Diabetic foot ulcers: treatment overview and cost considerations

Diabetic foot ulcers (DFUs) are deep tissue lesions associated with ischaemic, neuropathic, or combined neuroischaemic abnormalities and are a leading cause of morbidity and mortality.^{1,2} Of concern is that DFUs affect multiple areas of a person's functioning, including both physical and psychological distress.^{3,4} For example, inactivity due to a DFU can cause feelings of frustration, anger and guilt in patients.^{5,6} This distress has the potential to impair the immune response as well as impacting the quality of life (QoL).⁷⁻⁹

DFUs are often complicated by the presence of infection and this combined with abnormalities are a key cause of amputation in patients with DM, indeed up to 85% of lower extremity amputations are preceded by the presence of a DFU.¹⁰ Furthermore, even when treatment plans are followed, not all DFUs heal, and those that do have a high rate of recurrence.^{11,12}

Numerous epidemiological studies on DFUs have reported an elevation in the incidence of DFUs due to a greater life expectancy in patients with diabetes and an increasing worldwide prevalence of diabetes within an ageing population.^{10,13-15} DFUs are estimated to occur in one in every seven patients with diabetes.¹⁶⁻¹⁸ Furthermore, a recent systematic review showed the global prevalence of DFUs at 6.3% (95% confidence interval (CI): 5.4–7.3%), with the prevalence in North America, Asia, Europe, Africa and Oceania at 13.0% (95%CI: 10.0–15.9%), 5.5% (95%CI: 4.6–6.4%), 5.1% (95%CI: 4.1–6.0%), 7.2% (95%CI: 5.1–9.3%), and 3.0% (95% CI: 0.9–5.0%) respectively.¹⁹ The cost of DFUs varies depending on the degree of ulceration and the underlying pathologies which gave rise to the ulceration in the first place. The cost of DFUs increases with the severity of the lesion and is also dependent on the interventions used to treat them.²⁰

The management of DFUs is complex and multifaceted, thus, care delivery is best using a team approach.^{10,21-23} However, this complexity means that patients often must place significant restrictions on their daily lives. For example, it is usual that patients may be asked to attend multiple appointments with different specialists, restrict their physical movement, change their diet or take different medications, resulting in an impaired QoL.¹² Interestingly, patients with diabetic foot amputation with mobilisation capacity have a higher QoL compared with patients with a DFU.^{24,25}

The overall management of DFUs involves

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interventions to address the underlying systemic pathologies which give rise to the DFU. In addition, the local management of the ulcer revolves around the principle of offloading excess pressure, while using the TIME clinical decision support tool (CDST) would mean employing interventions such as debridement of

devitalised tissue, management of infection, achieving wound moisture balance, and stimulation of re-epithelialisation.²⁶ In addition pressure relief of the foot is extremely important.²⁷

What is a DFU?

Diabetic foot ulceration occurs primarily because of trauma to the foot in a patient with diabetes with either peripheral arterial disease (PAD), neuropathy, or both. In patients with neuropathy, the hallmark feature of such injury is a lack of pain. This lack of pain and awareness of injury causes the person to continue to mobilise on damaged tissue. This continued mobilisation causes increased pressure on the foot and the pressure is significant due to the altered proprioception which occurs concomitantly with neuropathy. In patients with PAD, the hallmark feature is the presence of pain in the foot and reduced tissue vitality which leads to damage usually at the borders of the foot. In patients with both neuropathy and PAD, also known as neuroischaemic, these lesions are characterised by reduced tissue vitality and a loss of pain and are currently the most prominent globally.²⁸

Irrespective of the underlying pathologies leading to the predisposition of DFU, once a wound is present on the foot the normal wound healing cascade is altered.²⁹ These wounds are often stuck in the inflammation phase and unable to progress from this.³⁰ Thus, the goal of any management strategy is to interrupt this altered process and return the wound to a normal healing cascade. In addition, interventions targeted at healing DFUs will also need to address the underlying pathologies that predisposed the individual to ulceration in the first place.³¹

Effects of a DFU

A DFU often takes time to heal, meaning that the patient is at an increased risk of developing an infection.³² Indeed, the longer a person has a DFU, the greater the chance of treatment failure, partly due to the ongoing complications of diabetes.³³ Infection is challenging to treat in patients with diabetes due to the polymicrobial nature of infections. A resultant outcome of this is that up to 80% of amputations are preceded by a DFU.³⁴

A DFU may have a significant impact on a patient's health-related QoL (HRQoL), namely on their relationship with others, mobility, loss of independence, increased amputation risk, and multiple, prolonged clinic visits.^{5,35,36} Studies have shown that patients with diabetes and foot ulcers are more depressed and have worse HRQoL than those without diabetic complications.^{37,38} For example, a cross-sectional study³⁶ included 200 patients with a DFU in a study group and 200 patients with diabetes in a control group. The authors used the RAND-36 questionnaire for evaluating QoL scores for the patients in both groups. The results showed that the diabetic foot was associated with severely impaired HRQoL in both physical and mental

health aspects, based on the RAND-36. Furthermore, in several other studies, many patients reported that ulcer pain interfered with sleep and that they should avoid putting pressure on the ulcer, even from bedding. Pain has also been reported when walking even short distances and during dressing changes.^{39–42} Clearly, pain has an obvious impact on HRQoL.

As mentioned, a DFU can be the precursor to lower extremity amputations.^{43,44} Another systematic review⁴³ aimed to explore the long-term outcomes of lower extremity amputations as a result of DFU. The authors found that re-amputations were 20.14%, 29.63% and 45.72% at one, three and five years, respectively. The weighted mean mortality at one, three and five years was 13.62%, 30.25%, and 50.55%, respectively, with significantly higher rates associated with major amputation, re-amputation and ischaemic cardiomyopathy. Another systematic review⁴⁴ focused on the role of DFU on mortality. The authors reported that the five-year mortality rate after ulceration was around 40%.

Cost of DFUs

DFUs impose a substantial health economic burden on individuals, healthcare systems and society.^{45–47} These costs are comparable to that of cancer in the US, each contributing to an almost similar economic burden.⁴⁷ In Europe, it is estimated that the economic burden of DFUs comes to US\$13,561 annually.²⁰ In the US, that the total medical cost for the management of DFUs varies from US\$9–13 billion in addition to the cost for management of diabetes alone.⁴⁶ A cohort study conducted in the Greater Toronto area showed that DFU was in the top five most costly conditions (\$10,169). The authors reported that the cost per patient with a DFU was \$22,754 while the cost per patient without a DFU was \$8350.

In terms of the burden of DFUs on individuals, a study conducted in five countries including Chile, China, India, Tanzania and the US found that the cost burden of a DFU amounted to a range of between six days to 5.7 years of patient income.⁴⁹ In the UK, it was found that DFU is responsible for 1% of the total NHS budget.⁵⁰ Therefore, implementing appropriate prevention and management strategies for DFU can contribute to the achievement of quality care standards, alleviate suffering, and decrease the financial burden on healthcare and society as a whole.^{2,51}

DFU costs encompass direct and indirect costs. Direct medical costs can be attributed to hospital admissions, emergency department visits, outpatient visits, home care, diagnostic testing, procedures, dressings, and antibiotics,^{52–54} whereas indirect costs are a result of reduced productivity and premature mortality.⁵⁵ In general, hospital admissions and longer durations of stay account for the largest segment of healthcare expenditure.⁵³ Indeed, when compared with other healthcare utilisation resources, including medications, hospital admissions have the highest unit costs.⁵⁶

Therefore, cost-effective measures are necessary to reduce intervention costs in treating DFUs and thus decrease the economic burden associated with them.^{57,58}

DFU management

A DFU arises because of a complicated interplay of multiple pathologies, all of which need to be addressed for the DFU wound to heal. Given the complexity of the DFU, care should be delivered using a multidisciplinary team approach. The TIME CDST is a model clinicians could adopt, using an ABCDE approach to ensure that each element of the care of the patient is addressed to maximise holistic patient outcomes.²⁶ The model includes the following key components:

- Assess patient and the wound
- Bring in multidisciplinary team and informal carers
- Control or treat systemic factors
- Decide appropriate treatment
- Evaluate and reassess wound treatment and outcomes.

This paper will address the ABC of the TIME CDST, the local wound management (D) will be addressed in a subsequent paper.

Assess patient and the wound.

Upon initial presentation, it is important to fully assess the patient, the underlying complications and pathologies, and the wound itself, and establish the presence of either PAD, neuropathy or both. To assess the level of hyperglycaemia, the measurement of glycated haemoglobin (HbA1c) is needed as is self-monitoring of blood glucose (SMBG). HbA1c can be measured either as a point of care test or with a laboratory assay, the latter showing greater accuracy.⁵⁹ The measurement of HbA1c shows a mean level of blood glucose in the preceding three months.⁶⁰

To assess the presence of neuropathy, bedside tests which are designed to ascertain the presence of a loss of protective sensation are employed. These tests include the use of a 10g monofilament, vibration perception threshold, light touch, and/or temperature.⁶¹ This is important in clinical practice as the presence of loss of protective sensation (LOPS) is associated with a lack of awareness of injury and, as such, with an increased risk of ulceration.^{62,63} A combined approach is advocated for utilising more than one testing modality in order to make a diagnosis of LOPS.^{62,64}

To assess for the presence of PAD, the initial test used is to palpate pulses as the absence of pedal pulses are associated with a high prevalence of PAD.⁶⁵ The palpation of pedal pulses, both the dorsalis pedis and the posterior tibial, appear in most clinical guidelines for assessing the presence of PAD.⁶⁶ Pedal pulses may still be palpable even in the presence of stenosis and non-specialists may not be clear about the location of the pulse. Studies have shown that the palpation of pedal pulses are not reliable or repeatable in specialists and non-specialists alike.⁶⁷ Non-invasive vascular testing may be a useful secondary inspection tool and

baseline levels of ankle-brachial indexes have been advocated in the literature, although in practice this does not necessarily happen.⁶⁵ The use of Doppler waveform may help to identify those at increased risk as it allows for the assessment of the medial arterial calcification (MAC).^{66,68,69} At the level of the wound, it is also important to assess the local factors which may impede healing. These are the presence of infection, excess pressure and devitalised tissue.

Bring in multidisciplinary team and informal carers

It is well recognised across different health systems that multidisciplinary teams (MDTs) organise and coordinate health and care services to meet the needs of individuals with complex care needs. Teams bring together the expertise and skills of different professionals to jointly evaluate, plan and manage care. Hospital and community-based, and networked with primary health care, MDTs are expected to work proactively to support individuals' care goals.^{70,71}

A DFU is a complex multisystem hard-to-heal wound, therefore, it requires a complex multidisciplinary approach.⁷² A systematic review by Musuuza et al.,⁷³ has shown that multiple single-centre studies have reported significant reductions in major amputations among patients with DFUs after initiation of multidisciplinary teams. After carefully analysing results, while multidisciplinary team composition was variable, their involvement reduced major amputations in 94% of the studies reviewed. Clinically, teams consistently focused on and addressed glycaemic control, local wound management, vascular disease and infection, in a timely and coordinated manner to reduce major amputation for patients with a DFU. Care algorithms and referral pathways were key tools to their success. On the other hand, an earlier review found that the evidence of MDTs in the management of people with a DFU is unclear as there is much heterogeneity in published studies and reviews.^{73,74}

Control or treat systemic factors.

The initial management plan for a DFU needs to address both the systemic challenges of hyperglycaemia, PAD, neuropathy and infection, in addition to the local management of the wound, which includes pressure relief, managing local debridement and infection, as well as ensuring the wound is dressed appropriately.¹²

To manage DFUs, there is a need to reduce hyperglycaemia associated with diabetes. Current guidelines recommend that the level of HbA1c should be no higher than 53mmol/l to prevent the development of complications.⁷⁵ Once complications have developed, the level should be maintained as close to 53mmol/l as possible to prevent further exacerbation of complications.⁷⁵

Complications can lead to the presence of PAD and neuropathy in patients which predispose and complicate DFU. PAD results in reduced blood flow in

the lower limb; this in turn complicates the wound by reducing levels of oxygenation in the foot.⁷⁶ The challenge in patients with diabetes is that the disease affects the distal arteries more than the proximal arteries. Additionally, the presence of medial arterial calcification which leads to longer lesions in the artery as well as a lesion in the middle of the artery rendering the disease more difficult to treat.⁷⁷ In order to effectively manage PAD, there is a need to ensure sufficient blood flow is restored to the foot to allow for any lesion to heal.⁷⁸ This can be achieved via either open or endovascular means, with no difference in outcomes reported.^{78,79}

Neuropathy is more challenging to address. The main symptom of neuropathy is that of neuropathic pain which can be very distressing as pain is felt in the absence of any lesion on the foot.¹⁷ Conversely, the presence of damage on the foot, especially to the plantar aspect, is rarely accompanied by pain.⁸⁰ Both the presence of PAD and neuropathy lead to an increased risk of infection. In neuropathy, with the lack of awareness of pain, patients may continue to mobilise despite having foot wounds, leading to an increased risk of infection. Indeed, the presence of infection in wounds with neuropathy is often the cause of treatment failure and the development of systemic infection including osteomyelitis.⁸¹ The identification of the infection is often masked in the patient with a DFU and neuropathy.⁸²

The presence of infection has important cost considerations as the extended use of systemic antibiotics is associated with high costs as well as increased rates of antimicrobial resistance.^{83,84} The combination of PAD, neuropathy and infection is strongly associated with a high incidence of major amputation.⁷⁸

Local treatment of infection is an area that has been under-researched and warrants further investigation.⁸⁵

The effectiveness of pressure reduction to the foot with a DFU is well established in the management of neuropathic forefoot plantar ulcers (DNFU).^{74,86,87} The gold standard treatment is total contact casting (TCC).

There is less evidence for pressure relief in non-neuropathic lesions although the use of offloading is still advocated in clinical practice guidelines.⁸⁸ Authors agree that TCC provides effective offloading of DNFBs but disagree on the mechanisms by which the offloading is delivered.^{10,89} Existing randomised controlled trials (RCTs) have small sample sizes and are generally underpowered and do not reflect normal practice.^{90–93} It has also been suggested that the use of offloading for all types of DFU is underutilised in clinical practice.^{91,94–96} While alternatives to TCC have been suggested,^{96–98} the evidence for their use is weak.^{90,99} Clinicians in practice need to balance the needs of the patient with the capability of the service in conjunction with published evidence.^{78,100}

Conclusion

This clinical paper has presented an overview of the treatment and cost considerations relating to DFUs. DFUs may have a significant impact on a patient's HRQoL, namely on their relationships with others, mobility, loss of independence, increased amputation risk and multiple, prolonged clinic visits. DFU costs encompass direct and indirect costs; direct medical costs can be attributed to hospital admissions, emergency department visits, outpatient visits, home care, diagnostic testing, procedures, dressings and antibiotics. The overall management of DFUs involves interventions to address the underlying pathologies of PAD, neuropathy, and control of hyperglycaemia related to diabetes, which reduces the risk of any further acceleration of disease. The goal of the management strategy is to interrupt this process and return the wound to a normal healing cascade. Interventions targeted at healing DFU will also need to address the underlying pathologies that predisposed the individual to ulceration in the first place. This paper used the TIME CDST model to highlight how DFU treatment could be approached. This is a model that should be evaluated further in DFU care and one clinicians could consider adopting as they strive to deliver holistic patient care and better outcomes. **JWC**

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