

FOOT PROBLEMS IN PATIENTS WITH DIABETES

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KEY POINTS:

- Diabetic foot problems remain the commonest cause of hospital admissions amongst diabetic patients in Western countries.
- Up to 50% of older Type 2 diabetic patients have risk factors for foot problems.
- Up to 85% of lower limb amputations are preceded by foot ulcers.
- All diabetic patients 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.

KEY WORDS:

diabetic foot, diabetic neuropathy, peripheral vascular disease, Charcot neuroarthropathy, foot ulceration.

ABSTRACT

Foot ulceration in diabetes is common with a diabetic patient having a 25% lifetime risk of developing an ulcer. Regular screening which should take the form of a careful clinical examination is essential to identify those at risk of foot problems who should then receive more regular follow up together with education in foot self-care. The key to management of diabetic neuropathic foot ulceration is aggressive debridement with removal of callus and dead tissue together with offloading the ulcer area in some form of cast. Any infection in foot ulcers should be treated aggressively and those patients with limb-threatening infections require urgent hospital admission, assessment of the vasculature and team management. The key to reducing ulceration and amputation in the future is regular screening, patient education and adopting a team approach to management both in the community and in hospital.

<H1> 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. Realising the global importance of diabetic foot disease, the International Diabetes Federation (IDF) focused on the diabetic foot throughout the year of 2005, during which there was a worldwide campaign to “put feet first” and highlight the all too common problem of amputation amongst diabetic patients 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 world-wide 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 diabetic patients during their lifetime (1).
- 2 Over 85% of lower limb amputations are preceded by foot ulcers and diabetes remains the commonest 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 healthcare professionals from all specialties realize that, as Dr Paul 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 recognised risk factors for the development of foot problems (4).

6 Diabetes is now the commonest cause of Charcot neuroarthropathy in western countries, another condition that should be generally preventable (3).

However, 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-review journals. Taken as a percentage of all PubMed listed articles on diabetes, those on the diabetic foot have increased from 0.7% in the 1980-88 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 recognised 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 diabetic patient with osteomyelitis but good blood supply: this was performed under the encouragement of RD Lawrence, himself diabetic, who was co-founder of the British Diabetes Association, now Diabetes UK (6).

In the last 2 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 pathological conditions that might affect the feet of people with diabetes. Initially the epidemiology and economic impact of diabetic foot disease will be 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 will be discussed, followed by a section on the management of foot ulcers. The chapter will close 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 (chapter 38), peripheral vascular disease (chapter 43), bone and rheumatic disorders in diabetes (chapter 48) and infection (chapter 50).

<H1> 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 epidemiological data for foot ulceration and amputation, originating from studies from a number of different countries (9-17), is provided in Table 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 do vary considerably as a consequence of different diagnostic criteria used as well as regional differences (19). As stated above, 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 1 were well conducted, methodological issues remain which make it difficult to do direct comparisons between studies/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 United Kingdom, 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, between 40 and 70% of patients fell into that category. Such observations clearly indicate the need for all diabetes services to have a regular screening programme to identify such high risk individuals.

<H2> HEALTH ECONOMICS OF DIABETIC FOOT DISEASE

In addition to causing substantial morbidity and even mortality, foot lesions in diabetic patients additionally have substantial economic consequences. Diabetic foot ulceration and amputations were estimated to cost US healthcare 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 United States suggests 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 therefore 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 healthcare systems.

H1 AETIOPATHOGENESIS 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 will also be briefly described.

<H2> 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 United States 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 1). Thus, minor injury and subsequent infection increase the demand for blood supply beyond the circulatory capacity and ischaemic ulceration and the risk of amputation ensues. In recent years, neuroischaemic 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.

<H2> DIABETIC NEUROPATHY

As discussed in chapter 38, the diabetic neuropathies represent the commonest 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 polyneuropathy and the autonomic neuropathies. It is the common sensorimotor neuropathy together with peripheral autonomic sympathetic neuropathy that together play an important role in the pathogenesis of ulceration and these will be discussed below.

<H3> 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 type 2 patients 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, paraesthesiae 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 fibre 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 self foot 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 exam after removal of shoes and socks, whatever the neuropathic history (27).

<H3> 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 however 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 Dr Paul 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 always emphasised to his students the power of clinical observation 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 realise that with loss of pain there is also diminished motivation in the healing of, and prevention of, injury.

<H3> 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 arterio-venous shunting leading to the warm foot. The complex interactions of the neuropathies and other contributory factors in the causation of foot ulcers are summarised in Figure 1.

<H2> OTHER RISK FACTORS

Of all the other risk factors for ulceration (Table 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%.

<H3> 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 normoglycaemic as a result of the pancreas transplant.

<H3> 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 healthcare professional.

<H3> ELEVATED FOOT PRESSURES

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

<H3> 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 2).

<H3> ETHNICITY AND GENDER

The male sex has been associated with a 1.6 fold increase of ulcers (33). With respect to ethnic origin, data from cross-sectional studies in Europe suggests that foot ulceration is commoner in European subjects when compared to 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 (34). Reasons for these ethnic differences certainly warrant further investigation. In contrast, in the southern United States, ulceration was much more common in Hispanic Americans and native Americans than in non-Hispanic whites (35). However, more recent data suggests this increased risk in Hispanics, that foot pressures are actually lower in this group (36).

<H2> PATHWAY TO ULCERATION

(Figure 1)

It is the combination of two or more risk factors that ultimately results in diabetic foot ulceration. Both Pecoraro et al (25) and later Reiber et al (37) 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 (eg 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 commonest triad of component causes, present in nearly two out of three incident foot ulcer cases, was neuropathy, deformity and trauma. Oedema and ischaemia 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, eg 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 neuroischaemic ulcers where the three component causes comprising ischaemia, trauma and neuropathy are often seen.

<H1> PREVENTION OF DIABETIC FOOT ULCERS

<H2> SCREENING

As stated above, 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 centre 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)” (38). The taskforce addressed and concisely summarised 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 neurological 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 (33,38). A summary of the key components of the CDFE is provided in Table 3. Whereas each potential simple neurological clinical test has advantages and disadvantages, it was felt that the 10g monofilament had much evidence to support its use hence the recommendation that assessment of neuropathy should comprise the use of a 10g monofilament plus one other test. In addition to those simple tests listed in Table 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 centres in both Europe and North America have such equipment. However, as can be seen from Table 3, this is not regarded as essential. Strong evidence does however support the use of vibration perception threshold as an excellent predictor of foot ulceration (39,40).

With respect to the vasculature, the Ankle Brachial Index was recommended although it was realised that many centres in primary care may not be able to perform this in day to day clinical practice.

<H2> 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 will now be discussed under a number of headings, the most important of which is education.

- <H3> EDUCATION

Previous studies have suggested that patients with foot ulcer risk lack knowledge and skills and consequently are unable to provide appropriate self foot care (41). 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. However, recent studies summarised by Vileikyte et al (42,43) 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 programme 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 3.

There have been a small number of reports that assess educational interventions, but these have mostly been small, single-centre studies. In the most recently published study, even though the foot care education programme was followed by improved foot care behaviour, there is no evidence that such targeted education was associated with a reduced incidence of recurrent foot ulcers (44). 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 colour from blue to pink if there is normal

sweating. The absence of sweating such as in a high risk foot, results in no colour change enabling patients to see that there is something different about their feet. A similar visual aid is the PressureStat (Podotrack) (46) (Figure 4). This is a simple, inexpensive, semi-quantitative footprint mat that is able to identify high plantar pressures. The higher the pressure, the darker the colour of the footprint. Similarly this can be used as an educational aid and might help the patient realise 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 randomised controlled trials. Further studies in this area are therefore urgently required.

- <H3> PODIATRY/CHIROPODY

Although not available in every country, regular nail and skin care from a podiatrist/chiroprapist 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. Chiroprapists and podiatrists should be attached to the foot care team if available and can also be educating the patient whilst treating the feet.

- <H3> FOOTWEAR/OTHOSES/HOSIERY

As stated above, inappropriate footwear is a common cause of foot ulceration in insensitive feet, whereas good footwear can reduce ulcer occurrence (41). This statement is supported by randomised controlled trials (47). 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 (48,49).

- <H3> 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, randomised controlled trial, Lavery et al (50) randomised patients with a history of neuropathic foot ulceration to one of 3 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% versus 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 (51).

- <H3> INJECTED LIQUID SILICONE

Injected liquid silicone under high pressure areas of the diabetic foot has been used for some years in the United States and is supported by a randomised controlled trial (52) 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 (53) confirmed that the effect of this “injectable orthosis” lasts for up to 2 years, although booster injections may be required from time to time.

<H1> FOOT ULCERS: DIAGNOSIS AND MANAGEMENT

<H2> 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 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 ischaemia 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 (54) but only a few will be described. The most widely used foot ulcer classification system worldwide at the time of writing is the Meggitt-Wagner grading, as shown in Table 4. Despite its wide use, this system does lack specificity: it does not refer to the neuropathic, ischaemic or infective status of the ulcers.

The newer University of Texas (UT) wound classification system is currently widely used (55) (Table5). This is based upon the Meggitt-Wagner system but in addition to grades of ulcers, stages each grade for the presence or absence of infection and ischaemia. In a comparative study of these 2 systems, the UT system was shown to be a useful predictor of outcome although the Meggitt-Wagner system was still confirmed to be useful (56). A high-risk foot with pre-ulcerative lesions (Wagner 0, UT1A) is shown in Figure 5. The 2 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 (54). Thus the UT system will be used to describe ulcer classification in this section.

<H2> WOUND HEALING IN THE DIABETIC FOOT

Wound healing is a tissue response to injury and passes through the phases of inflammation, chemotaxis, cellular proliferation, extra-cellular matrix deposition and finally wound re-modelling and scarring. Diabetes may influence foot wound healing in a number of different ways including an impairment of the peripheral circulation, altered leucocyte function, disturbed balance of cytokines and proteases and even chronic hyperglycaemia itself (3,57). Thus foot ulcers in diabetic patients are recalcitrant to healing due to many cellular and molecular aberrations. When compared to 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 (58-60). Most recently, it has been suggested that levels of matrix metalloproteinases (MMP) are important in predicting the likelihood of wound healing and a high level of MMP-1 seems essential to wound healing (60).

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.

<H2> 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 randomised controlled trials have compared the TCC with other removable offloading devices in plantar diabetic foot ulcers and invariably, healing is most rapid in those randomised to TCC treatment (3,61). However, as it is known that the Removable Cast Walkers (RCW) redistribute pressure in a similar manner to the TCC, 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 (62).

Subsequent to this observation, it was proposed that an RCW might be rendered irremovable by wrapping it with one or 2 bands of plaster of Paris, therefore addressing most of the disadvantages of the TCC but preserving irremovability. A subsequent randomised controlled trial of this modified, irremovable RCW versus the TCC showed that healing times were identical (63).

The impact of appropriate offloading on the histopathological features of neuropathic diabetic foot ulcers was reported by Piaggese et al (64). 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 (eg depression and anxiety) on wound healing in diabetic patients (65). 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 now 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 localised infection in neuropathic foot ulcers (Figure 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) (66).

For those patients treated with irremovable cast walkers, it is recommended that the cast be removed initially on a weekly basis for wound assessment debridement and cleansing. Healing can generally be 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 be extra depth or in the case of severe deformity, custom moulded.

<H2> DRESSINGS

The danger of dressings and bandages is that some healthcare 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 3 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, minimise the risk of infection and optimise 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 (67,68). There is little evidence that any specific dressing will have a major impact on the rate of wound healing.

<H2> 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 colonised 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 (69). Thus the presence of signs such as purulent discharge, erythema, local warmth and swelling which suggests infection requiring appropriate treatment.

<H3> 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 (70) have shown that with appropriate wound management, patients do equally well with or without systemic antibiotics in a randomised controlled trial. However, frequent review, debridement 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 ischaemic 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 ischaemia in the diabetic foot are a common cause of ultimate lower extremity amputation.

<H3> 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 (69,71,72). 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 (69). 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 (69). Most infective ulcers are polymicrobial, often with a mixture of anaerobes and aerobes. Unfortunately a systematic review of anti-microbial treatments for diabetic foot ulcers revealed that few appropriately designed randomised controlled studies have been conducted and it was difficult to give specific guidelines as to antibiotic regimens for specific infective organisms (73). 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 whilst waiting for sensitivity from the microbiology

department would include drugs such as Clindamycin or the amoxicillin/clavulanate combination (69).

<H3> LIMB-THREATENING INFECTION

Patients with limb-threatening infection usually have systemic symptoms and signs and require hospitalisation 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 debridement 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 colonising 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 (69). A recent study from France (74) showed the potential advantages of using this new technique in the rapid distinction between colonising 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 colonising 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 (69), which can be given parenterally or orally and are effective against such organisms. There is a suggestion that larval therapy (75) might be useful in eradicating MRSA that is contaminating diabetic foot wounds.

<H3> 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. However, in most clinical cases, the diagnosis is ultimately made by a plain x-ray of the foot. Magnetic resonance imaging (MRI) is playing an increasing role in the diagnosis as it has high sensitivity (76). The combination of an ulcer area > 2 x 2cm, 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 (77). 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 (78). Contrary to traditional teaching, it is increasingly recognised that some cases of localised osteomyelitis can be managed by long-term (10-12 weeks) antibiotic therapy (79). However, localised 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. However, it must be pointed out that data to inform treatment choices in osteomyelitis of the diabetic foot for randomised controlled trials are limited and further research is urgently needed (80).

<H2> 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 will be mentioned below but many were also recently reviewed by the International Working Group on the Diabetic Foot (81).

<H3> 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 (81). 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 randomised clinical studies (82), 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.

<H3> HYPERBARIC OXYGEN (HBO)

HBO has been widely promoted for the management of non-healing diabetic foot ulcers particularly in the United States, 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 (83). However, there have been several though small, well designed randomly controlled trials to assess the efficacy of HBO in ischaemic diabetic foot wounds (84). 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 (81,85).

<H3> NEGATIVE PRESSURE WOUND THERAPY (NPWT)

Over the past several years NPWT using vacuum-assisted closure has emerged as a commonly employed option in the treatment of complex wounds of the diabetic foot (86). Previous work has suggested that the application of negative pressure optimises blood flow, decreases local tissue oedema 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 (87) and more recently, in the management of complex but non-surgical diabetic foot ulcers (88). 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.

<H3> 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 is somewhat restricted by cost (81). 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 (89).

<H1> CHARCOT NEUROARTHROPATHY (CN)

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 aetiopathogenesis of this disorder in the last decade. It is clear that the classical neurotraumatic and neurotrophic theories for the pathogenesis of acute CN in diabetes do not address certain key features of the disease (90). If for example 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. Although CN is characterised by increased local bone resorption, the exact cellular mechanisms contributing to this condition remain unresolved. Recently, receptor activator of nuclear factor-kappaB ligand (RANKL) has been identified as an essential mediator of osteoclast formation and activation. It has been hypothesised that the RANKL/osteoprotegerin (OPG) pathway may play an important part in the

development of acute CN (90). 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 (91). 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.

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 hyperaemia have resolved and the skin temperature differential is one degree C or less, at which time custom moulded shoes with appropriate insoles are indicated (92). Bisphosphonates are potent inhibitors of osteoclast activation and intravenous Pamidronate has been shown to be useful in reducing disease activity in acute CN (93). However, larger randomised 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 (94)

<H1> FINAL 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 due to the global explosion in of the incidence 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 and colleagues pointed out that the outlook for those with diabetic foot disease is worse than many malignant diseases (95). However, there is increasing recognition of the multi-factorial nature of complications which led Young and el to review the survival of their patients with diabetic foot lesions over the last 13 years (96). 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 ischaemic 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).

<H2> 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 alone, and a number of reports over the last decade have promoted the benefits of a multi-disciplinary approach to diabetic foot care (97). 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 (98). 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 (99-102). The improved management of diabetic foot care in the district of Leverkusen, Germany, ultimately resulted in a 37% reduction in non-traumatic amputations in diabetic patients. However, this took more than 10 years after the establishment of

specialist foot care (99). Two studies from the UK (100,101) have reported reductions of up to 60% in diabetic amputations and both of these followed either the introduction of multi-disciplinary team work in the community or the improved organisation 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 (102).

The team approach, involving diabetologists working together with surgeons (orthopaedic and vascular), specialist nurses, podiatrists, orthotists and often many other healthcare professionals is therefore strongly recommended in the management of complex lesions of the diabetic foot. However, it is the patient at risk of, or with foot ulceration, that must be regarded as 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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Table 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 ^b	1.6	-	-	>40
	Bahrain	2007	1477	5.9	-	-	-	45
Al-Mahroos and Al-Roomi (10)	UK	2002	9710	1.7	1.3	2.2	-	>50
	Greece	2002	821	4.8	-	-	-	>50
Abbott et al (11)	Netherlands	2002	665	-	-	2.1	0.6	-
Manes et al (12)	USA	1999	8965			5.8 ^a	0.9 ^a	-
	Slovakia	1997	1205	2.5	0.9	0.6	0.6	-
Muller et al (13)	UK	1994	821	1.4 ^b	-	-	-	42
Ramsay et al (14)	USA	1992	2900	-	-	10.1 ^c	2.1 ^c	-
Vozar et al (15)								
Kumar et al (16)								
Moss et al (17)								

^aIncidence figures over 3 years; ^bActive ulcers: 5.4% past or current ulcer; ^cIncidence figures over 4 years

Table 2

Factors increasing risk of diabetic foot ulceration

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

Oedema

Ethnic background

Poor social background

More common contributory factors shown in bold

TABLE 3

Key Components of the Diabetic Foot Exam

* INSPECTION

- Evidence of past/present ulcers?
- Foot Shape?
 - prominent metatarsal heads/claw toes
 - hallux valgus
 - muscle wasting
 - Charcot deformity
- Dermatological?
 - callus
 - erythema
 - sweating

* NEUROLOGICAL

- 10g monofilament at 4 sites on each foot
+ 1 of the following
- Vibration using 128HZ tuning fork
- Pinprick sensation
- Ankle reflexes
- Vibration perception threshold

* VASCULAR

- Foot pulses
- Ankle Brachial Index, if indicated

TABLE 4

Meggitt-Wagner Classification

Grade 0:	No ulcer, but high risk foot (deformity, callus, etc)
Grade 2:	Deep ulcer, may involve tendons but not bone
Grade 3:	Deep ulcer with bone involvement, osteomyelitis
Grade 4:	Localised gangrene (eg toes)
Grade 5:	Gangrene of whole foot

Modified from 56

TABLE 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	+Ischaemia	+Ischaemia	+Ischaemia	+Ischaemia
D	+Infection and ischaemia	+Infection and ischaemia	+Infection and ischaemia	+Infection and ischaemia

CAPTIONS TO FIGURES

- Figure 1 Pathways to foot ulceration in diabetes (reproduced with permission from Boulton (7) twice.
- Figure 2 The “high risk” neuropathic diabetic foot demonstrating high arch, prominent metatarsal heads, clawing of toes and callus under 1st metatarsal head.
- Figure 3 The potential for education and self-care in prevention of neuropathic foot ulcers (courtesy L. Vileikyte MD. PhD).
- Figure 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.
- Figure 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.
- Figure 6 Radiograph from a patient with a deep neuropathic ulcer under the right 5th 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.
- Figure 7 This radiograph displays two main abnormalities: (a) changes of osteomyelitis and septic arthritis involving the first metatarsophalangeal 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.