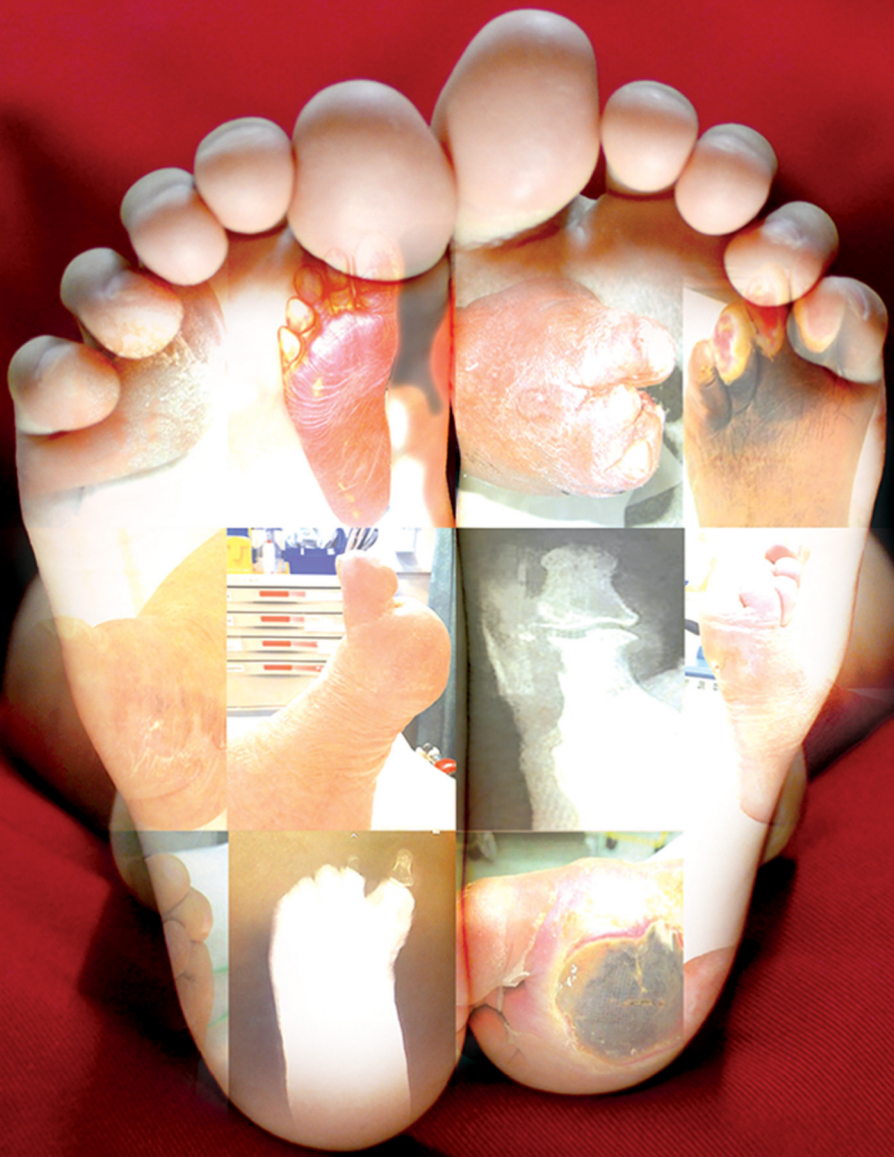
Diabetic Foot Management at the Primary Care Level

An Evidence-Based Approach



Edited by Hashim Mohamed

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This book is dedicated to a number of people, including my late father who passed away without realising his dream of seeing his young boy become a doctor, and to a unique lady, Badriya Al lenjawi, who is both my lovely wife and favorite coach, and our four children Ali, Houraa, Abdulla and Mohamed, and to those patients who suffered from diabetic foot ulcers, lost limbs, their families and those health care professionals who care for people with diabetic foot problems.

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CHAPTER 1

EPIDEMIOLOGY OF THE DIABETIC FOOT

DR HASHIM MOHAMED

Diabetic foot ulcer represents one of the most common complications of diabetes. Around 15% of individuals with diabetes will develop a foot ulcer during their illness [1-4]. However, the prevalence of diabetic foot ulcers varies between different populations, ranging from 2% to 10% [3,5-7]. On average, individuals with diabetic foot ulcers have around a 59% longer stay at the hospital compared to diabetic patients without ulcers [8]. Furthermore, approximately 85% of lower-extremity amputations are preceded by a diabetic foot ulcer [11-14]. Despite the recent advances in the management of type II diabetes, it is still the most common reason for non-traumatic lower-extremity amputations across the globe [2,3].

On average, the lower-extremity amputation rate is 50% higher in males compared to females and 15 to 40 times higher among individuals with diabetes compared to those without the disease [8,10,12,33]. Additionally, ethnic minorities, including African Americans and Hispanic Americans, carry a 1.5- to 2-fold higher risk of diabetes-related amputation than their Caucasians counterparts [3,4,16-19]. This could be related to several reasons, including poor education, lack of medical insurance, lower socio-economic status, cultural factors, lifestyle, healthcare-seeking behaviour and an external locus of control.

Survival rates post lower limb amputation are generally low in individuals with diabetes [3,4,13]. The average five-year survival rates are about 40%, with cardiovascular complications being the leading cause of death [17]. Recent data has demonstrated a 50% incidence of contralateral lower limb amputation within 2–5 years [3,13].

In the US, the total annual health care costs for individuals with diabetes was estimated to be $132 billion in 2002. The average price of treating a foot ulcer depends on several factors, including the country the patient is residing in, the status of the health system, medical insurance cover, ability to pay for treatment and comorbid conditions. However, in the US, the

average cost of foot ulcer treatment ten years ago was around $4,595 per ulcer [19,20]. There are additional costs related to having a diabetic foot ulcer or a lower limb amputation, including work days lost due to illness, low self-esteem, depression and poor quality of life.

1.1 Risk of ulceration

Risk factors for foot ulceration include improper footwear, foot deformities, trauma, peripheral neuropathy, peripheral vascular disease, limited joint mobility, abnormal foot pressures, impaired vision, and a history of ulceration or amputation [9,21,22]. Recent data revealed that peripheral sensory neuropathy in the face of unperceived trauma tends to be the leading cause of diabetic foot ulceration [8,23,24]. Neuropathy is responsible for 45% to 60% of all diabetic foot ulcerations, whereas 45% of diabetic foot ulcers have a combined neuropathic and ischaemic component [8,25].

Other types of neuropathy may contribute to the development of foot ulceration, including motor neuropathy manifested in atrophy or wasting of intrinsic muscles, ultimately leading to foot deformities such as prominent plantar metatarsal heads, hammer toe and foot drop [9,10,26-28]. Furthermore, the poorly-distributed weight of the body as a result of intrinsic muscle deformities and a reduced ankle motion will confer a higher-than-normal focal plantar pressure, especially at the forefoot, ultimately leading to ulceration, recurrence and/or recalcitrance of existing diabetic foot ulcers [29-32].

The situation is further aggravated when autonomic neuropathy leads to malfunctioning of the sweat gland leading to reduced moisture of the skin, consequently leading to dry skin, cracking and fissure formation, thereby creating a portal of entry for bacteria [33,34]. In individuals with a prolonged course of diabetes, especially if it is uncontrolled, may ultimately result in sympathetic and parasympathetic dysfunction. These are manifested by arteriovenous shunting, where the foot becomes oedematous and warm. Furthermore, in response to injury, the microvascular thermoregulatory dysfunction impairs normal tissue perfusion in the foot and its ability to heal. These deregulations may subsequently lead to diabetic foot ulcer formation [34-38].

Many factors, including injury, improper footwear and foot deformities resulting from neuropathy including hard callous formation, abnormal gait, prior ulceration, surgical interventions and reduced peripheral perfusion may result in an increased risk of ulceration [8,39-45]. The course and prognosis of diabetic foot ulceration are prolonged and complicated by the

presence of peripheral arterial disease imparting an elevated risk of amputation[12,44,45]. Individuals with peripheral arterial disease and/or those who continue to smoke will have an impaired ability to resolve infection due to low levels of oxygen as well as the reduced ability to deliver antibiotics to the site of infection. Hence, early aggressive management of lower-extremity ischaemia is of utmost importance for salvaging lower limbs [14, 45-47].

1.2. Mechanisms of injury

Although many pathophysiologic pathways have been suggested that lead to foot ulceration [48-51], two common mechanisms can lead to foot ulceration in individuals with diabetes [52,53]. The first mechanism of skin injury is related to repetitive shear prolonged low-grade pressure over a bony prominence (i.e. a hammer toe or bunion deformity). Classically, this happens if a person wears tight or ill-fitting footwear, thereby causing skin breakdown or formation of the wound over the bony area involved. Loss of protective sensation, coupled with footwear trauma in the presence of foot deformity and callous formation, becomes the leading cause of foot ulceration in individuals with diabetes [8,12,41].

The other common etiology of ulcer formation occurs due to prolonged repetitive moderate stress [52]. This usually happens on the plantar aspect of the foot and is related to anteriorly displaced or atrophied fat pads, prominent metatarsal heads and structural deformity of the foot. Structural risk factors related to ulcer development in the foot include rigid deformities such as hallux rigidus, hallux valgus, hammer toes, Charcot arthropathy and a limited range of motion of the small joints of the foot [11,41,45,54-56]. Various clinical studies have linked the likelihood of ulcer development with the presence of high plantar pressures [10,44,54,57].

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Case Study – I

A 61-year-old male patient with type II DM of 35 years duration, a chronic heavy smoker with coronary artery disease, hypertension, severe peripheral artery disease, chronic renal failure on haemodialysis, previous two episodes of myocardial infarction and left midfoot amputation presented with a non-healing right plantar foot ulceration with an exposed calcaneus. His investigations revealed Hb 6.7 gm/dl, HCT 6.6, MCV 19.4, creatinine 357 micromole/litre, urea 18.9 mmol/l. During his hospital stay he had a vascular assessment, which showed severe calcification of anterior and posterior tibial arteries.

He was treated previously in the hospital with intravenous antibiotics and insulin, and attended the podiatry clinic for dressing with advanced wound products, including a hydrogel and silver-based wound product before presenting at the primary care health centre.

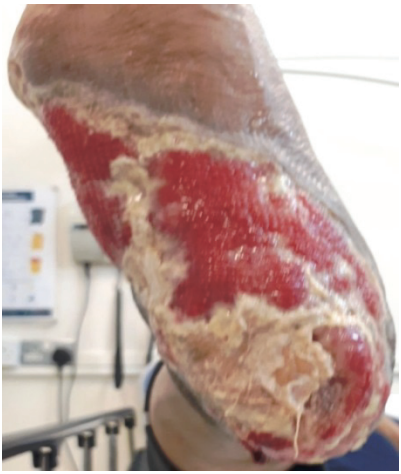

Figure 1-1: Exposed calcaneus and extensive necrotic tissue on presentation

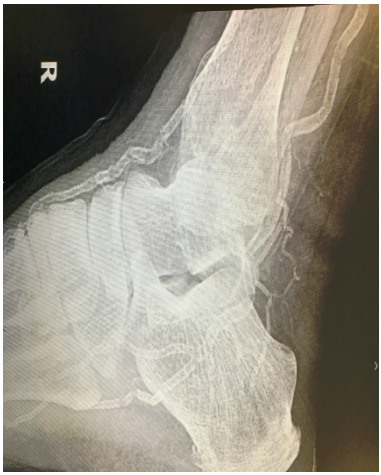

Figure 1-2: Showing complete calcification of anterior and posterior tibial arteries and its tributaries

The patient underwent extensive sharp debridement with a surgical blade (Figure 1-4); the wound was washed with normal saline via a 20 cc gauge syringe followed by the application of sterile raw honey, which was covered by a petroleum impregnated wound dressing. The wound was covered with cotton gauze and wrapped with a cotton bandage. The patient was instructed to strictly offload his foot using a pneumatic cast walker (Figure 1-3). An X-ray of the right foot revealed calcification of anterior and posterior tibial arteries (Figure 1-2). He was prescribed oral ciprofloxacin 500 mg bid for two weeks with daily dressing at the health centre. Eight weeks later, the plantar surface completely re-epithelized (Figure 1-5); however, the patient did not comply with the advice and removed the pneumatic cast walker and started to ambulate. This led to the haemorrhagic plantar surface with exposure of the calcaneal bone with subcutaneous bleeding and necrotic tissue formation (Figure 1-6).

The patient refused to go for angiography with the possibility of doing lower limb bypass and kept ambulating; this, in turn, led to the severe compromise of the blood flow to the toes resulting in the formation of dry gangrene of the second, third, fourth and fifth toes (Figure 1-7). The patient later stopped attending follow-up appointments.

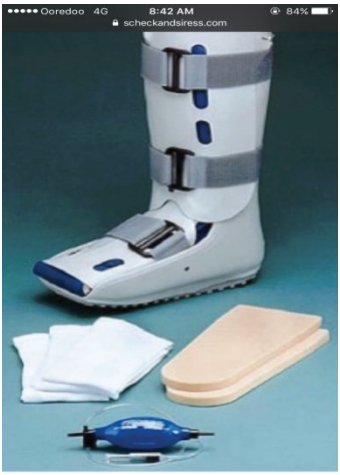

Figure 1-3: Showing pneumatic cast walker

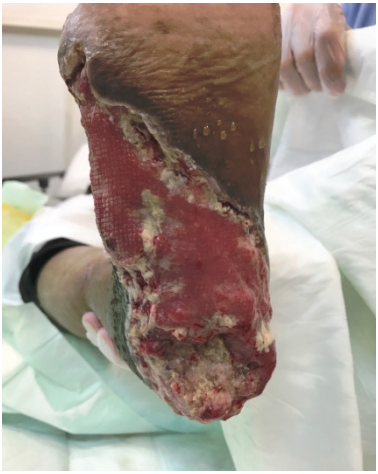

Figure 1-4: Plantar surface post debridement using surgical blade

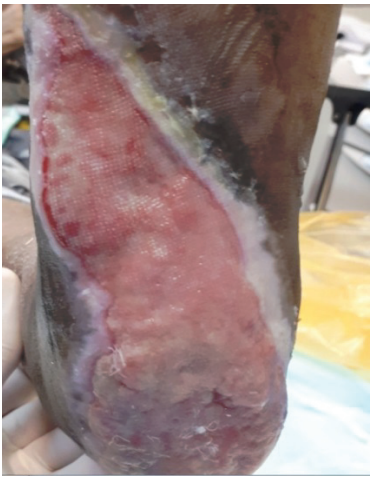

Figure 1-5: Complete epithelization of the plantar surface including the calcaneus eight weeks later

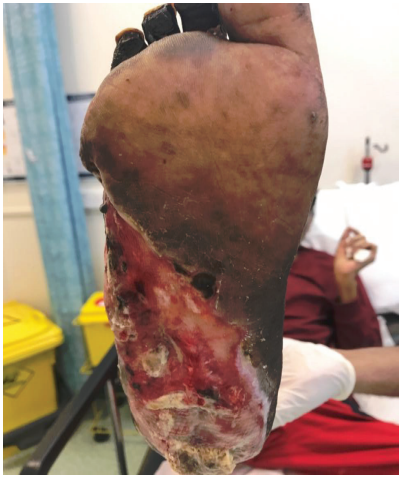

Figure 1-6: Trauma of plantar aspect leading to necrotic tissue and haemorrhagic spots formation and exposing of calcaneus with evident dry gangrene in the second, third and fourth toes

Figure 1-7: Dry gangrene of the second, third, fourth and fifth toes

Later upon inquiry, it was discovered that the patient was admitted by his family to the main hospital with an extensive lower limb infection and

was given intravenous meropenem antibiotic. He is waiting for below-knee amputation.

Case Study – II

A 73-year-old female suffering from type II diabetes for the past 30 years, with hypertension, hypercholesterolemia, and chronic end-stage renal disease (stage IV), presented with a non-healing wound on the right big toe she had had for one month. She received treatment in the neighbouring health centre, but the wound failed to heal. History revealed that she had suffered this injury after placing her foot on a hot pot while cooking traditional food. The ulcer was dressed in the neighbouring health centre with Betadine alternating with antibacterial dusting powder for one month resulting in an ulcer of Wagner's stage III (Figure 1-8). On examination, her general condition was stable except for a BP value of 160/94 mmHg, HbA1c value of 9%, erythrocyte sedimentation rate (ESR) 50 mm/first hour, random blood glucose of 12 mmol/l. She had neuropathic feet (loss of protective sensation documented by absent pressure sensation as tested by 10 g monofilament) with a normal ABI.

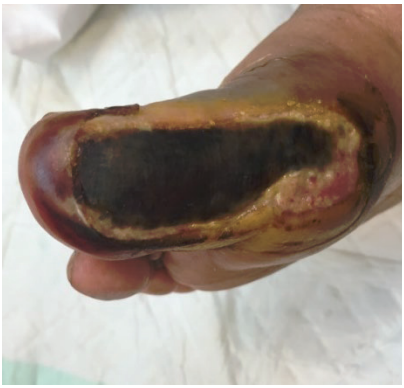

Figure 1-8: Thick black Escher formation with surrounding necrotic tissue, erythema and cellulitis

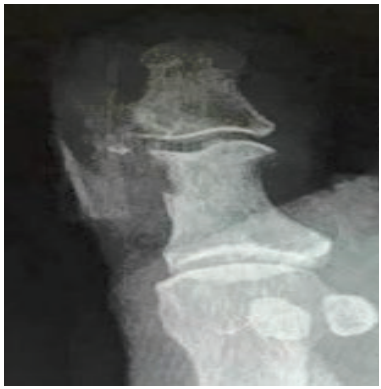

Figure 1-9: Showing punched out lytic lesion with cortical destruction of the shaft of the first proximal phalanx

After debriding the black eschar, the big toe revealed slough, necrotic tissue, and oozing pus with an exposed bone (Figure 1-8). The X-ray

revealed osteomyelitis of the first proximal phalanx shaft (Figure 1-9). She underwent daily dressing with natural honey and oral ciprofloxacin 500 mg twice daily for two weeks. The wound started to heal, but the area of necrotic bone (Figure 1-10) remained devoid of granulation tissue; hence curettage of osteomyelitis bone was performed using a sterile curette. Post curettage the wound was dressed with natural honey on a daily basis. Eight weeks later, the wound had completely healed and was covered by healthy skin (Figure 1-11). The patient was educated about her foot condition and how to examine it daily, including footwear, particularly therapeutic footwear.

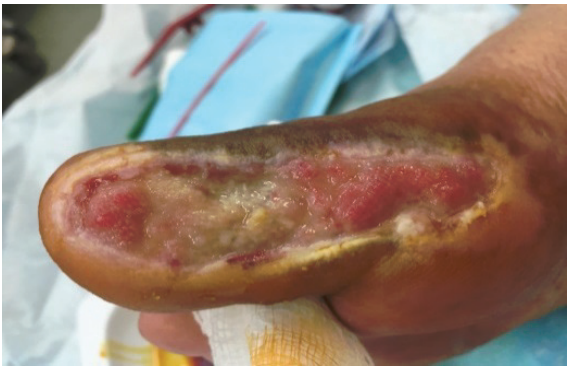

Figure 1-10: Showing healthy granulation tissue formation except in the proximal phalanx where necrotic tissue is apparent

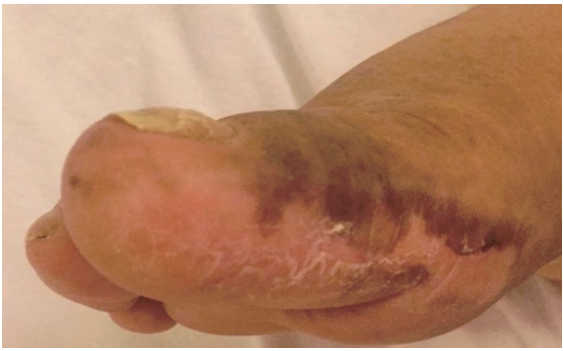

Figure 1-11: Complete healing of first big toe eight weeks later

Case Study – III

A 35-year-old female suffering from type II DM for five years duration presented with right big hallux lesion showing hyper granulation at the base of the nail following previous trauma which was neglected by the patient (Figure 1-12).The patient underwent excision of the hyper granulation tissue after application of digital block using Xylocaine injection along with the removal of the devitalized nail (Figure 1-13).

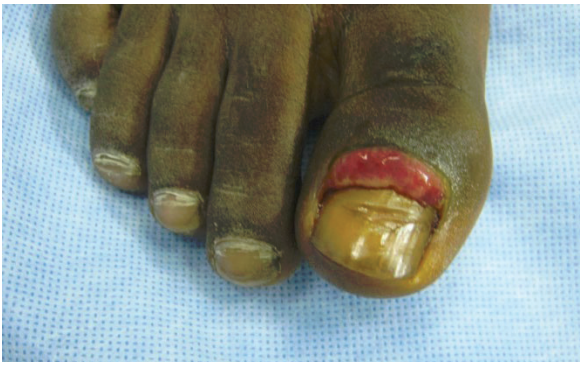

Figure 1-12: Right big hallux showing hyper granulation at the base of the nail

Figure 1-13: Post excision of the granulation tissue and nail

CHAPTER 2

DIABETIC FOOT INFECTION

DR HASHIM MOHAMED

2.1 Risk of infection

Individuals with diabetes have a higher risk of developing infections that are often more severe than in non-diabetics and carry a high risk of developing osteomyelitis[1]. Diabetic foot infections are usually polymicrobial in nature [2-8]. Prolonged impaired glycaemia results in dysfunction of the host leukocytes, thereby lowering their ability to fight bacterial pathogens, which is often complicated by the presence of peripheral vascular disease (ischaemia) because of reduced delivery of antibiotics to the site of infection.

As a result, the infection can spread rapidly and lead to significant and irreversible tissue damage [9]. Those individuals who do not have peripheral vascular diseases but suffer from peripheral sensory neuropathy will often experience a prolonged and problematic course of infection due to continued walking or delay in recognition [10,11]. Major predisposing factors leading to limb-threatening diabetic foot infections include prolonged hyperglycaemia, neuropathy, impaired immunologic responses and peripheral arterial diseases [12-14].

Foot infections are frequent among individuals with diabetes, especially following trauma; this, in turn, leads to increased risk of hospitalization and amputation. Diabetes confers a 30-fold higher lifetime risk of undergoing a lower-extremity amputation in individuals with diabetes compared with their counterparts [15,16]. Two-thirds of lower-extremity amputations are preceded by an infected diabetic foot ulcer [17,18], whereas infection-related lower-extremity amputation is surpassed only by the development of gangrene [19]. Statistically significant risk factors for developing a foot infection in individuals with diabetes include sustaining a foot wound, recurrent wounds that penetrated to the bone, peripheral vascular disease and wounds of long duration.

Additionally, neuropathy, previous history of amputation and peripheral vascular disease are each significantly and independently associated with infection, conferring 3.4-, 5.5- and 19.9-fold increased risk, respectively. Although studies in the developed world (USA) did not find any relationship between socio-economic factors, foot infections and ulceration, these findings cannot be mirrored in Third World countries where socio-economic factors are statistically linked to the development of foot ulceration [20].

2.2 Medical management of diabetic foot infections

2.2.1 Pathophysiology

Many predisposing factors related to the development of foot infections include immune system disturbances manifested by impaired phagocytosis, polymorphonuclear leukocyte migration, chemotaxis and intracellular killing [22].

Cellular immune responses, complement, and monocyte function is decreased as well [23,24].

2.2.2 Microbiological considerations

Before selecting suitable antimicrobial therapy, the clinician must be aware of the common etiologic agents responsible for diabetic foot infections along with any new antibiotic medications taken by the patient. Previous intake of antimicrobial agents can change the colonizing flora of skin ulcers [10,11]. It is worth noting that acute infections in previously untreated individuals often result from aerobic gram-positive cocci (often as monomicrobial infections). However, it is essential to be mindful that chronic ulcers often develop complex flora.

Determining the microbial aetiology of an infected wound will usually assist in subsequent management. The exact aetiologic agent(s) can be identified from specimens taken for culture and sensitivity. The sensitivity (true pathogens) can only be determined by obtaining deep tissue specimens aseptically by surgery. At a primary care level, an appropriate sample can be obtained by curettage or tissue scraping from the base of the ulcer with a scalpel after debriding the ulcer [10-13] unlike superficial swabs, which will only capture polymicrobial growing in the superficial flora.

The most common pathogen present in diabetic foot ulcers is *staph. aureus* [8]. Patients presenting at a primary care facility for daily dressing

may often be colonized with severe infections, including both aerobes and anaerobes [11,13]. Gram-negative Enterobacteriaceae usually colonize or are present in chronic or previously treated infections. In general, most patients are treated with wet dressings, including hydrogels or hydrotherapy. This approach confers a high chance of contracting *Pseudomonas* infections, especially in chronic wounds. Obligate anaerobic bacteria will usually colonize chronic wounds complicated by ischaemic necrosis or wounds penetrating deep tissues. Methicillin-resistant *S. aureus* is frequently isolated from hospitalized patients receiving antibiotic therapy [15]. However, they may present at primary care with a chronic wound in a patient attending a nursing home facility or even as an community-acquired infection in mobile patients.

2.3 Diagnosis and clinical presentation

Acute infection of a wound is usually diagnosed by the presence of systemic signs (e.g. chills, fever and leukocytosis), purulent secretions (pus), or two or more signs and/or symptoms of inflammation locally (warmth, pain, redness, induration and tenderness).

However, chronic wounds often have additional signs suggesting chronic infection, which include abnormal colouration, delayed healing, tissue friability, and on occasions, presence of foul odour. In patients with prolonged uncontrolled diabetes, peripheral neuropathy and/or ischaemia can either mask or mimic the signs and symptoms of inflammation and/or infection. Furthermore, chronic diabetic foot infections are often characterized by reduced signs of systemic toxicity, including low ESR level and reduced leukocytosis [19], even in those with limb-threatening conditions.

2.3.1 Clinical presentation

Evidence of peripheral vascular disease is present in almost two-thirds of patients suffering from a diabetic foot infection, with ~ 80% having lost their protective sensation [1]. Infections usually involve the forefoot, especially metatarsal heads, and the toes. Patients suffering from chronic diabetic foot ulcers do not often report pain, and more than half, including those with severe infections, do not have an elevated WBC count, C-reactive protein, and an elevated erythrocyte sedimentation rate or fever [19-21].

2.3.2 Assessing severity

The severity of the diabetic foot ulcer is assessed by the depth of the lesion, checking for ischaemia, and infection [22]. The diabetic foot ulcer must be thoroughly examined to look for necrotic material or foreign bodies and must be probed with a sterile metal probe or a cotton swab if a metal probe is not available. This is because deep-seated infections may often show a few superficial signs of infection.

Spread of infection to deep spaces must be suspected when there is inflammation distant from the skin wound, or when diabetic foot ulcers persist despite adequate antimicrobial therapy [23]. The primary care physician must be aware of what to keep and manage at the primary care level and what to refer urgently to the hospital when faced with a diabetic foot infection. Patients with a deep-seated infection must be admitted for possible surgical interventions at surgical podiatry clinics or hospital-based foot and ankle surgeons for incision and drainage, and metabolic control. The patient must be referred to the hospital if primary care has no offloading devices, if the patient is frail, suspected of having deep-seated infections and/or ischaemia, and is unlikely to comply with antibacterial therapy.

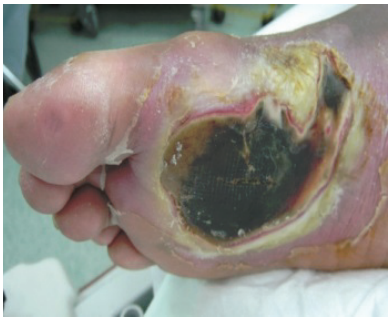

Figure 2-1: Deep infection of the forefoot and Escher formation on a neglected diabetic foot ulcer

2.3.3 Bone infection

Although diagnosing osteomyelitis is essential, it can also be challenging. Diagnostic, clinical and laboratory signs and symptoms are often unhelpful [36]. Osteomyelitis (contiguous spread of a deep soft tissue infection through the bone cortex to the marrow) may not be evident on plain X-ray during the first two weeks. Abnormalities commonly seen on X-ray are destructive bone

changes resulting from peripheral neuropathy (i.e. osteoarthropathy, neuroarthropathy) that are common in diabetes. Primary care physicians may request more sensitive imaging studies such as magnetic resonance imaging (MRI) or radionuclide scans, which may not be readily available [9-21]. A more practical and confidential approach that can be used in primary care was described in 1995 by Grayson et al. [22]. The technique involves introducing a sterile metal probe through the wound until it reaches a palpable bone. This technique has a positive predictive value of 89% [24-33]. Since its discovery, the probe-to-bone technique has been widely used worldwide for detecting osteomyelitis in diabetic patients with a foot wound. A recent study involving 356 patients with a diabetic foot ulcer showed a positive predictive value of 0.97, and a negative predictive value of 0.93 for the probe-to-bone test [37].

Primary care physicians managing a patient with chronic diabetic foot ulcer (> 4 weeks), which is large (> 2 cm), and deep (> 3 mm) and/or associated with a substantially elevated erythrocyte sedimentation rate (> 70 mm/h) should evaluate for possible osteomyelitis [38,39]. Obtaining plain radiographs for most patients with a diabetic foot infection is a must since many patients underestimate the duration of their wounds. Radiographic changes in infected bone generally take at least two weeks to become evident. the presence of osteomyelitis is suspected and the patient is stable, a repeat X-ray in two weeks is quite useful and will avoid requesting expensive imaging such as MRI.

Nonetheless, treating osteomyelitis is difficult for several reasons. Invading bacteria can escape attacks by inflammatory cells and cause osteolysis by interacting with host immune system cells [6]. Furthermore, the invading bacteria, especially *Staphylococcus aureus*, express receptors (adhesions) for bone matrix proteins [40] and become engulfed into a biofilm, thereby avoiding eradication by antibacterial agents. As a result, surgical resection of infected and necrotic bone becomes a necessity.

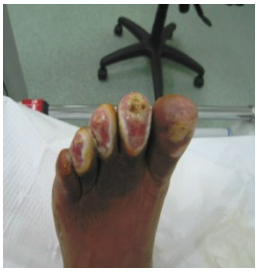

Figure 2-2: Osteomyelitis of distal phalanx of second left toe prior to excision

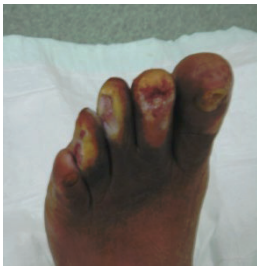

Figure 2-3: Post excision of distal phalanx of second left toe

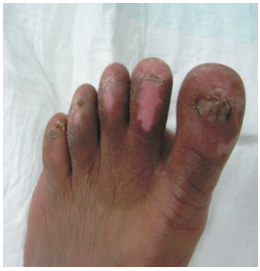

Figure 2-4: Complete healing post excision of the distal phalanx of the second left toe

If the osteomyelitis is caught, early antibiotic treatment may suffice when combined with minimal debridement. However, patients usually present late to the clinician and underestimate the duration of the ulcer history since they do not feel pain as a result of neuropathy. Hence, chronic osteomyelitis managed by antibiotics and limited debridement and drainage is largely unsuccessful [41-43]. Poor tissue penetration of older antibiotics, especially in the presence of limb ischaemia, are partly to blame. Experts in the field have stated that "curing osteomyelitis with antibiotics alone is difficult"[44] and that "surgical removal of infected bone down to living parts of the bone is of critical importance" [45].

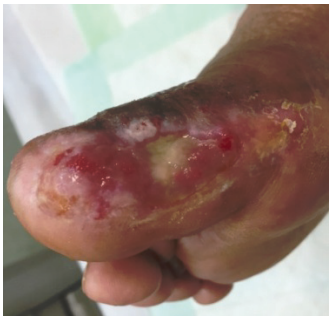

Figure 2-5: Failure of ulcer to heal despite antibacterial therapy for four weeks due to the presence of osteomyelitis (yellow necrotic tissue in the centre of the ulcer) of the right big hallux.

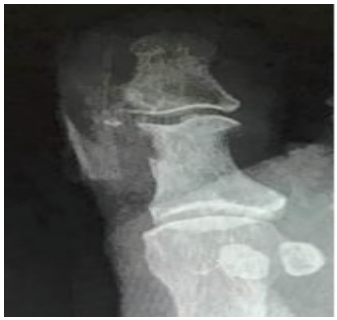

Figure 2-6: Showing necrotic bone (osteolysis) in the middle phalanx of the right big hallux of the same patient

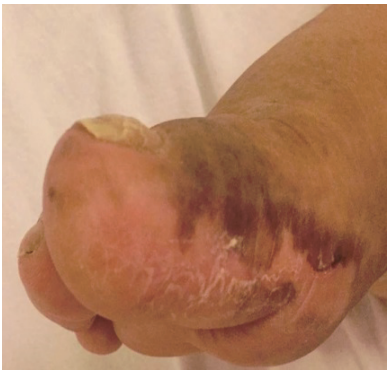

Fig 2-7: Complete healing of the right big toe following combined approach (antibiotic plus excision of necrotic bone)

Nonetheless, new antibiotics have better penetration capacity and the role of medical management of osteomyelitis may be favoured, especially in patients where debridement is contraindicated. New classes of antibiotics have a higher bioavailability and tolerability when taken orally (especially fluoroquinolones, clindamycin aminopenicillin/penicillinase inhibitor combinations, oxazolidinones and carbapenems). These new classes of antibiotics have the capacity to concentrate in the infected area after penetrating the glycocalix biofilm [23,25,45].

Recent evidence suggests that a combination of appropriate antibiotics and early surgery may be more effective than either approach when implemented individually. Ha Van et al.[46] documented that local excision increased the cure rate from 57% to 78%, compared with historical controls. If the diagnosis of osteomyelitis is in doubt, then other types of scans may be useful [39,41]. Bone scans (e.g. Tc-99) are sensitive (~85%) but lack specificity (~45%). Leukocyte scans (e.g. In-111 or ^{99m}Tc-HMPAO) have similar sensitivity and more specificity than bone scans (~75%). This scan can be used to assess if the infection has been arrested or not. However, MRI remains the diagnostic tool of choice, with a sensitivity of > 90% and a specificity of > 80% [44,45]. The best approach of identifying the causative bacteria is to take necrotic bone at the time of debridement and curettage, and send for both culture and histology. Many patients may have taken a variety of antibiotics for various lengths of time before the presentation to the clinician; therefore, culture results might be negative. As a result, the histopathological findings of leukocytes and necrosis will point towards infection. Most cases of osteomyelitis of the diabetic foot are polymicrobial in origin, with *S. aureus* being the most common invading bacteria (isolated in ~ 40% of cases). However, streptococci (~ 30%), *Staphylococcus epidermidis* (~ 25%), and Enterobacteriaceae (~ 40%) have also been isolated in some instances [39].

2.4 Treatment

2.4.1 Antibiotic therapy

Diabetic foot infections are usually treated empirically with broad-spectrum antibacterial regimens taking into account the renal status of the patient (estimated GFR), patient allergies, recent antibiotic therapy and local antibiotic resistance patterns. The prescribing clinician must select an antibiotic regimen that is active against staphylococci and streptococci. In severe cases or where the patient had been previously treated, prescribed

antibacterial agents must cover commonly isolated *Enterococcus* species and gram-negative bacilli. On the other hand, foul-smelling, necrotic or gangrenous wounds will usually require anaerobic antibacterial therapy.

Successful eradication of infection depends on obtaining a therapeutic antibacterial concentration at the site of infection.

2.4.2 Intravenous therapy

This approach usually achieves an adequate serum level of antibiotics, especially in the following situations where the patient

- has systemic signs of infection
- has a severe deep-seated infection
- is unable to withstand oral therapy
- has severe peripheral vascular disease and/or gangrene.

Once the patient is stabilized, and the infection is responding, they can be switched to oral therapy; most patients can have their treatment changed to oral therapy.

2.4.3 Oral therapy

This is less expensive, usually well-tolerated and has fewer side effects than the intramuscular or intravenous approach. It is reserved generally for mild to moderate cases of infection and when the patient can tolerate the drugs orally.

The practising clinician at primary care can avail of the available antibiotics, which include but not limited to fluoroquinolones and clindamycin, which are well absorbed orally and have adequate tissue concentration [47] even in inflamed tissues [48] due to their ability to penetrate the bacterial biofilm. In patients with the severe peripheral disease, therapeutic tissue concentration of antibiotics becomes an issue even when serum levels of the antibiotic are adequate [49].

Therefore, in these cases, the clinician is advised to refer the patient for an initial intravenous antibiotic for 1–2 weeks, then they can be switched back to an oral antibiotic for another 2–4 weeks. The use of an antiseptic rinse solution is contraindicated since it damages the newly granulating tissue. Similarly, topical antibacterial agents have no role since polymicrobial bacterial colonization is usually present on the surface of the

ulcer, and no published scientific data currently exist on their efficacy in treating diabetic foot infections.

On occasions, the infection may worsen despite adequate antibacterial coverage, hence the need to consider surgical intervention and/or invasive peripheral vascular supply assessment becomes a necessity.

Effective antibacterial agents used alone or in a combination that has been clinically proven in prospective trials targeting diabetic foot infections include [50]

- penicillin/β-lactamase inhibitor congeners (amoxicillin/clavulanate) orally [51-55];
- cephalosporins (cephalexin orally; cefoxitin and ceftizoxime parenterally) [25,56-60];
- fluoroquinolones (ciprofloxacin, levofloxacin, and ofloxacin, orally and intravenously) [61];
- clindamycin (orally and parenterally) [25,62,63].

2.4.5 Duration of therapy

Duration of antibiotic therapy for diabetic foot infections depends on many factors including the severity of infection, systemic manifestation, presence or absence of osteomyelitis, presence of necrotic tissue, types of pathogens isolated, and signs and symptoms of peripheral vascular disease. However, on average, for mild to moderate infections, a 1–2 week course is effective [64]. In contrast, more serious infections require therapy for longer than two weeks. The duration of antibacterial therapy is shortened if the wound is debrided, if necrotic tissue is removed and the wound is adequately offloaded. If there is an extensive infection, coupled with gangrene or inadequate vascular supply, a longer duration of therapy will be needed. Moreover, prolonged or intermittent suppressive antibacterial therapy will be required if the patient is unable or unwilling to undergo surgical resection.

2.4.6 Treatment of osteomyelitis

Ideally, bone culture results will decide the choice of antibiotic cover, especially because of the need for long-duration therapy [65]. Treatment of osteomyelitis requires an initial parenteral approach [66,67] for two weeks, followed by prolonged (at least six weeks) antibacterial cover.

Several retrospective studies have shown that around two-thirds of cases of osteomyelitis of the diabetic foot can be arrested with antibiotic therapy alone [68,69].

Due to their excellent bioavailability, the oral combination of clindamycin and fluoroquinolones may be adequate for most cases. Shorter duration of oral therapy will be required if all necrotic (infected) bone is removed.

2.4.7 Outcome of treatment

The practising clinician must realize that for adequately treated mild to moderate infection, a good clinical response is expected in around 80%–90% [70,71] of cases. For more extensive or deeper infections, the expected success rate is around 50%–60% [72,73]. Moreover, healing of diabetic foot infections is influenced by several factors including:

- peripheral vascular disease
- smoking
- degree of glycaemic control
- presence of comorbid conditions including Chronic obstructive pulmonary disease (COPD), nephropathy and retinopathy
- positive probe-to-bone test or exposed bone
- toe pressure of > 45 mm Hg or an ankle pressure of > 80 mm Hg
- low peripheral WBC count of < 12,000/mm^3 [19]
- the presence of oedema
- improper offloading
- compliance

Nonetheless, the practising physician must be alert to the possibility of foot infection if the patient suddenly develops redness of the skin, pain in a previously insensate foot, warmth and the classical signs and symptoms of foot infections.

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CASE STUDY – IV

A 55-year-old patient presented with post amputation of the right big hallux carried out in the main general hospital. The patient had been suffering from type II DM for the past eight years and sustained the initial injury after pulling the skin proximal to the first metatarsal head. This became inflamed, infected, and was ignored by the patient for two months because he was scared of going to the hospital until he developed a deep infection of the forefoot, including osteomyelitis of the first big hallux. Subsequently, he underwent disarticulation at the first metatarsophalangeal (MTP) joint.

He presented with a bad looking stump with necrotic tissue and subcutaneous bruises as seen in Figure 2-8. The necrotic tissue was debrided in the clinic, and the patient was offered cotton bandage instead of crepe bandage. The wound was washed with normal saline, after which natural honey was placed on the wound and was covered with a petroleum jelly-based dressing (Adaptic™).

This was done daily; a month later, healing progressed and filled the base of the wound with healthy granulation tissue, which is apparent (Figure 2-9). The patient continued the same dressing technique, and the wound almost closed in two months (Figure 2-10). Complete healing occurred ten weeks later (Figure 2-11).

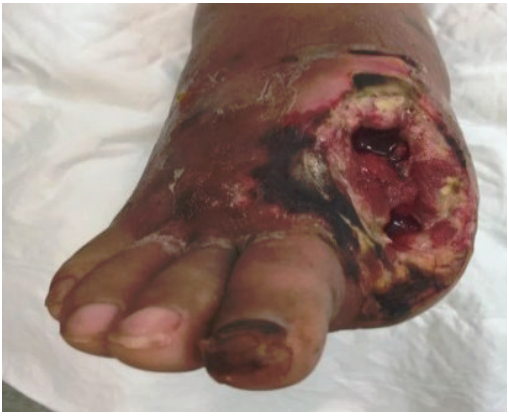

Figure 2-8: A deep ulcer of Wagner's grade III stage with necrotic tissue in the base and subcutaneous bleeding around the ulcer due to tight crepe bandaging

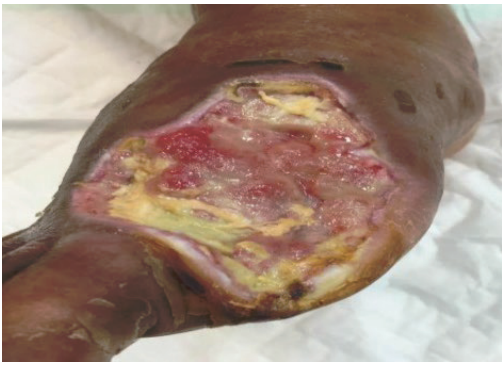

Figure 2-9: One month later showing recovery of subcutaneous tissue and filling in of the stump base with healthy granulating tissue

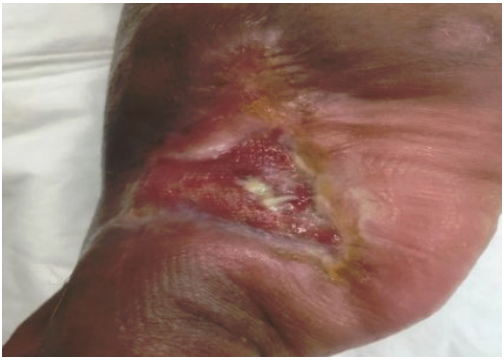

Figure 2-10: 90% reduction in the size of the ulcer two months later

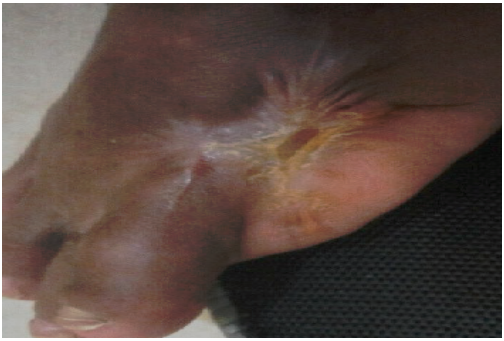

Figure 2-11: Showing complete healing ten weeks later

CASE STUDY – V

A 65-year-old heavy smoker, male, suffering from type II DM for the past 35 years, presented after being discharged from the hospital with a diabetic foot ulcer Wagner's grade IV, resulting in gangrene of the left fifth toe and a necrotic dorsal ulcer of the left foot. The wound started as a scratch on the dorsum of the foot three months earlier, which became infected and was ignored by the patient as he feared amputation. Later, the foot became swollen, tender and red, and the patient went to the main hospital where he had incision and drainage of the dorsal abscess.

During his hospital stay he developed fifth toe gangrene. On presentation to the health centre, the wound was showing yellowish devitalized tissue and dry gangrene of fifth toe (Figure 2-12). It was cleaned with normal saline, and devitalized tissue was debrided using a sharp scalpel.

The gangrenous toe was left to auto amputate as it was dry gangrene in nature. The patient was counselled about smoking cessation and optimizing his blood glucose level; meanwhile, an X-ray of the foot did not reveal any bony changes indicative of osteomyelitis.

Daily dressing continued with cleaning the wound with normal saline followed by application of natural honey, which was covered by a glycerine-based dressing (Adaptic (Acelity)) and wrapped with a cotton bandage. On occasions, the wound would become dry, and as a result, an alginate-based dressing (Nu-Gel™ (Acelity)) was used. Three months later, the wound reduced by 98% with auto amputation of the dry gangrenous toe (Figure 2-13). Daily dressing continued in the health centre, and complete healing was achieved after four months (Figure 2-14).

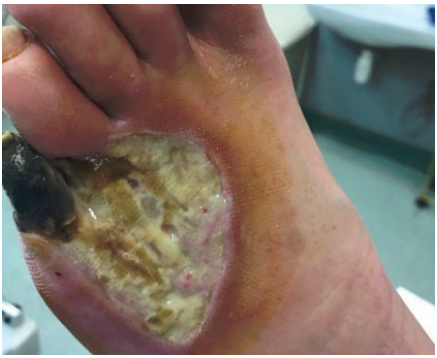

Figure 2-12: Gangrene of the fifth left toe and Wagner's grade IV ulcer of the dorsum of the foot showing thick yellowish devitalized necrotic tissues at the base of the ulcer

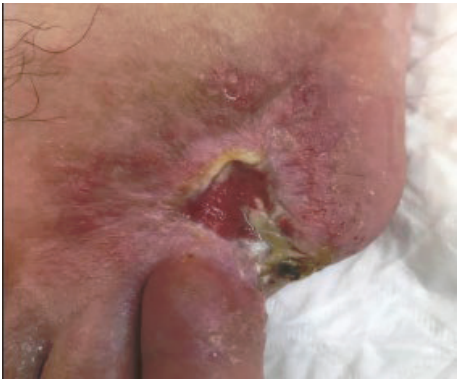

Figure 2-13: The wound has reduced in size by 98% after three months with auto amputation of the fifth gangrenous toe

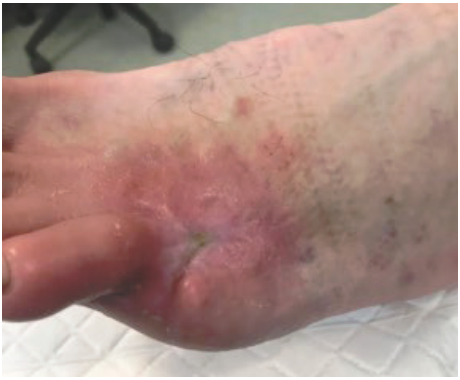

Figure 2-14: Complete healing achieved four months later

Case Study – VI

A 63-year-old male patient with type II diabetes complicated by long-standing peripheral neuropathy, chronic renal insufficiency and morbid obesity presented with a second-degree thermal burn (Figure 2-15), which he sustained after walking barefoot on hot tarmac. The wound was cleaned using a 20-gauge syringe; the peri-wound area was dressed using Betadine® solution to fight surrounding bacteria and to cause dryness of the macerated skin. Afterwards, natural honey was applied directly on the wound and covered by a secondary glycerine-based dressing (Adaptec), which was subsequently covered with cotton gauze and the final wrapping done using a cotton bandage. The foot was offloaded utilizing a custom-made offloading material consisting of multilayered incontinence sheets, and the patient was instructed to have minimal ambulation. Three days later, the wound looked less aggressive with the disappearance of the maceration in the peri-wound area (Figure 2-16). One week later, healthy skin covered the entire wound area (Figure 2-17).

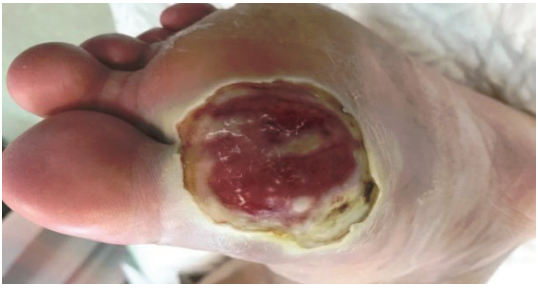

Figure 2-15 Upon initial presentation

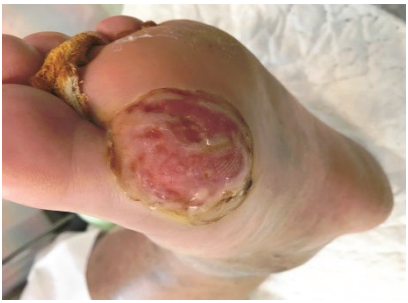

Figure 2-16: Three days later after offloading and application of natural honey; note the Betadine gauze in the first and second web spaces to dry the macerated areas

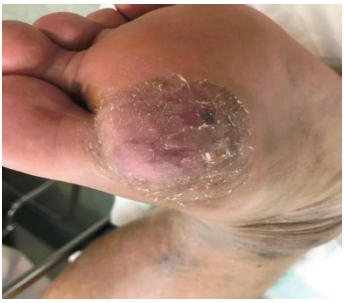

Figure 2-17: Complete healing one week later

CHAPTER 3

RISK OF ULCERATION

DR HASHIM MOHAMED

People with diabetes may suffer considerable morbidity as a result of ulceration and amputation [1]. Their suffering is worsened due to pain, sick days, financial burden, social isolation, depression, low quality of life and stigma. Various studies have demonstrated that foot ulcer is an important antecedent of lower-extremity amputation [2,3]. Different methods and techniques have been studied in predicting the risk of ulceration, including lower-extremity sensory testing, assessment of peak plantar pressure and thermography [5-7].

Unfortunately, these modalities are largely unavailable to primary care practitioners, especially in the developing world. Therefore, general practitioners must use inexpensive tools that predict the risk of ulceration, including the 10 gram monofilament, 128 MHz tuning fork and peak plantar pressure.

3.1 Peak plantar pressure

Increased plantar pressure, especially at the heads of the metatarsal–phalangeal joints (bony prominence), is associated with a higher risk of ulceration. A systemic review conducted by Crawford et al. (2007) examined four cohort studies and two case-control studies measuring peak plantar pressure, using four different dynamic measuring systems (Musgrave, F-scan, EMED and a pedobarograph). High plantar pressures constituted a risk of ulceration among patients with type II diabetes: SMD 0.98 N/cm (95% CI 0.63–1.33) for case-control studies, and SMD 0.47 N/cm (95% CI 0.24–0.70) for cohort studies [8].

Figure 3-1: Ink pad for measuring plantar pressure

3.2 Quantitative measurement

Traditionally, semi-quantitative measurement of plantar pressure used to be carried out using the ink pad on which the patient stands and, as a result, leaves an impression in different shades. Unfortunately, this method although very specific, is not very sensitive since it only measures the pressure while the patient is standing still and not in motion, which is the usual case for an ambulatory person. Currently, methods for quantitative assessment of plantar pressures use computer-based systems where the patient walks on the electronic pad and/or a specially designed sock or shoe fitted with transducers in a thin pliable layer that is in direct contact with the foot. As a result, information from the different parts of the foot is fed into the computer to find out which area of the foot bears the greatest pressure.

Other methods include the use of the vibration perception threshold meter, also known as the neurothesiometer or biothesiometer, which is a simple handheld instrument with a vibrating rubber tractor. The instrument is connected to a base unit displaying a linear scale of applied voltage, ranging from 0 to 100 volts [9,10]. The tractor is held vertically on the pulp of the big toe. The clinician increases the voltage gradually until the patient perceives a vibration. The vibration perception threshold for each foot is determined by calculating the mean of three readings that are measured in volts.

In a prospective four-year study, a vibration perception threshold greater than 25 was said to be an indicator of neuropathy, which is predictive of higher risk of ulceration with a sensitivity of 83% and a specificity of 63%.

Figure 3-2: Foot scan – measures plantar pressure

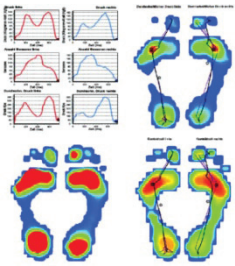

Figure 3-3: Foot scan showing increased plantar pressure under the metatarsal heads

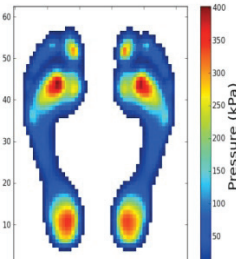

Figure 3-4: Plantar pressure graph (red areas are those with highest plantar pressure and green areas are those with the lowest plantar pressure)

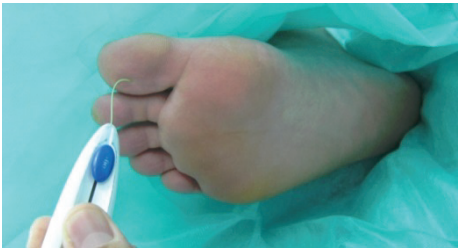

Figure 3-5: Use of 10 gram monofilament where the tip of monofilament should be held in a buckled fashion for 1–3 seconds

Figure 3-6: Use of 12 MHz tuning fork starting distally at the tip of the great toe or dorsal aspect of first metatarsal head and worked up proximally

Figure 3-7: An example of a commercially available biothesiometer

Risk factors for ulceration include:

- a higher level of A1C;
- sensory neuropathy;
- poor vision associated with higher risk of ulceration, which may be due to the impaired ability for self-care [13];
- history of previous foot ulceration and amputation [14];
- amputation producing changes in gait and weight distribution thereby increasing the risk of ulceration;
- foot deformities increasing the subsequent risk for foot ulcer [15] including bunions, overriding toes, hammer toes, and mallet toes;
- improper footwear (tight pointing coupled with neuropathy);
- presence of tinea pedis.

Sensory neuropathy is the main risk factor for ulceration according to prospective clinical studies [16-19] – it can be assessed quickly and cost effectively via the use of the standard 10 gram monofilament.

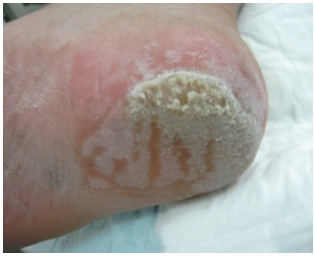

Figure 3-8: Hard callous formation on the heel

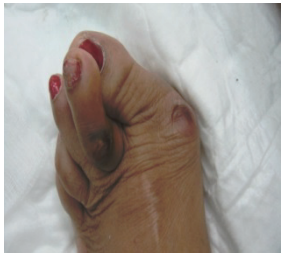

Figure 3-9: Overriding toe

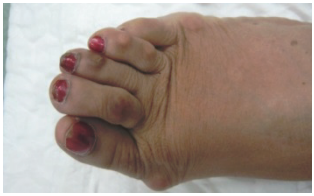

Figure 3-10: Hallux valgus known as bunion formation along with presence of dorsal corns on the second, third and fourth toes

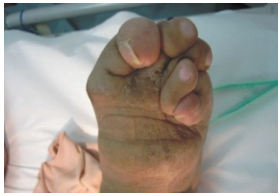

Figure 3-11: Severely deformed forefoot with Hallux valgus coupled with overriding toes and Charcot arthropathy of the midfoot

3.2.1 The monofilament technique

The 10 gram monofilament is a sensitive tool that assesses pressure sensation in the diabetic foot. It is widely accepted as a sensitive and specific tool that can be used in daily practice. However, physicians need to be aware that commercially available monofilaments are not as sensitive as the standard 10 gram Semmes-Weinstein monofilament. Therefore, the case of peripheral neuropathy might be missed if non-standardized monofilaments are used.

Semmes-Weinstein monofilaments are correctly calibrated, single-fibre nylon threads that generate reproducible buckling stress. If there is considerable loss of sensation, then the patient will not be able to feel the presence of the monofilament at buckling. The 10 g monofilament is one of the best indicators to assess the loss of protective sensation [22-24].

The process includes the following steps:

- Before examining the patient, show them the 10 g Semmes-Weinstein monofilament.
- The monofilament must be demonstrated on the inside of the clinician's forearm and then repeated at the same site on the patient with eyes open so that the sensation is appropriately understood.
- The patient is asked to say "yes" or "no" every time they feel the monofilament, and also, the patient must be asked to state the location of the touch with both eyes closed to avoid guessing.
- The patient is instructed to close both eyes, and then the monofilament should be applied and allowed to buckle for three seconds.

A standardized protocol must be followed, such as examining six sites on the plantar aspect of both feet [25]. These are the plantar aspect of the hallux, first, second, third, fourth and fifth metatarsal heads, avoiding callous [25], with loss of perception to one site indicating loss of perception to that weight of monofilament [26-29].

In each point of contact, the test must be repeated three times. If the patient answers incorrectly two or more times at that point, it should be considered as a definite symptom of neuropathy.

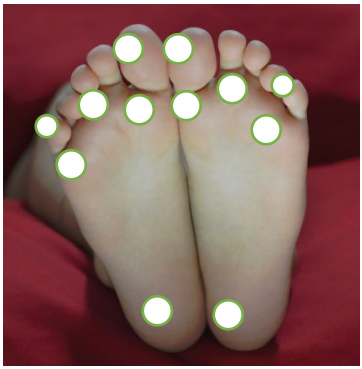

Figure 3-12: The following six sites should be tested

Many studies have utilized different screening criteria; some used as few as three sites, while others went up to ten sites. However, the sensitivity and specificity of the test increase when more sites are tested. Kamei, in his study, reported sensitivity and specificity using the 10 g Semmes-Weinstein monofilament at three points, of 5%–22.5% and 88.1%–97.6%, respectively [32]. Mason and colleagues, on the other hand, reported sensitivity and specificity of monofilament at 10 points, respectively 92.1%, and 100% [33]. Although the use of monofilament to detect neuropathy had been in use since 1995, the number of points that must be considered is still being debated. The monofilament must be rested for 24 hours after using on ten patients previously, as it will lose its sensitivity after the tenth patient [34].

Although prior studies showed a lower risk of diabetic foot ulcers among patients suffering from tinea pedis [6,20], a new sizeable prospective study involving 1,285 subjects showed a higher risk of ulceration in individuals suffering from fungal infections of the foot, especially onychomycosis and web spaces tinea pedis [21].

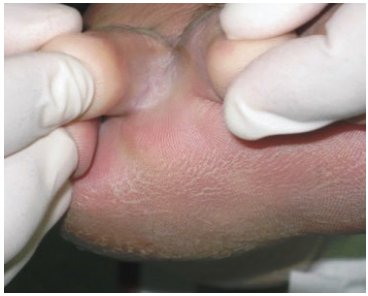

Figure 3-13: Tinea pedis in the second web space

3.2.2 The 128 MHz tuning fork technique

An initial assessment must be performed before performing the actual test. First, the clinician applies the 128 MHz vibrating tuning fork on the patient's forehead or sternum to understand the sense of vibration and not the tuning fork's contact with the body. Afterwards, the tuning fork is vibrated with a stroke on the palm for approximately 40 seconds and then placed on the bony prominence on the back of the thumb. The patient is then asked to report the perception of both the beginning of vibration sensation and the end of vibration on dampening [31]. With the patient's eyes closed, the clinician applies the tuning fork to the bony prominence of the dorsum of the first toe proximal to the nail. The procedure is repeated on the same foot, then twice on the other foot in an arrhythmic fashion, so the patient cannot guess when the tuning fork is to be applied. If the patient feels no vibration, move the fork proximally to the bony malleoli of the ankle, the tibia bone, tibial tuberosity and finally, the anterior iliac crest. If there is doubt whether that the vibration sense is intact or not, the physician can ask the patient to tell when the tuning fork has stopped vibrating.

Another sensitive way of testing for peripheral neuropathy is the use of the diabetic neuropathy symptom score (DNS), which can be administered to the patients on their follow-up visits. The DNS has a sensitivity of 65.4% and a specificity of 100%. In short, the DNS score is a four-item, validated symptom score that has a high predictive value to screen for diabetic peripheral neuropathy [38]. Four symptoms are elicited – unsteadiness while walking, neuropathic pain, paraesthesia and numbness. The presence of one symptom is scored as 1 point; the maximum score is 4 points. A score of 1 or higher is defined as positive for diabetic peripheral neuropathy (Table 3-1).

Table 3-1 Diabetic neuropathy symptom score (DNS)

In the last two weeks:	Yes	No
Are you experiencing unsteadiness in walking?		
Do you have burning, aching pain or tenderness in your legs or feet?		
Do you have a pricking or tingling sensation in your legs or feet?		
Are you experiencing any numbness or loss of feeling in your legs/feet?		
Each 'Yes' answer is scored as 1 point (score range = 0 to 4)		

A reduction of the rate of re-ulceration by up to 60% and lower limb amputation by up to 85% had been achieved by allocating adequate intervention modalities in high-risk patients with type II diabetes [29-31].

3.3 Conclusion

In 50% of patients with diabetes who suffer from peripheral neuropathy, up to half will have numbness as their only symptom, or they may be asymptomatic [3]. Diabetic peripheral neuropathy usually runs an insidious course. As a result, clinicians must be proactive in routinely assessing their patients during follow-up, especially those who already suffer from retinopathy or nephropathy. On each follow-up visit the patient should be questioned about different symptoms such as pain, numbness, tingling, burning and instability while walking. The patient should also be tested for signs of neuropathy with either a 10 gram standardized monofilament, a 128 MHz tuning fork or a biothesiometer, which may pick up diabetic peripheral neuropathy in asymptomatic patients. Since the main causative factor of both foot ulceration and amputation is peripheral sensory neuropathy, clinicians must choose inexpensive, quick, easy to administer and accurate methods/instruments to assess patients for risk of ulceration to allocate and distribute medical resources and personnel accordingly.

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CASE STUDY – VII

A 65-year-old male patient who had type II diabetes for the past 35 years, was morbidly obese and a non-smoker presented with a swollen foot after being managed in various hospitals, health centres and private clinics. His initial examination revealed a Charcot foot abnormality with amputated second and third toes (Figure 3-14). The plantar aspect of the foot revealed stage II Wagner's grade ulceration on previously grafted skin (Figure 3-15). An X-ray revealed a "crushed ice" appearance of the mid and hindfoot. The patient refused to offload. The ulcer was dressed using alginate (Nu-Gel™, Acelity) and petroleum jelly-based dressing (Adaptic™) and wrapped with cotton gauze. Unfortunately, the patient was non-compliant and refused strict offloading. He used to come to the health centre twice daily with bleeding from his wounds from stepping down on the floor. Three months later, the patient stopped attending the clinic and could not be contacted.

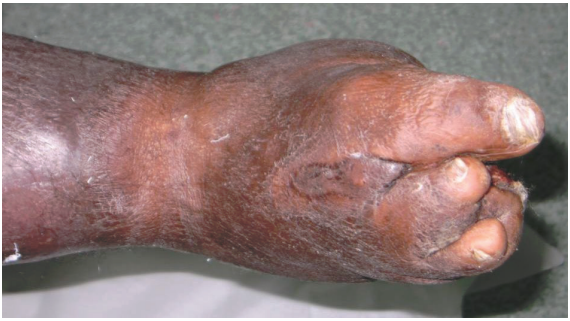

Figure 3-14: Showing deformed foot (rocker-bottom) foot due to Charcot arthropathy

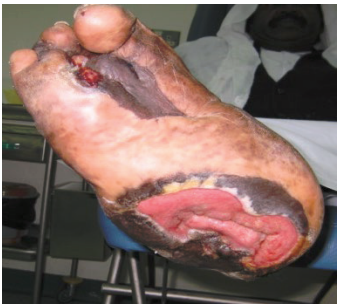

Figure 3-15: Showing deformed foot with huge ulcer 10 × 4cm Wegner's grade II in a previously grafted skin and a second ulcer at the second MTP joint

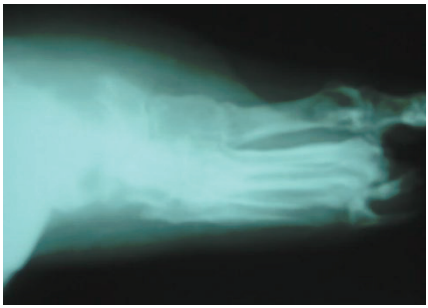

Figure 3-16: Showing complete destruction of the midfoot bones, the talus, and the calcaneus

CASE STUDY – VIII

A 55-year-old male presented with a second-degree thermal burn after placing his right foot in front of a hot charcoal fire (Figure 3-17).The patient was placed on oral ciprofloxacin to cover the possibility of *Pseudomonas* infection, and daily cleaning with normal saline was carried out followed by the application of natural honey, which was covered with a glycerin-based dressing (Adaptic-Acelity). The patient was offloaded using an ordinary three times folded incontinence pad, as removable cast walkers were not available. One month later, the wound reduced by 97% (Figure 3-18) with complete healing being achieved in six weeks (Figure 3-19).

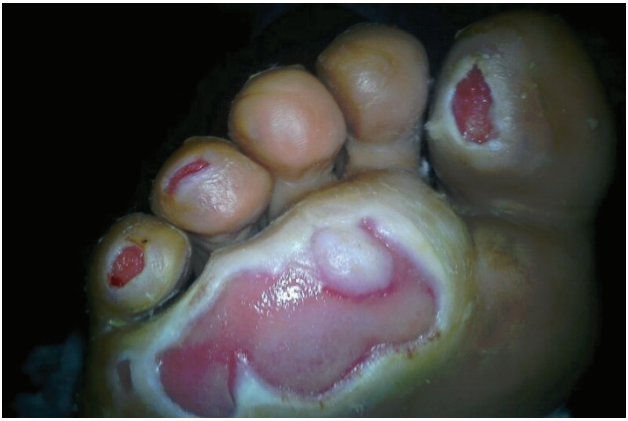

Figure 3-17: Second-degree burn involving first, fourth and fifth toes along with distal foot region

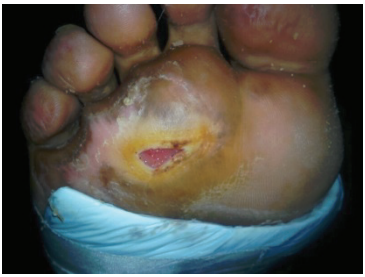

Figure 3-18: 98% reduction of the wounds with return of normal skin and no contractures

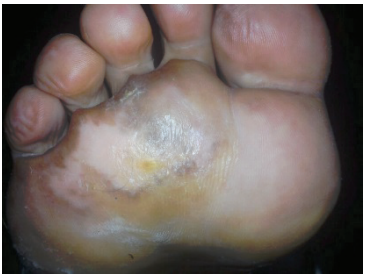

Figure 3-19: Complete healing with return of normal skin six weeks later

CASE STUDY – IX

A 55-year-old male patient with type II DM, hypertension and obesity developed contact dermatitis after wearing new leather sandals (Figure 3-20). The patient's wife had placed his feet in a hot water bath (whirlpool) (see Figure 3-21); the condition was further exacerbated by rubbing his feet with a volcanic stone (pumice) (Figure 3-22). The patient was placed on oral ciprofloxacin to target *Pseudomonas aeruginosa* which is common in patients with burns. The wound was cleaned with normal saline; natural honey was applied and covered with petroleum jelly-based dressing (Adaptic). The wound was dressed daily, and complete healing was achieved six weeks later (Figure 3-23).

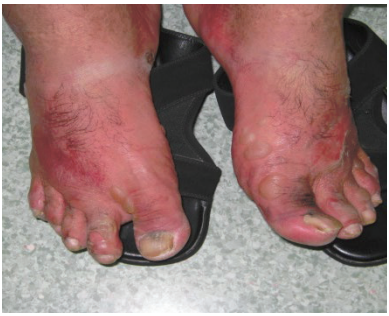

Figure 3-20: On presentation, the patient displayed contact dermatitis and second-degree burns with multiple vesicles and cellulitis after wearing leather sandals, and immersing the foot in a whirlpool!

Figure 3-21: Whirlpool soaking machine used by the patient

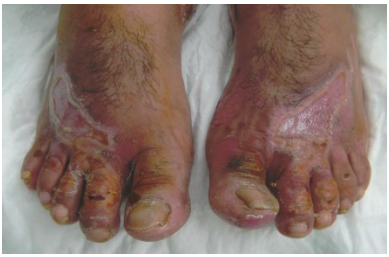

Figure 3-22: Later, two dorsal ulcerations became apparent after his wife rubbed the skin with a volcanic stone!

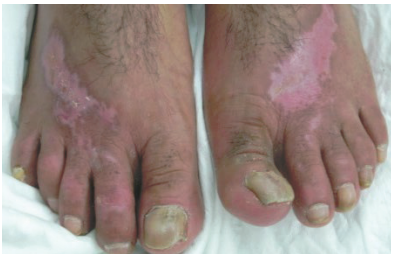

Figure 3-23: Complete healing six weeks later

CHAPTER 4

ASSESSMENT OF THE DIABETIC FOOT AT PRIMARY CARE LEVEL

DR HASHIM MOHAMED

While a thorough foot examination remains the pivotal component of foot assessment, history presents another vital piece of foot assessment. Vital components of the patient history include the duration of diabetes, footwear inside and outside the house, comorbid conditions such as hypertension, peripheral vascular disease, coronary artery disease, past cardiovascular surgeries and medications. The clinician must assess the patient for tobacco consumption since tobacco consumption is a significant risk factor for peripheral vascular disease and peripheral neuropathy. The patient must be asked about past ulceration or amputation, including neuropathic symptoms (numbness, pain, parasthesia, allodynia, burning sensation, aches, etc.) and peripheral vascular symptoms (exertion-induced calf muscle pain not present while the patient is at rest, which needed stopping, and resolves in 10 minutes or less after rest) [1,2], impaired vision and renal impairment.

4.1 General inspection

A careful inspection of the footwear is one of the first things to be carried out, and the clinician needs to inspect the feet in a well-lit room. Since foot deformities and inappropriate footwear are common causative factors for foot ulceration [3,4], the footwear must be inspected to find out if it is appropriate for the patient or not. Inappropriate footwear, for instance that is too small or too tight, can result in redness of the skin, blister formation, corns, callouses and ulceration, especially in patients with peripheral neuropathy.

Figure 4-1: Proper footwear (round, soft fibre, straps and no laces)

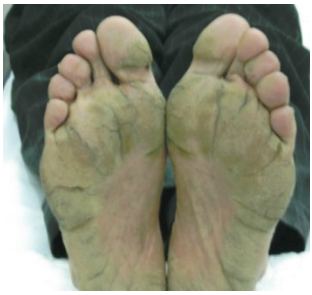

Figure 4-2: Excessive plantar callus formation due to inappropriate footwear and rubbing

4.1.1 Dermatological assessment

Both feet should be inspected for the presence of hair (the absence of which may signify peripheral vascular disease), skin colour (pallor and shiny skin representing ischaemia, whereas red skin, may represent cellulitis or dermatitis), and web spaces. The web spaces should be inspected for maceration and tinea pedis which may coexist at times with bacterial infection, especially *Pseudomonas aeruginosa*, giving rise to a light greenish-bluish discolouration on top of the whitish discolouration due to tinea pedis. Nails should be inspected for abnormal colour, contour, and thickness (nail dystrophy), including ingrowing toenails and onychomycosis. The clinician must be aware that on occasions, callous formation at the plantar aspect may hide subcutaneous haemorrhage underneath it. The temperature of the skin must be recorded using an infrared thermometer since high temperature, along with unilateral foot swelling, may indicate the presence of Charcot foot. On the other hand, skin temperature differences (lower than normal) may be predictive of peripheral vascular disease, which requires prompt referral to a vascular unit [5-8].

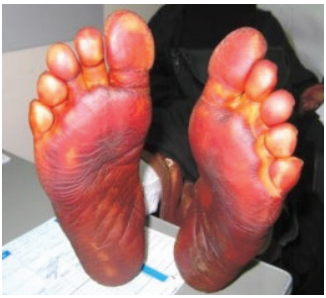

Figure 4-3: Excessive dryness of the feet due to the use of natural henna paste

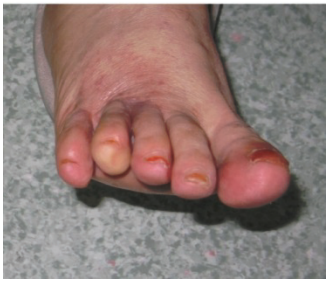

Figure 4-4: Inter digital third web space tinea pedis leading to dorsal fungal cellulites

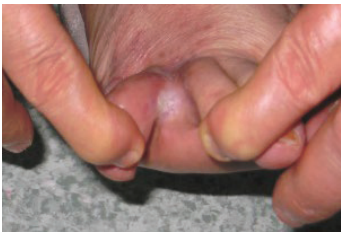

Figure 4.5: Evident third toe web space tinea pedis after proper examination

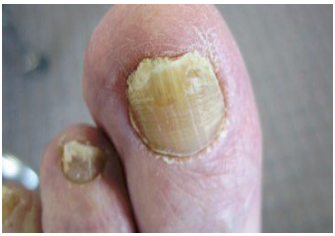

Figure 4-6: Thick, discoloured and dystrophic nails due to fungal infection (onychomycosis)

4.1.2 Musculoskeletal assessment

The musculoskeletal assessment of the foot should include examination for any gross deformity such as Charcot's foot (see Figure 4-9), overriding toes, high arched foot or digital amputation. Rigid deformities include overriding toes, hammer toes, mallet toes and claw toes.

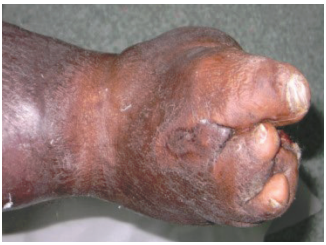

Figure 4-7: Grossly deformed foot with second and third toe amputation with Charcot deformity

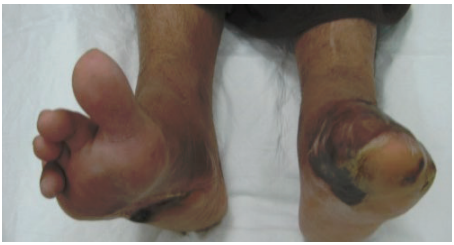

Figure 4-8: Left forefoot amputation

Rigid contractures of the digits (claw toes and hammer toes) are also important as they increase plantar pressures, thereby leading to skin breakdown and ulceration [9-11].

4.1.3 Neurological assessment

Peripheral neuropathy is the leading cause in the development of diabetic foot ulceration [1,3,4,12]. The clinical examination recommended by the American Diabetes Association is to detect the loss of protective sensation, usually by a 10 g monofilament and/or a vibration assessment using a biothesiometer, 128 Hz tuning fork, pinprick sensation and ankle reflexes.

4.1.4 10 g monofilaments

Standardized monofilaments must be used in any examination; prospective clinical data have shown that loss of pressure sensation using the 10 g monofilament is highly predictive of subsequent ulceration [3,21,22]. Monofilaments have been designed to buckle when a 10 g force is applied. It detects the loss of large-fibre nerve function explicitly. The inability to feel the pressure at one or more anatomic sites when the monofilament is buckled for 1–3 seconds is highly indicative of large-fibre neuropathy.

It is widely recommended that four areas (first, third and fifth metatarsal heads and the plantar aspect of the distal hallux) are tested on each foot. The clinician must test it on the patient's elbow first and then the patient's inner elbow so the patient will recognize the sensation. The four sites of each foot

may then be tested by asking the patient to respond “yes” or “no” and to locate the site being tested exactly. Areas of callous must be avoided when testing for pressure perception.

4.1.5 Pinprick sensation

An increased risk of ulceration among patients with diabetes is linked to the inability to perceive a pinprick sensation [4]. During this examination, the clinician uses a disposable pin and applies it just proximal to the toenail on the dorsal surface of the hallux, with mild (force) pressure to deform the skin. The inability of the patient to perceive the pinprick over either hallux is regarded as a positive sign of loss of protective sensation.

4.1.6 128 Hz tuning forks

Before the use of a tuning fork, the examiner must explain clearly to the patient what is being tested and that it is the vibration and not the touch of the tuning fork. The 128 Hz tuning fork must be applied to the tip of the great toe bilaterally. A test is abnormal when the patient loses the vibratory sensation of the tuning fork while the examiner can still perceive it when the fork is placed on the tip of the toe [13,14].

4.1.7 Ankle reflexes

Increased risk of foot ulceration is also associated with the absence of ankle reflexes [14]. Before examining the patient for ankle reflexes, the patient is asked either to kneel or rest on a couch/table. The Achilles tendon is stretched until the ankle is in a neutral position before striking it with the tendon hammer. Usually, patients are tense during examinations – especially while performing the ankle reflex – therefore if the initial response is negative the patient is instructed to hold their hands together and to pull so that the ankle reflexes can then be retested with reinforcement. This manoeuver will shift the attention of the patient from the ankles to his hands. The total absence of ankle reflex, either without or with support, is considered as an abnormal result.

4.1.8 Vibration perception threshold testing

The biothesiometer is an electronic handheld device that gives a semi-quantitative assessment of vibration perception threshold (VPT). The clinician holds the tip of the biothesiometer over the pulp of the big hallux. Before the test, the clinician holds the tip of the biothesiometer (stylus) on to the bony part of the elbow, the forehead or the sternum so that the patient can recognize the vibration. The patient is instructed to lie supine on the couch, and then the stylus of the instrument is placed over the dorsal hallux. Meanwhile, the clinician raises the amplitude until the patient can feel the vibration; the resulting voltage is called the vibration perception threshold (VPT). The mean of three readings is taken over each hallux. A VPT > 25 V is strongly predictive of subsequent foot ulceration [15,16] and is taken as a cut-off point, i.e. an abnormal result.

4.2 Vascular assessment

Narrowing of the peripheral arteries as a result of atherosclerosis is a chronic and slowly developing condition. Different severity of symptoms may occur depending on the degree of narrowing and the site involved. Although some patients may remain asymptomatic throughout their lives, on occasions acute events do occur, often associated with thrombus formation and/or embolism and/or occlusion of a minor or major artery. Usually, patients complain of pain in the calf region upon walking, which disappears after rest. However, in those with a more proximal level of arterial occlusion (i.e. the aortoiliac segment), patients may suffer from pain extending into the thighs and buttocks.

Interestingly, typical intermittent claudication can also be due to spinal canal stenosis in the lumbar region. In patients with diabetes, approximately one-third of foot ulcers are associated with peripheral arterial disease (PAD) and it is often an important risk factor linked to chronic wounds [4,17]. It is, therefore, important to assess the foot for the presence of PAD to determine overall foot risk status. Vascular assessment should start with a history of intermittent claudication, smoking history, previous cardiovascular studies, invasive procedures (angioplasty) and surgeries.

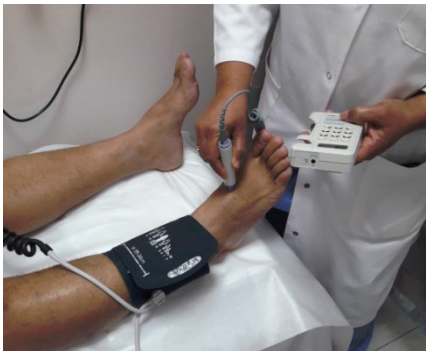

Figure 4-9: Application of handheld doppler on the dorsalis pedis prior to applying it on the posterior tibial artery during ABI measurement

The examination must start with an inspection of the foot for hair loss, nail status (dystrophy), skin colour (pallor), and palpation for temperature (cold to touch). The examiner should then proceed to digital palpation of the dorsalis pedis pulses and the posterior tibial artery [5,18], which should be classified as either "present" or "absent" [18]. The ankle-brachial index (ABI) measurement is another simple and reliable test for diagnosing peripheral artery disease, which should be done for patients where the pedal pulse is absent or where there are signs or symptoms of peripheral vascular disease. Such patients should be referred for a vascular assessment.

According to the European Society of Cardiology guidelines 2011 [21] for the diagnosis and treatment of peripheral artery disease, the ankle-brachial index is the first non-invasive test for the diagnosis of peripheral arterial disease (PAD). In healthy individuals, the ABI is > 1.0; an ABI of < 0.90 is usually taken as the diagnostic cut-off point to define PAD. The actual sensitivity and specificity of the ABI are 79% and 96%, respectively [19]. In a primary care setting, the diagnosis of PAD is considered when an ABI is < 0.8, or the mean of three ABIs is < 0.90 [20]. The degree of ABI correlates with the severity of PAD; there is a high risk of lower limb amputation when the ABI is < 0.50. A change in the value of ABI of > 0.15 is needed to consider the worsening of limb perfusion over time, or improving after revascularization [21].

4.2.1 The technique

A 10–12 cm sphygmomanometer cuff is placed just above the ankle (medial malleolus), and a handheld doppler probe (5–10 MHz) is placed on the posterior tibial artery or the dorsalis pedis of each foot.

Next, the brachial pressure should be measured using the same technique, i.e. a handheld doppler rather than a stethoscope to detect the brachial pulse.

The highest ankle systolic blood pressure is divided by the highest brachial systolic blood pressure, resulting in an ABI reading per leg.

An ABI value > 0.9 is considered normal, and an ABI value < 0.8 is seen as associated with claudication, whereas an ABI value < 0.4 is usually associated with ischaemic rest pain and tissue necrosis.

According to the American Diabetes Association Consensus Panel on Peripheral Arterial Disease measurement, ABI is recommended for patients over 50 years of age and with diabetes. Furthermore, ABI measurement should be considered in younger patients with multiple PAD risk factors, repeating normal tests every five years [(2)]. In a primary care setting, ABI measurement may be considered as part of the yearly foot exam in such patient subgroups.

It is worth noting that falsely elevated or suprasystolic ankle pressures may be recorded during ABI measurements in patients with diabetes because of the presence of medial calcinosis, which can render the arteries incompressible. In the presence of ABI > 1.3, due to the incompressible calf or ankle arteries, measurements of toe pressures (digital arterial systolic pressure) or transcutaneous oxygen tension may have to be carried out.

4.3 Risk classification and referral/follow-up

After completing the history and a thorough examination, the patient should be stratified [(22)] into a foot risk category (Table 4-1). These categories are designed to help clinicians direct management and subsequent referral, [(17,20)] including frequency of follow-up by the general practitioner or specialist.

The higher the category, the higher the risk for ulceration, hospitalization and amputation [(11)].

- Category 0 patients generally do not need a referral and should receive education and general foot care, including an annual comprehensive foot examination.
- Category (1) patients should be managed by a family physician or a podiatrist every 3–6 months.
- Category (2) patients should be managed by a podiatrist or a family physician with special training in diabetic foot management (special interest) every 2–3 months.

- Category (3) patients should be managed by a podiatrist or a family physician with special training in diabetic foot management (special interest) every 1–2 months.

Table 4-1. Risk stratification of the diabetic foot, LOPS = loss of protective sensation, PAD = peripheral artery disease

Risk stratification	Definition	Management recommendations	Recommended follow-up
0	No deformity, no LOPS, no PAD,	Patient, family education and appropriate footwear.	Annual follow-up (by family physician)
1	LOPS ± deformity	Advise the patient to get prescriptive footwear. In case of severe deformities, prophylactic surgery may be indicated. Continue patient education.	Every 3–6 months (by family physician or podiatrist)
2	LOPS ± PAD	Advise the patient to get prescriptive foot wear and advice for vascular consultation.	Every 2–3 months by (podiatrist or family physician with special training in the diabetic foot)
3	Previous history of ulcer or amputation	Same as risk stratification 1. Advise vascular consultation for combined follow-up if PAD present.	Every 1–2 months (by podiatrist or family physician with special training in the diabetic foot)

4.4 Conclusions

Diabetic foot complications are common and costly in terms of human suffering, financial aspects and a burden on the health system, therefore a

proactive, integrated and aggressive approach is needed in preventative assessments by family physicians and podiatrists. In general, all patients with diabetes should be considered at risk unless proven otherwise. Hence comes the need for patients with diabetes to have their feet examined at least annually for the presence of risk factors that may lead to ulceration and amputation, including improper footwear, foot deformities, neuropathy and vascular disease.

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CASE STUDY – X

A 65-year-old obese male patient with type II DM and hypertension presented with severe dry feet due to improper footwear (Figure 4-10).The patient's feet were soaked with normal saline impregnated gauzes for one hour, and a sharp surgical scalpel was used to debride the thick callous, which was 4 mm thick (Figure 4-11). The feet were then cleaned with normal saline, and 20% urea cream was applied directly on the skin and covered by Adaptic. The patient was advised to wear cotton socks and prescription footwear and apply 20% urea cream to the soles of the feet and to avoid the toes' web spaces to prevent maceration and secondary fungal infection (tinea pedis). Following two weeks of proper footwear and 20% urea cream application, the feet regained their normal skin texture (Figure 4-12).

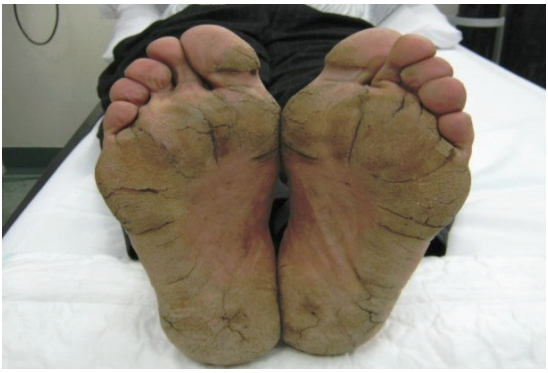

Figure 4-10: Dry, thick plantar skin complicated by fissuring due to improper footwear

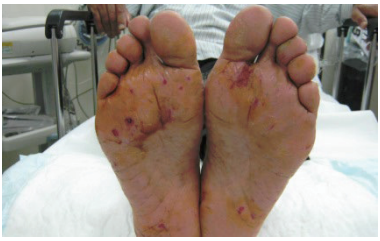

Figure 4-11: The same feet after sharp surgical debridement and proper footwear

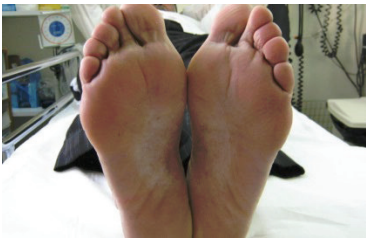

Figure 4-12: The foot after application of 20% urea cream and proper socks, and prescription footwear

CASE STUDY – XI

A 54-year-old male suffering from type II diabetes for the past eight years, who was obese with a history of hypertension, coronary artery disease and a nicotine addiction of 40 cigarettes per day presented at the health centre. The secondary care hospital told him that his toes needed to be amputated. He could not recall when the injury was sustained. On examination, he was in a good general condition, febrile, a pulse rate of 80/minute with a BP of 140/95 mmHg. His biochemical profile revealed an fasting blood glucose (FBG) of 21 mmol/l and HbA1c of 11% with a creatinine value of 2mg/dl.

. Local examination of the left foot revealed necrotic toes and dystrophic nails involving all the toes (Figure 4-13). The foot was debrided using a sharp surgical blade removing all necrotic tissues. Post debridement, the second toe revealed a necrotic distal phalanx signifying chronic osteomyelitis (Figure 4-14). Subsequently, the necrotic bone was excised, and natural honey was applied and wrapped with cotton gauze in order to achieve healing by primary intention (Figure 4-15). Following the daily application of natural honey, the toes achieved complete healing in two months (Figure 4-16).

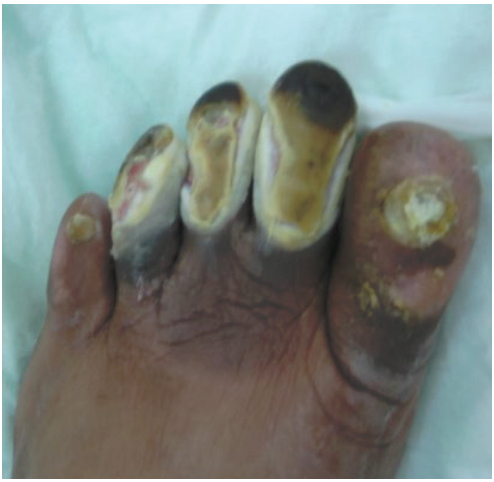

Figure 4-13: Showing necrotic toes and onychomycosis of the big hallux

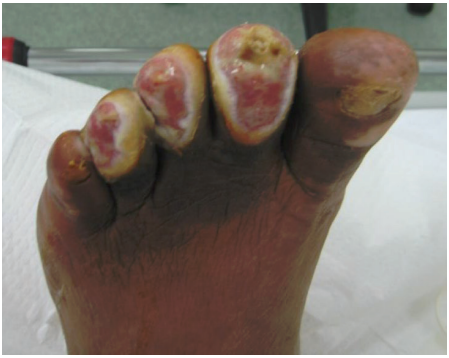

Figure 4-14: Post debridement of necrotic tissue with a visible osteomyelitis at the distal phalanx of the second left toe

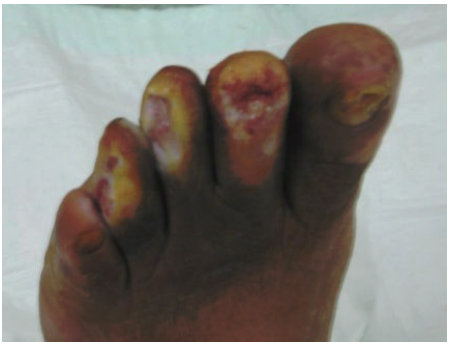

Figure 4-15: Post excision of osteomyelitis bone and healing of the second toe by primary intention

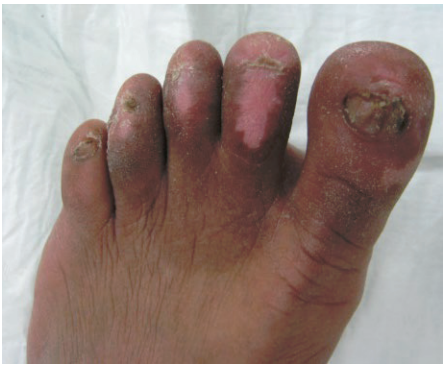

Figure 4-16: Complete healing of toes eight weeks later

CHAPTER 5

CLASSIFICATION OF DIABETIC FOOT ULCERS

DR HASHIM MOHAMED

Nearly 15% of all patients with diabetes are at risk of developing foot ulceration during their lifetime, and an estimated 70% of healed ulcers are likely to recur within five years [1,2]. The main causative factors leading to diabetic foot ulcerations and amputations include peripheral neuropathy, foot infection, peripheral vascular disease and elevated plantar pressure load [3,4]. Due to the high economic and human cost of diabetic foot wounds [5,6], several classification systems have been developed in an attempt to help assess the severity of the disease.

In accordance with the International Working Group on the Diabetic Foot (IWGDF) guidance, an adequate classification system for clinical use should enhance communication between health care providers, guide daily management and furnish ample information about the healing capacity of a wound [7]. One of the most commonly cited wound classification systems is the one explained by Meggitt in 1976, which was popularized five years later by Wagner [9] in 1981.

The prevention of diabetic foot complications is possible, according to recent evidence. Risk classification and stratification are some of the useful and pivotal tools for population-based screening and disease management. The IWGDF proposed that the prediction of morbid outcomes in patients with diabetes is possible using inexpensive, readily available tools that would stratify patients into different risk groups.

As a result, clinicians can allocate educational sessions, therapeutic footwear and clinical visits to patients at the highest risk of adverse events. Several validated classifications systems exist in the literature [10-12]. The majority of them incorporate a history of ulceration or amputation, neuropathy, bony foot deformity or various combinations of these [13-19] while three of them have included peripheral vascular disease [11,17]. Currently, the most used classification systems are Wagner's classification,

the IWGDF classification and the University of Texas Treatment-Based Diabetic Foot Classification System [10,18,19].

Although these classification systems are important, they are often seen as being complex, especially in a busy clinic. They may not apply to all countries, especially in the Third World, where resources are limited. Even in developed countries, there is some data to suggest that there is a suboptimal quality of diabetic foot examinations [20,21]. The complexity of most of the classification systems might make them hard to implement globally.

However, this does not diminish the fact that these classifications are useful tools in the assessment of diabetic foot ulcers, especially for research purposes. A recent study [22] documented that the IWGDF classification system has shown that patients are 34 times more likely to ulcerate if they are in the higher-risk group compared to patients in the lowest-risk group. Similarly, in three years follow-up of patients from the high-risk group, the classification system has shown that patients were 17 times more likely to receive an amputation compared to those patients in the lower-risk group. Additionally, the risk of re-ulceration is more than 100 times more likely in those with a previous amputation compared to those patients with no amputation. Patients at high risk are characterized by having a more extended history of uncontrolled diabetes, foot deformity, worsening neuropathy and increased plantar pressures. They usually tend to be males, with a history of alcohol abuse as well as microvascular complications, such as nephropathy and retinopathy.

5.1 Wagner's classification

The well-established and widely used Wagner wound classification system provides descriptions of ulcers to varying degrees; it is easy to use by clinicians and provides a guide for planning management strategies.

The Wagner system is based on the following parameters – ulcer depth, presence of osteomyelitis and/or gangrene – by using the following grades:

- Grade 0 high-risk foot and no ulceration (pre-or post-ulcerative lesion);
- Grade 1 (superficial or full-thickness ulcer);
- Grade 2 deep ulcer (probing to tendon or capsule) but not reaching bone;
- Grade 3 (deep ulceration with osteitis and/or abscess);
- Grade 4 (partial foot gangrene);
- Grade 5 (whole foot gangrene) [23]. (Table 5-1)

The most commonly used classification system worldwide, especially in the Third World, is the Wagner–Meggitt classification, which defines wounds by the depth of ulceration and the extent of gangrene. However, it does not consider scores of neuropathies, pressure load or ulcer size.

Table 5-1. Wagner's classification for diabetic foot disease (Adopted and modified from Boulton and VileiKyte [23]).

Grade 0	*High-risk foot and no ulceration. (pre or post-ulcerative lesion)*
Grade 1	Superficial or full-thickness ulcer
Grade 2	Deep ulcer (probing to tendon or capsule)
Grade 3	Ulceration with osteomyelitis or abscess
Grade 4	Partial foot gangrene
Grade 5	Whole foot gangrene

5.2 The University of Texas classification

This classification system assesses the ulcer depth, presence of infection and presence of clinical signs of lower limb ischaemia. The system consists of a matrix of grades on the horizontal axis with the stages on the vertical axis. The grades are as follows:

- grade 0 (pre-or post-ulcerative site that has healed),
- grade 1 (superficial ulcer),
- grade 2 (ulcer reaching tendon or capsule),
- grade 3 (ulcer probing to bone or joint).

Within each wound grade, there are four stages: stage 1 (clean wounds), stage 2 (non-ischaemic infected wounds), stage 3 (ischaemic non-infected wounds), and stage 4 (ischaemic infected wounds) (Table 5-2).

The University of Texas classification system combines grade and stage making it more comprehensive, and it shows a higher association with increased clinical outcomes, i.e. higher risk of ulceration, amputation and prediction of ulcer healing in comparison with Wagner's classification.

Table 5-2: Texas University Classification system assessment

TEXAS UNIVERSITY CLASSIFICATION

	GRADE 0	GRADE 1	GRADE 2	GRADE 3
STAGE 1	Preulcerative or post-ulcerative lesions completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating tendon or capsule	Wound penetrating to bone or joint
STAGE 2	Infection	Infection	Infection	Infection
STAGE 3	Ischaemia	Ischaemia	Ischaemia	Ischaemia
STAGE 4	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia

5.3 Diabetic foot ulcer clinical evaluation, treatment and prevention

An extensive assessment of any ulcer is essential and should guide management [24], An adequate description of ulcer characteristics such as appearance, size, depth and location also provides the clinician with a map of progress during treatment [25].

The clinical assessment should determine the aetiology of the ulcer – whether it is neuropathic, ischaemic or neuro-ischaemic.

The inability to perceive the pressure of a standardized 10 g monofilament is a valid indicator of the presence of peripheral sensory neuropathy and loss of protective sensation [26,27]. Other common modalities that can be used to detect neuropathy are a standard tuning fork (128 MHz), a neurothesiometer and a neurologic reflex hammer.

After describing the appearance and the dimensions of the ulcer, the clinician should probe the ulcer with a blunt sterile instrument or a cotton swab. Careful probing can detect undermining of ulcer margins, an extension of the ulcer into tendon sheaths, bone, or joints and/or sinus tract formation.

Osteomyelitis is highly likely in patients with a positive probe-to-bone test [28]. Failure of wound healing is often due to failure to diagnose underlying osteomyelitis. The clinician must note the existence of malodour and the nature and amount of exudate along with the presence and extent of cellulitis [29].

Cellulitis extending beyond 2 cm from the ulcer perimeter is defined as a lower-limb-threatening infection, including osteomyelitis, deep abscess and/or critical ischaemia [24,25,30].

Adequate specimens (deep, zig-zag, tissue specimens) must be sent to the lab for aerobic and anaerobic bacterial infections whenever there is a strong suspicion of infection, including signs and symptoms such as new onset of pain in an insensate foot, or presence of inflammation or purulence [25].

Since all ulcers have microbial contamination, the culture of a non-infected ulcer is generally not recommended [6,14] Severe diabetic foot infections are characterized by polymicrobial infections, which include a variety of aerobic gram-positive cocci, anaerobes and gram-negative rods [31,32].

Patients presenting with deep ulceration of extended duration (one month or more) must have a radiological assessment performed to rule out osteomyelitis; however, one must be mindful that plain X-ray is not always a very sensitive indicator of acute osteomyelitis [25,33]. Whenever the plain X-ray is negative, and there is a strong clinical suspicion of osteomyelitis, additional leukocyte or bone scanning helps rule out bone involvement. Challenges sometimes arise in the neuropathic patient with a deep ulcer where the bone scans are often falsely positive due to the presence of Charcot's arthropathy or hyperemia. In this case, magnetic resonance imaging is a better alternative since it has high specificity [33]. However, the gold standard is to take a bone biopsy to establish the diagnosis of osteomyelitis.

During ulcer evaluation, a careful vascular assessment must always be undertaken since the presence of ischaemia is a sign of poor prognosis unless vascular intervention is considered.

Adequate arterial perfusion to the foot is defined by the presence of pedal and popliteal pulses on palpation. Failure to palpate pedal pulses in the presence of a palpable popliteal pulse is a classic sign of diabetic peripheral arterial disease, due to the selective involvement of the tibial arteries below the knee [25,30].

Non-invasive studies, including duplex ultrasound of the arterial tree, should be utilized to supplement the clinical examination if necessary; however, these tests may underestimate the severity of arterial insufficiency [30]. Whenever there is a significant suspicion of ischaemia, vascular surgical consultation must also be considered.

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CASE STUDY – XII

A 55-year-old male was complaining of a burning sensation in his feet which was not responding to petroleum jelly application and made worse by moisturizing cream. This condition is due to tinea pedis, which can be mistaken as a case of dry feet. As a result, the patient may receive moisturizers to treat the dryness. However, the condition is made worse since moisture makes it more favourable for fungi to grow.

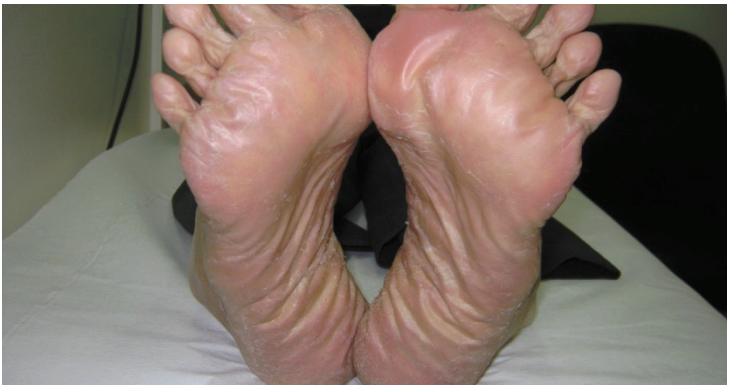

Figure 5-1: Shiny hyperemic and scaly skin due to tinea pedis of the plantar aspect of the feet, usually mistaken by clinicians as dry feet

CASE STUDY – XIII

A 75-year-old female presented at the health centre who had been suffering from type II diabetes mellitus for the past 35 years, was obese and had hypertension. She was on a short visit from her home country Egypt to Qatar and presented with a Charcot foot ulcer which she had for the last two years.The patient had been told by her physicians that the ulcer will never heal. On examination the patient was in a good general condition, obese with a BMI of 43 kg/m^2, HbA1c was 8% with a chronic kidney disease stage II. Examination of the left foot revealed a Charcot foot with a chronic midfoot ulcer of one year duration (Figure 5-2). The ulcer was debrided using a sharp scalpel, cleaned with normal saline followed by topical application of raw natural honey and covered with a secondary petroleum jelly-based dressing. The wound was covered with a cotton bandage, and the dressing was changed daily. Meanwhile, the patient was instructed not to ambulate except in a wheelchair. Two months later, the wound had completely healed (Figure 5-3).

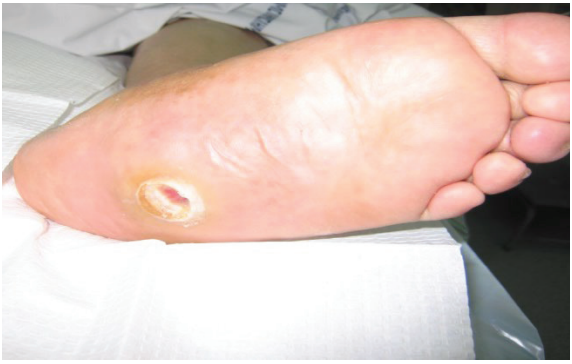

Figure 5-2: Showing classical "rocker-bottom" foot with an ulcer at the midfoot region

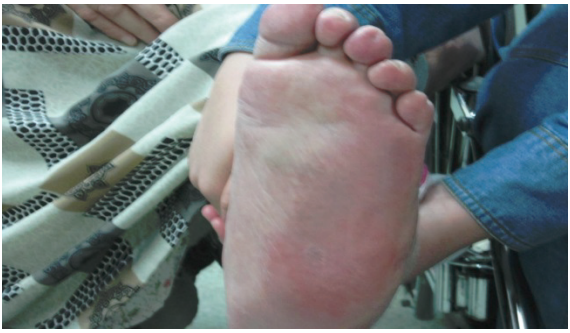

Figure. 5-3: Showing complete healing of ulcer two months later

CHAPTER 6

THE PATHOPHYSIOLOGY OF WOUND HEALING

DR HASHIM MOHAMED

The wound-healing process is made up of four highly overlapping and integrated phases: haemostasis, inflammation, proliferation and tissue remodelling or resolution [(1)]. In order for a wound to heal, these phases and their biophysiological functions must happen in the proper sequence, at a designated time, and continue at an optimal intensity for a specific duration [(2)].

Failure to progress through the normal stages of healing will lead to delayed acute and chronic wounds. Such wounds usually suffer from a state of pathologic inflammation due to an incomplete, uncoordinated or delayed healing process.

About 3–6 million people in the United States suffer from non-healing wounds, with the majority (85%) happening in people 65 years and above.

Optimal wound healing in adults consists of the following events:

- Fast haemostasis;
- Appropriate inflammation;
- Mesenchymal cell differentiation and proliferation followed by migration to the wound site;
- Proper angiogenesis;
  Fast re-epithelialization;
- Adequate synthesis, alignment and cross-linking of collagen to provide adequate strength to the healing wound [(1,2)].

The first phase after the injury is haemostasis manifested by vasoconstriction and fibrin clot formation. The surrounding wound tissue and the clot will release pro-inflammatory cytokines and growth factors such as the platelet-derived growth factor (PDGF), the transforming growth factor (TGF-β), the epidermal growth factor (EGF) and the fibroblast growth factor (FGF).

Once bleeding is under control, inflammatory cells tend to migrate into the wound (chemotaxis) and enhance the inflammatory phase, which is manifested by the sequential infiltration of macrophages, neutrophils and lymphocytes [1,2,3].

An essential and critical role of neutrophils is the clearance of invading pathogens and cellular debris in the wound area. However, these cells often produce certain substances, including proteases and reactive oxygen species (ROS), which cause further damage. During wound healing, macrophages play multiple roles. In the early stages, macrophages will release cytokines, thereby promoting the inflammatory response by activating and recruiting additional leukocytes. Macrophages pave the way for the resolution of inflammation by clearing apoptotic cells (including neutrophils). Lastly, as macrophages begin to clear these apoptotic cells, they go through a phenotypic transition to a reparative state that enhances fibroblasts, keratinocytes, and angiogenesis to stimulate tissue regeneration [5,6]. In this process, macrophages stimulate the transition to the proliferative phase of healing.

Following the inflammatory stage, T-lymphocytes and macrophages migrate into wounds, and peak in the late-proliferative/early-remodelling phase. The precise function of T-lymphocytes is not fully understood and is under intensive investigation.

Previous laboratory studies suggest that decreased T-cell concentration in the wound site and delayed T-cell infiltration is linked to impaired wound healing, while others have reported that CD4+ cells (T-helper cells) have a positive and essential role in wound healing and CD8+ cells (T-suppressor-cytotoxic cells) play an essential inhibitory function during wound healing [7,8]. The proliferative phase of wound healing usually follows and overlaps with the inflammatory phase, and is manifested by epithelial proliferation and migration over the provisional matrix inside the wound (re-epithelialization).

In the reparative dermis, endothelial cells and fibroblasts are abundantly present to enhance capillary growth, the formation of granulation tissue and collagen formation at the site of injury. In the wound bed, fibroblasts produce glycosaminoglycans, collagen and proteoglycans, which are essential elements of the extracellular matrix (ECM).

After the proliferation and ECM synthesis, the wound-healing process enters the final remodelling phase, which may last for years. Regression of many of the newly formed capillaries happens during the remodelling phase; therefore, the vascular density of the wound is enabled to return to normal size.

An essential feature of the remodelling phase is ECM remodelling to a structure that resembles that of the normal tissue. Meanwhile, the wound starts to undergo physical contraction all along the wound-healing process, which appears to be facilitated by contractile fibroblasts (myofibroblasts) [1,3].

The stem cells' (SC) role in tissue regeneration and cutaneous wound healing is currently under scrutiny, with the main focus on the function of adult stem cells such as bone marrow (BM)-derived cells (BMDCs) and epidermal stem cells.

Epidermal stem cells are found in the bulge area in hair follicles and in the epidermal basal layer, which gives rise to the keratinocytes that start migrating and ultimately end up re-epithelializing wounds.

One of the target organs for BMDCs is normal skin. The bone marrow has two main stem cell populations: the mesenchymal SC (MSC) and the haematopoietic SC (HSC). A BM-MSC scan differentiates into various cell types, including osteoblasts, adipocytes, fibroblasts, chondrocytes and keratinocytes [9,10].

Endothelial progenitor cells (EPCs) originating from the HSC lineage are essential cells that give rise to neovascularization. Both EPCs and BM-MSCs are vital for the cutaneous wound-healing process. During hypoxia, the wound triggers the mobilization of bone marrow EPCs to the circulation, thereby playing a vital role in the process of neovascularization [11,12].

Various cell types play a key role in the wound-healing process, and, as explained above, the cellular activities of any specific cell type may also change during various stages of wound repair.

The coordination and complexity of the wound-healing process are huge obstacles to therapeutic interventions since any therapeutic option must effectively target the appropriate stage.

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CASE STUDY – XIV

A 45-year-old male patient presented at the health centre with type II diabetes mellitus. He was obese, and had venous insufficiency manifested by a left foot varicose vein ulceration above the left medial malleolus, known as the Gaiter's area. He was managed previously in the hospital, but his varicose vein ulceration failed to heal. On examination, there were three painful superficial venous ulcers in the left lower limb with inflamed skin surrounding the ulcers and prominent tortuous superficial varicose veins (Figure 6-1). The wound was cleaned gently with normal saline and dressed with natural honey and secondary petroleumjelly-based dressing wrapped with cotton wool bandaging followed by application of interrupted bandaging starting from the toes upwards. Meanwhile, the patient was warned of the possibility of a stinging sensation due to the acidic nature of honey, which can last up to 5 minutes; after this the leg was covered with normal crepe bandage. The patient was prescribed Daflon micronized purified flavonoid fraction (MPFF, 450 mg diosmin plus 50 mg hesperidin – 500 mg) twice daily and was instructed to lose 3–5 kg of his original weight. One week later, the ulcers started to fill from the inside out (Figure 6-2). The patient continued with the change of dressing in the health centre. The dressing was changed every three days, and the dressing was soaked with normal saline to minimize pain during the removal of the old dressing. There was a healing of two of the adjacent ulcers two weeks later (Figure 6-3). One month later, all ulcers healed completely (Figure 6-4).

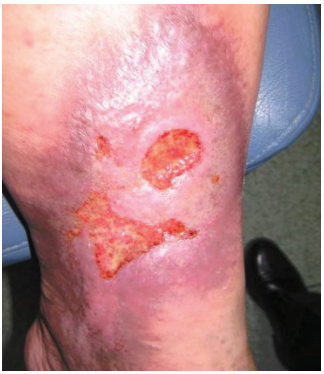


Figure 6-1: An inflamed varicose vein superficial ulcer with an “inverted champagne bottle appearance” with evident varicosities. A venous ulcer classically occurs proximal to the medial malleolus in the “Gaiter’s area” region

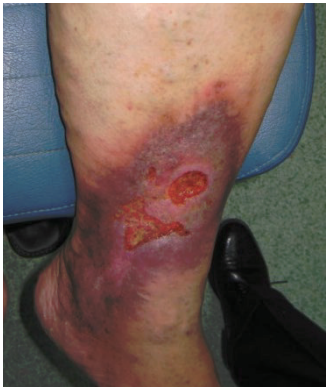


Figure 6-2: Less inflamed ulcer with filling up of the venous ulcer

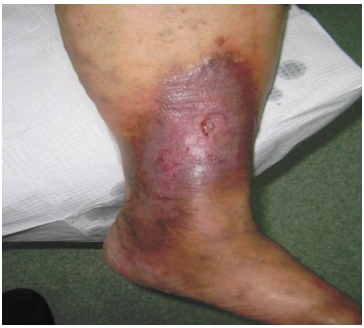


Figure 6-3: There is healing of some of the previous larger ulcer two weeks later

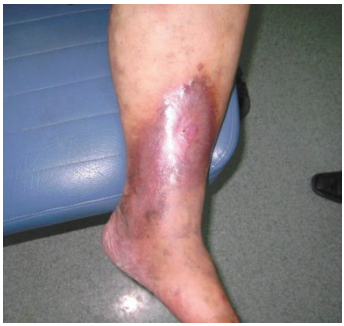
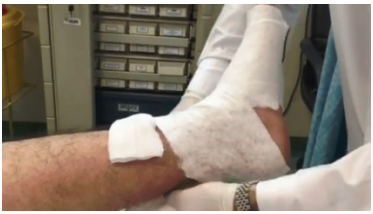
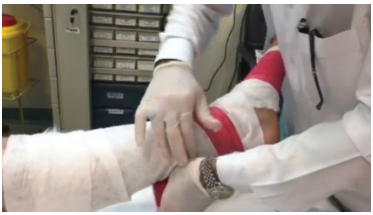


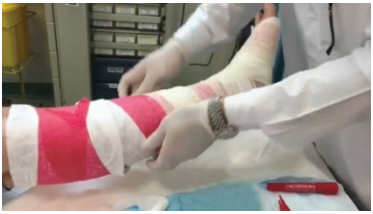
Figure 6-4: Complete healing of ulcer and regression in the size of the oedema of the leg one month later



Step 1. The wound was cleaned gently with normal saline and dressed with natural honey and secondary petroleum jelly dressing



Step 2. Dressing and wrapped with cotton wool bandaging followed by application of interrupted bandaging



Step 3. Application of full bandaging from the toes upwards

Figure 6-5: Interrupted bandaging

Case Study – XV

A 65-year-old male patient with type II diabetes of 35 years duration and heavy smoker of two packets per day for the last 45 years, with chronic renal failure stage III and severe peripheral vascular disease self-referred to the health centre. His general condition was reasonable, with a BP of 130/75 mmHg. The examination revealed amputated second, third and fourth toes with a gangrenous fifth toe of the right foot (Figure 6-6). He was informed in the past by the vascular surgeon that he needs below-knee amputation. Palpation of the pulses in the lower limb revealed a palpable femoral artery pulsation and feeble posterior tibial and dorsalis pedis pulsations. The ankle-brachial index was 0.6 on the right side and 8.5 on the left side.

The wound was cleaned with normal saline, and necrotic tissues were debrided using a surgical scalpel and dressed with honey daily, covered by secondary petroleum jelly-based dressing (Adaptic). A cotton wool bandage was used to cover the foot. One month later, the wound decreased in size by 50% (Figure 6-7); meanwhile, the fifth toe assumed a dry gangrene state and was left untouched in order for it to auto amputate. Two months later, the fifth toe auto amputated, and the wound size reduced by 75% (Figure 6-8). Three months later, the wound was completely healed (Figure 6-9).

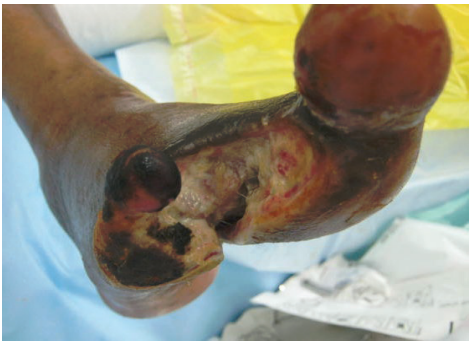


Figure 6-6: Presented post amputation of second, third and fourth toes with necrotic tissue and gangrenous fifth toe

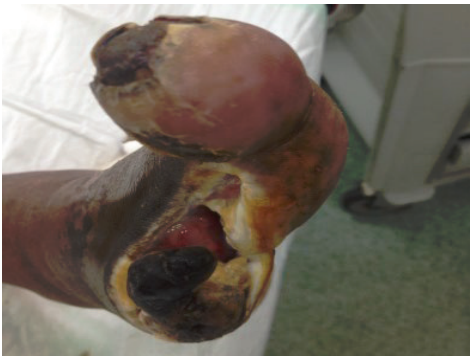


Figure 6-7: One week post debridement of necrotic tissue with dry gangrene of the fifth toe and necrotic tip of the big hallux

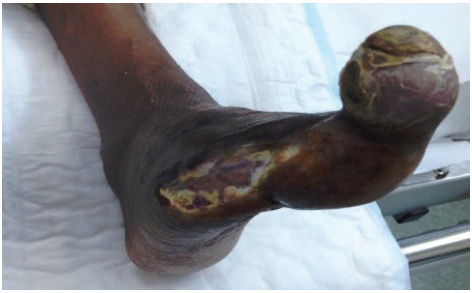


Figure 6-8: Auto amputation of the fifth toe and reduction of the size of the ulcer by 50%

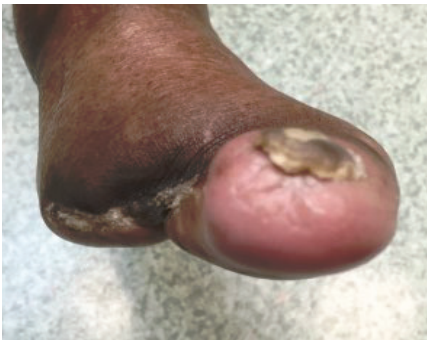


Figure 6-9: Complete healing of the ulcer with healthy skin appearance around the big hallux

CASE STUDY – XVI

A 65-year-old male, a chronic heavy smoker, presented at the health centre following amputation of the second and third toes at the main general hospital. On examination, the wound had necrotic tissue that was badly macerated (Figure 6-10). The wound was cleaned with normal saline, and the peri-wound area was dried using Betadine® solution. Meanwhile, a sharp debridement of necrotic tissue was carried out, and natural honey was applied and covered by Adaptic and a cotton gauze dressing to contain the natural honey in the site of the wound. Four weeks later, there was 90% healing of the wound, and the skin of the peri-wound area had gone back to its normal status (Figure 6-11). Six weeks later, the wound has completely closed by secondary intention (Figure 6-12).

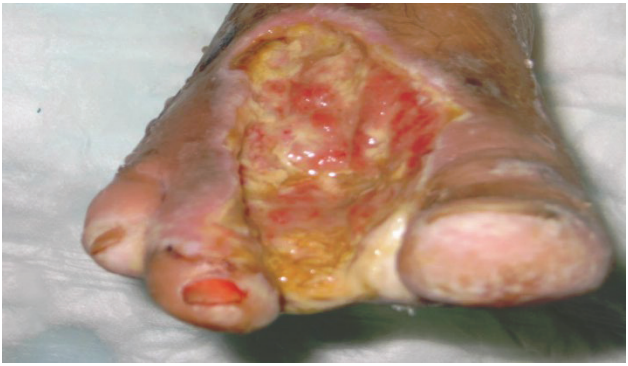


Figure 6-10 Post-surgery wound showing macerated edges, necrotic tissue and islands of granulation tissue

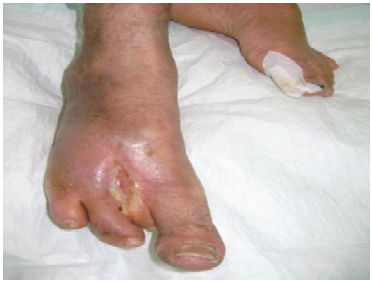


Figure 6-11: Showing 90% healing of the ulcer

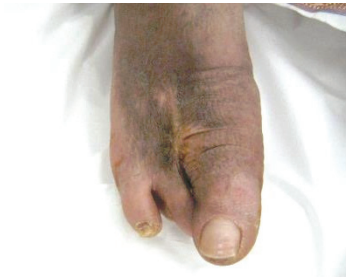


Figure 6-12: Complete healing of the ulcer with inward movement of the fourth toe

CHAPTER 7

DIAGNOSIS AND MANAGEMENT OF DIABETIC NEUROPATHY IN PRIMARY CARE

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7.1 Why is it important to detect diabetic neuropathy in primary care?

Diabetic neuropathies are the most common long-term complications of diabetes that can affect 50-90% of people with diabetes [1-4]. The most common and most studied forms of diabetic neuropathy are distal symmetrical polyneuropathy (DSPN) [5] and diabetic autonomic neuropathy (DAN) [6].

There are several compelling reasons why primary care physicians should recognize and manage diabetic neuropathies [7-10]:

- To prevent the development of foot ulceration and amputation in patients with loss of sensation. People usually only go to see their doctor if they have pain, but with sensory loss, they have no symptoms. The primary care physician is ideally placed to undertake early screening to identify the person with early neuropathy and the 'at-risk' diabetic foot.
- To correctly identify patients with painful diabetic neuropathy and associated sleep disturbance and depression, which are common presentations of painful diabetic neuropathy.

- To correctly identify and differentiate diabetic neuropathy from other neuropathies enabling early and appropriate referral to neurology.

The primary strategy to effectively manage diabetic peripheral neuropathy (DPN) is the early and accurate diagnosis and timely management of this condition [10]. Primary care physicians can play an essential role in early diagnosis and reduction of appropriate risk factors (glucose, blood pressure, lipids) to prevent the progression of DPN [5,11]. The earlier the treatment is implemented, the more likely it is that discomfort and disability is minimized. DPN is characterized by pain and/or numbness and can go undiagnosed until the patient presents with a foot ulcer [12,13]. The severe pain of DPN (pDPN) is often misdiagnosed and either treated inappropriately with non-steroidal anti-inflammatory drugs (NSAIDs) or sub-therapeutic doses of medications for pDPN. If left untreated or undertreated, it may significantly limit general activities of daily living, the ability to exercise or walk, and cause sleep disturbance [7-9]. Symptoms are often most intense at night, which can lead to depression and anxiety. A reduction in pain severity of 30-50% is achievable with combination therapy for most patients [7]. It is important to distinguish between neuropathic and nociceptive pain to provide the appropriate treatment.

7.1.2 How common is diabetic neuropathy and painful diabetic neuropathy in the MENA region?

The worldwide prevalence of DPN in people with diabetes has been reported to be up to 50% 90% [1-4,14,15] and pDPN to around 21% to 34% [14,15]. In the Middle East and North Africa (MENA) region, the prevalence of DPN varies from 9% to 53%, reported from 15 countries (Figure 7-1), and pDPN varies from 14% to 65% reported from eight countries (Figure 7-2) [16]. This wide range can be attributed to different criteria used to identify neuropathy and whether the patients are from primary or secondary care. It is clear that both DPN and pDPN are widely underdiagnosed and often poorly treated due to the lack of systematic screening in primary care [16].

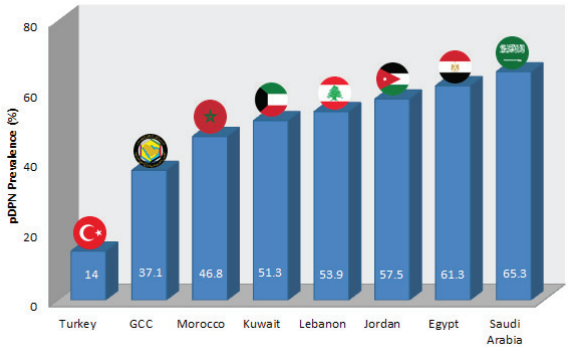

Figure 7-1. Prevalence of diabetic neuropathy in the MENA region (adapted from reference [16]).

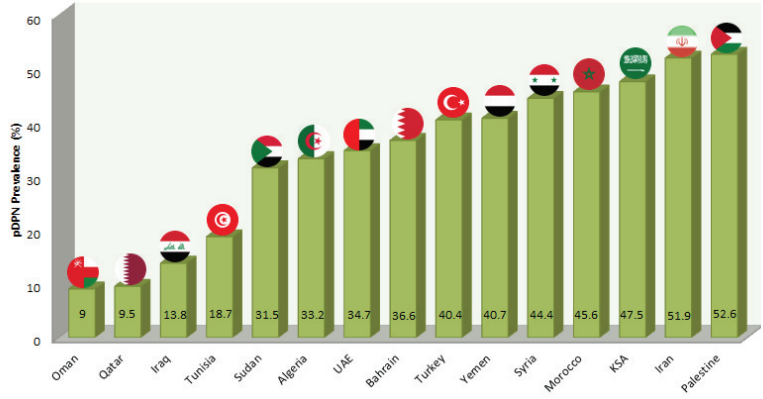

Figure 7-2. Prevalence of painful diabetic neuropathy in the MENA region (adapted from reference [16])

7.1.3 What are the risk factors for diabetic neuropathy?

The primary reported risk factors for DPN include hyperglycaemia, hyperlipidaemia, hypertension, inflammation, insulin resistance and vitamin D deficiency [17-20]. Height, smoking, and alcohol consumption have also been identified as risk factors for DPN [21]. While the aetiology of pDPN is less clear, it may be also be attributed to the standard risk factors of hyperglycaemia, dyslipidaemia, and hypertension [22,23], but additional risk factors include diabetes duration > 10 years, age > 65, BMI > 30 and being female [24].

7.2 How to diagnose diabetic neuropathy

The diagnosis of DPN is based on a combination of numbness or painful symptoms and neurological deficits, which comprises distal sensory loss [5,6,12]. Up to half of the patients may be asymptomatic, and a diagnosis may only be made when the patient presents with a painless foot ulcer or Charcot neuroarthropathy [25]. It is incumbent on all physicians who manage patients with diabetes that they assess them for the presence and severity of DPN. According to the 2017 American Diabetes Association consensus statement on DPN, all patients should undergo screening for DPN at diagnosis of type 2 diabetes, and after five years of type 1 diabetes, and annually after that [6]. Also, subjects with pre-diabetes should be screened if they have symptoms of peripheral neuropathy. Based on pragmatic goals, the assessment includes a careful history and 10 g monofilament testing along with at least one of the following tests: assessment of temperature, pinprick, or vibration sensation (128 Hz tuning fork) [26]. The 10 g monofilament assesses the patient's ability to feel light pressure at 4–6 sites on each foot. Failure to detect light pressure at more than one of the designated testing sites indicates severe loss of protective sensation and an increased risk of foot ulceration and amputation. A 128-Hz tuning fork is applied to the apex of the big toe to detect loss of vibration perception [27]. It is important to note that both monofilament insensitivity and/or loss of vibration perception by the tuning fork detects moderate to severe neuropathy in large nerve fibres [28]. They should not be used to detect early or mild neuropathy and especially should not be used to exclude a small fibre neuropathy in patients with painful diabetic neuropathy.

7.2.1 Clinical examination

There are several validated screening tests which can be undertaken in primary care to diagnose and risks stratify patients with DPN (Table 1):

The Toronto Clinical Neuropathy Score (TCNS) includes an assessment of symptoms, sensory loss and reflexes. Symptom are graded as 1 = present, 0 = absent; sensory tests are graded as 0 = normal and 1 = abnormal; reflexes are graded as 0 = normal, 1 = reduced and 2 = absent. A score of 6–8 signifies mild neuropathy, 9–11, moderate neuropathy, and ≥ 12 severe neuropathy [29].

The Michigan Neuropathy Screening Instrument (MNSI) consists of 15 self-administered questions adapted from the neuropathy symptom profile [30]. A score of ≥ 7 is considered abnormal [31]. The MNSI test is based on

foot inspection: each foot with an ulcer is given a score of 1, and a foot with dry skin, infections, callouses, fissures or deformities is also scored 1. Using a 128 Hz tuning fork, a score of 0.5 is given if the vibration can be felt on the toe for ≥ 10 s and 1 if absent. Achilles reflexes are scored 0.5 if a reflex is attained following the Jendrassik manoeuver and 1 if the reflex is absent [31].

The neuropathy disability score (NDS) is a composite measure of four tests:

1. *Vibration perception,* using a 128 Hz tuning fork: score 1 for each foot if the individual cannot detect vibration at the apex of the big toe.
2. *Thermal perception,* using a cold and warm metallic rod: score 1 for each foot if the individual cannot distinguish cold from warm on the dorsum of the foot.
3. *Pinprick testing,* using a sharp pin applied proximal to the big toenail, with sufficient pressure to deform but not break the skin: score 1 for each foot if the individual cannot distinguish between sharp and blunt.
4. *Achilles tendon reflex*: score 0, 1, or 2 if the ankle reflex is present, present with reinforcement or absent.

The NDS can be used to stratify the severity of DPN as none (0–2), mild (3–5), moderate (6–8) and severe (9–10).

Nerve conduction studies (NCS) are objective measures of peripheral nerve function [32,33]. It requires referral to a neurophysiology clinic to quantify peripheral nerve conduction velocity and amplitude (commonly peroneal, sural and tibial nerves), which represents the impact of demyelination and axonal loss, respectively. Recently, more detailed neurophysiological evaluation to identify an abnormality in rate-dependent depression (RDD) of the H-reflex has been shown to identify diabetic patients with disruption of spinally mediated pathways of pain, who may be more responsive to drugs like duloxetine [34].

Quantitative sensory testing (QST) is a psychophysical test that generates specific physical vibratory or thermal stimuli to detect somatosensory deficits (Figure 7-3) [35,36]. Stimulators generate the vibration with a designed frequency and adjustable amplitude. The thermal stimulus is generated by the Peltier principle [37]; the thermode contacts the skin, and the patient is asked to report the sensation of temperature change, or cold or heat pain. QST assesses the function of large Aα and Aβ (vibration perception threshold), small Aδ (cold perception thresholds) and C (warm perception thresholds) fibres [38]. The sensitivity and specificity of QST vary

between the different tests: 64% and 97% for VPT [39], 44% and 87% for CPT [40] and 43%, and 76% for WPT [41]. Because QST is dependent on the patient's response and concentration, and has moderate sensitivity and specificity with poor reproducibility, it is not recommended as a standalone test for the diagnosis of DPN or pDPN [42].

Figure 7-3: TSA II neurosensory analyser (Medoc Ltd., Ramat Yishai, Israel) for testing thermal perception and pain thresholds

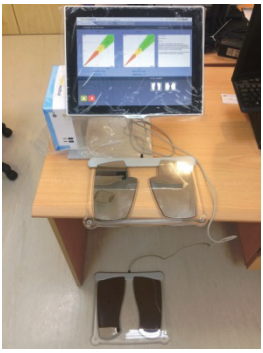

Figure 7-4: A Sudoscan with monitor and two sets of large-area nickel electrodes for the hands and feet

The Sudoscan (Impeto Medical, Paris, France) measures sudomotor function based on sweat chloride concentrations through reverse iontophoresis and chronoamperometry (Figure 7-4) [43] and detects DAN in patients with diabetes [44]. The Sudoscan measures the electrochemical skin conductance (ESC), expressed in microSiemens (μS) and can be used to define sudomotor dysfunction: > 60 μS = no dysfunctions; 60–40 μS = moderate dysfunction; < 40 μS = severe dysfunction. It has a sensitivity of 78% and specificity of 92% to detect diabetic neuropathy [45].

Corneal confocal microscopy (CCM) is a rapid non-invasive ophthalmic imaging technique (Figure 7-5), which quantifies small sensory nerve fibres and can detect sub-clinical neuropathy in subjects with impaired glucose tolerance [46] and correlates with the severity of DPN [47]. Furthermore, CCM can predict the development of clinical neuropathy [48] and foot ulceration as well as Charcot [49]. It also has a very high sensitivity (91%) and specificity (93%) for identifying DPN [50].

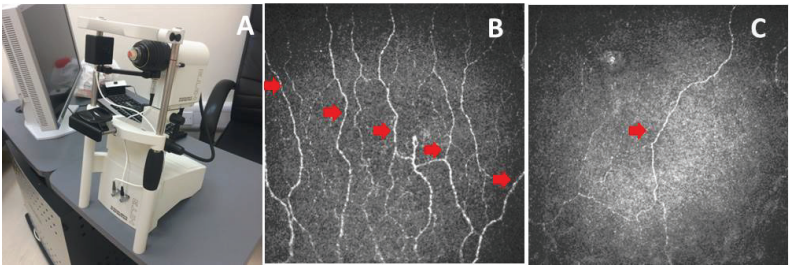

Figure 7-5. A corneal confocal microscope (Heidelberg HDR III) instrument (A) with a corneal confocal microscopy image from a control participant (B) with normal corneal nerve fibre density (red arrows) compared to an image from a person with diabetes showed a marked loss of nerve fibres (C).

7.2.2 Skin biopsy

The technique of skin punch biopsy with measurement of intraepidermal nerve fibre density (IENFD) can detect early DPN (Figure 6) [51]. A reduced IENFD is associated with neuropathic pain, and serial skin biopsies are useful in predicting the progression of neuropathy [52,53], but is not feasible. This is an invasive procedure, which requires an experienced laboratory for accurate immune histological staining and quantification

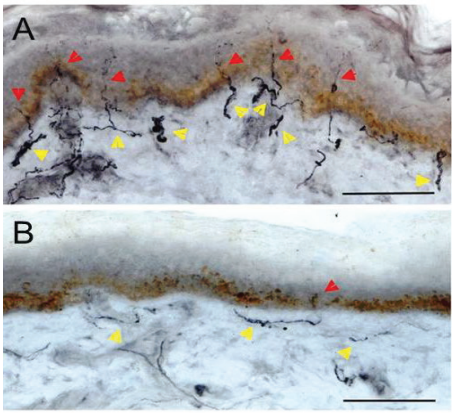

Figure 7-6. Skin punch biopsy specimens immunostained for PGP9.5

(A) shows numerous intraepidermal nerve fibres (red arrows) reaching the upper level of the epidermis with a well-developed subepidermal nerve plexus (yellow arrows) in a healthy control participant

(B) Sscant subepidermal and intraepidermal nerve fibres in a patient with diabetic neuropathy.

Table 1. Summary of the advantages and limitations of diagnostic tests to detect diabetic peripheral neuropathy.

Diagnostic techniques	Advantages	Limitations
Clinical examination	Simple and does not require a dedicated instrument	Lack of sensitivity and reproducibility
Nerve conduction studies [32,33]	Objective	Evaluates large nerve fibres only, needs neurology referral
Quantitative sensory testing [35,36]	Relatively easy to perform, detects small and large nerve fibre damage	Subjective, requires dedicated instrument, moderate reproducibility
Sympathetic skin response	Simple, rapid, objective	Low sensitivity, semi-quantitative, not widely available
Quantitative sudomotor axon reflex test [44]	Sensitive, objective, reproducible	Requires dedicated instrument, not widely available
Neuropad [54]	Easy to perform and interpret when entirely normal or abnormal	Subjective, moderate sensitivity and specificity
Skin biopsy [51]	Sensitive, quantifies small nerve fibres	Invasive, requires specialist histological techniques and expert interpretation
Sudoscan [44]	Non-invasive, easy to perform, objective	Moderate sensitivity, requires a dedicated instrument
Corneal confocal microscopy [46, 47]	Reproducible, rapid, sensitive, quantifies small nerve fibres, objective	Requires a dedicated instrument, expert operator
Corneal confocal microscopy [46, 47]	Reproducible, rapid, sensitive, quantify small nerve fibres, objective	Dedicated instrument, expert operator

7.3 Autonomic neuropathy

Autonomic neuropathies affect the parasympathetic and sympathetic fibres and are associated with a variety of clinical manifestations including hypoglycaemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhoea, faecal incontinence, erectile dysfunction, neurogenic bladder and sudomotor dysfunction with either increased or decreased sweating. It is important to remember that there is a wide range of other causes of autonomic neuropathy, which should be excluded especially in symptomatic patients, and include: inherited neuropathies, amyloid neuropathy, porphyria, SLE, alcoholic neuropathy, HIV and chemotherapy-induced neuropathy.

7.3.1 How to diagnose painful diabetic neuropathy

The diagnosis of pDPN can be made from a history of neuropathic symptoms and/or signs of neurological deficits after the exclusion of other causes [12,13]; pDPN is related to small fibre dysfunction. It is characterized by continuous pain, which is commonly described as a burning, cold sensation, and episodic pain, which lasts for seconds and is usually described as a shooting, electric shock, or pins and needles [55]. Evoked pain can be tested by light touch, mild pressure, heat or cold, and manifests as allodynia or hyperalgesia. Allodynia is pain caused by non-painful stimuli, and hyperalgesia is an increased response to painful stimuli due to an abnormally low pain threshold. Loss of sensation may coexist with pDPN and is commonly described as numbness or itching [55]. The diagnosis and severity of pDPN can be identified using validated questionnaires, which can also distinguish between neuropathic and nociceptive pain.

There are several validated screening tests for the diagnosis of pDPN:

- The Douleur Neuropathique 4 (DN4) is comprised of seven questions on the characteristics of the pain: 1) burning, 2) painful cold, 3) electrical shock, 4) tingling, 5) pins and needles, 6) numbness and 7) itching, and a physical exam which includes examination of 8) touch and 9) pin hypoaesthesia and a soft brush to test for 10) dynamic tactile allodynia [56]. One point is awarded for each positive item, and deficit and neuropathic pain is diagnosed when the total score is ≥4 [57]. It has a sensitivity and specificity of 83% and 90%, respectively.
- The Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS) has seven aspects: five are symptoms, and two are signs with a sensitivity and specificity ranging from 82% to 91%, and 80% to 94%, respectively [58].
- The Neuropathic Pain Questionnaire (NPQ) is interview-based (12 questions) and does not incorporate physical tests. It has a sensitivity and specificity of 66% and 74%, respectively [59].
- The Neuropathic Pain Symptom Inventory (NPSI) is interview-based (12 questions), and does not incorporate physical tests that can be used to assess treatment effect [60].
- The Neurological Symptom Score (NSS) assesses sensory, motor, and autonomic deficits (17 questions) [61,62].
- The Diabetic Neuropathy Symptom score (DNS) consists of four questions related to unsteadiness in walking, burning or aching, prickling sensations and numbness in the legs or feet, which must

have been experienced several times a week for the previous two weeks [63].

7.3.2 The pathophysiology of DPN

Damage to the nerve fibres can occur due to hyperglycaemia-mediated hyperactivity of the polyol pathway, oxidative stress and microangiopathy. Most studies in patients with diabetic neuropathy demonstrate demyelination and axonal degeneration with a loss of myelinated fibres, which ranges from minimal in early neuropathy to extreme in patients with type 1 diabetes and autonomic neuropathy [33]. Unmyelinated fibre pathology is characterized by a reduction in axon density and diameter, and an increase in the unassociated Schwann cell profile density with axonal sprouts [64]. Endoneurial microangiopathy is most prominent in patients with advanced diabetic neuropathy and is characterized by luminal narrowing, endothelial cell hyperplasia and hypertrophy, pericyte cell loss, and basement membrane thickening [65]. Nerve damage can lead to a change or alteration in ion channel expression and hyperexcitability of neurons leading to neuropathic pain. Multiple neuropathic pain models have demonstrated the up-regulation of voltage-gated sodium channels (NaV) and activation of transient receptor potential channels [66,67].

Not all patients with diabetes and neuropathy have diabetic neuropathy. Although the most common neuropathy of diabetes is DSPN, one should be aware of other 'atypical' neuropathies and, indeed, other co-existing neuropathies, which require different treatment approaches. Other causes of neuropathy should be actively excluded by undertaking a family and medication history, and performing relevant investigations (e.g. serum B_{12}, folic acid, thyroid function, complete blood count, metabolic panel and protein immune electrophoresis). Electrophysiological testing or referral to a neurologist is rarely needed for the diagnosis of DPN, even when the clinical features are atypical:

- motor greater than sensory deficits
- asymmetry of symptoms and signs
- rapid progression

A different aetiology should be suspected, and early referral to neurology is recommended [6]. While the frequency of chronic inflammatory demyelinating polyneuropathy (CIDP) in diabetes remains controversial, the occurrence of a rapidly progressive disability warrants awareness of the association and the need for urgent immunomodulatory therapy. CIDP is an

immune-mediated neuropathy resulting from aberrant immune responses to peripheral nerve antigens and is histologically characterized by inflammation, nerve oedema, endoneurial infiltration with macrophages and perivascular infiltration with T cells as well as increased expression of cytokines and other inflammatory molecules in cerebrospinal fluid and blood [68-70]. CIDP is treated with IVIg or corticosteroids as main first-line therapies and plasma exchange as a third-line therapy [71].

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) (diabetic amyotrophy) and diabetic cervical radiculoplexus neuropathy (DCRPN) should be easy to recognize with the acute onset of proximal pain and weakness in the thigh or arm, although they may sometimes be painless and more extensive. Their course is monophasic, and the prognosis is generally favourable with improvement over 12–18 months [6]. Although there are no randomized trials, case series and case reports do show a dramatic response to corticosteroids, IVIg and plasma exchange.

7.4 Treatment of diabetic neuropathy

There remains a lack of treatment options that effectively target the underlying pathophysiology of DSPN. While many pathogenetic pharmacotherapies have been investigated in clinical trials of DSPN, there are currently no Food and Drug Administration (FDA) approved treatments [72,73]. While maintaining a good glycaemic control is essential to prevent the progression of DPN, there is no evidence to suggest that it can reverse DPN [10,74]. Essential therapies for those with DSPN include treating with an ACE inhibitor, irrespective of blood pressure [75], and/or a fibrate, irrespective of triglyceride levels [76], smoking cessation and a reduction of BMI to a target of < 25 kg/m^2 [21].

7.5 Treatment of painful diabetic neuropathy (Table 2)

The MENA guidelines for the treatment of pDPN are now dated as they recommend pregabalin, gabapentin, and tricyclic antidepressants as first-line treatment and duloxetine and opioid analgesics as second-line [77,78]. The International Association for the Study of Pain, Neuropathic Pain Special Interest Group (NeuPSIG) guidelines consider pregabalin, duloxetine, gabapentin and tricyclic antidepressants as first-line treatments with capsaicin 8% patches, lidocaine patches and tramadol as second-line treatments for neuropathic pain [77,78].

The 2017 American Diabetes Association (ADA) guidelines for the management of painful diabetic neuropathy recommend pregabalin or duloxetine as first-line medication [6,17], as the FDA approved both medications for the treatment of pDPN. However, other medications such as gabapentin and tricyclic antidepressants that are not approved by the FDA for pDPN are also recommended as first-line therapies due to lower costs, but with caution due to the high risk of serious side effects. The FDA approved tapentadol for the treatment of pDPN, but the ADA does not recommend it as a first or second-line treatment due to the high risk of addiction and safety concerns compared with its modest pain relief. Furthermore, patients who are unresponsive to other medications and may benefit from opioids should be referred to specialized pain clinics. The ADA also recommends combination therapy at lower doses if high doses of single drugs are not tolerated [79,80].

7.5.1 Anticonvulsants

Pregabalin and gabapentin are anticonvulsant drugs that are commonly used in treating pDPN. They function by inhibiting the calcium voltage-gated channels by binding to the alpha2delta-1 subunit, which results in reducing pain associated with DPN [81]. They have been shown to reduce mean daily pain scores and improve sleep quality associated with pDPN, but can cause dizziness and somnolence [82]. Furthermore, two studies showed that pregabalin could also be used to treat pDPN for reducing pain and improving sleep quality compared to the placebo group. Side effects noted in the studies included headaches, infection and dry mouth. Other side effects were dose-dependent dizziness, somnolence and peripheral oedema [82]. However, gabapentin and pregabalin should not be administered with azelastine (nasal), orphenadrine, oxomemazine, paraldehyde and thalidomide due to the enhanced risk of oversedation [83].

7.5.1 Antidepressants

This class of drugs functions by increasing the synaptic concentration of serotonin, norepinephrine and dopamine. Amitriptyline, imipramine and nortriptyline are tricyclic antidepressants (TCA) that can aid in reducing pain associated with pDPN. Drug interactions that need to be taken into account include any drugs that are metabolized by cytochrome P4502D6 such as cimetidine or phenothiazines, and class 1C antiarrhythmics. SSRIs can also affect the metabolism of TCAs by inhibiting cytochrome P4502D6

and elevate the drug plasma levels to toxic concentrations [84]. Adverse side effects associated with TCAs include anticholinergic symptoms such as dry mouth, orthostatic hypotension, constipation, blurred vision and cardiac arrhythmias. Contraindications to TCA include myocardial infarction within six months, long QT syndrome, cardiac conduction disease and history of ventricular arrhythmias. Older patients may also experience cognitive impairment and difficulties in balance. Anticholinergic drugs such as aclidinium, cimetropium, eluxadoline, glucagon, glycopyrrolate (oral inhalation), ipratropium (oral inhalation), oxatomide, potassium chloride, potassium citrate, tiotropium, and umeclidinium should be avoided due to additive anticholinergic effects [85]. CNS depressants such as azelastine (nasal), orphenadrine, oxomemazine, paraldehyde and thalidomide should also be avoided due to enhanced CNS depression [83].

Duloxetine and venlafaxine are both antidepressant drugs that inhibit the reuptake of both serotonin and norepinephrine. Compared to the TCAs, these drugs do not have muscarinic, histaminic or adrenergic side effects [6]. Significant drug interactions to consider when prescribing duloxetine or venlafaxine include serotonin modulators such as dapoxetine and methylene blue due to the increased risk of serotonin syndrome (SS) [86]. Serotonin syndrome, characterized by the sudden onset of cognitive/behavioural changes (e.g. confusion, agitation, lethargy, coma), autonomic instability (e.g. hyperthermia, tachycardia, diaphoresis, nausea, vomiting, diarrhoea, dilated pupils), and neuromuscular changes (e.g. myoclonus, hyperreflexia, rigidity) [86]. Concomitant use of other SNRIs such as linezolid, methylene blue, and monoamine oxidase inhibitors may also result in SS [87]. CYP1A2 inhibitors can increase serum duloxetine concentration [88].

7.5.3 Opioids

Tramadol is an analgesic drug that acts as a weak agonist of the μ-opioid receptor and as a serotonin and norepinephrine reuptake inhibitor, and is effective for pDPN. However, because patients may develop dependence, it is considered second or third-line treatment [6,89]. CNS depressants such as azelastine (nasal), orphenadrine, oxomemazine, paraldehyde and thalidomide should not be prescribed with tramadol as there is a risk of enhanced CNS depression [83]. Also, co-administration of serotonin modulators such as dapoxetine, duloxetine or methylene blue can lead to serotonin syndrome [86]. Eluxadoline, indicated for diarrhoea – predominantly irritable bowel syndrome – should not be prescribed with opioid analgesics as it can cause severe constipation [90]. Carbamazepine can decrease the serum concentration of tramadol by inducing its metabolism, and conversely, tramadol can induce

Table 7-2. Drugs used in painful diabetic neuropathy with their principle indication, recommendation, interaction and side effects.

Drug	Drug class	1st line	2nd line	Drug Interactions	Common side effects	Major side effects
Gabapentin	Anticonvulsant	MENA, NeuPSIG, ADA		CNS depressants	Somnolence, dizziness, peripheral edema, headache, ataxia, fatigue, xerostomia, weight gain	Angioedema, hepatotoxicity, rhabdomyolysis, suicidal thoughts, seizures after rapid discontinuation, thrombocytopenia
Pregabalin	Anticonvulsant	MENA, NeuPSIG, ADA		CNS depressants	Somnolence, dizziness, ataxia, fatigue	Stevens-Johnson Syndrome, suicidal thoughts, seizures after rapid discontinuation
Duloxetine	Antidepressant	NeuPSIG, ADA	MENA	Serotonin modulators, serotonin/norepinephrine reuptake inhibitors, CYP1A2 inhibitors	Nausea, somnolence, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia, headache, diaphoresis, insomnia, fatigue, decreased libido	Stevens-Johnson Syndrome, hepatotoxicity, hypertensive crisis, gastrointestinal hemorrhage, delirium, myocardial infarction, cardiac arrhythmias, glaucoma, suicidal thoughts, shift to mania from bipolar, seizures, severe hyponatremia, fragility bone fracture, serotonin syndrome, neuroleptic malignant syndrome
Venlafaxine	Antidepressant	NeuPSIG, ADA	MENA	Serotonin modulators, serotonin/norepinephrine reuptake inhibitors	Same as above	Same as above

Amitriptyline	Tricyclic antidepressant	MENA, NeuPSIG, ADA		Anticholinergic drugs, CNS depressants, Serotonin agonists	Nausea, somnolence, dizziness, constipation, xerostomia, anorexia, headache, insomnia, fatigue, orthostatic hypertension, urinary retention, blurred vision, altered accommodation disturbance, mydriasis, weight gain	Delirium, cardiac arrhythmias, conduction abnormalities, myocardial infarction, heart failure exacerbation, stroke, seizures, hepatotoxicity, bone marrow suppression, suicidal thoughts, shift to mania in bipolar disorder, neuroleptic malignat syndrome, serotonin syndrome, severe hyponatremia, fragility bone fracture
Desipramine	TCA antidepressant	MENA, NeuPSIG, ADA		Same as above	Same as above	Same as above
Nortriptyline	TCA antidepressant	MENA, NeuPSIG, ADA		Same as above	Same as above	Same as above
Tramadol	Opioid		MENA, NeuPSIG	CNS depressants, serotonin modulators, eluxadoline, carbamazepine, moclobemide	Somnolence, nausea, vomiting, constipation, light-headedness, dizziness	Confusion, seizure, cardiac arrhythmias, hypertension, hypersensitivity reaction, Steven-Johnson syndrome

seizures, diminishing each other's efficacy [91]. Moclobemide's serotonergic effect can be increased by tramadol, resulting in serotonin syndrome [92].

Oxycodone, a slow-release opioid, may also be effective for pDPN although a risk–benefit ratio has not been firmly established [6,89]. Oxyocodone can also interact with azelastine (nasal), orphenadrine, oxomemazine, paraldehyde and thalidomide, and increase CNS depression [83]. Conivaptan, fusidic acid (systemic), and idelalisib are CYP3A4 inhibitors, which can result in high levels of serum oxycodone [93].

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CASE STUDY – XVII

A 58-year-old male patient suffering from type II DM of 35 years duration, obese with hypertension, with severe diabetic retinopathy and coronary artery disease, presented at the health centre. He was also on renal haemodialysis. The patient recently returned from Thailand, where he was treated for a left foot infection. On examination he was in a good general condition, BP 135/78 mmHg, afebrile, and his HbA1c was 7%. He was taking basal insulin (Glargine) 36 units in the evening and 15 units of a fast-acting insulin analogue (Novo rapid) 10 minutes before main meals. The foot had a rocker-bottom appearance due to Charcot arthropathy with Wagner's grade II ulcers involving the midfoot and the heel where necrotic tissue was in the middle of the wound (Figure 7-7). The attending family physician with a special interest in diabetic foot management debrided the necrotic tissue, applied Betadine® to the peri-wound area, and applied natural honey to the wounds. The dressing was changed daily, and the patient meanwhile was instructed to have minimal ambulation. Two weeks later, the wound looked healthy with pink granulation tissue (Figure 7-8). The patient continued his dressing daily and three weeks later, the wound reduced in size by 50% (Figure 7-9). The heel ulcer continued to improve and started to fill from inside outwards (Figure 7-10), and complete healing took place two months later (Figure 7-11). Although the midfoot plantar ulcer reduced by 75%, (Figure 7-12), the patient failed to come for further treatment due to finishing his contract in the country.

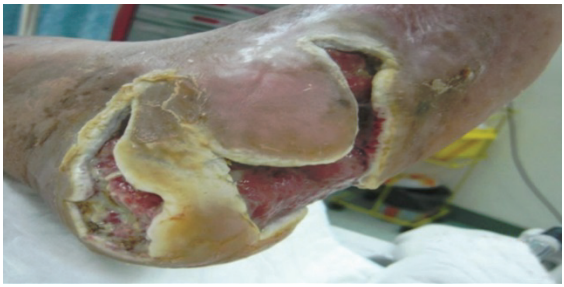

Figure. 7-7: Left foot showing classical “rocker-bottom foot” deformity with extensive surgical debridement due to deep soft tissue infection with necrotic tissue in the heel region

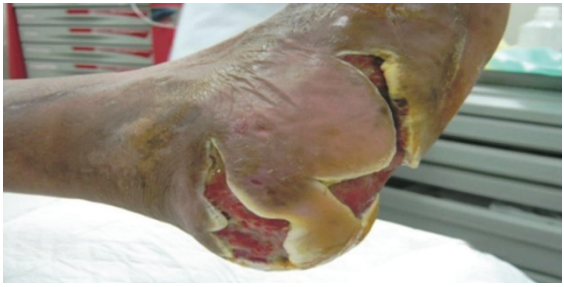

Figure 7-8: Post application of raw honey showing a reduction in the size of the ulcer with apparent healthy granulation tissue two weeks later

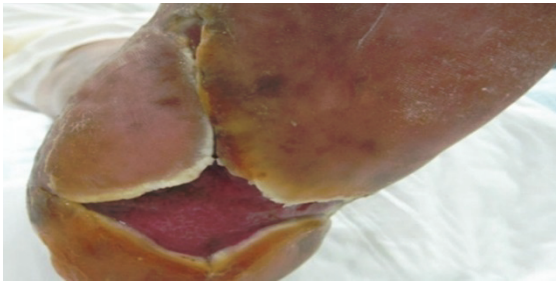

Figure 7-9: Almost 50% reduction in size of ulcer four weeks later

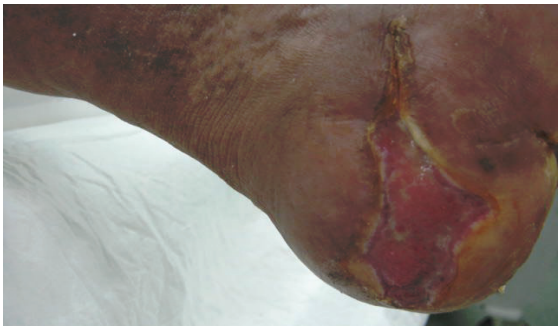

Figure 7-10: The heel ulcer is filling from down upwards with healthy granulation tissue

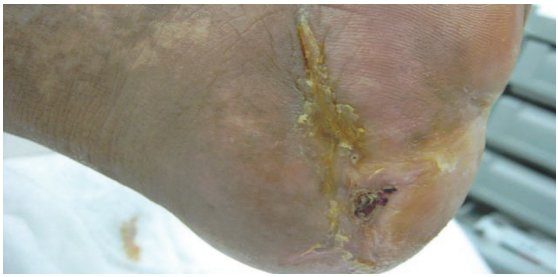

Figure 7-11: Complete healing of the heel ulcer

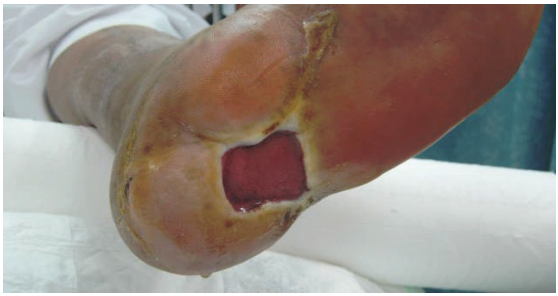

Figure 7-12: Reduction in the midfoot ulcer by 75%

CHAPTER 8

PRINCIPLES OF MANAGEMENT OF ACUTE AND CHRONIC DIABETIC WOUNDS

DR HASHIM MOHAMED

8.1 Acute wounds

A wound is said to be in an acute stage when there is a disruption in skin integrity, and underlying structures are expected to heal in an orderly and timely fashion.

8.2 Chronic wounds

Management of patients with chronic diabetic wounds and their long-term consequences presents an equal challenge for both the practitioner and the patient. The utilization of evidence-based treatment pathways within a multidisciplinary approach centred on patient and family education, along with the provision of medical and social support, may prove invaluable.

8.2.1 Definition and pathology

Wounds are defined as being chronic if they fail to proceed through a timely and orderly reparative cascade to restore anatomic and functional integrity over three months [4]. Any wound is liable to become chronic, therefore identifying and treating the underlying aetiologies of the wound is essential. The underlying factors could be arterial insufficiency, diabetes, unrelieved pressure or systemic factors such as immune suppression, nutritional status and infection. These can lead to poor wound healing [1-4].

A simplified algorithm for the management of chronic wounds is demonstrated in Figure 8-1 [1]. The most frequently seen chronic wound is

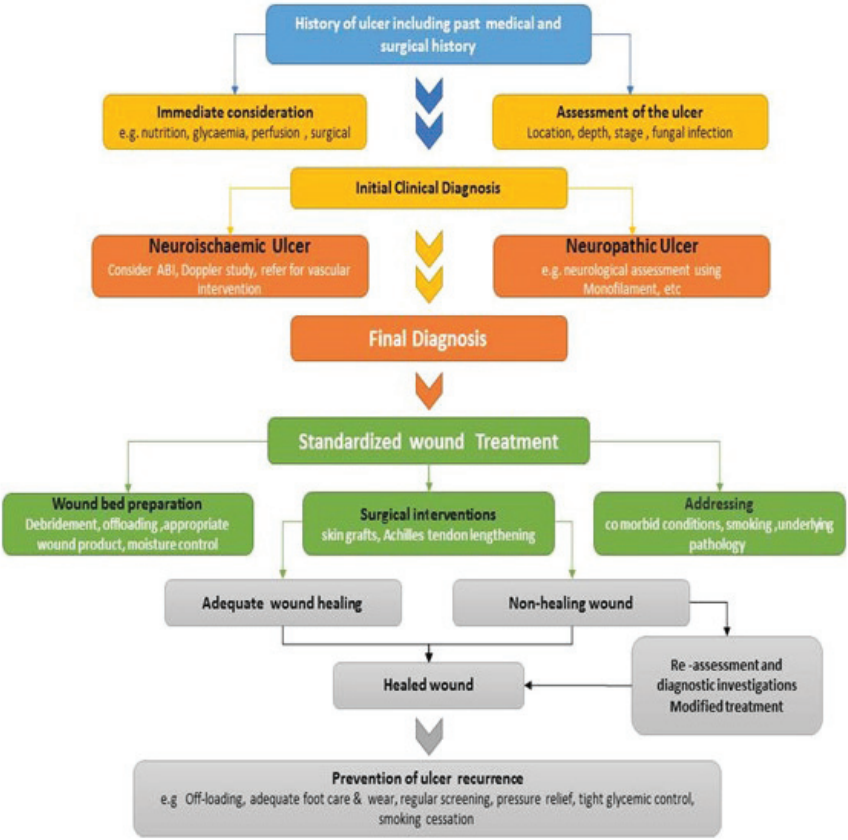

Figure 8-1: Diabetic foot ulcer management algorithm

the lower limb ulcer; these are usually diabetic or vascular in nature, and are responsible for up to 98% of all lower limb wounds [5].

The identification of a chronic wound is often carried out through the occurrence of a raised, hyperproliferative, yet non-advancing wound margin.

Fibroblasts found in the wound bed of chronic diabetic wounds are typically premature, senescent or of a differentiated phenotype, which respond inadequately to normal stimulatory messages [4,6,7]. Chronic wounds are typically characterized by a wound bed which is rich in pro-inflammatory cytokines and inflammatory products leading to the creation of an imbalanced enzymatic milieu made up of an abundance of matrix

metalloproteinases and a significant reduction of their inhibitors, ultimately leading to the destruction of the extracellular matrix [6].

This profound inflammatory state is considered to be a major factor in delaying healing. As a result, this state of chronic inflammation is a hallmark of a "failing to heal" wound, which may ultimately predispose these wounds to have malignant changes. Additionally, reduced perfusion leading to local cellular hypoxia with a recurrent ischaemia-reperfusion insult is thought to be a common pathogenesis in the development of chronic wounds [6].

8.3 Diabetic ulcer

Several factors lead to the development of diabetic wounds and their chronicity. Although classically diabetic foot ulcers were once considered to be mainly a disease of small vessels, a currently contribution of large vessel disease is gaining recognition [4]. Generally speaking, neuropathic diabetic foot ulcers need therapeutic interventions aimed at several causative factors including optimal glycaemic control, infection control, treatment of the neuropathy, revascularization and local wound management as well as prevention strategies [4].

Effective wound management is achieved through improving perfusion, medical management for neuropathy along with surgical decompressions [4,8]. Tight glycaemic control, infection resolution, education, prevention and offloading are highly significant [8]. All patients with neuropathic diabetic foot ulcers should receive pressure offloading [4-8,10]. Offloading devices may include crutches, wheelchairs, walkers, felt padding and protective footwear. In addition to the various classical mainstream medical wound products, alternative therapies such as natural honey and curcuma are making a strong impact.

This is coupled with new technologies, including the use of living skin equivalents, platelet-derived growth factors and cytokines, which are showing varying degrees of success in treating diabetic ulcers after rigorous wound bed preparation [4].

8.4 Local wound management principles

Regardless of the nature of the wound type, the general wound management principle applies to a wide array of chronic wounds [4]. The Wound Healing Society proposed the TIME acronym, which is a

comprehensive, yet simple method for communicating, defining and targeting principal factors linked to impaired wound healing [15].

T I M E

"T" refers to *tissue* (deficits, presence of necrotic or devitalized tissue)
"I" refers to *inflammation* or *infection* (in the wound or peri-wound area)
"M" refers to *moisture* balance (which ranges from maceration to desiccation)
"E" refers to the nature of the wound *edge*, usually heaped up, non-advancing and hyperkeratotic in the chronic wound setting, along with describing the amount of re-epithelialization) [15].

8.4.1 Tissue

The first step in the treatment of any chronic wound is to eliminate the local barriers to wound healing by removing devitalized tissue, necrotic tissue and excessive microbial (bacterial) burden [15]. Adequate wound bed preparation requires aggressive and yet judicious debridement, preserving vital tissue while removing devitalized tissue and excessive bacterial load.

By doing so, we convert the poorly healing or non-advancing chronic wound state to one resembling an acute wound [15,16]. Numerous modalities exist nowadays for debriding wounds. They range from sharp debridement using surgical tools (scalpels), electromechanical instruments such as the curettage and waterjet, autolytic debridement wound dressings like hydrocolloid, and occlusive wound dressings enzymatic agents like papain-urea derivatives and collagenase, along with biological agents such as maggots [15-17].

Currently, no definitive data exists in establishing any single type of debridement as more superior in improving healing time. Sharp surgical debridement is generally considered as an effective and fast method, especially in patients with diabetic pressure and related venous wounds [16]. In cases where peripheral pulses are not palpable, indicating arterial insufficiency, sharp surgical debridement should be deferred until the vascular status is assessed and modified (revascularization) unless complicated by sepsis [5].

8.4.2 Infection

In a wide range of chronic wounds, failure to heal is due to self-sustaining and uncontrolled inflammatory mechanisms [18].

Control of local and systemic inflammatory mediators is best facilitated by decreasing the bioburden to sub-infection levels.

Chronic wounds are characterized by polymicrobial colonization, therefore quantitative tissue biopsies and validated adequate deep swab techniques may provide objective evidence of the extent and nature of the offending pathogen.

Impaired wound healing and surgical closure have been associated with bacterial concentration exceeding $10^{(5)}$ or $10^{(6)}$ bacteria colony-forming units per gram of tissue or any value of β-haemolytic streptococci [5].

The nature of the offending pathogen in chronic wounds varies from one country to another; however, the most prevalent pathogen worldwide, including the United States and Europe, is *Staphylococcus aureus*. However, recently methicillin-resistant *Staphylococcus aureus* (MRSA) has also been seen in 20% to 50% of cases in US hospitals. Also, community-acquired MRSA is frequently noticed in primary care-based clinics too.

Surgical debridement, along with flushing the wound with normal saline or water, is effective in reducing a bacterial bioburden. Although topical antibiotics have been reported to lower the number of bacteria in chronic wounds effectively, rigorous multicentre randomized controlled trials are still lacking in this area.

Similarly, the systemic administration of antibiotics does not effectively reduce a bacterial bioburden in granulating wounds [20]. Many antimicrobial dressings and agents are available on the market, and wound care dressing companies have been rigorously influencing and targeting wound care specialists for decades. The use of ionic silver-based products has increased dramatically over the past years due to enormous and sustained pharmaceutical campaigns quoting multiple reports suggesting improved rates of healing. However, to date, three clinical randomized control trials have failed to demonstrate a significant increase in complete wound healing [21].

8.4.3 Moisture

In order to cleanse the wound, a non-irritating and non-toxic solution should be used to minimize additional trauma through cytotoxicity. Current wound dressings combine elements of wound bed preparation, that is, antimicrobial activity, with debridement with moisture control. The best topical environment for an open wound is a moist (non-macerated)

environment which needs to be maintained in order to achieve optimal healing [13,22].

Selecting an adequate wound dressing should address the current stage of wound healing, its cost, ease of removal, acceptability, specific temporal requirements and efficacy, as well as potential side effects. Ideal dressings should be easy to apply, should not compromise healthy granulating tissue when removed, and should cause minimal pain. Additionally, dressings must prevent shear and friction while offering protection to the peri-ulcer tissue and skin [13]. A recent literature review advocates using hydrogels for the debridement, a foam dressing at the granulation stage, and the use of either low-adherence dressing or hydrocolloids for the epithelialization phase [13].

Interestingly, a recent literature review advocated the use of a single modality therapy consisting of either a saline-moistened dressing or paraffin gauze dressing, which can also be effectively utilized [22].

At present, there is little solid evidence based on data from randomized clinical trials to prove the superiority of expensive modern dressings in terms of efficacy or general performance criteria (ease of use, pain, avoidance of tissue trauma on removal, and ability to absorb and contain exudates) [22].

8.4.4 Edge of the wound

Ideally, the caregiver should monitor the wound's progress regularly. A reduction in ulcer size should be noted if appropriate therapeutic intervention is employed; if not, other pathologies need to be considered, including autoimmune ulcers, squamous cell carcinoma and pyoderma gangrenosum. A biopsy is warranted in order to rule out these conditions. Drug-related ulcers should also be taken into consideration [5].

Wound healing is normally characterized by the formation of new skin cells that are added to the base and the edges until it closes up. A key indicator of a healing wound is the progression (migration) of the wound edge in terms of the epidermal cell (keratinocyte) and contraction of the wound. Chronic neuropathic diabetic foot ulcers are usually characterized by the presence of hyperkeratosis or a thick callous at the wound periphery which will act as an obstacle, thereby preventing keratinocyte migration and, as a result, prevent epithelialization. Many reasons account for this, including the presence of abnormal skin cells at the base and the edges of the wound due to excessive walking or failure of the caregiver to debride the edges of the ulcer, or the presence of inhibitory elements in the wound exudate (fluid).

Many chronic diabetic feet display a wound edge that is damaged or worn away (i.e. undermined); as a result, new skin cells may not adhere properly. Chronic wound closure may be enhanced by addressing inflammation, tissue viability and moisture levels in the wound. Surgical repair is of two kinds, those that lead to definitive closure of the wound and those that manage the underlying disease process.

Nutritional status, glycaemic control, offloading bacterial burden, haemodynamic status and vascular supply all play essential roles in the timing of optimal surgical repair.

Exposed functional structures, including neurovascular structures, tendons and bone, require immediate surgical preservation and protection. Occasionally chronic wounds are complicated by severe lipodermatosclerosis, thereby requiring thorough excision, debridement and bacterial bioburden control followed by free flap reconstruction, which has been demonstrated to accelerate healing [25]. Whenever pressure ulcers fail to heal in a timely fashion despite optimal efforts at prevention and optimization, a surgical closure is generally required [4,25].

8.5 Adjuvant agents

A broad range of commercially available adjuvants is marketed to enhance the healing of chronic wounds. Unfortunately, multicentre high-quality randomized controlled trials are non-existent to support promotion and application.

Improved perfusion, functional status and quality of life have been proven with the use of cilostazol for the treatment of arterial ulcers [26]. The use of bilayered artificial skin dressings [5] and pentoxifylline [27], both utilized in combination with interrupted high-compression bandaging for the treatment of venous ulcers, has been validated. Similarly, the application of platelet-derived growth factors for pressure ulcers [5] and neuropathic ulcers [28] has also been validated.

The use of Regranex® gel has raised recent concerns regarding malignancy [29]. Ultrasound, electrical stimulation, spinal cord stimulation, low laser energy and hyperbaric oxygen therapy are promising modalities with preclinical studies advocating their use [5]. Challenging chronic wounds has shown some benefit with the application of negative pressure [5]. However, phototherapy and laser therapy do not significantly improve wound healing [5].

8.6 Ulcer recurrence

The recurrence rate for most chronic ulcers remains high, ranging from 24% to 57% for venous ulcers, 23% to 40% for pressure ulcers and upward of 60% for diabetic ulcers, suggesting the importance of continuous preventive efforts [14,30,31].

Accurate and timely diagnosis and management, addressing risk factors, management of co-morbidities including psychosocial support and education, remain vital for effective prevention of recurrence [5,14,30,31]. Patients with type II diabetes usually require optimal glycaemic control, antiplatelet therapy, smoking cessation, management of hypertension and hyperlipidaemia to promote healing [5,30,32].

The reduction in the incidence and complications linked to diabetic foot ulcers is related to the use of protective footwear and proper foot care practices, including adequate bathing and nail trimming [5,8,34].

Nutritional assessment and optimization are vital in the management of patients with chronic wounds, especially among the elderly patients who usually suffer from chronic systemic diseases, traumas, immunosuppressive states, malignancies and adverse drug reactions.

Wound management requires adequate education of patients and family members. Patient education is linked to improved quality of life, compliance, frequency and efficacy of dressing changes, as well as prevention of recurrence [5,37]. Finally, updating medical staff while critical for optimal management remains an often-neglected factor in treating and preventing chronic wounds [38].

8.7 The future

Emerging novel technologies present alternative modalities for future wound care. Currently, new technology is being used in gene therapy, which allows genes or gene-derived messengers to be directed into the wound at various points in time [41]. Ethical issues, however, remain an obstacle in the application of the skin and composite equivalents from embryonic and bone marrow-derived stem cells in certain countries [42].

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CASE STUDY – XVIII

A 65-year-old male patient known to have malignant melanoma of the plantar aspect of the left foot presented at the health centre by self-referral after his skin graft had fallen off. On examination, the plantar aspect of the left foot revealed a wound of 6 × 5 × 3 cm with plantar aponeurosis evident in the middle of the wound (Figure 8-2). After applying honey daily, the wound was covered with healthy granulation tissue (Figure 8-3). By three weeks, the wound started showing growth of new skin at the periphery of the wound (Figure 8-4). Three months later, 90% of the wound had healed with areas of hypergranulation evident at the 9 o'clock position (Figure 8-5). The hypergranulation tissue was cauterized using a cautery pen (Figure 8-6). Three months later, the patient achieved 100% healing (Figure 8-7).

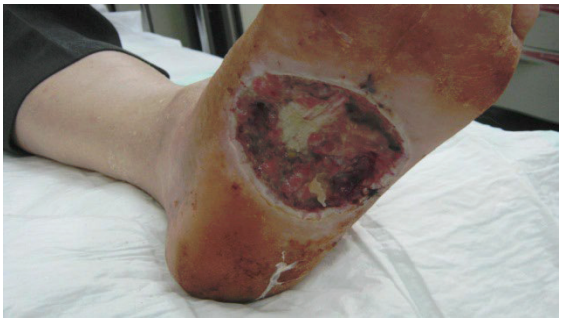

Figure 8-2: Wound size of 6 × 5 cm showing areas of skin where the clips have been removed along with evident plantar aponeurosis in the middle of the wound.

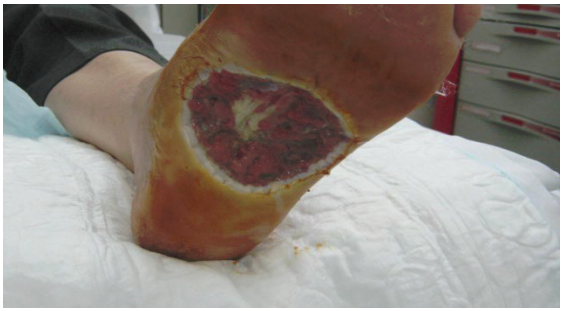

Figure 8-3: One week later healthy granulation tissue appears evident even on the plantar aponeurosis

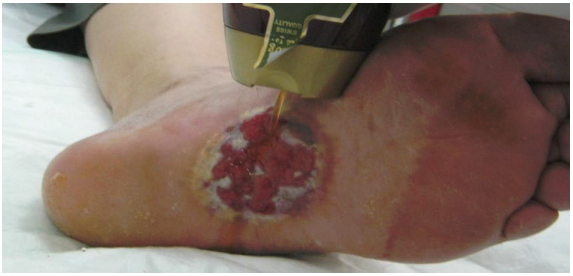

Figure 8-4: Three weeks later, areas of new skin formation are evident along with a reduction in the size of the ulcer by 35% and the application of natural honey.

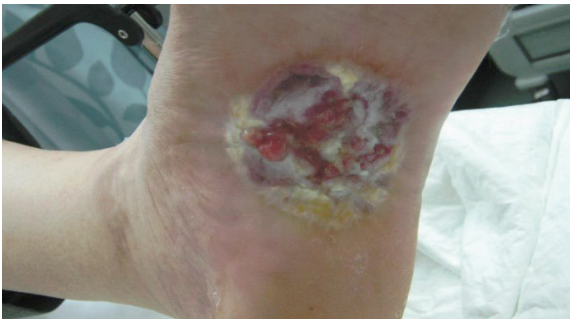

Figure 8-5: Two months later, there is a 90% reduction in wound size along with new skin formation. However, there are areas of hypergranulation seen in the 9 o'clock position.

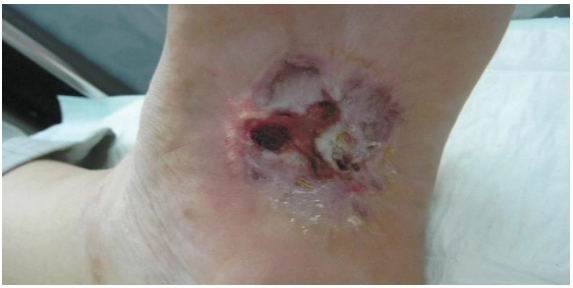

Figure 8-6: The foot after cauterization of the hypergranulation tissue using a handheld disposable cautery pen

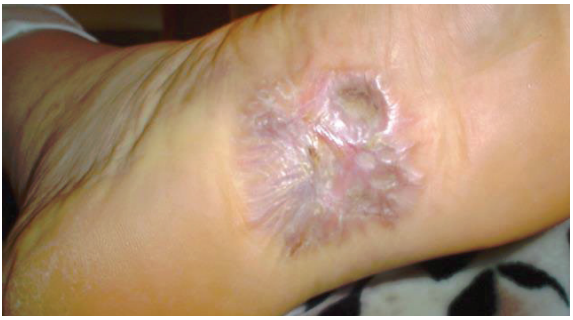

Figure 8-7: Showing complete healing three months later.

CHAPTER 9

WOUND CARE PRODUCTS: THE PAST, PRESENT AND THE FUTURE

DR BADRIYA AL LENJAWI

9.1 Introduction

Wound care discipline contains as many different management modalities and options as the number of health care workers caring for the wounds. Although many wound care specialists depend on tried and tested management options, there seems to be an endless flow of new wound care products and technologies in the field. Many of these wound care products are enhanced and updated versions of previous modalities, whereas others are the end products of entirely new scientific clinical research. The race to introduce new and novel wound products often precedes rigorous clinical trials, and the efficacy is then determined by clinical judgement. This may lead to unanswered questions regarding indications, side effects, and appropriate use and cost.

The objective of this review is to discuss alternative wound care products, modern-day dressings and several new technologies about chronic diabetic foot ulcerations, burns and various other wounds.

Silver dressings are potent antimicrobials and have been used for centuries in wound care. Although new forms of delivery are continuously being developed to increase their efficacy, some concerns regarding their in vitro cytotoxic safety remain. Lasers and ultrasound devices are relatively new in wound care management, and their applications are continually growing to include new options for wound management that previously had very few alternatives. Wound healing conditions are optimized in the wound environment with the help of advanced wound care products. With the discovery of tissue engineering and biosynthetic, skin substitutes are proving to be novel and effective therapies that provide temporary wound coverage, leading to a change in the paradigm of wound care. Wound

healing is modulated or augmented with biologic substances and growth factors although infection, cost and failure are a concern. Finally, natural honey can provide an alternative treatment modality to the above wound healing options, particularly in chronic wounds that are not responding to other management strategies.

Around 370 million people worldwide have diabetes, and this number is increasing [1]. Diabetes UK estimates that by 2030 approximately 552 million people worldwide will have diabetes [2]. Among diabetes complications, diabetic foot ulcers (DFUs) are relatively common; in the UK alone, 5%–7% of people with diabetes currently have, or have had, a DFU [3]. Economies worldwide are burdened heavily by the cost of treating DFUs. The average estimated cost of an outpatient-treated DFU was estimated at $28,000 (US dollars) over two years, according to a study conducted in 1999 in the US [4]. Another study, conducted in 1997, revealed that the average inpatient cost of lower limb complications was $16,800 for DFU, $25,241 for toe or toe plus other distal amputations, and $31,436 for major amputations [5,6].

DFUs are usually chronic and complex in nature, resulting in a significant impact on the mortality, morbidity and quality of patients' lives [7,8]. Patients who are affected by a DFU are at an increased risk of myocardial infarction, premature death, peripheral vascular disease and fatal stroke compared to those without a history of DFU [9]. Unlike other chronic wounds, the onset and progression of a DFU are often aggravated by a multitude of diabetic changes, including vascular disease, neuropathy and altered foot dynamics.

Individuals suffering from a DFU often neglect foot care and adopt an unhealthy lifestyle due to a negative attitude stemming from concomitant depression. Furthermore, DFUs are characterized by altered protein synthesis and defective neutrophil function, along with the diminished tissue perfusion that frequently accompanies diabetes [7]. Consequently, health workers are challenged with unique and specific management dilemmas.

As a discipline, wound management possesses a wide variety of management modalities and options. For example, the number of new dressings available on the UK Drug Tariff increased from 4 in 1988, to 57 in 1998 and 262 by February 2007 [7].

Historically, wound dressings have varied tremendously from potato peel and cotton to biosynthetic, skin substitutes and tissue engineering. Health care professionals may be confused by this unprecedented number of wound care options that are constantly pouring in. Besides, complications like bacterial resistance to treatment and increased costs add to further confusion. An ideal wound dressing should provide an optimum environment to allow epithelialization, angiogenesis and a moist environment promoting

healing without scar formation, while being aesthetically acceptable and cost-effective [10-12].

Wound management depends on a variety of factors such as the nature and duration of wounds being treated, co-morbidities, age of the patient, type of wound dressing, nutritional status, perfusion, oxygenation, existence of biofilm, the physical and chemical properties of the available dressings, offloading, socio-economic status [10], psychological well-being of the patient and the logistics of the health care setting.

It is important to remember that wound products should be assessed and tested in relation to their physical, biological and chemical properties, and clinical efficacy for a certain type of wound and the stage of wound healing, before inclusion in routine clinical practice.

This review discusses the current, state-of-the-art wound healing products as well as more traditional products such as natural honey and other alternative wound management products.

Wound care products are discussed in terms of their advantages and shortcomings. Furthermore, the need for dressings with improved properties is also debated. With the wide range of wound care products available, the aim should be to find the most appropriate modality to optimize wound healing.

9.2 Classification of dressings

There are various ways of classifying wound care products (dressings) depending on their mechanism of action in the wound environment (i.e. occlusive, adherence, absorbent, debridement) [11], the nature of the material used to produce the dressing (e.g. alginate, hydrocolloid or collagen) [12] and the physical nature of the dressing (e.g. film, foam, ointment or gel) [13,14]. Alternative classification criteria include traditional, modern and advanced dressings, skin replacement products and wound healing devices.

These classifications, like the preceding ones, do not consider alternative or complementary dressings used worldwide. Some of these alternatives – complementary elements and dressings – are considered below.

9.2.1 Silver

The medical use of silver to prevent and treat wound infection has been used through the ages. The use of silver is recorded as early as 69 BC, and it remains among the most widely used current therapeutic options.

Regardless of the form of a silver-containing product, elemental silver needs ionization for it to be an effective antimicrobial agent [15].

Maintaining silver in an adequate concentration with long enough residual activity is the critical factor in formulating the most effective product where silver ions readily bind to protein and chloride in the wound bed fluid [16].

Wound products containing silver have maintained their place in wound management due to silver's broad-spectrum coverage, particularly against antibiotic-resistant bacteria. Silver also has a very broad spectrum of microbial coverage against mould, yeast and fungi when used in adequate concentrations for an appropriate length of time [17].

To prevent resistance against healing, silver requires maintenance in the wound in a high concentration and with lasting residual activity. Hence, silver products such as silver nitrate require around 12 applications per day to maintain activity. Silver sulfadiazine has a similar activity. Both can provide high enough initial concentrations (3,176 mg/L and 3,025 mg/L, respectively) [18].

Despite silver being noted for its broad-spectrum antimicrobial coverage, bacterial resistance has been documented as early as 1975 [19,20], specifically among burn patients where silver salts had been used as an antiseptic agent. Silver-resistant strains include *E. coli*, *Enterobacter cloacae*, *Pseudomonas stutzeri*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *salmonella typhi* [19-21]. A salmonella strain that was resistant to silver caused septicaemia and the death of three patients, which led to the closure of the burns unit at the Massachusetts General Hospital [22].

Nanocrystalline silver, on the other hand, is more efficacious than silver sulfadiazine and silver nitrate. Wright (1998) and colleagues demonstrated that a nanocrystalline silver dressing killed MRSA in 30 minutes, whereas other silver preparations did not affect it. Similarly, Yin et al. showed that nanocrystalline silver killed *Staphylococcus aureus* after one hour, while silver sulfadiazine took 4–6 hours [23,24].

Several studies show that nanocrystalline silver leads to faster wound healing, decreased need for antimicrobials, decreased cellulitis and less burn sepsis [25-27].

However, nanocrystalline silver has also been shown to cause cytotoxicity, especially towards fibroblasts and keratinocytes, which leads to inhibition of keratinocyte growth and delay in re-epithelialization. In vitro studies have further shown nanocrystalline silver to be specifically toxic to cultured skin substitute [28-30]. Studies carried out by Du Toit and Page (2009) [31] had shown significant cytotoxicity when nanocrystalline silver was applied to keratinocytes and fibroblasts, the essential cells needed

for tissue repair. These findings align with those of Poon (2004), Burd (2007) and Frazer et al. (2004) [32-34].

A study by Paddle-Ledinek et al. (2006) [35] demonstrated cell toxicity arising from wound dressings such as Contreet-H (Coloplast), Avance® (Mölnlycke Health Care), and Aquacel® Ag (Convatec). Rapidly proliferating cells, such as donor sites and superficial burns, are therefore at risk of cytotoxicity if exposed to nanocrystalline silver.

A recent literature review conducted by Khundkar et al. (2010) [36] expressed a word of caution comparing nanocrystalline silver to other silver preparations; only 1 in 31 articles was rated at a level of evidence 1 (randomized controlled trial (RCT) of sufficient size for a narrow confidence interval), with the majority of articles rated at level of evidence 5 (expert opinion or based on bench research).

Utilizing Medaline® (Ovid), Greer et al. (2012) [37] conducted a systematic review of RCTs published from 1995 to August 2012. Four fair quality RCTs (n = 280 randomized) of silver products were identified; three were silver versus different advanced wound care products. In one study (n = 66), ulcers managed with silver ointment were more likely to heal than those managed with standard care (39% versus 16%; absolute risk difference (ARD) = 23%, 95% confidence interval (CI) 2% to 43%). Healed ulcers with mixed results were reported in three studies. Additionally, in two studies there was no difference in healing between silver products (dressing or cream) versus oak bark extract or a calcium-based dressing.

9.2.2 Skin substitutes

Bioengineered skin substitutes, both cultured autologous engineered skin and biosynthetic skin substitutes, are available to provide skin coverage for participants with significant body surface area burns leading to decreased mortality and increased survival. Although skin substitutes are available in large quantities with negligible immunologic reaction or risk of infection, they are expensive.

Biobrane® is a new, temporary wound dressing made of knitted nylon mesh attached to a thin silicone membrane and covered with porcine polypeptides. It is used to cover donor sites in split-thickness skin grafting and on clean, superficial and mid-dermal deep burns. Its efficacy is equivalent to silver sulfadiazine in wound healing without the frequency of dressing change [38,39].

Transcyte® has a similar composition to Biobrane with human fibroblasts cells added to it. It can be used as a temporary cover for excised

burns before grafting, or as a dressing for superficial burns that do not require skin grafting.

Where burns are concerned, especially facial burns, Transcyte has shown to be superior to sulfadiazine or antibiotic creams in terms of infection, healing time and scar formation [40,41].

Apligraf® is made of an epidermal layer of allogenic neonatal fibroblasts and keratinocytes from neonatal foreskin on layered type 1 bovine collagen. Apligraf leads to acceleration in healing times if used as an adjunct covering to an autograft. It can also be used alone in chronic wound ulcers demonstrating accelerated healing times when compared to controls [42,43].

Dermagraft® is composed of a bioabsorbable polyglactin mesh, which contains neonatal fibroblasts. It can be used as a temporary or permanent cover for excised burns wounds, pressure ulcers and venous ulcers. Fibroblasts produce growth factors dermal collagen and fibronectin to aid wound healing. Studies demonstrate that it is similar in efficacy to an allograft for healing time, wound infection and graft take [38,39,44,45]. Although this advanced wound product seems to be efficacious, the cost and controversy associated with its use regarding legal and ethical issues limit its use in everyday clinical practice.

Integra® is a temporary semi-biologic, bilayer dressing consisting of a matrix of glycosaminoglycan and type 1 bovine collagen under a superficial silicon sheet [38,46]. The patient's endothelial cells and fibroblasts migrate through the pores (70–200 micrometre). The silicon sheet is removed upon granulation of the wound, and a superficial autograft layer is implanted above the neodermis to cover the wound area. Full and partial thickness wounds are the primary indications for its use along with pressure ulcers and vascular and complex traumatic soft tissue reconstruction of overexposed soft tissue and joints [47].

The medical field has witnessed various successes with the use of skin substitutes; however, serious issues remain, including a high failure rate, irritation, cross-contamination, and religious and ethical issues. They are relatively expensive compared to cadaveric skin from skin banks. Biological skin equivalents were assessed via a literature review carried out by Greer et al. [37], which included seven randomized controlled trials. In these clinical studies (n = 576 randomized), Dermagraft demonstrated statistically significant healing time in two of the studies (30% versus 18% in one study and 305 versus 185 days in the other). Subjects receiving metabolically active Dermagraft demonstrated significant healing in the third trial. However, a pooled analysis showed an overall non-significant benefit of Dermagraft compared to standard care for wound healing (RR = 1.49, 95% CI 1.20 to 2.08, I2 = to 0.0%) [37].

Apligraf was compared to standard care in two moderate-quality trials (n = 339 randomized), and they demonstrated a significant advantage in wound healing (55% versus 34%: ARD = 21%, 95% CI 9% to 32%, RR = 1.58, 95% CI 1.20 to 2.08) [36]. Despite the fact that advanced wound products have an essential role in a variety of wounds, their inclusion in routine medical practice is hampered not only by cost, but also by the risk of cross-infection including hepatitis and HIV, antigenicity, and legal and ethical issues surrounding stem cell research [48].

9.2.3 Growth factors and biological wound dressings

The wound healing process is regulated by a variety of mediators including cytokines, eicosanoids, growth factors and nitric oxide. Eicosanoids are arachidonic acid metabolites such as thromboxane, prostaglandins and leukotrienes. Prostaglandin E1 is well known, and inhibits platelet–neutrophil activation, decreases blood viscosity and causes vasodilation [47]. Inflammation is regulated by cytokines, which modulate haematopoietic cells. Cytokines include interleukins, lymphokines, interferons and colony-stimulating factors. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is the most widely examined.

Fibroblasts and keratinocytes are stimulated by growth factors via transmembrane glycoproteins [49]. They are classified into five main categories, the most famous being the FDA-approved platelet-derived growth factor (rhPDGF-BB), which has been studied by Steed based on 118 subjects suffering from DFUs [50]. In this study, statistically significant wound healing was demonstrated (48% versus 25%) and a greater reduction in wound size.

These findings were supported by additional studies that demonstrated increased odds of wound healing and decreased risk of amputation in patients suffering from diabetic foot ulceration [51,52]. Greer et al. examined nine RCTs (n = 990) comparing PDGF to placebo gel or standard ulcer care (n = 6), an advanced wound care therapy (n = 2) or both (n = 1) [36]. Two of these trials were of high quality, five were moderate and two were poor. At study completion, the PDGF group showed a greater percentage of wound healing in comparison to standard care (seven trials). However, there was evidence of marked heterogeneity (58% versus 37%; ARD = 21%, 95% CI 14% to 29%; RR = 1.45, 95% CI 1.03 to 2.05). The PDGF-treated group had significantly less time to healing in four trials (29 versus 41 days) with one trial reporting no difference. However, when compared to biologic dressing, carboxylmethylcellulose gel or silver sulfadiazine, there was no significant difference in relation to the time of healing or percentage of

ulcers healed. Although encouraging clinical results were reported by Khan and Davies [53] examining the potential role of growth factors in managing chronic leg ulcers, inconsistent clinical endpoints and small sample size prevented definite conclusions from being drawn [54].

The PDGF treatment is not without its critics. The National Institute for Health and Clinical Excellence (NICE) recommends that autologous platelet-rich plasma gel and PDGF should not be offered as a treatment for diabetic foot problems unless they are part of a clinical trial [7].

9.3 Herbal wound therapy

Herbal wound therapy varies across cultures and nations. These include, but are not limited to, boiled potato peel [55], fenugreek and garlic, as well as various herbal combinations used by the Egyptians in 100 BC, including turmeric and castor oil. Traditional Chinese and Indian medicines contain a variety of herbs still widely used in clinical practice for a variety of both acute and chronic wounds. Different herbal medicines used in wound care management include *Parkia biglobosa* (Jacq.) and *Bridelia ferruginea*, which are thought to increase the proliferation of dermal fibroblasts. *Carapa guianensis* leaves are found to enhance skin breaking strength due to their hydroxyproline content, thereby enhancing wound healing potential and contraction [56].

Improved wound healing was also demonstrated using methanol extracts of *Heliotropium indicium Linn.* [57]. *Melaleuca alternifolia* and tea tree oil are used in wounds for their antiseptic, antiviral and antifungal properties [58]. Historically, burns have been treated by aloe vera, but clinical evidence remains unclear. The clinical use of aloe vera for burn wounds was studied by Maenthaisong et al., who conducted a systemic review [59] after searching MEDLINE, CINAHL, Cochrane Library, DARE, Health Star – a Chinese database – and several Thai local databases (1918–2004) including burn studies only. The review included four clinical trials that were fit for inclusion criteria (n = 371), and the duration of wound healing was used as an outcome measure. The summary weighted mean differences in the healing time of the aloe vera group was 8.79 days shorter than those in the control group ($p = 0.006$).

There is insufficient data to draw firm conclusions from these studies, mainly due to a lack of standardization of products used and outcome measures. However, cumulative evidence tends to favour using aloe vera for first and second-degree burns. According to Krishan [60], aloe vera is the sole herbal wound material that showed apparent efficacy in vitro, during

animal and human trials. Zhou et al. searched English and Chinese databases for oriental medicine and chronic wound care [61] in their systemic review. They identified and selected 17 RCTs on venous ulcers, 26 RCTs on pressure ulcers, and 93 RCTs on diabetic ulcers. They concluded that individual herbs and herbal formulas appear to be efficacious in treating chronic wounds.

9.4 Ultrasound

To stimulate normal physiological response to injury, a low therapeutic intensity (0.125–3 w/cm^2) ultrasound is used to stimulate tissue repair by stimulating fibroblasts to synthesize collagen. In the medical literature, only a few published clinical trials have demonstrated that ultrasound can accelerate wound healing, including those due to varicose vein insufficiency [62,63].

Galitsky and Levina [64] demonstrated that trophic ulcer sites had enhanced 'take' of skin graft when therapeutic ultrasound was used. Similarly, McDiarmid et al. [65] had used therapeutic ultrasound in managing infected pressure ulcers, which led to an improvement in the healing rate of treated wounds. Clinical studies had utilized non-contact, low-frequency ultrasound (NLFU) in the management of a variety of wounds since 2006 with various success rates, including ischaemic wounds [66,67]. Eight published trials reporting the effect of NLFU-treated patients were included in a meta-analysis conducted by Driver and colleagues [68]. They concluded that using NLFU was associated with a substantial and consistent wound reduction and a faster healing rate. Healing rate over time indicated that 32.7% of wounds healed on average by six weeks (95% CI 23.5%–42%) and 41.7% by twelve weeks.

However, most of these studies were of a non-comparative design, had a small sample size, and lacked blinding. Positive findings need to be confirmed through rigorous placebo-controlled randomized controlled trials.

9.5 Lasers and wound healing

Applying low doses of laser energy resulted in the stimulation of regeneration of mechanically induced wounds and burns [72]. In vitro studies demonstrated that wounds exposed to low-level laser therapy (LLLT) had increased epithelial growth, fibroblast migration, proliferation and

enhanced collagen synthesis. Furthermore, enhanced keratinocyte cell motility [69,70], growth factor release and transformation of fibroblasts to myofibroblasts [71] were attributed to using low-level laser therapy during in vitro studies. Although the efficacy of LLLT in wound healing has been demonstrated in many clinical studies [72], others have failed to replicate these findings [73,74,75].

To confuse the situation further, fibroblast proliferation was not demonstrated during in vitro studies by many researchers after using LLLT on a variety of wounds [76-78]. These conflicting results may be attributed to variation in treatment protocols, lack of control groups and non-binding investigators [78,79]. One plausible explanation may be that certain tissues (cells) may absorb light while others do not, and the intensity of light absorption also varies from one tissue to another, as well as the cell size and composition. Although laser therapy is used extensively in the cosmetic field, its use may be associated with the formation of non-viable atypical cells and chromosomal damage [80]. Additionally, a low-level laser has been found to stimulate growth areas and tumour cell proliferation [81].

A systematic review was conducted by Cullum et al. [82] examining 19 electronic databases, including Cochrane controlled trials, CINAHL, Embase and MEDLINE. Randomized controlled trials were selected if they included objective outcome measures such as wound healing rate or wound incidence. They concluded that there is insufficient reliable evidence to support using laser therapy in chronic wound healing.

9.6 Natural honey and wound healing

The honey, a natural product of bees of the genera *Apis* and *Meliponinae* since antiquity, has been considered for its medicinal properties. Surgical dressings impregnated with honey were used by the Ancient Egyptians to promote wound healing [83]. Judeo-Christian and Islamic traditions have considered honey as a gift from God. The Islamic Holy Quran has also described honey as a medicinal agent: “And your Lord revealed to the bees: Make hives in the mountains and the trees and in what they build. Then eat of all the fruits and walk in the ways of your Lord submissively. There comes forth from their bellies a beverage of many colours, in which there is healing for mankind. Verily in this is a sign for those who give thought.” [The Quran, Surah Al-Nahl, verses 68 and 69]

Since first introduced in 1999, licensed medical wound care products containing medical-grade honey are now widely used in the medical field. Silver-containing wound care product sales rose 200% between 1999 and

2009 as a result of large companies backing strong marketing campaigns [84].

In vitro studies have demonstrated that natural honey has comparable antibacterial efficacy to silver, yet it has none of the cytotoxicity related to silver use [31], especially affecting keratinocytes and fibroblasts essential for tissue repair. Furthermore, Frazer et al. (2004) and Poon (2004) have shown similar evidence of keratinocyte cytotoxicity upon exposure to silver. Natural honey, by comparison, was not shown to be toxic and favoured cell proliferation [31] and angiogenesis. Natural honey has long been recognized for its antimicrobial activities [85] both for in vitro and in vivo studies. Its texture, water content and constituents make it an ideal cost-effective dressing. Natural honey has been shown to exert a broad range of antimicrobial activity against bacteria, fungi and viruses [86,87]. Gram-positive bacteria often cause wound infection, and a very low concentration of natural honey is effective in inhibiting the growth of *Staphylococcus aureus*, the most common cause of wound infection [88-90]. Furthermore, natural honey inhibits the growth of vancomycin resistant *Staphylococcus aureus* (VRSA), methicillin-resistant *staphylococcus aureus* (MRSA) [91-94] and coagulase-negative staphylococci [95].

A recent study demonstrated growth inhibition of 15 cultures of streptococcus species isolated from a variety of wounds [96]. In vitro studies have demonstrated the inhibitory activity of natural honey against most commonly implicated bacteria in wound infection, such as *Pseudomonas aeruginosa* [88,91,93], enteric bacteria [97], Stenotrophomonas species [98] and *Acinetobacter baumannii* [89,92].

Chronic DFUs are characterized by biofilms [99]. In vitro studies have shown that natural honey disrupts established biofilms and inhibits their formation, especially those of VRSA and MRSA [88]. Interestingly, natural honey has demonstrated antiviral activity during in vitro studies [100] and reduced duration and pain threshold, and crusting of genital herpetic infections [101].

The exact mechanism in which natural honey exerts its antimicrobial activity remains unclear, although honey may destroy bacteria mainly through the release of hydrogen peroxide. This is produced by glucose oxidation catalyzed by the action of the bee enzyme glucose oxidase. Additional antimicrobial activity is linked to the release of methylglyoxal, defensin-1, low pH and flavonoids, which cause inhibition of adenosine triphosphate (ATP) metabolism and nucleic acid synthesis.

Honey is composed of approximately 40% fructose, 30% glucose, 5% sucrose and 20% water. It also contains several amino acids, antioxidants, vitamins, minerals and glucose oxidase. Glucose oxidase produces

hydrogen peroxide and gluconic acid, which gives honey its acidic pH of 3.2–4.5. Hydrogen peroxide is released at 1/1000th the concentration of wound rinse solution, just enough to kill bacteria without compromising keratinocytes or fibroblasts – the very cells required for the development of granulation tissue. Honey has a unique property of providing a moist wound healing environment because 17%–20% of its content is water. Natural honey also has a hyperosmolar medium. This leads to the absorption of water out of bacterial cell walls, resulting in the death of bacteria through the destruction of its cell wall [102-111].

Medical literature reports hundreds of case studies explaining the efficacy of natural honey in chronic wound management, including diabetic foot ulcers [112-114,119, 121-129]. However, there are few RCTs to support this. In one RCT, honey was demonstrated to promote improved wound debridement compared to the hydrogel [102]. Furthermore, natural honey has other bioactivities including a deodorizing action [103], an osmotic effect, anti-inflammatory activity [104], enhanced rate of healing [105,106], provision of water to the wound bed [103], provision of an external barrier to pathogens [107] and antioxidant activity [108,109] by reducing the release of reactive oxygen intermediates [110].

Although recently, the number of publications reporting use of honey has increased, systematic reviews have been critical of their study design [115-117]. Moore et al. (2001) [115] concluded that clinical evidence to support using honey in the treatment of superficial wounds and burns was of low quality.

By contrast, a review of 19 RCTs with a total of 2,554 participants suggested that honey improved healing times in mild to moderate superficial and partial thickness burns when compared to conventional dressings [117]. This was supported by a meta-analysis of systematic reviews of topical and systematic antimicrobial interventions for wounds. A total of 44 Cochrane reviews out of 149, which had been graded into five categories based on their size, homogeneity and the effect size of the outcome, were selected. In 109 evidence-based conclusions, robust evidence was found to support using topical honey to reduce healing times in burns [118].

A recent systemic review [130] examining published RCTs and controlled clinical trials (CCTs) using two electronic databases, PubMed and ISI Web of Science, looked at the efficacy of honey compared to other dressing materials. Four RCTs and two CCTs met the inclusion criteria for the effect of honey on chronic ulcers. The authors stated that more evidence could be noticed for the wound healing stimulating capacity of honey, for which two out of four RCTs report a statistically significant reduction in wound size, and two CCTs support the positive effect of honey on wound healing. Most

evidence had been found for the wound size reducing the effect of honey, which was statistically significant in favour of honey.

A 2014 systemic review [135] searching six electronic databases – including PubMed, the Cochrane Library, ISI Web of Science, and CNKI (China National Knowledge Infrastructure) – evaluating natural honey in chronic DFUs, looked at RCTs comparing natural honey to other treatments [131]. They found a total of four RCTs involving 258 participants. Three trials involving 228 participants met the quantitative analysis, and one study involving 30 participants met the qualitative analysis. Results of meta and descriptive analyses showed pooled differences in overall treatment time between the honey dressing group and control groups [SMD = −1.28, 95% CI (−2.46, −0.07), P = 0.04]. Pooled differences in mean purge time of wounds after intervention revealed a significant difference between the honey dressing and control groups [SMD = −0.92, 95% CI (1.27, −0.57), P = 0.00]. Pooled differences in the germ purge ratio in different treatment periods after intervention revealed significant differences between the honey dressing and control groups [RR = 2.32, 95% CI (1.51, 3.57), P = 0.00; RR = 1.70, 95% CI (1.02, 2.83), P = 0.04; RR = 1.56, 95% CI (1.19, 2.04), P = 0.00]. Healed areas of ulcers pooled differences after intervention revealed a significant difference in favour of honey compared to the control groups [SMD = 1.45, 95% CI (0.59, 2.31), P = 0.00].

Another recent review [117] of 33 RCTs noted that participants using honey had increased from 1965 in 2006 to 3556 in 2011, with a broadening range of wound types included, the choice of dressings available to clinicians and the types of honey employed. With such variations, it is difficult to make generalized deductions about clinical efficacy.

In 2012, Kamaratos and colleagues conducted a randomized controlled trial (RCT) investigating the effect of manuka honey-impregnated dressings on the healing of chronic diabetic foot ulcers. Sixty-three subjects with type 2 diabetes were randomized into two groups: group I patients were managed with honey, and group II patients were managed with conventional dressings (CD). Subjects were seen every week for four months. Mean healing time was 31 ± 4 days in group I versus 43 ± 3 days in group II ($P < 0.05$). In group I patients, 78.13% of ulcers became sterile during the first week versus 35.5% in group II patients; the corresponding percentages for weeks 2, 4 and 6 were 15.6% versus 38.7%, 6.25% versus 12.9% and 0% versus 12.9% respectively. The percentage of ulcers healed did not differ significantly between groups (97% for honey and 90% for conventional dressings).[132]

It seems that natural honey can be considered a credible alternative dressing for many reasons, including its broad-spectrum antibacterial

activity, its antifungal and antiviral action, ease of use, acceptability by both patients and health professionals alike, its cost-effectiveness, provision of moisture, anti-inflammatory activity, stimulation of angiogenesis and cell proliferation. To date, no honey-resistant bacteria have been isolated from wounds [120].

Honey-based treatments have been found to be preferential to silver or iodine due to a comparative lack of toxicity [31]. Du Toit and Page (2009) [31] observed that silver-impregnated dressings are potentially cytopathic and cytotoxic to proliferating cells in vitro, and this may be relevant in the clinical decision-making process. A newer role for honey in wound healing involves immune modulation [121], leading to a limitation of inflammation and pain modulation [122], Natural honey is cost-effective compared to advanced wound products [123,124], provides moisture and vitamins, and deodorizes the wounds.

9.7 Conclusion

Honey has been used for thousands of years as an adjuvant to wound healing. Every year new studies further elucidate the precise action of honey in wound healing and demonstrate its efficacy in treating various wounds. While many modern-day physicians are likely to remain sceptical about the benefits of honey until larger, RCTs support its use, one cannot overlook the vast body of literature that associates honey with significant wound healing benefits.

It is difficult to understand that by the twenty-first century, no evidence is yet available. Current evidence suggests that caution still needs to be exercised. Nonetheless, this review should be helpful in designing new, large RCTs, with blinded assessment and useful clinical outcomes compared with standard wound treatments for all types of wounds.

These studies will not be easy. With honey, one needs to be aware that it is a natural product, and that those characteristics associated with wound healing may be affected by species of bee, geographical location and botanical origin, as well as processing and storage conditions. While these trials would be relevant to industrialized countries to compare honey with conventional and advanced treatments, it would be helpful to conduct them in developing countries, where costs are a vital factor.

The discipline of wound management is growing with rapid advances in technology. New wound healing modalities and products increase the choices for health professionals as they tackle all features of wound management. While there is still no notable alternative for reconstruction

using patients' own tissues and carefully carried out meticulous reconstructive procedures, natural honey can help accelerate wound healing. By offering antibacterial properties, enhancing tissue repair factors, maintaining a moist environment and promoting epithelialization ultimately resulting in optimal wound repair, natural honey may represent an optimal alternative treatment approach in wounds of different etiologies.

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CASE STUDY – XIX

A 67-year-old obese female with type II diabetes, COPD, DPNP, CAD, PVD and obstructive sleep apnoea presented at the health centre with a non-healing ulcer previously managed at the local hospital. On examination, there was a Wagner's grade II ulceration at the right heel with no probing to the bone (Figure 9-1). Vascular assessment revealed impalpable pedal pulses with a weak popliteal pulse. The ankle-brachial index measured was 0.6. The patient was referred to vascular surgery for angiography and possible angioplasty. Two weeks later, the patient returned with palpable pedal pulses after undergoing angioplasty. The patient had honey dressing daily combined with offloading achieving 50% healing of the ulcer size (Figure 9-2). The same management was continued at the health centre, and the patient achieved 100% healing eight weeks later (Figure 9-3).

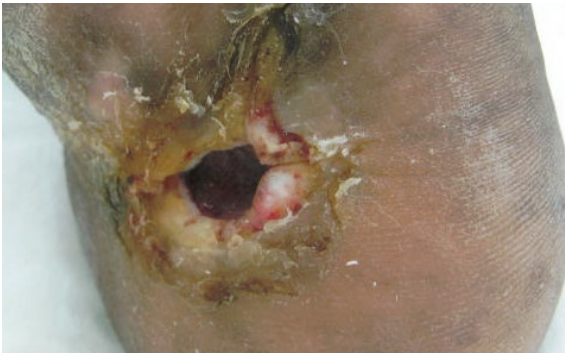

Figure 9-1 Upon presentation, there is a heel ulcer Wagner's grade II which was followed up in the main general hospital for one year, and no healing occurred

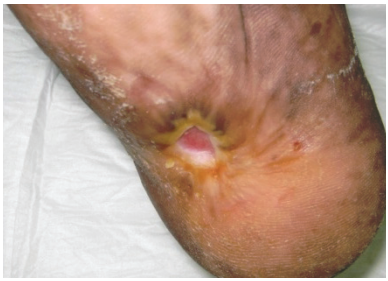

Figure 9-2
Post angioplasty, sharp debridement, daily natural honey application and offloading the ulcer has a healthy pink base with a reduction in the size of the ulcer by 50% four weeks later

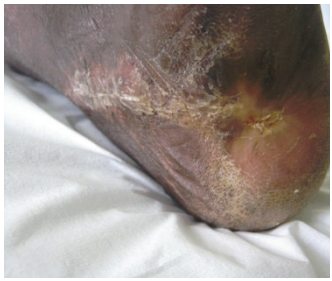

Figure 9-3
Complete healing eight weeks later

CHAPTER 10

THE CHARCOT FOOT IN DIABETES

DR HASHIM MOHAMED

Charcot foot is not a single entity but rather considered as a syndrome which is a serious complication of diabetes and may potentially lead to future amputation as a consequence. It is characterized by a state of inflammation with various degrees of bone and joint disorganization and destruction due to underlying trauma, neuropathy and disturbance of bone metabolism. The Charcot foot in diabetes presents a diagnostic challenge for most clinicians since little is known about its pathophysiology as well as there being scant evidence about its management.

10.1 Pathogenesis

Charcot foot is a condition that affects bones, soft tissues and joints of the foot, which is manifested by uncontrolled inflammation in its early stage. The Charcot foot occurs as a result of diabetic neuropathy, where several components interact and result in this condition including long-standing diabetes, autonomic neuropathy, trauma, sensory-motor neuropathy and metabolic abnormalities of bone. This, in turn, will end up causing acute and localized inflammation leading to various degrees of bone destruction, joint subluxation and dislocation.

The most common manifestation associated with Charcot foot is midfoot collapse, described as a “rocker-bottom” foot (Figure 10-1). Nonetheless, Charcot foot may affect other parts of the foot, including the heel and the forefoot.

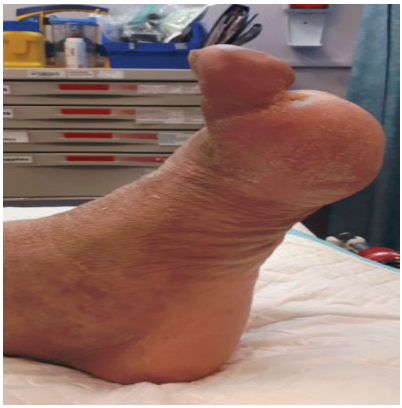

Figure 10-1: Charcot foot involving the left fore foot

During the active (acute) stage of Charcot foot, discomfort and pain may be present, but the degree of discomfort and pain may be less in individuals with normal sensations.

It has been postulated that during the acute inflammatory stage, there will be osteolysis, increased peripheral blood flow leading to progressive bone fracture and joint dislocation that characterizes its presentation [(1)].

As the bone is fractured, it will release pro-inflammatory cytokines, which in turn potentiates the maturation of osteoclasts from osteoclast precursor cells and leading to further osteolysis [(1)]. Individuals developing acute Charcot foot may suffer already from loss of pain sensation due to peripheral neuropathy. This in turn will allow for continuous ambulation, thereby leading to repetitive trauma, thus compromising the foot further. Besides, loss of protective sensation will increase the susceptibility of the foot to further trauma; meanwhile, motor neuropathy may result in altered mechanics and ultimately alter the shape of the foot (claw toes and exaggeration of the plantar arch). Inflicted patients may recall the onset of Charcot foot being precipitated by minor trauma [(2)], osteomyelitis, previous ulceration or recent foot surgery.

10.2 Diagnosis

Initially, Charcot foot is mild in nature and is not recognized by either patient or clinician but becomes apparent later with unperceived repetitive trauma. In order to make a clinical diagnosis, several clinical findings must be present including neurological, musculoskeletal, vascular and radiographic changes. A patient suffering from peripheral sensory neuropathy coupled

with the reduced sensation of pain is the main predisposing factor that leads to the development of Charcot foot [3-6]. Classically, Charcot foot manifests by being warm, swollen, and at times coupled with erythematous skin with mild to moderate discomfort or pain [5-10].

The underlying bone and joint injury is manifested initially as an acute local inflammation [11]. This initial presentation is often misdiagnosed as acute gout, cellulitis or deep-vein thrombosis. The inflicted foot has a higher temperature of several degrees compared to the normal foot [10,14]. The affected foot has a preserved or even increased arterial blood flow, and the pedal pulses will be bounding unless dampened by accompanying oedema. In patients with chronic Charcot foot, there will be various bony and foot deformities depending on the chronicity of the condition, which may even lead to bones protruding through the skin and may subsequently develop limb-threatening ischaemia [6-9,12]. Patients with Charcot foot most often present with classic rocker-bottom foot representing a severe chronic deformity [12-14].

10.2.1 Imaging of the Charcot foot

During the initial stages of Charcot foot, X-rays may be normal or show subtle fractures and dislocations, but as the condition progresses, overt fractures and subluxations may become apparent. Nonetheless, X-ray changes of Charcot foot have low sensitivity and are typically delayed [15]. In the early stages of the disease, magnetic resonance imaging (MRI) allows detection of subtle changes that can be missed on X-ray. Technetium bone scans, on the other hand, are highly sensitive for active bone pathology. However, if the patient suffers from peripheral vascular disease, then the diminished circulation can lead to false-negative results. Nowadays, clinicians are utilizing positron emission tomography for diagnosis and differentiating Charcot foot from osteomyelitis [15,16].

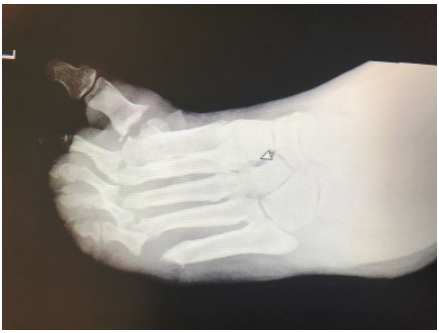

Figure 10-2: Charcot arthropathy leading to fractured metatarsal heads

10.3 Medical treatment

Medical treatment of Charcot foot involves educating the patient about the importance of strict offloading of the involved foot, treating bone disease and preventing further foot fractures [17].

10.3.1 Offloading

Offloading is the most critical management strategy in the acute phase in order to arrest the progression to deformity. The offloaded foot should be immobilized in a total contact cast (TCC) or pneumatic cast walker, with replacement every three days, and then examined once a week after that. Following offloading in the first few weeks, the oedema starts to reduce. The patient should be counselled regarding the importance of offloading (avoiding weight bearing) and should be encouraged to use either crutches or a wheelchair if TCCs or pneumatic cast walkers are not available. Clinicians must encourage the patient to continue using the TCC or the pneumatic cast walker until the oedema has resolved, and the temperature of the involved foot is within 2°C of the contralateral foot [18].

Duration of offloading and cast application should be guided by clinical assessment of the Charcot foot in relation to erythema, oedema and changes in the skin temperature [16,18,19].

Reduction of skin temperature, along with evidence of healing on X-rays or MRI, encourages the clinician to transform the patient from cast to prescription footwear. After the resolution of the acute Charcot condition, prescription footwear is essential in preventing the recurrence of ulceration and/or further bony damage, and the patient must be counselled regarding wearing the prescription footwear at all times − even in the house − and it

should not be taken off apart from before going to sleep. This approach can be consolidated by health education and counselling to both patients and family members alike.

10.3.2 Antiresorptive therapy

During active Charcot foot, some clinicians may opt to use antiresorptive drugs since bone turnover is excessive. Their use has been studied in the treatment of Charcot foot in small randomized, double-blind controlled trials [20,21].

Intranasal calcitonin is another antiresorptive agent that has been used in the treatment of active Charcot disease. Calcitonin offers a safer alternative to bisphosphonate in patients with renal failure [22,23]. Ongoing regular follow-up is needed to monitor for signs of recurrent or new Charcot foot episodes.

10.3.3 Surgical treatment

Surgery is generally not advised during the active inflammatory stage because of the theoretical risk of mechanical failure of fixation and/or wound infection. However, once the active stage is over, surgical intervention in Charcot foot may be warranted for removing bony prominences that could not be managed with prescription footwear or custom-made orthoses, and resecting osteomyelitis bone which has failed systemic antibiotics [23].

Several experts are suggesting Achilles tendon lengthening combined with total contact casting in order to decrease the deforming forces at the midfoot and ultimately reduce the morbidity associated with Charcot foot [24-27].

10.3.4 Charcot arthropathy of the ankle

Surgical correction of deformity at the level of the ankle is carried out using internal fixation followed by prolonged periods of immobilization and non-weight bearing in neuropathic patients who sustain acute ankle fractures [28-31].

Currently, there is inconclusive evidence to suggest one form of fixation over another (i.e. internal, external or combined) for a non-infected Charcot foot.

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CASE STUDY – XX

A 45-year-old female with peripheral neuropathy and traumatic ulceration of both feet who previously had a skin graft on both feet due to previous ulceration (Figure 10-3) presented at the health centre. The patient reported that she sustained the ulceration in both feet (Figure 10-4) while walking using leather sandals during a visit to India. The ulcers were cleaned with normal saline, and natural honey was applied directly, followed by Adaptec (Acelity); meanwhile, the patient was instructed to offload using a pneumatic cast walker (Figure 10-5). The patient continued her dressing at home and had weekly follow-ups at the health centre. Three months later, the wound achieved 98% healing after strict bed rest (Figure 10-6).

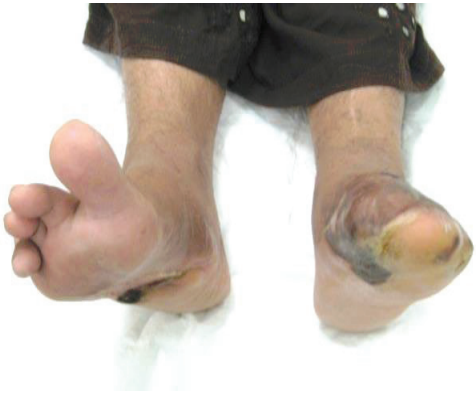

Figure 10.3: Amputated left forefoot with skin grafting of both feet as indicated by dark patches in the plantar aspect of both feet

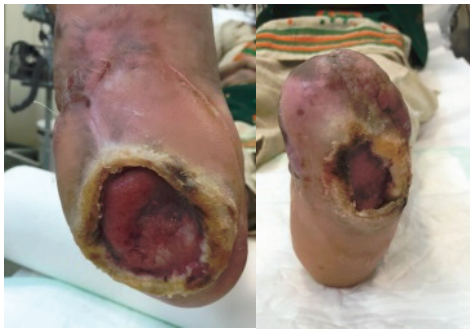

Figure 10-4: Bilateral Wagner's grade II ulceration with thick necrotic borders

Figure 10-5: Patient wearing pneumatic cast walker to improve offloading

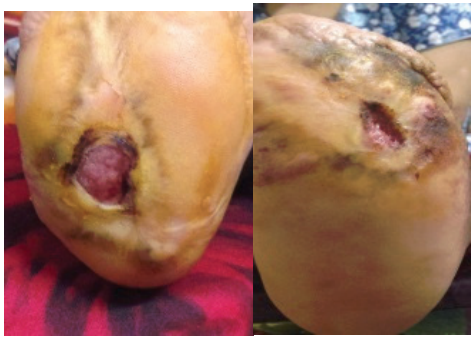

Figure 10-6: 98% healing after strict bed rest three months later

CHAPTER 11

SURGICAL MANAGEMENT OF DIABETIC FOOT INFECTIONS: A STEPWISE APPROACH

DR HUDA AL DHUBAIB

Diabetes is a global problem with massive health, socio-economic implications, morbidity and mortality [1,2]. Diabetes is the single most significant factor leading to lower-extremity amputation in Europe and the US [3-6], mainly due to diabetic peripheral neuropathy and loss of protective sensation of the feet. Neuropathic foot ulceration is the main antecedent factor predisposing to diabetic foot infection [7] and precedes 85% of all non-traumatic lower limb amputations in the US [8].

We intend to present a concise stepwise approach to the management of diabetic foot infections, emphasizing the importance of appropriate and timely surgical intervention. Ideal management often involves an interdisciplinary team approach (Fisher et al., 2010) [9] that involves the collaboration of various specialties; these may include family medicine, podiatry, infectious disease, vascular surgery, diabetic foot nurse, radiology, prosthetics/orthotics and physical therapy.

11.1 The stepwise approach

Diagnosing the presence and severity of infection is the initial step in its management. Simple, clinically relevant tools to classify diabetic foot infections have been validated by Lavery et al. [10]. These include the International Working Group on the Diabetic Foot and the Infectious Diseases Society of America diabetic foot infection classification system (Table 11-1), which allows accurate assessment of risk classification and identifies high-risk patients who are likely to develop adverse outcomes and increased risk of lower limb amputation [9].

11.2 Diabetic foot infections management using a stepwise surgical approach

Many diabetic foot infections may be regarded as superficial since they do not extend beneath the superficial fascia [10]. However, on occasions the infection may penetrate more deeply into the underlying soft tissue, thereby creating a deep space abscess [11,12]. As a result, surgical intervention is warranted to drain the abscess, debride the wound in order to remove necrotic tissue, thereby minimizing the risk of further extension. In this synopsis, we highlight steps such as incision, investigation, debridement of the wound, lavage and closure.

Table 11-1: Important classification schemes for diabetic foot infections

Clinical description	Infectious Diseases Society of America	International Working Group on the Diabetic Foot
Wound without any manifestations of inflammation or purulence	Uninfected	1
≥2 Manifestations of inflammation (purulence or erythema, induration, tenderness, warmth or pain); erythema extending ≤2 cm around ulcer, or any cellulitis and infection is limited to skin or superficial subcutaneous tissues; no local complications or systemic illness	Mild	2
Infection in a systemically well and metabolically stable patient but has ≥ 1 of the following: cellulitis extending > 2 cm; spread beneath fascia; lymphangitis, deep tissue abscess; tendon, muscle joint or bone involvement; gangrene	Moderate	3
Infection in a patient with signs and symptoms of systemic toxicity and/or metabolic instability (e.g. fever, chills, leukocytosis, hyperglycaemia, tachycardia, hypotension, confusion, vomiting, acidosis or azotaemia)	Severe	4

11.2.2 Incision

The attending clinician must consider the concept of fascial spaces when considering performing an incision and drainage of the foot. Although simple infections do not require surgical interventions, other more deep and extensive infections require staged procedures; therefore, before making the initial skin incision and dissection, surgical plans must be taken into

consideration [13]. Grodinsky discovered three main plantar spaces: the central (superficial and deep), lateral and medial spaces. He proposed performing a medial surgical approach due to the potential discomfort and pain of a plantar incision [14]. However, Loeffler and Ballard documented success using a plantar-based incision when draining foot infections [15]. They proposed starting proximally, posterior to the medial malleolus, and extending laterally and distally towards the midline, stopping between the heads of the first and second metatarsals.

Another alternative approach includes a distal to proximal approach in emergency and limb-threatening diabetic foot infections. The clinician must start with the distal-most area of ulceration or infection and extend proximally. The incision should continue until viable, healthy, granulating tissue is seen, or evidence of infection has been eradicated. This conservative approach avoids unnecessarily long incisions, which may pose future problems, especially in a patient with peripheral vascular disease. The clinician must consider plans for future reconstruction. Regardless of the approach, the infected space(s) has to be evacuated completely along with debriding any necrotic tissue. A second thorough examination must be performed post evacuation and debridement [10] in order to locate further abscesses, exposed bones, tendons or sinus tracts.

Deep diabetic foot infections are best managed using the Loeffler-Ballard incision, which exposes all five central plantar compartments using a single-incision approach. This incision should start at the distal end of the first intermetatarsal compartment and proceed proximally towards the medial malleolus via the medial longitudinal arch. The natural anatomy of the foot (flexor tendons and soft tissues) is followed when utilizing this approach.

A proposed modified approach by Fisher et al. (2010) involves stopping the incision into each of the affected interspaces (see Figure 11-2).

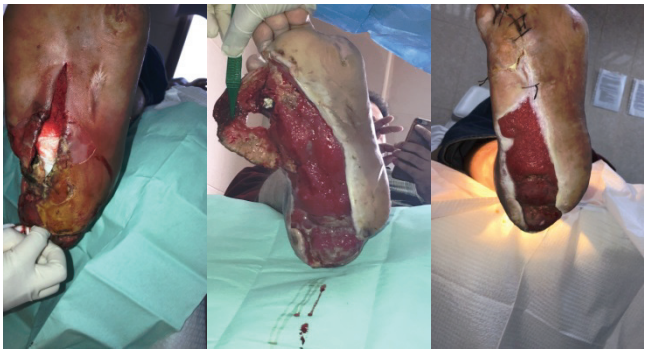

Figure 11-1: Example of plantar incision for draining, debriding and secondary closure of diabetic foot infections

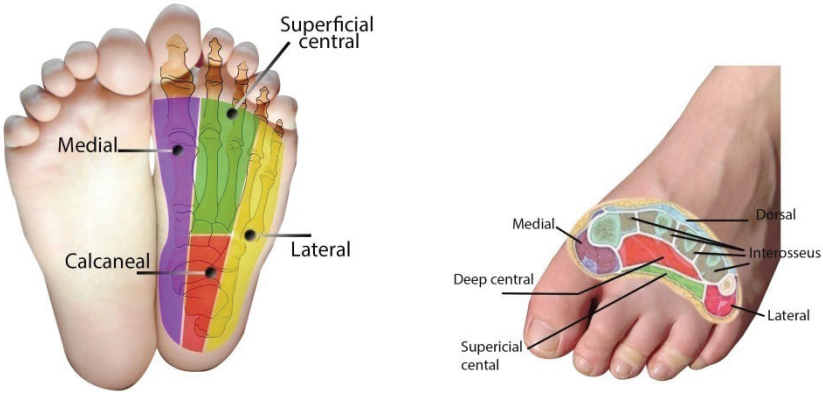

Figure 11-2: Surgical compartments of the foot anatomy

11.2.3 Exploration

Wound assessment must include consideration regarding its size, degree of soft tissue involvement, presence of abscesses, sinus tracts or any foreign bodies. Appropriate tissue planes must be followed when performing surgical exploration in order to allow the surgeon to examine the compartments for any possible remaining infection. The possibility of necrotizing fasciitis is high if tissue planes are easily separated, which is an indication for potential debridement [16].

11.2.4 Debridement

Following wound exploration and assessing tissue planes and foot compartments that are compromised, all non-viable tissue and bone should be completely debrided regardless of quantity and size [17,18].

Debridement should start with the removal of all devitalized tissues, including necrotic (grey, black), sloughed and ischaemic-looking (purple) tissues. Exposed tendons must be removed following soft tissue debridement in order to reduce the spread of infection along the tendon sheaths (Fisher et al., 2010) [9]. In post tissue debridement, exposed bone is often evident, and surgeons usually recommend removal of the exposed bone although medical practitioners may opt for medical therapy of osteomyelitis, including the use of intravenous antibiotics for 2–4 weeks and then switching to oral antibiotics for another 4–6 weeks. On occasions, multiple surgical debridement may be needed in order to remove all devitalized tissue, which is usually associated with faster healing times and improved outcomes [17,19].

11.2.5 Wound lavage

Wound irrigation or lavage is achieved via a steady flow of a solution across the open wound surface in order to remove debris and cellular pathogens, to hydrate and assist with the visual inspection. Ideal irrigation solutions should be isotonic, non-toxic, non-haemolytic, transparent, inexpensive, odourless and easy to sterilize. Many irrigation solutions used by surgeons all over the world, such as hydrogen peroxide, povidone-iodine and chlorhexidine, may be cytotoxic to healthy granulating tissues which may negatively impact on acute wound healing (Leesa et al., 2010; Barnhart, 2005).

Cleansing the wound post-surgical debridement of infected tissue appears to be safe and has been documented as a good adjunct to systemic antibiotics in decreasing the incidence of continued infection [10]. However, due to the lack of appropriate systematic reviews and adequate randomized controlled trials, there is no consensus regarding the most effective solution(s) to be used. The irrigation of infected wounds by normal saline in animal studies appears to be effective in reducing the bacterial (load) counts compared with untreated controls; saline has also performed favourably when compared with cefazolin solution and povidone-iodine solution [20,21].

11.2.6 Closure

Wound closure is usually considered once clinical signs and symptoms of infection have been eliminated. However, re-debridement to a higher level is often needed in heavily contaminated wounds and/or previous amputation sites [10]. Wound closure is classified into three categories: primary, secondary intention and delayed primary closure. While primary closure indicates closing the wound at the time of the first surgical intervention secondary closure, on the other hand, indicates leaving the wound open post-surgical intervention in order for it to granulate and contract. Delayed primary closure indicates leaving the wound open at the time of the initial surgical intervention, usually for the wound to be free from infection with a plan to close it later. The delayed primary approach is usually performed in conjunction with wet-to-dry dressings and/or negative pressure wound therapy (NPWT) to promote wound granulation before closure, and is shown to have fewer wound complications in comparison to primary closure [24,25]. Other available options for proper wound closure include the use of local flaps, pedicle flaps, muscle flaps, split-thickness skin grafts and muscular tendinous flaps.

11.2.7 Contraindication to sharp debridement

Clinicians caring for patients with diabetic foot should refrain from debridement if there is severe peripheral vascular disease, arterial occlusion, arterial ulceration, inability to feel a pulse or a weak pulse, an ankle-brachial index less than 0.5, signs and symptoms of peripheral vascular disease such as loss of hair on the toes, thickened and dystrophic nails and shiny pale skin.

11.3 Conclusion

Diabetic foot ulcers complicated by a deep infection have a high chance of ending with amputations, thereby resulting in a huge socio-economic and psychological burden on society. Optimal management of infected diabetic foot ulcers requires accurate identification of offending pathogens, appropriate selection and duration of antimicrobial therapy, improved diagnostic modalities and an interdisciplinary team approach involving the patient and caregivers.

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CASE STUDY – XXI

A 65-year-old obese female patient with uncontrolled type II DM of 35 years duration, and an HbA1c of 11%, hypertension, peripheral neuropathy and chronic kidney disease stage V presented at the health centre. The patient had two previous cerebral vascular accidents involving the left side of the body resulting in weakness of both upper and lower limbs. The patient also had a stage II Wagner's ulceration of the left big hallux (Figure 11-3), which was managed previously in a neighbouring health centre. This thermal ulcer was developed after contact with a hot cooking pot, following which the patient was dressed with Betadine® solution and dry gauze in the neighbouring health centre. The wound was debrided using a sharp scalpel resulting in the removal of devitalized tissues. The wound was cleaned daily using normal saline followed by application of natural honey and covered with Adaptic™ (Acelity) and wrapped with a cotton bandage. One month later, the wound improved by 80% with a return of healthy skin (Figure 11-4). Six weeks later, the wound completely healed (Figure 11-5).

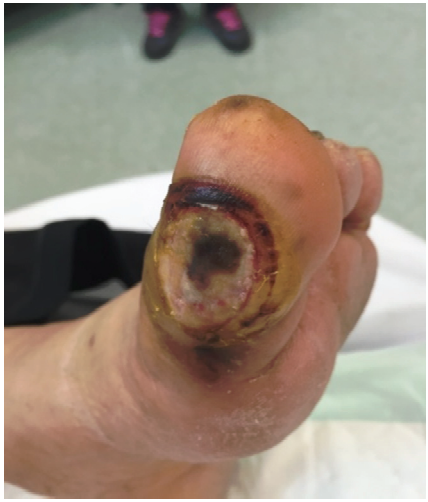

Figure 11-3:
Left big hallux showing necrotic ulcer with a size area of 2 × 3 cm showing necrotic base with devitalized tissue and surrounding discoloured thick skin

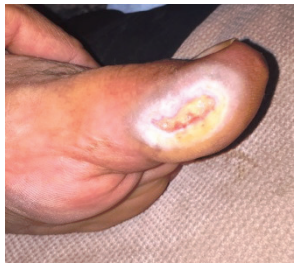

Figure 11-4:
Reduction of the wound size by 80% one month later

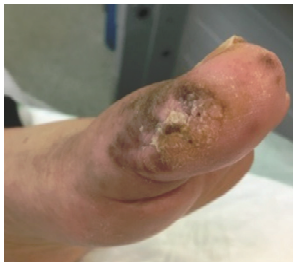

Figure 11-5:
Complete healing of left big hallux six weeks later

CHAPTER 12

DIABETIC FOOT RADIOGRAPHIC IMAGING

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Radiology is a science that deals with imaging diseases. The radiological tools commonly used in diabetic foot imaging include plain radiographs, ultrasound, computed tomography and magnetic resonance imaging. Although considered by many clinicians and radiologists to be inadequate to diagnose diabetic foot pathologies, plain radiographs can offer beneficial diagnostic clues regarding diabetic foot complications that are mainly related to the bone.

Plain radiographs are used mainly to detect bony changes. Diabetic foot lesions that mainly affect the bone are easily detected with specific radiographic features (e.g. osteomyelitis). Soft tissue calcification can also be well demonstrated in plain radiographs (e.g. vascular calcification due to chronic atherosclerosis).

It is essential to bear in mind that an interval of 2–3 weeks is needed for the bone density to change in radiographs; it means that osteomyelitis shows its classical sign of bone destruction 2–3 weeks after the initial infection. To detect osteomyelitis earlier, magnetic resonance imaging is required. The osteomyelitis process can be active, and the plain radiograph shows no bone destruction up to 10 days after the initial infection. As previously stated, plain radiographs should be used initially to investigate diabetic foot bone lesions, but a normal plain radiograph does not always mean that there are no bony lesions and the patient is normal.

12.1 The radiographic densities

Too many clinicians' radiographs are a challenge to interpret; the reason sometimes lies in lack of proper training in radiology. In plain radiography,

the density of water is considered the main density of the tissues, since the body is made up of 70% water by weight. Water density is the main greyish contrast detected in a plain radiograph. The important densities to note are the two densities below it (giving dark shades) and two densities above it (giving whitish shades). The shades below water are: fat (dark areas compared to the rest of the grey soft tissue shades), and air (pure dark areas in a radiograph). In contrast, the shades above water are bone (showing as whitish areas compared to the rest of the grey soft tissue shades), and metal (pure white areas in a radiograph).

In conclusion, there are only five densities to be interpreted in a radiograph: air, fat, water, bone and metal. With these five densities in mind, it is easy for the non-radiologists to point out the area of abnormality within a radiograph.

12.2 Diabetic angiopathy

According to the World Health Organization (WHO), diabetic foot is defined as the foot with ulceration, infection and/or destruction of the deep tissues, associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb

Poor diabetic controls result in peripheral arterial disease (PAD). PAD is almost three times more common in diabetic patients in comparison with age- and sex-matched individuals. PAD tends to exhibit a diffuse pattern of distribution, and the lesions are more extensive, frequently bilateral and tend to involve arteries below the knee level. Peripheral ischaemia plays an essential role in diabetic foot ulceration (almost 50% of cases) and prolonged healing time, increasing the risk of amputation.

Arterial pathologies detected in peripheral vascular disease, classically in diabetes mellitus, can be divided into three groups as a function of size and structural features:

1) Large elastic arteries: these include the aorta and some of its major branches such as the subclavian, common carotid and iliac arteries. Large arteries in diabetes mellitus are typically affected by atherosclerosis, which is characterized by the formation of fibro-fatty and calcific intimal plaques that can cause luminal narrowing of blood vessels. On radiographs, atherosclerosis is detected as multiple, coarse, irregular and patchy calcifications in large and medium-sized vessels. They are not contiguous, being dispersed more randomly along the course of the artery.

2) Medium-size (muscular) arteries: these include the peripheral vessels of the extremities. In diabetes mellitus, muscular arteries are typically affected by Monckeberg's sclerosis, and are characterized by more diffuse and continuous calcification within the media of medium-sized muscular arteries. There is no involvement of the intima, which is the most striking feature of atherosclerosis.
On a radiograph, Monckeberg's sclerosis is detected as a pipe-stem appearance from contiguous, dystrophic, granular calcifications deposited throughout the media. Superimposed, regular rings of denser calcification can cause the vessel in a longitudinal projection to resemble a tram track (characteristic) (Figure 12-1)

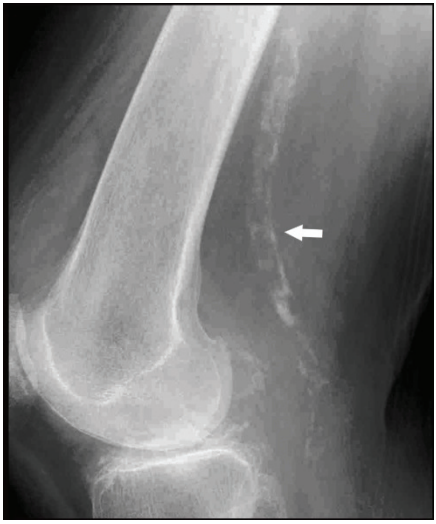

Figure 12-1: Lateral plain radiograph of a knee demonstrating tramline-like calcification of the popliteal artery (arrow)

3) Arterioles: the smallest arteries, which are within the substance of tissues and organs; these end-vessels terminate in capillary beds. The arterioles and the capillary beds in diabetes mellitus are affected by arteriolosclerosis, which is a disease of small arteries and arterioles.

12.3 Diabetic osteopathy

In diabetes, the bone is affected in two major ways: atrophic (osteolytic) osteopathy, and hypertrophic (Charcot's joint) osteopathy. Each type has its own pathophysiologic basis and radiological features.

12.3.1 Atrophic osteopathy

This classically arises when sympathetic dystrophy affects bones of the foot. Sympathetic dystrophy, also known as complex regional pain syndrome type I and Sudeck's atrophy, is a disease where the sympathetic supply of a limb is injured, causing sympathetic dysautonomia that leads to reactive bone marrow oedema and bone resorption due to the effect of the sympathetic supply on osteoclasts (increases their action). On radiography, an atrophic joint often shows patchy or diffuse osteoporosis of the affected bone (Figure 12-2), with or without resorption of the metatarsal distal ends resulting in "pencil and cup" or "sucked candy stick" deformities, similar to those seen in leprosy.

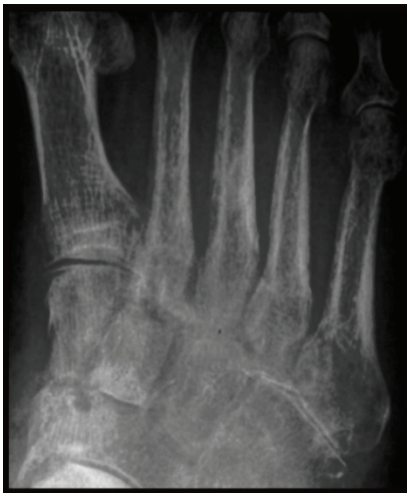

Figure 12-2: Anteroposterior forefoot radiograph that shows diffuse demineralization of the foot due to sympathetic dystrophy

12.3.2 Hypertrophic osteopathy

This type of diabetic osteopathy, also commonly known as Charcot's joint, arises due to denervation of the neuronal supply to the bone, causing multiple microtrauma formation in the bone. The body will try to heal desperately by forming callous, which will result in joint hypertrophy. On radiography, Charcot's joint is characterized by "5Ds": *d*istention, *d*islocation, *d*isorganization, *d*ebris and increased bone *d*ensity. Due to the amount of destruction often depicted on radiographs of Charcot's joint, hypertrophic osteopathy is often mistaken for chronic osteomyelitis. One of the helpful tips in radiography to differentiate the two pathological

processes is to look at the area of the foot affected. Osteomyelitis typically affects the fore- and hindfoot (areas of pressure); in contrast, Charcot's joint classically affects the midfoot (area of balance) (Figure 12-3).

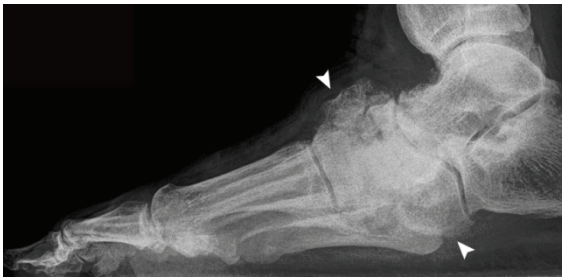

Figure 12-3: Lateral plain radiograph of a patient with Charcot's joint showing increase density, debris and increase density of the midfoot (arrowheads)

Other uncommon osteopathic findings in the diabetic foot include metatarsal fractures (e.g. Lisfranc and Chopart fractures) and osteonecrosis (e.g. Freiberg's disease). Freiberg's disease is a disease characterized by infarction of the metatarsal heads. The disease typically develops 3–4 times more frequently in women than men during late childhood or adolescence. Patients present clinically in the acute phase with local foot pain confined to the area of the metatarsal heads with tenderness.

On radiographs, Lisfranc's fracture is diagnosed when the second metatarsal bone is displaced laterally > 2 mm from its articulation with the intermediate cuneiform bone (Figure 12-4).

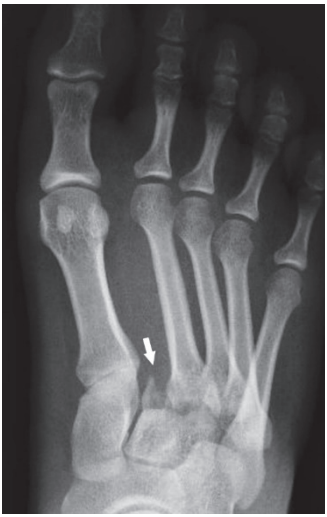

Figure 12-4: Anteroposterior forefoot radiograph that shows fracture of the second metatarsal bone (Lisfranc's fracture) (arrow)

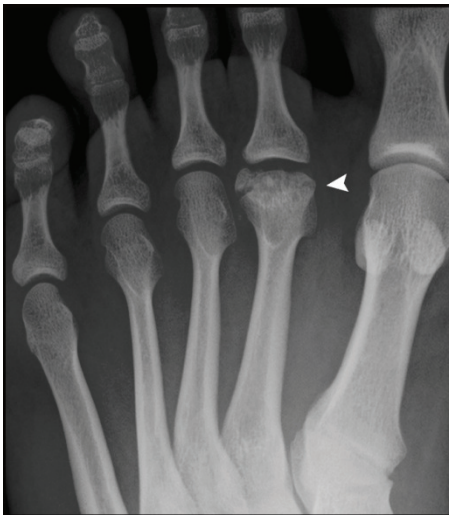

Figure 12-5: Anteroposterior forefoot radiograph that shows flattening and fragmentation of the second metatarsal head (Frieberg's infarction – arrowhead)

In Figure 12-4, an anteroposterior forefoot radiograph shows a fracture of the second metatarsal bone (Lisfranc's fracture, arrowed) while Frieberg's infarction is detected as subtle flattening and sclerosis of the metatarsal head with the widening of the metatarsophalangeal joint. The most common metatarsal head involved is the second metatarsal head (sometimes referred to as second ray syndrome) (Figure 12-5).

12.4 Diabetic infections

People with diabetes are prone to foot infections due to compromised immunity, skin ulceration and diabetic peripheral neuropathy. Diabetic foot infections can be categorized anatomically into the following types.

A. Cellulitis: defined as the spreading of inflammatory reactions occurring along subcutaneous and fascial planes with oedema and hyperaemia. Cellulitis usually results from a streptococcus pyogenes or *Staphylococcus aureus* infection. Cellulitis may occur

in conjunction with superficial thrombophlebitis and may progress to pre-abscess or abscess formation. Cellulitis essentially is a clinical diagnosis. However, radiographs in cellulitis, abscess and/or necrotizing fasciitis can show soft tissue swelling with or without radiolucent gas formation within the soft tissues (Figure 12-6).

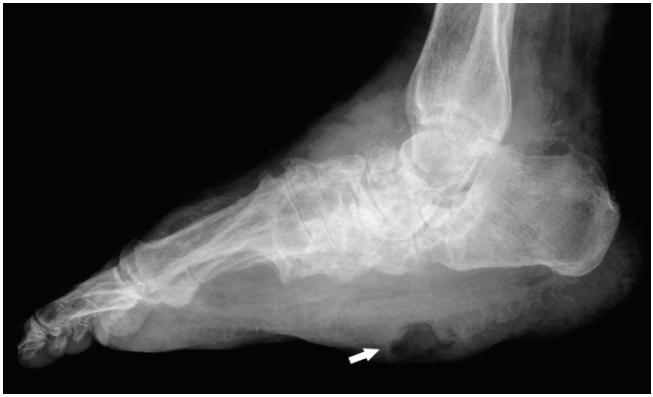

Figure 12-6: Lateral plain radiograph of a patient with cellulitis showing gas radiolucent shade inside a soft tissue swelling of the plantar fascia, characteristic of cellulitis (arrow)

B. Thrombophlebitis: a term used to describe infection of the vein walls, causing localized erythema, pain and thrombosis. Patients with superficial thrombophlebitis typically present with localized erythema, pain, and painful, tender, prominent, thread-like veins.
C. Pyomyositis: defined as a suppurative bacterial infection of muscle, most commonly affecting the larger muscles of the lower limbs. Muscle trauma and haematoma may be precipitating factors. Clinically, there is fever, myalgia and localized muscle tenderness. *Staphylococcus aureus* is the causative organism in more than 90% of cases.
D. Tendinitis: this is inflammation of the tendons.
E. Enthesitis: inflammation of the entheses sites, which is the place where tendons or ligaments attach to a bone.

12.5 Osteomyelitis

Osteomyelitis is defined as an infectious process of the bone that involves both the cortex and the medullary cavity (cancellous bone). When the infection is confined only to the cortex, the condition is called ostitis. Osteomyelitis sources can be via the blood (haematogenous) or spread to the bone from an adjacent infectious source (contiguous focus).

Staphylococcus aureus accounts for most cases of suppurative osteomyelitis. It occurs most often in children under the age of 12 and is more common in males. Most foci are in the metaphyses, probably because of the rich blood supply. It is because of the break in the cortical bone that ultrasound can be used in the assessment of osteomyelitis

Osteomyelitis produces changes in the contiguous soft tissues, which can be seen on ultrasound. They occur very early and could be detected within 24 hours of the onset of symptoms. On radiographs, acute osteomyelitis shows soft tissue swelling and osteolytic bone destruction (Figure 12-7) that requires 10–14 days to appear on radiographs, when 35%–50% of bone destruction occurs. Subacute osteomyelitis appears as an abscess within a bone (Brodie's abscess).

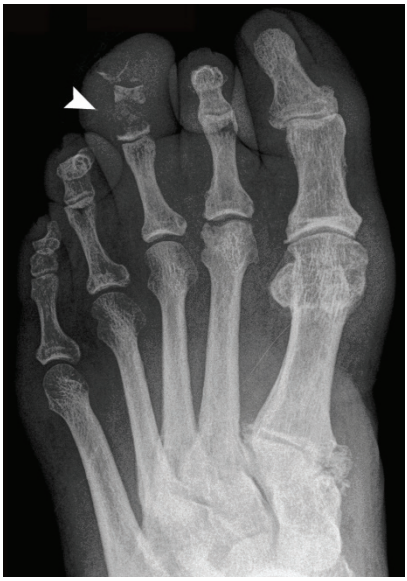

Figure 12-7: Anteroposterior forefoot radiograph that shows soft tissue and osteolytic bone destruction of the third toe distal phalanx, characteristic of acute osteomyelitis (arrowhead)

Chronic osteomyelitis will show mixed osteolytic and osteosclerotic changes with hypertrophic bony changes that mimic Charcot's joint. Sequestrum formation requires at least three weeks to form, and it is a sign of chronic osteomyelitis (see Figure 12-8).

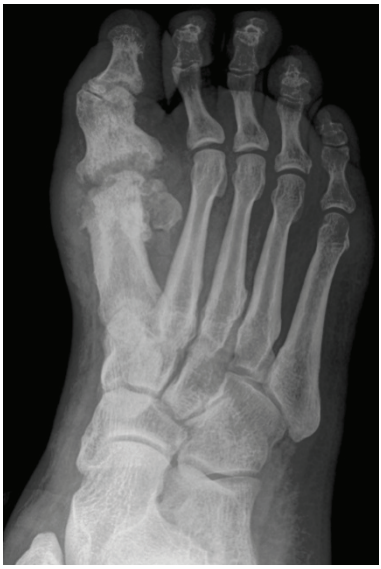

Figure 12-8: Anteroposterior forefoot radiograph that shows hypertrophic changes of the big toe with mixed osteolytic/osteosclerotic changes with disorganization of the first proximal interphalangeal joint in a patient with chronic osteomyelitis of the big toe

Cierny-Mader osteomyelitis anatomical classification:

- Stage 1 (medullary) osteomyelitis: the infection is confined to the medulla with no cortical involvement. It arises due to haematogenous sepsis.
- Stage 2 (superficial) osteomyelitis: the bone's surface is necrotic and exposed (e.g. overlying ulcer).
- Stage 3 (localized) osteomyelitis: this type is characterized by full-thickness cortical sequestration.
- Stage 4 (disseminated) osteomyelitis involves the bone cortex at multiple sites.

Types of organisms in osteomyelitis:

- Bacteria: *Staphylococcus aureus* and streptococci (70%), salmonella (sickle cell disease), *Pseudomonas* species (drug-addicted and puncture wounds).
- Fungi: blastomycosis, cryptococcosis, coccidiodiomycosis, aspergillosis and candidiasis. Fungal osteomyelitis is difficult to treat and may require amputation.
- Mycobacteria: TB osteomyelitis is seen in 1% of patients with TB infection. It has a higher incidence in patients with renal transplant.

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CASE STUDY – XXII

A 65-year-old male with type II DM of 35-year duration, post chronic heavy smoker and peripheral vascular disease presented with left big toe ulcer of two months duration after wearing improper foot wear. The ulcer showed a necrotic base with the positive probe-to-bone test (Figure 12-9), and the X-ray showed signs of osteomyelitis, after which the patient was placed on oral ciprofloxacin.

The feet showed impalpable pedal pulses following which the patient was sent to the main general hospital for angiography to assess his vasculature. The patient underwent angioplasty of the anterior tibial artery with the restoration of the dorsalis pedispulse; as a result, the wound started to heal following daily dressing with saline and honey (Figure 12-10). One month later, the wound healed completely (Figure 12-11).

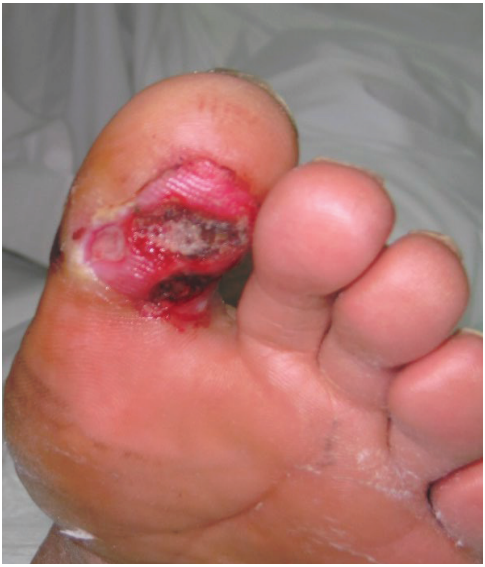

Figure 12-9: Showing grade II neuro-ischaemic ulceration of right big toe

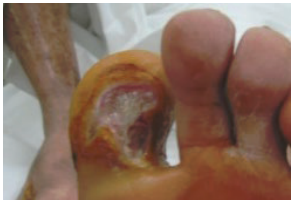

Figure 12-10: The ulcer is beginning to heal post angioplasty

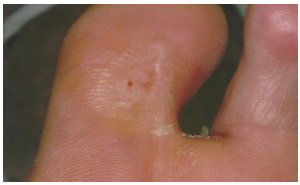

Figure 12-11: Complete healing one month later

CHAPTER 13

LOCAL WOUND CARE AND DRESSINGS FOR DIABETIC ULCERS

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Introduction

Local wound care and proper wound dressing selection are essential components of diabetic foot ulcer management. Diabetes-related lower limb amputations often start with a foot ulcer, which is preventable. Diabetic foot ulcers (DFU) occur in 19%–34% of diabetic patients during their lifetime, creating a challenging problem for patients and care providers. The recurrence after healing is estimated to be 40% during the first year and 60% within three years [1]. Early detection and treatment of DFU are critical to save a limb or save a life of patients with DFU. Preventing diabetic foot ulcers by routine foot exams, identifying high-risk diabetic foot and educating the patients about proper foot care is part of an important proactive approach. If an ulcer develops, treatment should include proper offloading, infection control, debridement, proper dressings and the control of the underlying systemic diseases, including diabetes [2,3,4].

Wounds should be classified as healable, maintenance or non-healable. The healing wound can heal with a good vascular supply. The maintenance wound is considered conditionally healable with adherence to a management plan, including wearing offloading devices and adequate skin

protection [5]. Local care should include debridement of devitalized tissue and the control of infection and inflammation, and the use of proper dressings (DIM) [2,3,4].

13.1 Cleansers

Cleansing the surface of the wound is about removing the inflammatory material and debris. The optimal cleanser is of low toxicity to the healthy tissue, thus minimizing the mechanical and chemical injury to healing tissue. Isotonic normal saline, short contact acetic acid and water are of such quality; detergents and soaps can interfere with the healing process. Sterile isotonic normal saline is a safe choice for most wounds, and sterile water or even tap water (in countries with clean water) can be another substitute [2,3].

The conventional methods for cleansing are soak, compress or irrigation. A soak is when the saline saturated gauze is applied over the surface of dried eschar hydrating. It draws the fluid net flow from the gauze. The compress is using the wet gauze after it is squeezed and then applying it over the wound to remove the exudate. These can be repeated around 3–5 cycles, of a minute each. The irrigation method is using a fluid stream to wash out the wound surface and cavity. Its use is discouraged for deep wounds, which may lead to the collection of fluid inside the wound [5].

13.2 Debridement

Standard debridement is removing callous, foreign materials, necrotic tissue and exudates. This would help the wound heal properly and lessen the chance of infection; [2,4,5] also, it gives the care provider accurate assessment of the wound and the surroundings [4]. Recently, debriding has included the removal of bacterial biofilms, unresponsive fibroblasts and keratinocytes [2]. Debridement is one of the mainstay treatments of DFU and associated with a higher rate of healing [2,6]. Steed et al.'s (2014) study showed increased healing of diabetic foot ulcers with the use of recombinant human platelet-derived growth factor (rhPDGf) and was even higher in a patient with frequent debridement. As an example, 83% of wounds healed completely in one centre whose debridement rate was 81% of patient visits [2,3].

Various methods for debridement are used depending on the condition and the preference of the patient and care provider. Surgical debridement is the gold standard for DFU. Other methods include autolytic, mechanical, enzymatic or biological [2,3,5].

Mechanical debridement, for example, by wet-to-dry dressing, is applying a gauze soaked with saline over the wound until it is dry then removing it, taking off the attached tissue. This method is not favoured as it is painful and non-selective in removing even the viable tissue [4]. Wound irrigation and hydrotherapy are the other two methods that fall under mechanical debridement [5].

Studies have shown a higher healing rate with autolytic debridement compared to standard wound care [4]. The moisture provided by some dressings promotes the autolytic debridement giving an environment suitable for the endogenous enzymes in helping the migration of cells and formation of a matrix [3]. Dressings providing such purpose include alginates, hydrocolloids and hydrogels [7]. Autolytic debridement can be an option for healable wounds but not for deep or infected wounds [5]. The advantage of autolytic debridement is that it is less painful and atraumatic; however, this method is much slower than surgical debridement [7].

Enzymatic debridement involves the use of enzymes to facilitate the lysis of necrotic tissue in the wound. It acts by digesting collagens, elastin and other components of the matrix [5]. The evidence to support different enzymatic debridement options are limited, and the only FDA-approved one is the collagenase Santyl® [8].

Biological debridement, as in the use of maggot larva to digest the necrotic tissue in the wounds, has been mentioned in several studies; however, the evidence is limited. This method has not shown a significant reduction in the healing time nor the amputation rate [9].

Surgical debridement is the preferable method and has been well studied [3]. Callous can be removed precisely by the sharp instrument, helping in the reduction of pressure on and around the wound (offloading). Also, this technique is a fast and selective way to remove the necrotic tissue. The common goal in the wound tissue debridement is reaching the bleeding tissue [2]. This, in turn, helps to convert a chronic ulcer to an acute wound [5]. The main drawback is pain, which can be controlled by topical or local anaesthetics [5]. Hingorani et al. suggested that debridement should be carried out at 1–4 week intervals using a sharp surgical method as the optimal way of care [4].

13.3 Topical antibiotics and antiseptics

The DFUs are often contaminated with the presence of bacteria in the tissue. The colonization can be termed critical if it starts to invade the tissue causing damage, and usually if growth reaches a threshold of 10^5 bacteria per gram of tissue [2].

Antibiotic therapy is reserved for clinical infection, and there is no evidence that antibiotics would benefit wounds if clinically uninfected [6]. Lavery et al. recommend sufficient debridement, and if there is still growth of more than 10^5 CFU/g of tissue in the wound then topical antimicrobials may be used to decrease bacterial burden [3].

Topical antimicrobials should preferably be of low toxicity to normal healing tissue. The use of topical antibiotics has limited evidence and increases the risk of contact dermatitis [2,6]. Risk of bacterial resistance and cytotoxicity to tissue limit the use of topical antibiotics to only selected cases [3].

Topical antiseptics have a significant role in reducing the bacterial burden, carry a low risk of bacterial resistance and have a less toxic effect on the host tissue; therefore, antiseptics are preferred for critical colonization. It is available as topical or integrated with dressings. Antiseptics suppress the growth of microorganisms by several cellular metabolic levels; therefore, they are less likely to have bacterial resistance [5] and they also have an action against other microbes such as fungi and viruses [2]. Antibiotics and antiseptics along with debridement help in eradicating the bacterial biofilms that impend wound healing [6].

The antiseptics with the lowest toxicity and broad antimicrobial coverage include silver, iodine, chlorhexidine derivatives, honey, hypertonic saline, gentian violet and crystalline blue [5]. Iodine with low molecular weight has a good penetration to biofilms [2]. There are concerns regarding the toxicity for the granulation tissue and wound healing inhibition; however, the low-releasing forms (e.g. cadexomer iodine) have minimal in vivo tissue toxicity [5,10].

Silver products have been used for a long time and have activity against various organisms; moreover, they have an anti-inflammatory effect [5]. There is limited evidence that silver may help wound healing [4]. Furthermore, it is available in a dressing with slow release for longer wearing time. A meta-analysis by Lo showed that it reduces the odour, exudate and healing time. However, the Cochrane review shows no statistical significance if the goal is complete healing of the wound or infection prevention. Thus, topical therapy should be used for selected cases [5].

13.4 Dressings

Generally, dressings function as a protective barrier and provide a good wound healing environment by moisture balance. The moist environment for wounds favours healing by promoting the migration of cells, autolytic debridement and formation of a matrix [3]. The choice of dressing depends on wound assessment. Wounds with high exudate need absorptive dressing, while dry wounds need dressings that give extra moisture by water donation or preservation. Several aspects should be addressed regarding the choice of dressing, including pain, odour, exudate level, microbiology and location [2] as well as the cost and the potential side effects. The latter, when absorption is not enough, may cause maceration to the skin around the ulcer, thereby impeding healing. Also, if the dressing does not fit, it may injure the wound by friction [3].

The occlusive dressings should be used with caution and avoided if any concern exists about skin infection [2]. For other types of dressings, other factors, including offloading, should be addressed.

Different dressing types are utilized according to their properties. They include acrylics, calcium alginates, films, foams, hydrocolloids, hydrofibres and hydrogels. These types of dressings vary in their absorption, moisture donation, occlusion and other characteristics, yet are termed moisture retentive dressing or traditionally passive dressings [10]. The current evidence is not enough to support one dressing over another in terms of speeding up the healing of wounds [4]. In this section, some common dressing will be discussed in more detail (Tables 1 and 2).

13.4.1 Alginates

The alginates are natural polysaccharides made from seaweed with high absorbing ability [2,10]. Reverse exchange happens between the calcium in the alginate dressing and sodium from the wound fluids. The result is that sodium alginate gel adds moisture to the wound surface and subsequently can cause autolytic debridement. It has a haemostatic effect through the release of calcium during ion exchange. Alginate can remain in situ for days and is secured by a secondary dressing [10].

13.4.2 Gelling fibres (hydrofibres)

These are similar to alginates but with higher absorption. They are made up of carboxymethyl cellulose fibres that, when they absorb wound fluids,

turn to gel and promote autolytic debridement. Compared to alginates, gelling fibres are less likely to macerate the surrounding skin due to the vertical absorption of fluid [10]. Gelling fibres need secondary dressing and can be removed without inducing trauma [2].

13.4.3 Films

Films are thin transparent materials that are adhesive and made of polyurethane or similar materials. They are semipermeable, allowing the exchange of gas and water vapour, therefore increasing O_2 for tissues to heal and preventing maceration of healthy skin, bypassing sweat and insensible water. However, films do not allow larger molecules to pass through their pores. Therefore, they prevent bacteria and wound fluid from crossing the dressings [10].

The transparency of the film allows the visual inspection of the wound without removing it. Other advantages are the reduction of pain and enhancement of re-epithelialization – demonstrated in studies – for donor sites by 25–45%. Among the drawbacks, it may adhere to the wound while it dries, potentially disrupting the new epithelium upon removal, thus it is advised to leave it to fall off by itself in 1–2 weeks. Films only attach to healthy skin and usually have some difficulty in placement as the film may adhere to itself. Wrinkling of the film should be avoided as it can be an opening for bacterial invasion or exudate leak [10].

13.4.4 Foams

These are usually made of bilaminate polyurethane or silicone, and composed of two layers. The outer hydrophobic backing is semipermeable, protecting against bacteria and proving some moisture comparable to films. Inner hydrophilic absorbing foam is permeable to gas. Typically, foams are non-adherent and may need secondary dressings, although foam dressings with an adhesive border are available as well [10].

They are used for wounds with moderate exudates and usually need to be changed every 1–3 days. They are comfortable as they are non-adherent, easy to change and usually not expensive. The silicon-based rubber foams can be used for cavities and deep wounds as they can be moulded to the shape of the wound. Some disadvantages are opacity, unsuitability for dry wounds and high frequency of changing [10].

13.4.5 Hydrocolloids

Commonly used hydrocolloid dressings have a hydrophilic colloid base made of a mixture of carboxymethyl cellulose or guar, karaya, pectin and an adhesive material (e.g. polyisobutylene or ethylene-vinyl acetate). Moreover, they have an outer layer that is semipermeable like polyurethane [10].

Hydrocolloid dressings are waterproof and do not require secondary dressings. They come in sheets that can be cut according to the wound size. Another advantage is the cushioning effects that are increased further with fluid absorption. The result of fluid absorbsion is colloidal gel hence it protects the wound base from attaching to the dressings. Disadvantages include malodorous gel – as seen in alginates – and risk of skin maceration. The latter could potentially result in contact dermatitis or even excess granulation tissue formation [10].

13.4.6 Hydrogels

Hydrogels are mainly water, reaching up to 96% of their content. The hydrogel is a network of hydrophilic crosslinked polymers (e.g. polyvinyl alcohol and polyacrylamide). This dressing can be used as an amorphous gel, impregnated dressing or as sheets. Visual examination of the wound is possible as it is semitransparent. A secondary dressing is needed as it is only partially adherent or even non-adherent, and it provides protection against bacteria that can penetrate hydrogels. It maintains a moist environment for the wound to heal and has good absorptive capacity although slow in onset [10].

The major advantage of the hydrogel is the increased rate of healing of superficial DFU compared to basic dressings [9]. Also, it reduces pain and inflammation postoperatively. Disadvantages include frequent dressing changes and its unsuitability for infected wounds [10].

13.5 Advanced therapies for DFU

These options are used for wounds where the healing has stalled; the wounds have failed to reduce by more than 50% of their size after four weeks of standard care, and are less likely to heal by week 12. A re-evaluation must be done for every patient for the vascular supply of the wound, signs of infection and adherence to offloading therapy. Recommendation for a specific type of advanced therapy and choice is

made according to clinical settings and cost-effectiveness [4]. Available adjunctive therapies include topical growth factors, skin equivalents, negative pressure wound therapy, electrical stimulation and extracorporeal shock wave therapy [3].

Becaplermin is a platelet-derived growth factor (PDGF) proven to be useful for accelerating wound healing in DFU, and it is FDA approved. It promotes angiogenesis, increases the activity of fibroblasts and enhances the migration of epithelial cells [4]. A meta-analysis of 922 DFU patients showed a healing rate of 83% when it was used as an adjunctive therapy at a daily dose of 100 mcg with standard wound care [2].

Autologous skin grafting is an available advanced treatment for many countries, in contrast to the other advanced therapies. Furthermore, reconstructive surgery can be a solution to cover bones and weight-bearing points [2] Skin equivalents such as Apligraf® are derived from neonatal fibroblasts and epidermal keratinocytes. Apligraf has been shown to increase the DFU healing rate and reduce the incidence of osteomyelitis [2,4]. Cells in Apligraf secrete many growth factors (e.g. fibroblast growth factor, PDGF and vascular endothelial growth factor) all of which promote wound healing [3,4]. Dermagraft® is another example of skin substitutes proven to increase the healing of DFU, and it is made from neonatal dermal fibroblasts [2,4].

Hospital-based negative pressure wound therapy uses sub-atmospheric pressure delivered by a vacuum pump with a sealed dressing and applied to the wound bed. This suction system promotes the proliferation of cells and wound healing [2]. Negative pressure wound therapy (NPWT) is an effective and safe modality for the treatment of DFU. Randomized control trials demonstrated a reduction in healing time, hospital stay and secondary amputations [4].

Hyperbaric oxygen therapy is the use of 100% oxygen that is administrated to the wound using an airtight chamber. This is usually given once to twice daily for 4 to 5 days per week [2]. The pressure is more than one atmospheric pressure (usually 1–2 times greater), and duration ranges from 45 to 120 minutes [5]. This system improves wound healing and reduces the risk of amputation [3,4].

Also, stimulation using electrical current applied to the wound has been used to enhance wound healing. Another modality is the extracorporeal shock wave therapy, which was found to benefit wound healing [3].

13.6 DFU local wound care recommendations (4)

Prevention of DFU by educating the patients and families about proper foot care and regular foot examination with care providers is vital.

Offloading devices and therapeutic footwear are recommended for a risky diabetic patient (e.g. having neuropathy or deformity). Adequate control of diabetes and other general conditions is critical to avoid developing DFUs.

DFU must be frequently examined at 1–4 week intervals. At every visit, the wound size should be monitored, and evaluation for signs of infection or delay of healing must be carried out. Furthermore, cleaning and debriding the wound, as well as the use of proper dressings, should also be performed.

Dressings should provide moisture to the wound bed, control the exudate and should not macerate the healthy skin. Wound debridement for the necrotic tissue and callous should be carried out, preferably by a surgical method, especially at the initial visit. However, any of the methods for debriding the wound can be used depending on the clinical experience and patient preference. Wound size should be monitored and should reduce by more than 50% in four weeks with proper standard wound care. Failing to do so leads to the option of using the advanced treatments if available. Before using the advanced therapies, a re-evaluation must be done for infection, offloading therapy and vascular supply.

13.7 Conclusion

DFU needs interdisciplinary care addressing the general patient conditions as well as the local wound care. Offloading therapy, infection control, debridement and proper dressings are the main local care for the DFUs. Reassessment of the vascular supply, signs/ symptoms of infection, and proper offloading therapy should be done if the ulcers are not healing. After maintaining the standard care for DFUs the advanced treatments can be used if ulcer is failing to reduce in size by more than 50% after four weeks. Choice of any treatment modality should be made in accordance with availability, clinical settings and preference.

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CASE STUDY – XXIII

A 64-year-old male with type II DM of 14 years duration and hypertension presented to the health centre with post excision dorsal ulcer of necrotizing fasciitis of the right foot, measuring 3 × 4 cm (Figure 13-1). The wound was cleaned with normal saline and dressed in natural honey daily; two weeks later the wound started to fill from the inside out with a reduction in the size of the ulcer by 35% (Figure 13-2). Healthy granulation tissue appeared three weeks later with a reduction in the ulcer size by 50% (Figure 13-3). One month later, the wound healed by almost 98% (Figure 13-4). Dressing continued in the health centre with complete healing achieved six weeks later (Figure 13-5).

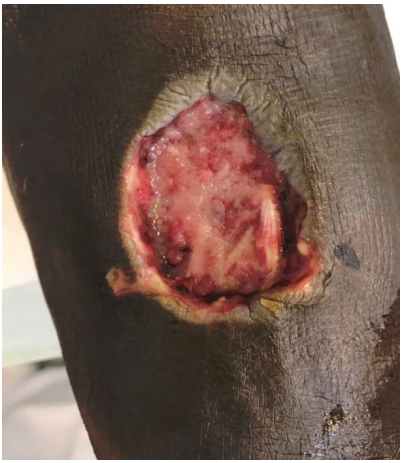

Figure 13-1: Showing a post excision ulcer of necrotizing fasciitis with indrawn ulcer edges with apparent tendon

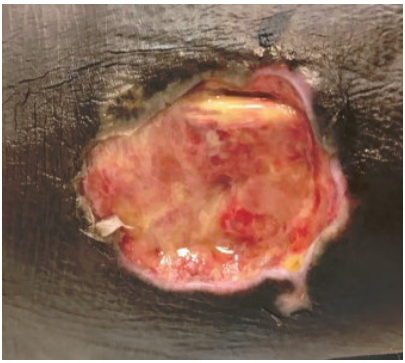

Figure 13-2: Showing improved ulcer size by filling from inside out

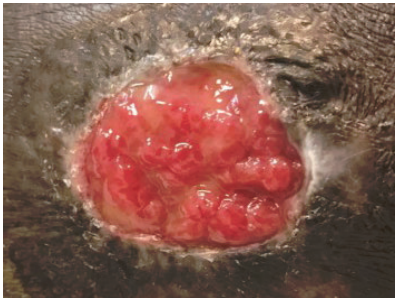

Figure 13-3: Reduction of size of ulcer by 50% and formation of healthy granulation tissue three weeks later

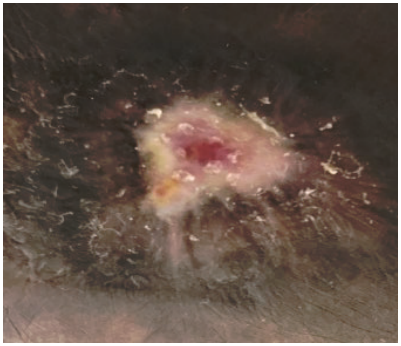

Figure. 13-4: Improvement of wound size by almost 98%

Figure 13-5: Complete wound healing achieved six weeks later

APPENDIX:
MISCELLANEOUS CASES

Composed of, or containing, a variety of cases undergoing studies and observation

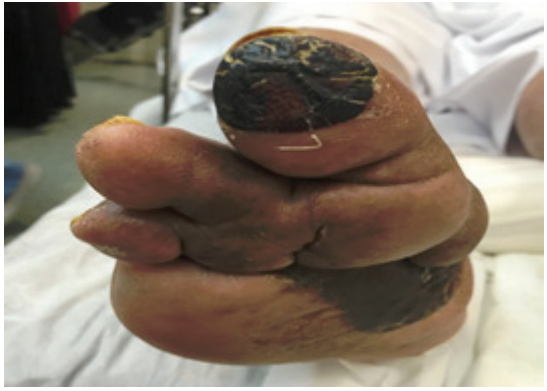

Figure A1: A 55-year-old male patient with type 2 DM with skin graft in the midfoot region and a dry haemorrhagic bullae dermatosis in the tip of the big toe due to the side effects of heparin

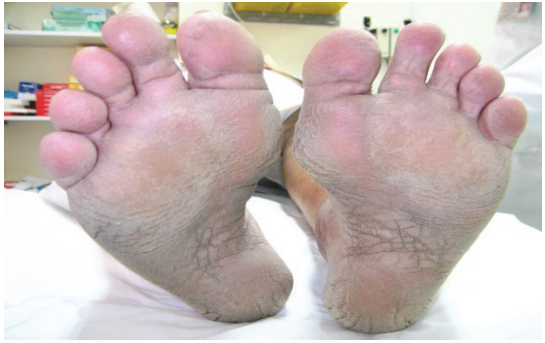

Figure A2: Severely dry and fissured feet

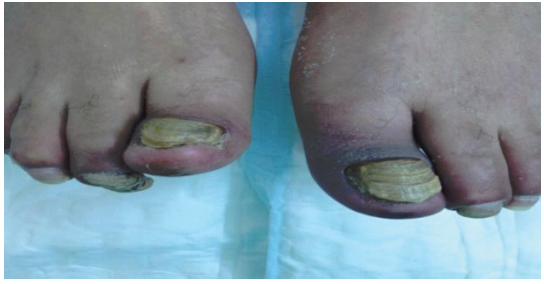

Figure A3: A 55-year-old female with chronic onychomycosis and clawing of toes

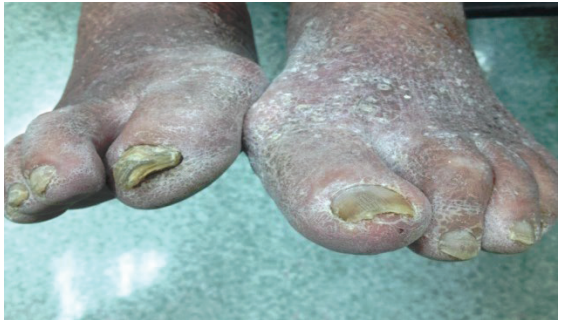

Figure A4: A 64-year-old male with severe onychomycosis leading to the disfigurement of nails of the right big hallux, chronic tinea pedis associated with bilateral bunions

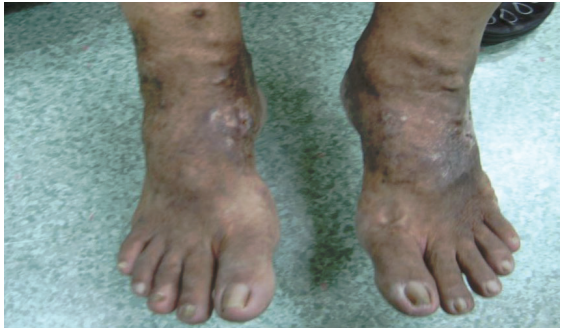

Figure A5: A 65-year-old male with diabetic dermopathy and varicose vein eczema, and thick, discoloured toenails due to onychomycosis

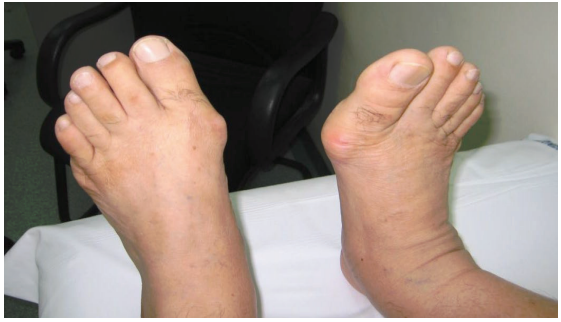

Figure A6: Bilateral bunion of both feet

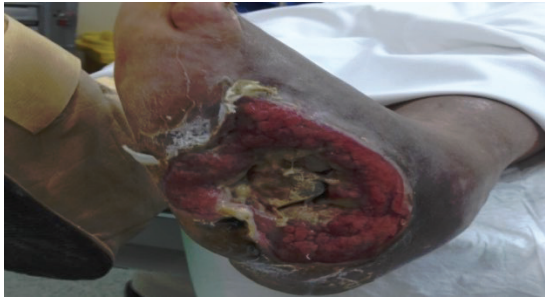

Figure A7: A 56-year-old male with Charcot foot and osteomyelitis of the midfoot bones

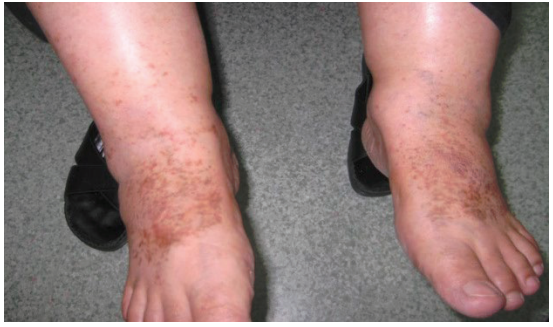

Figure A8: A 70-year-old male with diabetes mellitus presenting with brownish discolouration representing diabetic dermopathy

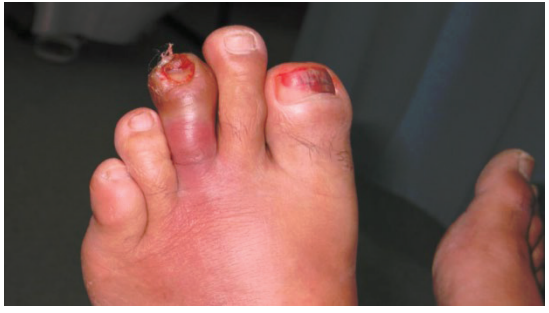

Figure A9: A 55-year-old female with type II diabetes and left foot swelling along with third left toe swelling, redness, cellulitis and ascending lymphangitis. The patient has applied red tincture iodine, as can be seen on the third and first (big) toes.

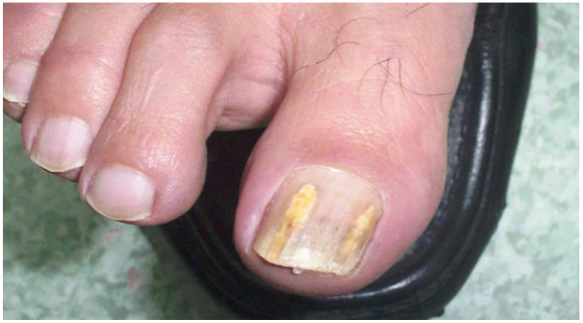

Figure A10: Onychomycosis involving the right big hallux

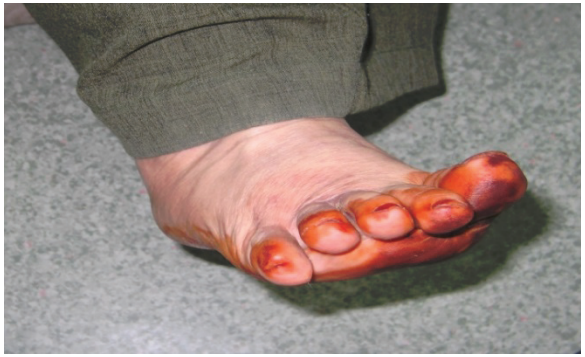

Figure A11: Interdigital tinea pedis with dorsal extension and discoloured foot due to henna paste application

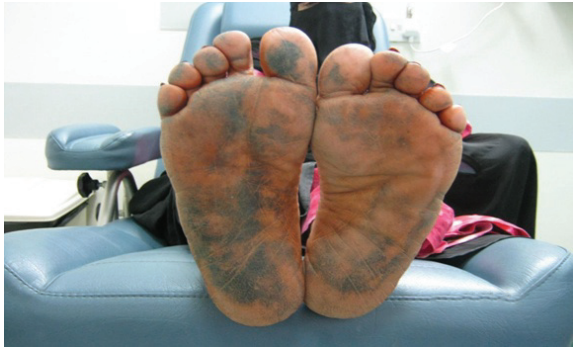

Figure A12: Black discolouration of the soles due to natural henna mixed with petroleum to give it a dark appearance when applied to the skin

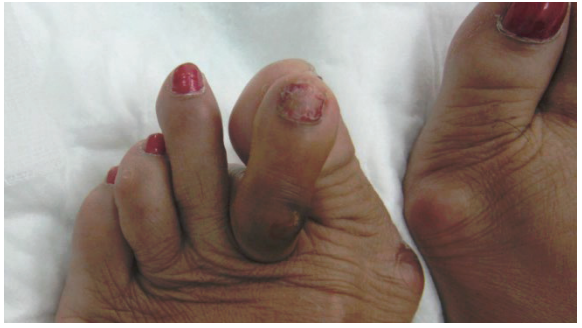

Figure A13: Overriding second toe deformity of the left foot showing redness and stage 1 Wagner's ulceration on the dorsalis pedis of the second toe with apparent bilateral bunions

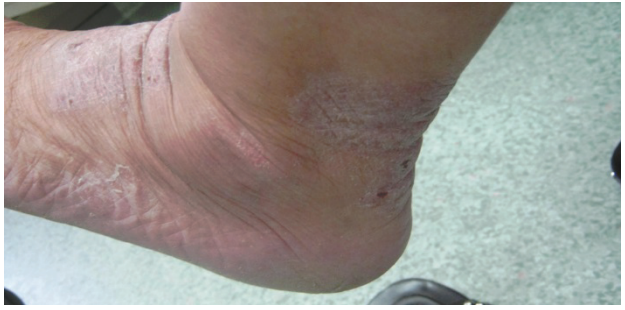

Figure A14: Extensive dry, circumscribed and scaly lesions of the dorsum of the feet and the Achilles region due to tinea pedis

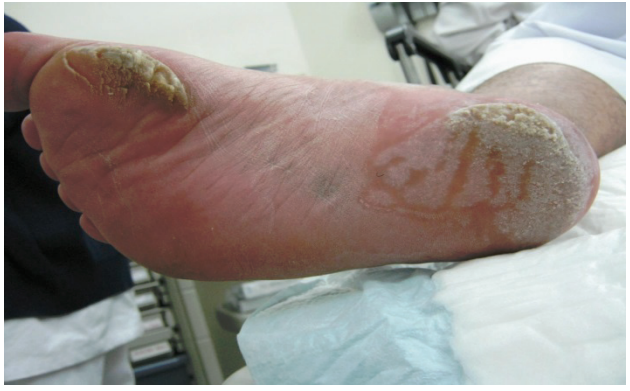

Figure A15: Thick callous at the forefoot heel area due to improper footwear and misdistribution of pressure on the foot

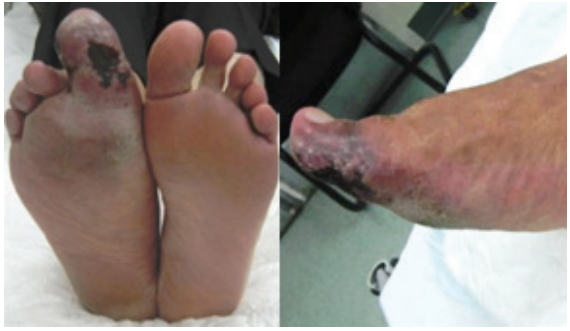

Figure A16: A 65-year-old male with right foot ulceration showing a dusky coloured right big hallux representing reduced peripheral circulation to the big hallux along with superficial ulceration, which can be an impending sign of gangrene of the right big hallux.

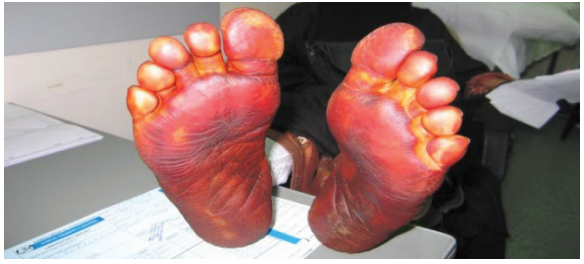

Figure A17: A 55-year-old female presented with burning feet at night so she applied natural henna on her feet thinking it would cool her feet

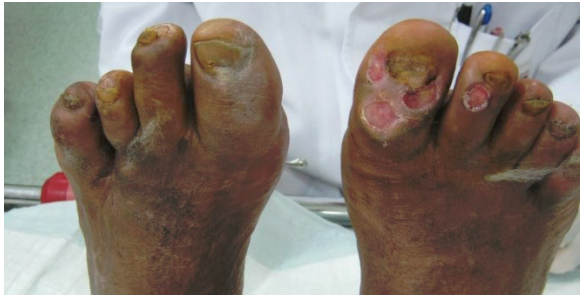

Figure A18: Multiple superficial ulcerations on the right big hallux and second toe due to improper footwear along with chronic onychomycosis affecting all the toenails along with an amputated left fifth toe

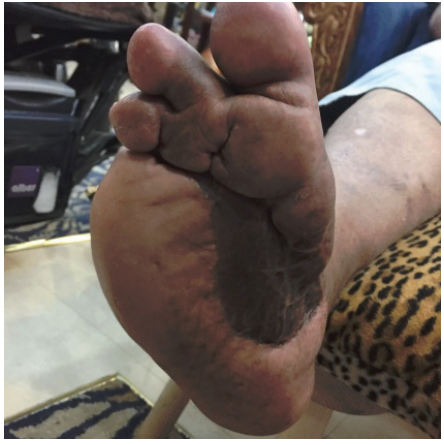

Figure A19: A case of the right foot showing Charcot deformity with a skin graft

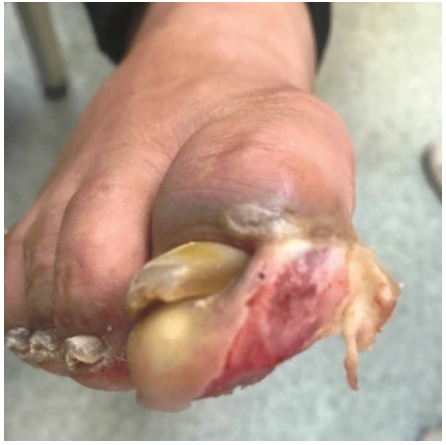

Figure A20: Traumatic injury of the right big hallux and swelling of the big hallux due to osteomyelitis

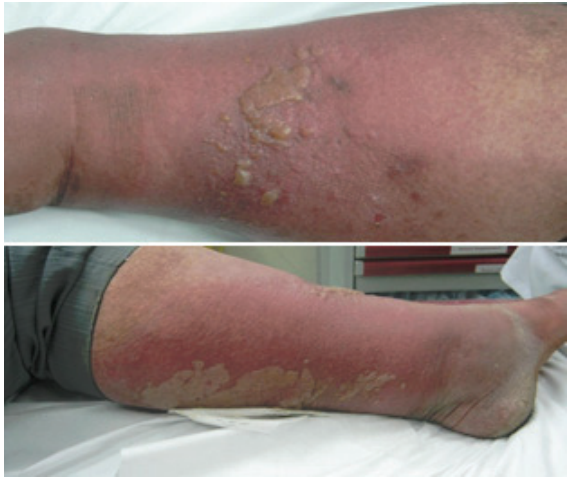

Figure A21: Multiple vesicles on the left shin of a person with diabetes, morbidly obese patient due to lymphatic circulation dysfunction complicated by cellulitis

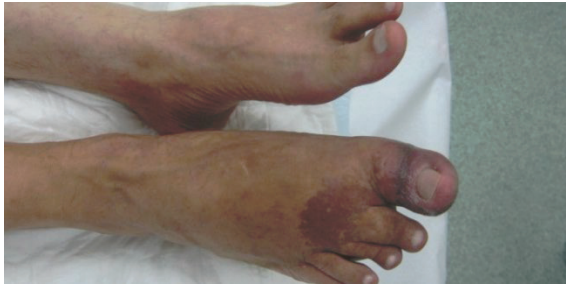

Figure A22: The right foot is showing healed chronic osteomyelitis feet involving the big hallux and second toe where both digits are swollen compared to the contralateral foot, and the third toe is showing “mallet deformity”