Impaired wound healing in the diabetic foot

Diabetic foot ulcers and their consequences are a tragedy for the person affected and a considerable financial burden on healthcare services and society. This article considers why diabetic foot ulcers fail to heal and considers appropriate, evidence-based, management strategies to overcome barriers to healing.

"Amputation is not an inevitable sequela of a diabetic foot ulcer; up to 85% of amputations can be avoided when an effective care plan is adopted."

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Diabetes mellitus is a complex metabolic disease characterised by persistent hyperglycaemia (high blood sugars) over a prolonged period of time. The American Diabetes Association (ADA, 2017) argues that while classification is important for determining therapy, the traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes occurring only in children and younger adults is no longer accurate, as both diseases are increasingly being observed within both cohorts. Type 1 and type 2 diabetes are heterogeneous diseases in which clinical presentation can vary considerably. Once chronic hyperglycaemia occurs, however, all patients are known to be at risk of developing the same complications, although the rates of disease progression may differ (ADA, 2017).

Diabetes requires ongoing medical care that focuses on good glycaemic control and risk reduction strategies to prevent long-term complications (ADA, 2017). As the number of people with diabetes is increasing globally, its consequences are worsening. One of the key areas of morbidity and mortality associated with diabetes is diabetic foot disease (DFD) (Hingorani et al, 2016). Diabetic foot ulcers (DFUs) and their consequences represent a major personal tragedy for the patient and a considerable financial burden on healthcare services and society. According to US data, at least 25% of these ulcers will not heal, and up to 28% may result in some form of lower-extremity amputation (Hingorani et al, 2016). In the UK, diabetes is the most common cause of non-traumatic lower-extremity amputation; approximately 7,400 lower-limb (major and distal) amputations happen each year in England alone. This equates to 140 amputations per week, or 20 per day in England (Diabetes UK, 2016).

Amputation is not an inevitable sequela of a DFU; it has been suggested that up to 85% of amputations can be avoided when an effective care plan is adopted (International Best Practice Guidelines, 2013). It is, therefore, imperative that all clinicians who are involved in managing DFUs have a sound understanding of the pathogenesis, understand the reasons why these wounds fail to heal and possess the necessary knowledge and skills to apply optimum, evidence-based management strategies, which will ultimately improve patient outcomes. This article considers the long-term complications of diabetes, including the pathogenesis of DFD, explores the reasons why diabetic foot wounds fail to heal and considers appropriate, evidence-based, management of DFUs.

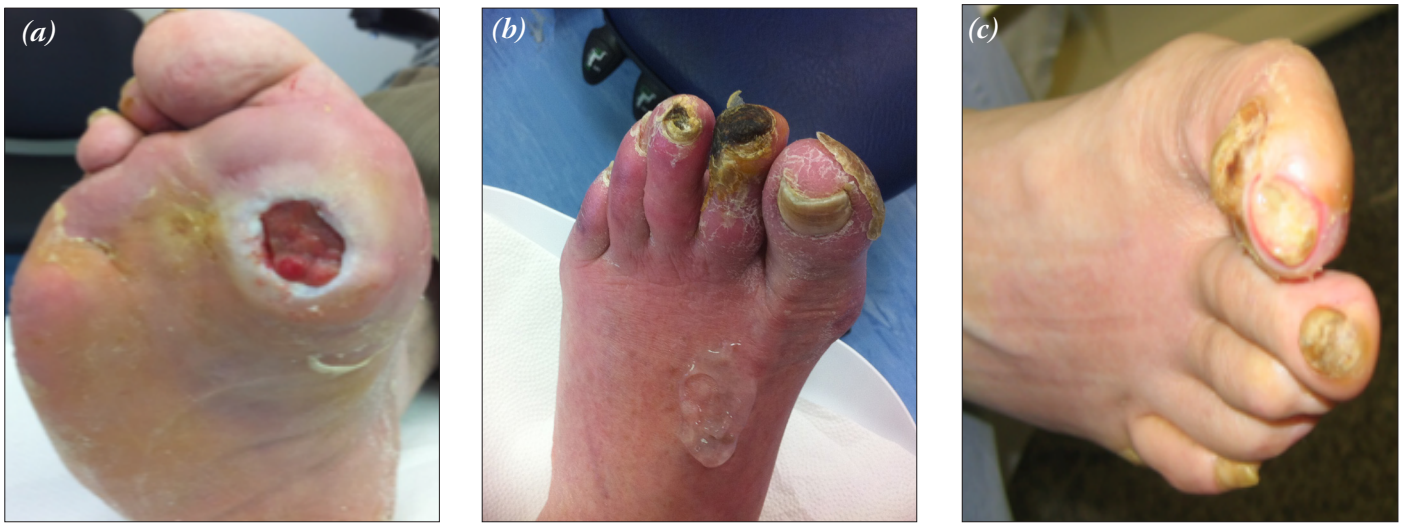

Figure 1. Diabetes can result in (a) neuropathic ulceration (b), ischaemic ulceration, or (c) neuroischaemic ulceration.

The long-term complications of diabetes

Poorly controlled diabetes can give rise to several long-term complications that subsequently contribute to the pathogenesis of DFD. The injurious effects of chronic hyperglycaemia on the vascular tree are a major source of morbidity and mortality. Vascular problems associated with diabetes can be separated into macrovascular and microvascular complications (disease of the large and small blood vessels, respectively) (Fowler, 2008).

Macrovascular complications

The pathology of macrovascular disease in diabetes generally involves atherosclerosis (the deposition of fatty plaques within the arteries), which leads to narrowing of the arteries throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral and/or coronary vascular system (Fowler, 2008). Diabetes, therefore, increases the risk of a person developing cardiovascular disease. Indeed, cardiovascular disease is the primary cause of death in people with diabetes (Fowler, 2008).

Microvascular complications

Microvascular complications are associated with the magnitude and duration of hyperglycaemia and include (Fowler, 2008):

- Diabetic retinopathy (damage to the retina), a leading cause of visual impairment and blindness
- Diabetic nephropathy (damage or disease of the kidney), a leading cause of renal failure
- Diabetic neuropathy (damage to peripheral nerves, most often affecting the legs and feet).

Diabetic foot disease and ulcers

DFD can be defined as the presence of several characteristic diabetic foot pathologies, including neuropathy and ischaemia, which contribute to the pathogenesis of diabetic foot ulceration. DFUs are multifactorial. Both macro- and microvascular disease are major contributors in the pathogenesis of DFD and DFUs. In most patients, peripheral neuropathy and peripheral arterial disease (PAD) (or both) play a central role, therefore DFUs are commonly classified as:

- Neuropathic, due to loss of nerve sensation (*Figure 1a*)
- Ischaemic, due to poor blood flow *(Figure 1b)*
- Neuroischaemic (due to the combined effect of diabetic neuropathy and ischaemia in the diabetic foot (*Figure 1c*).

Hingorani et al (2016) suggest that the pathophysiological mechanism of DFUs has changed during the past 20 years, with an increasing proportion of ischaemic and neuroischaemic ulcers. It is estimated that at least 65% of DFUs have an ischaemic component – nearly double that reported in the early 1990s. This change has implications in the provision of care and outcomes because patients with ischaemic ulcers suffer from a higher recurrence rate and double the amputation rate compared with patients with neuropathic ulcers (Hingorani et al, 2016).

DFU is a marker of serious disease and comorbidities in the person with diabetes (International Best Practice Guidelines, 2013). Without early and optimal intervention, foot ulcers can rapidly deteriorate, leading to amputation of the affected limb. Mortality following amputation increases with the level of amputation and ranges from 50–68% at 5 years, which is comparable to or worse than for most malignancies (International Best Practice Guidelines, 2013).

Why DFUs fail to heal

The healing of a wound requires the well-orchestrated interaction between complex biological and molecular events that include cell migration, cell proliferation and the deposition of extracellular matrix (Falanga, 2005). It is useful to divide the repair process into four overlapping phases of coagulation,

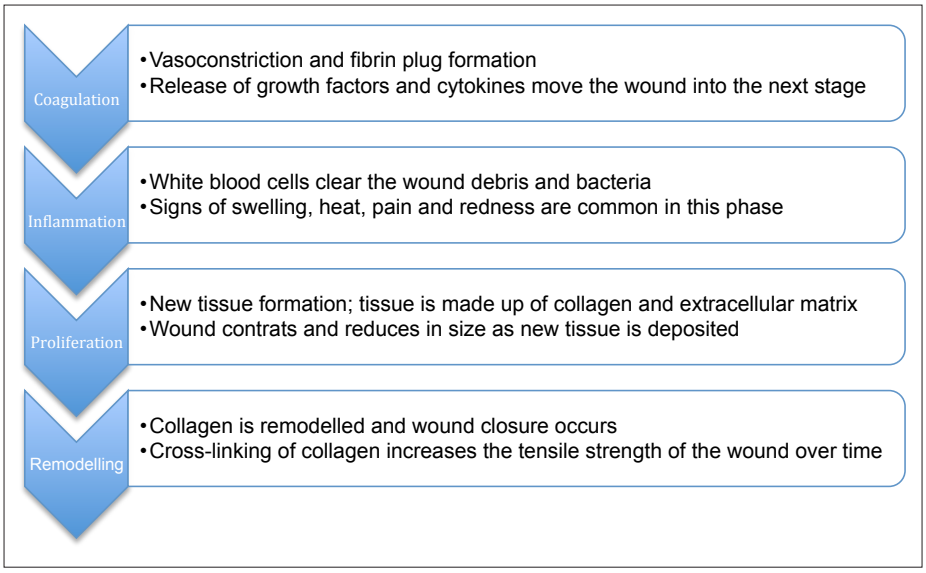

Figure 2. The four phases of wound healing (Falanga, 2005).

inflammation, proliferation (including matrix deposition) and remodelling (see *Figure 2*). Acute, uncomplicated, wounds tend to follow this phased progression; however DFUs, and other types of chronic wound, do not. Instead, the chronic wound may be 'stuck' in different phases, having lost the ideal synchrony of events that leads to rapid healing (Falanga, 2005).

In DFUs impairment of healing is known to be caused by various intrinsic factors (primarily neuropathic and vascular problems) and extrinsic factors (wound infection, callus formation and excessive pressure to the site). Traditionally, this set of predisposing abnormalities in diabetes has been referred to as the 'pathogenic triad' of neuropathy, trauma and ischaemia; however, Falanga (2005) argues that this is an oversimplification omitting infection, which is a major contributor to healing impairment, hospitalisation and limb loss.

Factors affecting healing

Neuropathy

Diabetes-related peripheral neuropathy is a common microvascular complication of diabetes that can affect different nerve pathways, namely sensory, motor and autonomic nerves.

Sensory deficits in diabetes are a direct consequence of hyperglycaemia and can cause numbness, loss of sensation, paraesthesia (pins and needles) and pain in the feet and lower limbs. The insensate foot is particularly vulnerable to trauma because the person affected by sensory neuropathy lacks the protective mechanisms (i.e. pain) that guard against tissue damage. Thus repetitive or inadvertent trauma can initiate the development of a foot ulcer (International Best Practice Guidelines, 2013).

Motor neuropathy occurs if the motor nerves, which control movement, are damaged. Symptoms include muscle weakness, atrophy (muscle wasting), poor coordination and balance problems. Motor nerve dysfunction in diabetes leads to further physical stress on the insensate foot, the development of anatomical deformities (arched foot and clawing of toes) and might play a part in the development of infection, since bacterial growth is enhanced in tissues under high compressive forces (International Best Practice Guidelines, 2013).

Autonomic neuropathy occurs when there is damage to the nerves that manage the autonomic nervous system. This system manages essential body functions including heart rate, blood pressure and sweating. In the diabetic foot, autonomic neuropathy can manifest as dry skin, lack of sweating, distended veins and skin fissures. Reduced bone density and the presence of Charcot's neuroarthropathy have also been attributed to increasing severity of autonomic neuropathy in the presence of diabetes (Brown and La Fontaine, 2004).

Ischaemia

Diabetes is a major risk factor for PAD; people with diabetes are twice as likely to have PAD as those without diabetes (International Best Practice Guidelines, 2013). Hingorani et al (2016) argue that the combination of diabetes and PAD is a sinister one, with an associated 5-year mortality rate of nearly 50% – a figure higher than for many forms of cancer. PAD is also a key risk factor for lower extremity amputation. Patients with diabetes have greater macrovascular disease than the non-diabetes population, with more distal distribution from the superficial femoral artery and tibial arteries to the pedal arch (Hingorani et al, 2016). The mortality of a patient with PAD and diabetes who suffers an amputation is reportedly 50% at 2 years (Hingorani et al, 2016). Microvascular deficiencies can occur early in diabetes. These abnormalities include: a reduction in capillary size; thickening of the basement membrane of blood vessels, which interferes with physiological exchanges; and altered migration of white blood cells, increasing infection risk (Hingorani et al., 2016).

Infection

Infection is an extremely important cause of morbidity, hospitalisation, amputation and impaired healing in diabetes. Falanga (2005) highlights the role of trauma, stress and compressive forces favouring overgrowth of bacteria, decreased function of white blood cells – specifically macrophages and neutrophils – and vascular abnormalities. It is likely a combination of these factors that increase infection risk. Infection can spread rapidly in the diabetic foot. Limb-threatening cellulitis, abscesses and osteomyelitis (bone infection) are common and require immediate attention (Falanga, 2005).

Optimal management strategies

A holistic approach to the management of DFUs is imperative to overcome the many barriers to healing and optimise patient outcomes. For the non-specialist practitioner, the key skill required is knowing when and how to refer a patient with a DFU to the multidisciplinary foot care team. Patients with a DFU should be assessed by the team within 1 working day of presentation, or sooner in the presence of severe infection (International Best Practice Guidelines, 2013).

The multidisciplinary team approach

Diabetes is a complex disease and the management of DFUs requires input from a wide range of clinical specialties. A multidisciplinary team approach is key to understanding the linear relationship between uncontrolled diabetes, vascular compromise, foot deformity, diabetic foot infection and other comorbidities. The burden of care and spectrum of services required for sustainable success in diabetic foot care requires a team of organised and unified specialists. A team effort, along with a systematic approach towards controlling ischaemia, wound severity and foot infection, will help reduce the risk of amputation and facilitate the healing of DFUs (World Union of Wound Healing Societies (WUWHS), 2016).

Glycaemic control

Hyperglycaemia defines diabetes and glycaemic control is fundamental to diabetes management (ADA, 2017). Patients with poorly controlled diabetes may be subject to acute complications of diabetes, including microvascular complications, increased infection risk and poor wound healing (ADA, 2017). Hingorani et al (2016) discuss the findings of several large trials that have suggested survival benefit and lower overall morbidity with tight glycaemic control. For example, the UK Prospective Diabetes Study showed that intensive glycaemic control decreased mortality and microvascular complications compared with standard regimens (Hingorani et al, 2016). Better glycaemic control is associated with significantly decreased rates of development and progression of microvascular (retinopathy and diabetic kidney disease) and neuropathic complications (Hingorani et al, 2016). The ADA (2017) therefore recommend achieving HbA_{1C} targets of 8.57 mmol/L, where appropriate, to reduce microvascular complications of diabetes.

Education and lifestyle management

Treatment goals and plans should be created with patients based on their individual preferences, values and goals. The management plan should take into account the patient's age, cognitive abilities, health beliefs, support systems, social situation, financial concerns, cultural factors, diabetes complications, comorbidities, health priorities, care preferences and life expectancy. Various strategies and techniques should be used to support patients' self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management (WUWHS, 2016). Practitioners should ensure patients with DFUs understand the aims of treatment, how to recognise and report the signs and symptoms of (worsening) infection and the need for prompt treatment of new wounds (International Best Practice Guidelines, 2013).

Recognition and management of infection

Diabetic foot infections are a serious complication of diabetes. Early diagnosis, prompt recognition and rapid initiation of antimicrobial therapy is vital to minimise adverse outcomes including osteomyelitis, limb-threatening infections and amputations (McIntosh and O'Loughlin, 2016).

Neuropathy and PAD can mask signs and symptoms of infection in DFUs. In fact the WUWHS (2016) has reported that up to 50% of patients do not present with the classic signs of infection, such as redness, heat, swelling and pain. In such cases, diagnosis of infection may rely on the recognition of more subtle local signs of infection, which may include:

- Increased exudate
- Friable or dull granulation tissue
- Undermining of wound edges
- Malodour.

It is important that clinicians involved in the management of DFUs recognise these signs. In severe infection, systemic signs such as fever or hypothermia, increased heart and respiratory rates, and high or low white cell counts may also occur (WUWHS, 2016).

Vascular control

The ADA recommends that all people with diabetes and a foot wound should have the blood supply to their feet assessed by ankle brachial pressure index (ABPI) and either toe pressure or transcutanous oxygen measurement (Hingorani et al, 2016). ABPI <0.8 increases amputation risk in the presence of a foot wound in a patient with diabetes. Diminishing degrees of perfusion increase amputation risk, especially when ABPI is <0.4 and toe systolic pressure is <30 mmHg.

'Subcritical' degrees of ischemia need to be considered and may warrant intervention in a patient with diabetes and a foot wound who does not respond to adequate offloading and debridement (Hingorani et al, 2016). Any patient presenting with a non-healing DFU and suspected PAD should be referred to the vascular team for further investigation and intervention.

Optimal wound care

After the initial wound assessment, subsequent assessments should focus on changes in wound size, wound bed, exudate levels and signs of infection (WUWHS, 2016). Signs of deterioration should be investigated to determine cause (e.g. developing infection, poor glycaemic control or suboptimal pressure redistribution) and to indicate referral or further treatment as appropriate. Four weeks after the start of treatment, a wound area

reduction of <50% indicates that the DFU is unlikely to heal and that the patient and wound should be reassessed fully, with changes made to management as appropriate (WUWHS, 2016).

Management of exudate is important for maintaining a moist wound bed for healing. Keep necrotic tissue dry to prevent infection and allow for auto-debridement. Dressings must be able to cope with the amount of exudate present and withstand the weight-bearing forces of the foot during gait (WUWHS, 2016).

Regular debridement is an important component of DFU management and aims to remove nonviable tissue and hyperkeratotic wound margins (callus). Debridement also facilitates drainage of exudate, while removal of nonviable tissue reduces infection risk by decreasing bacterial burden (Hingorani et al, 2016). Sharp debridement carried out by experienced clinicians with specialist training is widely used but should be carried out with caution in a patient with an ischaemic foot (WUWHS, 2016).

Offloading

Pressure generated during walking and trauma from ill-fitting or inappropriate footwear are important contributors to the development of DFUs. As a result, a fundamental principle of the management of DFUs is to redistribute pressure (offload) from vulnerable areas of the foot and provide protection. Effective offloading is essential to facilitate healing. A number of offloading modalities are available. These range from irremovable and removable devices through to insoles and orthoses. Choice of modality will be dependent on a range of patient-related factors, e.g. concordance with the device, the patient's mobility and his/her daily, regular activities (WUWHS, 2016).

Prevention of recurrence

The annual risk of a person with diabetes developing a DFU is 2%. In patients with a history of DFU, however, the risk of another appearing in the next 3 years ranges from 17%–60% (WUWHS, 2016). A patient with a healed DFU should therefore be considered in remission rather than cured and management plans must focus on secondary prevention (WUWHS, 2016).

Conclusion

A DFU is a marker of serious disease and comorbidities. Due to underlying disease processes and various intrinsic and extrinsic factors, DFUs often fail to follow an orderly and reliable progression to healing. Chronic non-healing DFUs are a leading cause of limb-threatening infection and non-traumatic lower extremity amputation. The adoption of a holistic approach to wound healing, with multidisciplinary involvement, can facilitate healing of DFUs and prevent adverse outcomes, including amputations. WE

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