs such as a sausage-shaped toe or the ability to probe to bone may suggest this diagnosis) should have a radiograph taken of the infected foot and possibly further investigations (see below and Chapter 50). The

antibiotic prescription for a clinically infected non-limb-threatening foot ulcer without evidence of osteomyelitis should be guided by sensitivities after these are available from tissue specimens: when sensitivities are known, targeted appropriate narrow-spectrum agents should be prescribed. Suitable broad-spectrum antibiotics to start as soon as the clinical diagnosis of infection is made while waiting for sensitivity from the microbiology department would include drugs such as clindamycin or the amoxicillin–clavulanate combination [68].

Limb-threatening infection

Patients with limb-threatening infection usually have systemic symptoms and signs and require hospitalization with parenteral antibiotics. Deep wound and blood cultures should be taken, the circulation assessed with non-invasive studies initially, and metabolic control is usually achieved by intravenous insulin infusion. Early surgical débridement is often indicated in such cases, and initial antibiotic regimens should be broad-spectrum until sensitivities are determined from cultures. Examples of initial antibiotic regimens include: clindamycin and ciprofloxacin, or flucloxacillin, ampicillin and metronidazole. One problem with interpreting sensitivities is the question as to whether the organism isolated is simply a colonizing bacteria or is it a true infecting organism? One technique, the polymerase chain reaction (PCR) assay has been shown to be effective at identifying many virulent organisms [68]. A recent study from France [73] showed the potential advantages of using this new technique in the rapid distinction between colonizing and virulent infecting organisms.

An increasing problem in diabetic foot clinics is the antibiotic-resistant pathogens such as methacillin-resistant *Staphylococcus aureus* (MRSA). In most cases, MRSA is isolated as an opportunistic colonizing organism following the treatment with often inappropriate long duration broad-spectrum antibiotics. If MRSA is felt to be an infecting organism, there are useful new agents such as linezolid [68], which can be given parenterally or orally and are effective against such organisms. There is a suggestion that larval therapy [74] might be useful in eradicating MRSA that is contaminating diabetic foot wounds.

Osteomyelitis

As discussed in Chapter 50, the diagnosis of osteomyelitis is a controversial topic, and several diagnostic tests have been recommended. Amongst these, "probing to bone" has been shown to have a relatively high predictive value whereas plain radiographs are insensitive early in the natural history of osteomyelitis. In most clinical cases, however, the diagnosis is ultimately made by a plain X-ray of the foot (Figure 44.7). Magnetic resonance imaging (MRI) is having an increasing role in the diagnosis as it has high sensitivity [75]. The combination of an ulcer area $>2 \times 2$ cm, a positive probe to bone test, an elevated sedimentation rate and an abnormal radiograph are most helpful in diagnosing the presence of osteomyelitis in the diabetic foot whereas a negative MRI makes a diagnosis much less likely [76]. The most recent review on this topic suggests that a combination of clinical and laboratory findings together can significantly improve diagnostic accuracy for osteomyelitis in the diabetic foot: the specific combination of ulcer depth with serum inflammatory markers appears to be particularly sensitive [77]. Contrary to traditional teaching, it is increasingly recognized that some cases of localized osteomyelitis can be managed by long-term (10–12 weeks) antibiotic therapy [78]; however, localized bony resection after appropriate antibiotic therapy remains a common approach. Those cases with osteomyelitis confined to one bone without involvement of a joint are most likely to respond to antibiotic therapy particularly in the absence of peripheral vascular disease. It must be pointed out that data to inform treatment choices in osteomyelitis of the diabetic foot for randomized controlled trials are limited and further research is urgently needed [79].

Adjunctive therapies

A number of newer approaches to promote more rapid healing in diabetic foot lesions have been described over the last two decades. Some of those are mentioned below but many were also recently reviewed by the International Working Group on the Diabetic Foot [80].

Growth factors

A number of growth factors and other agents designed to modify abnormalities of the biochemistry of the wound bed or surrounding tissues have been described, but there is still no consensus as their place in day-to-day clinical practice [80]. One example is platelet-derived growth factor (PDGF) which is available for clinical use in a number of countries. Whereas there is some support for their use for randomized clinical studies [81], their expense together with the fact that most neuropathic ulcers can be healed with appropriate offloading, have limited their use. Unfortunately, PDGF together with other topically applied agents such as epidermal growth factor do not have sufficient robust data to support their day-to-day use in routine clinical practice.

Hyperbaric oxygen

Hyperbaric oxygen (HBO) has been widely promoted for the management of non-healing diabetic foot ulcers particularly in the USA, for some years. Many of the reported studies have been poorly designed or anecdotal and have given rise to serious concerns about the widespread use of this treatment [82]; however, there have been several small well-designed randomized controlled trials to assess the efficacy of HBO in ischemic diabetic foot wounds [83]. Whereas the systematic review of the International Working Group that considered HBO accepted that there was some evidence to support its use, it is clear that more data are required from larger controlled trials not only to confirm efficacy but also to clarify which wounds might best benefit from this expensive treatment [80,84].

Negative pressure wound therapy

Over the past several years negative pressure wound therapy (NPWT) using vacuum-assisted closure has emerged as a com-

monly employed option in the treatment of complex wounds of the diabetic foot [85]. Previous work has suggested that the application of negative pressure optimizes blood flow, decreases local tissue edema and removes excessive fluid and pro-inflammatory exudates from the wound bed. There is now controlled trial evidence for the use of NPWT in both local postoperative wounds in the diabetic foot [86] and, more recently, in the management of complex but non-surgical diabetic foot ulcers [87]. It is clear that this treatment helps promote the formation of granulation tissue, but its cost will limit its use to those complex diabetic foot wounds not responding to standard therapies.

Bioengineered skin substitutes

Similar to other treatments in this group of adjunctive therapies although there is some evidence to support the use of bioengineered skin substitutes in non-infected neuropathic ulcers, its use of somewhat restricted by cost [80]. A systematic review on this topic concluded that the trials assessed were of questionable quality and until high quality studies were performed, recommendations for the use of these skin substitutes could not be made [88].

Charcot neuroarthropathy

Charcot neuroarthropathy (CN) is a non-infective arthropathy that occurs in a well-perfused insensate foot. Although the exact mechanism underlying the development of CN remains unclear, progress has been made in our understanding of the etiopathogenesis of this disorder in the last decade. It is clear that the classic neurotraumatic and neurotrophic theories for the pathogenesis of acute CN in diabetes do not address certain key features of the disease [89]. If the former theory were correct, CN would be much more common and should be symmetrical: in contrast, acute CN is relatively rare amongst patients with neuropathy and is usually asymmetrical, although there is an increased risk of developing CN in the contralateral foot some years later.

CN occurs in a well-perfused insensate foot. Typically, patients present with a warm, swollen foot and contrary to some of the earlier texts, may be accompanied by pain or at least discomfort in the affected limb. The affected patient tends to be slightly younger than is usual for the patient presenting with a diabetic foot ulcer and typically presents with a warm swollen foot which may or may not be painful. Although a history of trauma may be present, the trauma is rarely of sufficient severity to account for the abnormalities observed on clinical examination (Figure 44.7). Although CN is characterized by increased local bone resorption, the exact cellular mechanisms contributing to this condition remain unresolved. Recently, receptor activator of nuclear factor κB ligand (RANKL) has been identified as an essential mediator of osteoclast formation and activation. It has been hypothesized that the RANKL/osteoprotegerin (OPG) pathway may play an important part in the development of acute CN [89]. It has subsequently been confirmed that peripheral blood monocytes isolated from patients with CN and cultured in the presence of macrophage colony-stimulating factor led to an increased osteoclast formation when compared to healthy and diabetic controlled monocytes [90]. These observations suggested that RANKL-mediated osteoclastic resorption occurs in acute CN. Thus, the RANKL-dependent pathway is important in the pathogenesis of acute CN suggesting that in the future, inhibition of RANKL might be useful in management.

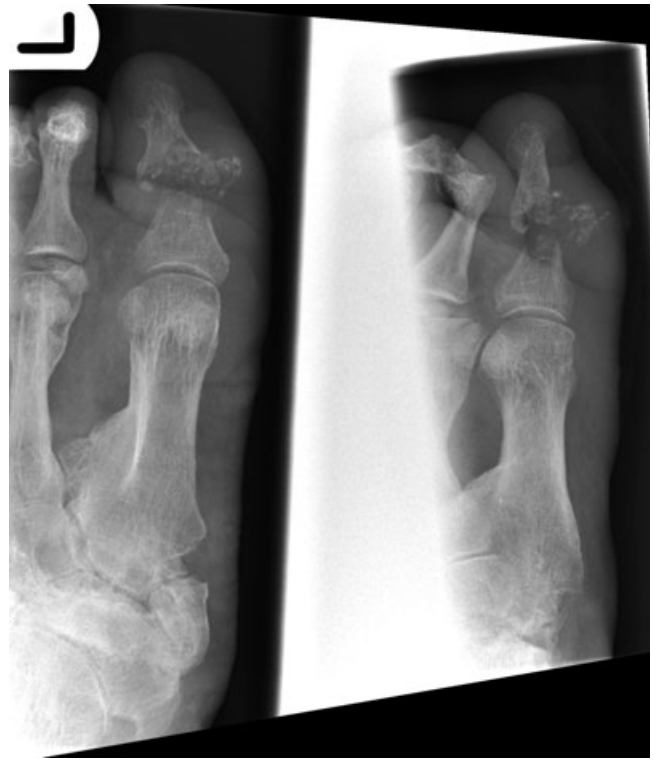

Figure 44.7 This radiograph displays two main abnormalities: (a) changes of osteomyelitis and septic arthritis involving the first metatarso-phalangeal joint, with destruction of the distal first metatarsal and proximal area of the proximal phalanx of the great toe; and (b) chronic changes of Charcot neuroarthropathy in the first cuneiform/metatarsal area.

As discussed in Chapter 48, the treatment of the foot in CN depends upon the stage in which the disease is diagnosed. In the acute phase, there is evidence that offloading of the affected foot by use of a plaster cast is the most effective method of reducing disease activity and local inflammation. Use of the cast should continue until the swelling and hyperemia have resolved and the skin temperature differential is 1°C or less, at which time custom moulded shoes with appropriate insoles are indicated [91]. Bisphosphonates are potent inhibitors of osteoclast activation and intravenous pamidronate has been shown to be useful in reducing disease activity in acute CN [92]. Larger randomized controlled trials are required to confirm these preliminary observations.

The management of advanced CN with bone deformity requiring reconstructive surgery is beyond the scope of this chapter and the reader is referred to recent reviews [93].

Conclusions

There can be no doubt that despite our efforts in early identification, prevention and aggressive treatment of diabetic foot problems, that the incidence of diabetic foot disease is likely to increase in the next few decades with the global explosion in of the prevalence in type 2 diabetes reviewed elsewhere in this book. It is also clear that diabetic foot disease carries not only a significant morbidity, but even mortality: Armstrong *et al.* [94] pointed out that the outlook for those with diabetic foot disease is worse than many malignant diseases. There is increasing recognition of the multifactorial nature of complications which led Young *et al.* [95] to review the survival of their patients with diabetic foot lesions over the last 13 years. They reported that survival has improved and this has been accompanied by the adoption of an aggressive cardiovascular risk management policy which should be encouraged in all patients with diabetic foot disease. The ultimate prognosis for the limb with a diabetic foot lesion depends upon the presence or absence of an ischemic component: it has been shown that patients with higher Wagner or UT gradings and severity are more likely to end up with minor or even major amputation. Thus, neuropathic foot lesions generally carry a good prognosis, whereas those with a significant ischaemic components are more likely to require the input of the vascular surgeon (see Chapter 43).

The team approach

It should be clear that the spectrum of diabetic foot problems requires the involvement of individuals from many specialties. The diabetic foot cannot be regarded as the sole responsibility of the diabetologist, and a number of reports over the last decade have promoted the benefits of a multidisciplinary approach to diabetic foot care [96]. This started in the early 1990s when the concept of the "annual review" was adopted by most national diabetes societies. This requires that all patients with diabetes be screened on an annual basis for evidence of long-term complications [97]. There is increasing evidence from a number of long-term studies that the adoption of this approach not only in hospital but in community care, has been associated with a reduced incidence of foot problems [98–101]. The improved management of diabetic foot care in the district of Leverkusen, Germany, ultimately resulted in a 37% reduction in non-traumatic amputations in patients with diabetes; however, this took more than 10 years after the establishment of specialist foot care [98]. Two studies from the UK [99,100] have reported reductions of up to 60% in diabetic amputations and both of these followed either the introduction of multidisciplinary team work in the community or the improved organization of general diabetes care. Finally, a sustained reduction in major amputations has been reported from Sweden over the last 20 years suggesting that a substantial decrease in diabetes-related amputations can not only be achieved, but maintained over a long period of time [101].

The team approach, involving diabetologists working together with surgeons (orthopedic and vascular), specialist nurses, podiatrists, orthotists and often many other health care professionals is therefore strongly recommended in the management of complex lesions of the diabetic foot. It should be remenbered, however, it is the patient at risk of, or with foot ulceration, who must be regarded as the most important in this team. Without the patient's willing participation, there is little that other team members can achieve to improve the overall outlook for the diabetic foot in the 21st century.

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