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REVIEW

Hard-to-heal diabetes-related foot ulcers: current challenges and future prospects

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Abstract: Diabetes-related foot ulceration is a frequent cause for hospital admission and the leading cause of nontraumatic lower limb amputation, placing a high burden on the health system, patient, and their families. Considerable advances in treatments and the establishment of specialized services and teams have improved healing rates and reduced unnecessary amputations. However, amputation rates remain high in some areas, with unacceptable variations within countries yet to be resolved. Specific risk factors including infection, ischemia, ulcer size, depth, and duration as well as probing to bone (or osteomyelitis), location of ulcer, sensory loss, deformity (and high plantar pressure), advanced age, number of ulcers present, and renal disease are associated with poor outcome and delayed healing. To assist in prediction of difficult-to-heal ulcers, more than 13 classification systems have been developed. Ulcer depth (or size), infection, and ischemia are the most common risk factors identified. High-quality treatment protocols and guidelines exist to facilitate best practice in the standard of care. Under these conditions, 66%–77% of foot ulcers will heal. The remaining proportion represents a group unlikely to heal and who will live with a non-healing wound or undergo amputation. The authors have applied their experience of managing patients in this discussion of why some ulcers are harder to heal. The article explores the effects of patient non-adherence to treatment, comorbid mental illness, a failure of research to be translated into the everyday practice of many clinicians, and the impact of delayed access to specialized treatment. These factors when combined with the main published risk factors of size, infection, ischemia and pressure are perceived as critical barriers to healing.

Keywords: diabetic foot, healing, infection, delayed treatment, referral

Introduction

Diabetes and its complications represent a major health challenge in both the developed and developing countries, with an estimated 415 million adults affected globally.[1] A largely underestimated complication of diabetes is diabetes-related foot ulcer (DFU), which carries a lifetime risk of 15% of all persons with diabetes[2] and is responsible for much morbidity and mortality.[3] The International Diabetes Federation has studied the impact of this complication and estimates that an amputation due to diabetes occurs every 4 seconds somewhere in the world. For this reason, there has been a large amount of effort directed to coordinated approaches to the prevention, identification, and management of DFUs. The implementation of treatment guidelines such as those published by the International Working Group on the Diabetic Foot (IWGDF),[4] The National Institute for Health and Care Excellence,[5] Australia's National Guidelines,[6]

and many other notable documents has resulted in better organized care, prevention of amputation, and improvement in patient outcomes.[7,8] While direct comparisons should be made with caution because of differences in measurement and ascertainment of diabetes incidence across countries, it is evident that there is high variation between and within countries.[9–11] This suggests that universal adoption of best practice and equity of access to contemporary foot care for people with diabetic foot complications are still a work in progress and may not be adequately prioritized in some regions.

It is well recognized that DFUs are notoriously hard to heal; however, when treatment is provided according to the evidence-based practice guidelines (EBG) whereby there is identification and management of infection and ischemia, in combination with wound debridement, pressure offloading, and appropriate patient and health professional (HP) education, many patients will achieve healing. Results from large studies and wound registries with a 1-year follow-up period have reported healing rates of 66%–77%, respectively.[12,13] While such studies provide an overall benchmark for expected percentage of ulcers healed, they point to over a quarter of DFUs failing to heal. Why this occurs is not certain. The time to healing and risk of amputation for individual patients are known to vary markedly based on patient and ulcer factors such as infection, ischemia, ulcer size, and ulcer duration, as well as more difficult to quantify extrinsic factors such as the standard of foot care provided[14,15] and patient adherence to prescribed foot ulcer care. Therefore, we need to identify and explore what makes a wound "hard to heal" and to mitigate the barriers to healing from the perspective of HPs involved in the care of people with DFU.

The purpose of this article is to discuss some of the issues we (HPs and research workers) believe contribute to the poor prognosis of some DFUs and make them hard to heal. These are shown schematically in Figure 1. While the physical risk factors for delayed or non-healing of DFU are largely well described and evidenced, other issues we explore are difficult to quantify and have no proven causal relationship. We include issues relating to the health care provider in terms of translation of evidence into everyday practice and patient behavior, both of which affect the timeliness and quality of treatment. These factors are complex and many are interrelated. Each warrants due consideration if healing outcomes are to be improved.

Defining the hard-to-heal DFU

The measureable risk factors to delayed healing or amputation, which define DFUs that will be hard to heal, have now been extensively studied across patient populations. Analysis

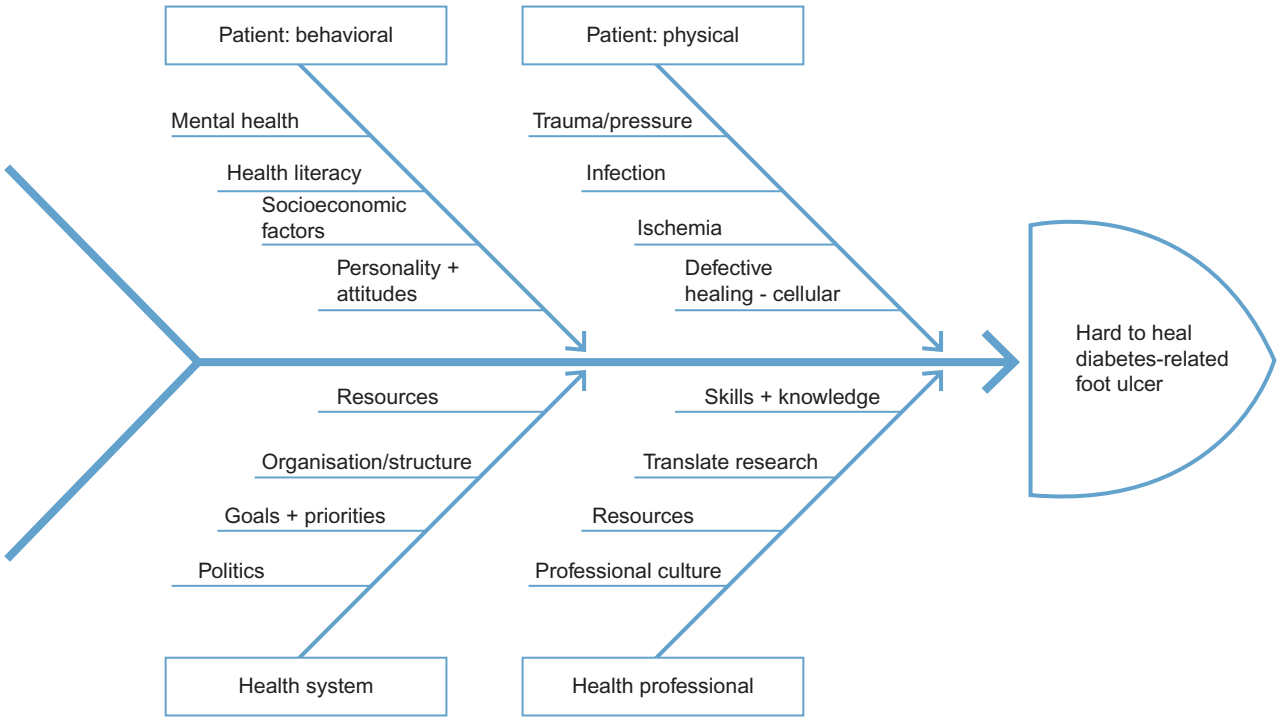

Figure 1 Ishikawa diagram of suspected issues, which contribute to the problem of the hard-to-heal DFU.
Abbreviation: DFU, diabetes-related foot ulcer.

of different variables has informed predictive models, and at least 13 grading or classification systems have been proposed for use in research and clinical practice including the University of Texas (UT), PEDIS (perfusion, extent, depth, infection and sensation), S(AD) (size (area, depth)), SAD (sepsis, arteriopathy and denervation), and MAID systems.[16–18] The documented factors most strongly associated with poor outcomes are advanced age,[19] infection,[12,16,20] biofilm presence,[21] the presence of ischemia,[12,16,18,20,22] wound duration,[18,23,24] large wound size (depth and circumference),[16,18,24–26] site,[27] having multiple ulcers,[18,22,24] end-stage renal disease,[12] heart failure,[12] male sex,[12] immobility,[12] and depressive symptoms.[28]

The use of predictive data in grading and classification of wounds is useful in guiding management, aids communication between HPs, and helps describe the case mix for the purpose of reporting and evaluating performance of a particular service. Importantly, use of predictive grading informs conversations with patients and their families regarding the goals of treatment based on ulcer severity and prognosis.

Wound fluid analysis may also have utility in predicting wound healing for individual patients to guide treatments. In particular, increased wound fluid levels of matrix-degrading enzymes called matrix metalloproteinases (MMPs) have been detected in human non-healing wounds including DFUs, and measurement of wound fluid MMP-9 in combination with transforming growth factor β and the MMP inhibitor TIMP-1 can predict future poor healing with high sensitivity and specificity.[29] Other possible wound fluid factors that have received less attention in diabetic wounds include pH and endotoxin levels both of which are known to be altered in chronic non-healing wounds.[30–32]

Health professionals and health system

Translating evidence into clinical practice

The translation of quality research into the clinical environment ensures that HPs are fully informed and treatment is evidence based. The application of evidence-based practice has further potential to improve health outcomes and strengthen health systems by providing more efficient and cost-effective care.[33–35]

To support the translation of the high volume of studies and often-complex information, EBG citing quality evidence together with expert consensus (where evidence is lacking) have been developed. However, despite evidence that support a prompt referral to a multidisciplinary team with standardized clinical practices when a hard-to-heal DFU is identified,[6,36,37] HPs do not consistently implement these processes.[38,39] A broad illustration of this is the 2008 report of the Eurodiale Studies, which documents that across 14 treatment centers, a quarter of patients had delayed referral to multidisciplinary teams of >3 months, the majority had no or inadequate offloading, and almost half the patients with severe ischemia had no vascular imaging.[39] This suggested widespread lack of adoption of the well-known "International Working Group, Diabetic Foot Consensus Guidelines"[4] or those of other peak organizations by established treatment centers within developed countries and also by their referrers.

Understanding the reasons why EBG are not successfully translated into practice could help inform funding and policy decisions with potential to support better health outcomes for people with DFU and reduce associated costs. Key individual HP attributes associated with translation of research into clinical practice are open-mindedness and capacity for critical thinking; however, for many HPs, experiential learning, formal education, and discussions with other HPs will inform their practice more than professional journals.[40] At an organizational or system level, historical precedence has been shown to influence how knowledge translation is valued and developed and how HPs are supported during its implementation. Resistance from professional groups to the introduction of EBG and the degree to which recommendations are implemented by clinicians are often raised as a reason that positive change is not forthcoming.[41,42] This lack of change may be explained within the general health community by HPs finding the continual introduction of new practice information difficult to implement within a constantly changing environment.[43] To address this, a system-based approach that introduces behavior change support is suggested as a viable means of facilitating required changes in practice.[42] Factors that impede implementation of EBG include cost of the intervention (including where too expensive or too resource intensive), the research not being applicable to the particular patient population,[44] HPs lacking skills and equipment to apply recommendation, or changes being inconsistent with desired practice of the HP.[41]

To be adopted, evidence and EBG must be known to HPs and health system administrators, and as with any change, the adoption of best practice requires a motivating force, as well as alignment of the goals of the organization and available resources. The utilization of inexpensive, passive approaches, which rely on publication, mail outs, and email, is only minimally effective in ensuring the uptake and utilization of EBG by HPs.[44] These approaches fail to capture and engage all the stakeholders who have a role in both the provision of the resources and the planning required for implementation of EBG and ongoing reinforcement of their

practice. Ultimately, successful application of EBG depends on adequate funding as well as political and organizational support around developing an environment that is able to fully implement best practice. A range of strategies that identify and target modifiable barriers is important, and effective implementation methods should be employed.[41] A system-based approach that includes performance measurement, point-of-care access to practical information on treatment including where to refer, education for HPs, and adequate resources are approaches likely to improve translation of research and achievement of sustainable benefits in terms of patient outcomes.[42]

Performance monitoring through auditing processes is a recommendation of the IWGDF[45] for all foot care services. Monitoring and reporting process and patient outcomes has been shown to be effective in influencing positive change on a large scale and represents a future prospect for improvement of care and patient outcomes.[36,46] Data on costs and better prevalence information arising from initiatives such as the UK's DFU registry and US Wound Registry will provide incentives for investment in these approaches at an organizational level. Training of HPs is also essential. The International Diabetes Federation "Train-the-Foot-Trainer" program, teaching DFU management and how to set up and use data to monitor outcomes, has achieved gains largely through education.[47]

Some of the most important evidence for improving outcomes for people with DFU comes from the establishment of specialized or dedicated, multidisciplinary foot care teams (MDTs).[48,49] This multidisciplinary approach requires the alignment of many disciplines. While this is challenging, many countries have achieved significant improvements in patient outcomes with this approach.

Within our region, reinforcement of best practice through a multifaceted approach and standardized data collection has contributed to reduced rates of lower extremity amputation and hospital admission in Queensland, and development of an Australian Register for DFU is underway.[36,50] With the establishment of these services comes the imperative that patients have prompt and equitable access.

Delayed referral to multidisciplinary services

A coordinated MDT is supported in EBG, but universal access to a MDT is not yet a reality. Even in countries where specialized treatment centers exist, practical reasons such as locality, resources, and patient mobility may prevent attendance. Therefore, a proportion of DFUs are managed outside the multidisciplinary team, and under the care of the patient's primary care doctor, nurse, or podiatrist.

Key circumstances where MDT management is of a necessity include ulcers probing to tendon, joint, or bone, ulcers that fail to reduce in size after 4 weeks, ischemia, and ascending cellulitis.[51] At its most critical stage, such as when the DFU is complicated by limb- or life-threatening sepsis, particularly in the presence of critical limb ischemia, hospital admission is essential. However, if EBG were implemented fully, earlier treatment by an MDT in the ambulatory or outpatient setting, such as high-risk foot service (HRFS), would avert the need for hospitalization in most cases.

Treatment delay is a risk factor for amputation and is associated with longer treatment time,[15,39] increased wound size,[23] and poorer outcomes.[52] Conversely, improved outcomes for patients with a DFU are largely attributed to wounds presenting at a stage when they were more "prognostically favorable", suggesting earlier access to care.[8,53] Time to presentation to a HRFS for patients with a DFU has been reinforced as a key performance indicator for our service[54] since local data (unpublished) showing increased ulcer severity with delayed referral.

Reasons for treatment delay are often ascribed to patient behavior, but HPs behaviors explain at least some of the delay. In Europe, 27% of all patients had been treated for >3 months before referral to a specialized multidisciplinary foot service, and a primary care physician had treated close to half of these until referral.[39] Sanders et al reported a median delay of 7 days (0–279 days) between the first HP consulted for DFU and referral to a podiatrist. Despite this relative brief delay and the small study size, they detected an associated increase in the time to healing.[55] Given the data supporting ulcer duration as a risk factor for poorer outcomes,[19,22,24,26] it is likely that prompt referral would reverse this effect.

HPs play a significant role in ensuring that delayed treatment is not a barrier to healing by ensuring they conduct routine foot examinations in their patients and are prompt to act when ulcers meet criteria for referral. Education of patients and carers is important, as is instilling in patients the understanding that foot problems are serious and deserve attention.[45] One of the most powerful ways to convey this must be for HPs to perform routine foot assessments according to EBG. To help overcome the barrier of time required for busy clinicians to complete foot screening, Woodbury et al[56] have recently reported on their simplified 60-second diabetic foot screening tool. This tool was designed as a fast and reliable assessment, particularly for health care

workers in low- and middle-income countries, to aid timely identification and referral for patients who are at risk of or currently have a DFU.

It is also vital that specialized services promulgate their existence and measure access and time to treatment of patients, so that they can ensure they are being appropriately utilized. In evaluation of service impact, Ellis et al[57] found that only 33% of patients admitted to hospital for DFU had accessed the region's MDT and Plusch et al[58] found that 75% of patients with an acute hospital admission for DFU had been admitted without prior treatment by the HRFS. In the UK, increased admission days for diabetic foot complications were associated with reduced podiatry resourcing, which impacted on early access to treatment.[59] This observation, when reported on, motivated health administrators to fund the reinstating of the podiatry workforce, after which the trend reversed.

This delay in referral leads us to seek a solution but demands our recognition of the complex, interrelated, progressive, and location-specific factors that must be addressed to remove the inequity of access to specialist foot care as a mitigating factor in making wounds harder to heal.

Once referred, the healing of a DFU involves the management of the complex physical, biological, and behavioral aspects of this disease.

Patient factors – physical

Defective healing and chronic inflammation

Inflammation is required for normal wound repair, and the process in normal wound healing is tightly regulated both temporally and spatially.[60] Any pathological process, many of which are present in DFUs (eg, impaired immune response, bacterial burden, and/or ischemia), can interfere with this physiological process and result in a non-healing wound. The effect of diabetes on wound healing can be seen from the very first moments of injury. The normal three-phase process of inflammation (Lewis–Flare) is partly mediated by stimulation of C nociceptive small nerve fibers, which secrete substances to enable vasodilation following injury. This process is impaired in patients with diabetes and neuropathic foot ulcers[61] and is believed to contribute to their vulnerability and poor wound healing.

Chronic and hard-to-heal DFUs are characterized by a chronic inflammatory state, which is manifested by imbalances in 1) proteases and their antiproteases and 2) proinflammatory cytokines and their natural inhibitors.[62–65] These imbalances occur because of sustained production of inflammatory mediators and influx of inflammatory cells, which prevent matrix synthesis and remodeling essential for progression to a healed wound.[66–68]

Having established the role of inflammation in delayed healing, we now need to better understand the mechanism by which healing fails and find evidence for treatments to address this. Despite intensive research, most therapeutic strategies have not been as successful in humans as in animal studies. Why this occurs is likely due to a number of factors including 1) animal models that do not fully replicate the conditions present in DFUs especially where the etiology of the ulcer is different (eg, diabetic neuropathic ulcer vs vascular insufficiency), 2) patient compliance with treatment regimens, 3) variability in wound care, and 4) variability in delivery of therapeutics with problems of retention. There does appear some hope that new therapies directed to molecular defects (eg, addition of stem cells) can impact on hard-to-heal DFUs. Treatments such as the inclusion of growth factors (eg, platelet-derived growth factors)[69] and the use of neutraceuticals added either topically or to wound dressings[70] may also have some utility in the treatment of hard-to-heal DFUs.

Infection

The defects in the early immune response in people with diabetes also delay wound healing by increasing the risk of infection.[71] Typically arising in neuropathic, ischemic, or neuroischemic wounds, diabetic foot infections (DFIs) are the most frequent diabetes-related complication requiring hospitalization[72,73] and greatly increase probability of amputation.[72] Prompt identification and grading of infections from mild, involving superficial structures, moderate to severe limb and/or life threatening using validated criteria as a key step in the appropriate management of infection is therefore paramount.[74] In addition to identification of the presence of infection, it has become clear that bacteria can form organized communities that are encased in a polymeric substance called biofilm. Biofilm exists on the surface of most chronic wounds, and its presence protects bacteria from the effects of most conventional antimicrobial treatments.[21,75] The presence of biofilm is difficult to identify, highlighting the need for improved detection technology. Additionally, it is clear that frequent debridement that can physically remove biofilm as well as prevent biofilm formation also improves wound healing.[75,76]

Management of DFI is well documented, including most notably, the freely available Infectious Diseases Society of America and the IWGDF CPG and Bader and Brooks in

2012.[77–79] These highlight the need for assessment of clinical signs of inflammation to identify infection, appropriate methods for assessing severity, debridement, assessment of peripheral arterial disease (PAD), and correct technique in collection of tissue samples for the analysis of bacterial phenotype. Empiric systemic antibiotic therapy can be commenced while awaiting formal culture results to inform ongoing selection of antimicrobial therapy, and this is particularly important for severe infections when failure to treat infection rapidly threatens limb and life.

Current reliance on traditional microbiological sampling, culture, and sensitivity testing, which takes several days, would delay treatment if not for recommendations of empiric prescription. However, concerns arise that widespread use of poorly targeted therapy contributes to antimicrobial resistance and poor outcomes. The evidence is unclear about the efficacy of one treatment over another. Methods using DNA analysis, which can assess the polymicrobial nature of the wound bacteria, have already demonstrated that traditional techniques underdetect important pathogens and do not capture the full diversity of organisms present in wounds and biofilms.[76,80] In future, widespread use of methods for detecting infecting organisms based on more accurate and rapid analysis of bacterial DNA may lead to more targeted and effective treatment. In chronic wounds, DNA tests detect a wide variety of genotypically distinct bacteria often present in biofilms.[80] How this new information will be translated to more targeted therapeutics is not as yet clear, although a recent study has shown that personalized treatment based on type of bacteria present, identified by DNA analysis, can improve wound healing and at reduced cost.[81]

All major guidelines recommend referral and management of these patients via a dedicated MDT.[82,83] Delay in referral has been identified as a risk factor for lower extremity amputation[15] and can be due either to the underrecognition of infection by the primary care physician or the patients' delay in seeking care, or both. Healing rate is not only affected by bacterial number but also by the type of bacteria present. Gram-positive cocci, most notably Staphylococci, are the most commonly detected organisms.[84] The factors that affect the pattern of sepsis (such as the presence of Gram-negative and/or Gram-positive organisms or diversity of the bacterial biofilm) are not yet clear. Metabolic control has been shown to play a role[85] as has delayed referral.[86] More recently, studies using animal models suggest that insulin therapy may promote antibiotic resistance in two important species commonly implicated in DFI, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[87,88]

Of particular importance is the prompt treatment of infected DFU complicated by PAD present in a high proportion of DFU.[89] Diminished blood flow and neuropathy often result in dampening of the visual cues of infection. These deficits, especially in a patient with sensory neuropathy who also lacks the ability to sense pain or warmth, can delay awareness of an infection by the patient and the HP. DFI in wounds complicated by ischemia will often rapidly result in a contiguous spread to the adjacent bone if they are not managed promptly.[90] With osteomyelitis comes a high probability of non-healing and amputation.[72]

In general, urgent action to overcome barriers and enhance collaboration among the various specialties involved in managing DFI is needed. Given the propensity for neurological and vascular impairment to mask signs of infection, in these conditions, high levels of suspicion for infection are needed to detect early changes.

Ischemia

Ischemia or PAD is present in up to 50% of patients with DFU.[91] PAD is an independent baseline predictor of non-healing and also an independent risk factor for both ulcer recurrence and amputation.[89] When caring for patients with DFU, reliably identifying PAD and knowing when to refer and how to provide best management will greatly influence the healing potential of a DFU.

The identification of PAD begins with checking for history of intermittent claudication or rest pain and palpation of pedal pulses. However, symptoms may be absent due to peripheral neuropathy,[92] and palpation of pulses alone is an unreliable sign for determining PAD.[93] Hence, noninvasive bedside assessments that largely exclude PAD should be conducted. Significant PAD may be excluded using the following criteria: ankle brachial index (ABI) is 0.9–1.3, toe brachial index ≥0.75, and triphasic pedal Doppler arterial waveforms[94] are present or there is adequate perfusion demonstrated with transcutaneous oximetry. ABIs need to be interpreted with caution due to the prevalence of arterial calcification that can falsely elevate results, reducing the sensitivity of the test in people with diabetes and neuropathy.[95,96] While the toe brachial index and ABI closely correlate and ABI is still widely recommended,[94,97] the digital arteries are less likely to be calcified, and therefore, toe brachial index detects more people with PAD (increased sensitivity) in people with diabetes.[98] As a guide, patients with DFU will generally heal if toe pressure is >55 mmHg[92] but should be promptly referred for further vascular imaging and revascularization if toe pressure is <30 mmHg.[99] Irrespective of noninvasive

bedside vascular assessment results, referral for further vascular imaging is indicated if a DFU fails to improve within 6 weeks of standard care.[99]

Literature to date does not provide a definitive guide to which patients will benefit most from revascularization or whether open bypass or endovascular procedures are optimal. However, the recent review by the IWGDF indicates that overall ~60% of ulcers when revascularized proceed to heal.[99] The 1-year survival rates are 80%–90% for open bypass and 70%–85% following endovascular procedures.[91] Despite some variability in results, the increased accessibility to endovascular procedures provides a window of hope for healing of DFUs even if the resultant increased perfusion is temporary. However, many patients will continue to experience slow healing and frequent re-ulceration due to failure of the stent[100] and the progressive nature of the PAD. For patients with critical limb ischemia for whom revascularization is unsafe or not appropriate, for example, in severely frail patients or in those whose life expectancy is <6–12 months[101] or those who decline intervention, there is evidence that healing can still be achieved. In their prospective study of patients with ischemia and PAD, deemed unsuitable for or who declined revascularization, Elgzyri et al[102] showed a 50% rate of healing without major amputation in an average of 27 weeks. This suggests that time and good care without revascularization can be appropriate management for some patients with ischemia.

The presence of PAD is of course due in part to modifiable risk factors. Earlier intensification of preventive measures (including smoking cessation, management of dyslipidemia, hyperglycemia, and hypertension) are all likely to improve outcomes. Additionally, data are emerging to support a role for long-term lipid-lowering treatment and a reduction in risk of amputation.[103]

Neuropathy, deformity, and offloading

In the presence of peripheral neuropathy, chronic repetitive mechanical stress on areas of high pressure such as those frequently created by foot deformity is a common pathway to DFU.[104,105] The alleviation of localized pressure on the ulcer site is integral to successful healing irrespective of the injury being a consequence of chronic mechanical stress and acute physical, thermal, or chemical trauma. Without effective off-loading, other therapies, including advanced treatments, are unlikely to succeed.[106]

Most evidence to date supports total contact casting and irremovable walking casts for plantar DFUs because they provide effective pressure relief to the plantar aspect of the forefoot and compliance is forced.[107,108] This is reinforced by the IWGDF and other peak bodies recommending offloading in an irremovable knee high device with an appropriate foot interface for plantar neuropathic ulcers or other modalities such as felt or felted-foam deflective padding[109] and footwear when these treatments cannot be used.[51,110]

As with other areas of clinical management, there is a significant gap between evidence and practice. Most (77%) of the patients in the Eurodiale[89,111] studies had no or inadequate offloading at study entry, and only 35% of patients were treated with some form of casting. Surveys in both the USA and Australia have shown the relative infrequency of the most recommended treatment by HPs; 68% of Australian podiatrists working in HRFS only used non-removable below-knee casts or walkers 11.2% of the time.[112] Similarly in the USA, most HP's reported use of total contact casts in <25% of patients.[113] While lack of training and experience may be implicated, this was not considered a major driver in choosing other offloading devices in the Australian survey. In practice, irremovable devices are not prescribed for all patients for a range of reasons including nonacceptance by the patient or unsuitability of the treatment based on wound factors (infection, ischemia, fluctuating edema, depth, and location), patient behaviors that render an irremovable device unsafe, instability of gait, vision impairment, or the need to drive or a physical environment not conducive to wearing a cast. A lack of reimbursement for devices was suggested as a barrier in the USA and Australia.[113,114]

A lack of transferability of research to the clinic population may exist due to the nature of clinical trials, whereby researchers may need to exclude the very patients who clinicians have difficulty treating. The use of practical trials, which increase the applicability of research outcomes to real world, has been proposed to address this issue.[44]

Therefore, the authors agree with Armstrong et al[107] that "thoughtful patient selection and diligent monitoring" are important. When irremovable devices are not deemed suitable, HPs must seek alternatives, often creatively and extrapolating from available evidence and experience. There are also reports of good healing outcomes achieved with devices such as felt deflection and healing shoes.[109,110,115] Emerging reports support surgical offloading to prevent recurrence where foot deformity is the cause of ulceration, and other treatments to heal or prevent recurrence have failed.[116,117] This is reflected in the latest international guidelines from the IWGDF, which recommend surgical procedures to achieve pressure offloading.[110]

Future research in the area of pressure offloading will need to focus on individualized treatments, using patients who are representative of the cohort, testing commonly used modalities that have potential clinical effect, and using patient-focused outcomes such as acceptability in addition to healing outcomes.

Patient factor – behavioral

Adherence to treatment

It is widely acknowledged by HPs that poor adherence to treatment is common in patients with DFU and that this makes it harder to heal a wound. People with DFU are of course a heterogeneous group, and there are a multitude of reasons why the rigorous treatment regimens recommended are not fully complied with. Patient non-adherence can take many forms, including the failure to keep appointments, follow recommended dressing and offloading instructions, make alterations to lifestyle including weight-bearing activity, and follow other aspects of treatment. There are two concepts to consider when exploring non-adherence to treatment regimens: unintentional and intentional, and in each case, it is important to determine the cause of non-adherence before commencing efforts to address it.[118,119]

Unintentional non-adherence applies when patients have an inadequate understanding of the disease or treatment regimen to competently complete the given tasks, whether due to poor literacy skills, lack of affordability, poor comprehension, reduced cognitive function, not acknowledging the seriousness of the condition due to lack of pain or other causative factors. Cognitive function must be considered since increased prevalence has been documented in patients with DFU.[120,121]

As the day-to-day care of the wound rests in the hands of the patient, reviewing our behavior, as clinicians, in order to engage, empower, and provide an optimal patient-centered experience for our patients has been shown to influence healing.[118,119] Simple education and knowledge exchange strategies can be effective when managing people who unintentionally do not follow advice, and it is the responsibility of the clinician to ensure the patient is equipped with adequate information and that the type of communication is optimized and individualized. Advice and instructions need to be:

- Clear and unambiguous;
- Use nontechnical, everyday language;
- Limited to three or four major points during each discussion;
- Include written materials to support information;
- And involve the patient's family members and friends.[118,119]

However, education and information alone will not always address the cause of non-adherence, particularly in the case of intentional non-adherence. Intentional non-adherence is a complex and at times incredibly frustrating encounter for clinicians. Intentional non-adherence is a deliberate and purposeful choice of patients to modify or reject treatment regimens for reasons important to themselves.[118,119] As with all human behavior, progress can be cyclic, with individuals oscillating between making positive progress in their behavior change to "regressing" back to previous negative behaviors. Determining their motivation for doing so is the key to improving adherence. Motivating factors can include:

- Not taking their condition seriously enough;
- Patients feeling the side effects of the treatment outweigh the benefits; and/or
- The patient may not believe that the treatment is working.[118,119]

Most behavior change interventions are targeted toward intentional non-adherence, as it is widely accepted that motivation is a dynamic state that can be influenced.[122] However, there is little evidence of sufficient efficacy to conclude that one method of behavior change intervention has a clear advantage over the others.[119] As such, multifaceted approaches should be used until greater evidence is established. Importantly, motivation and patient adherence fluctuate in response to clinicians' counseling style and communication methods.[123,124] Therefore, a shift in our traditional role as an authoritative HP to a more collaborative "health coach", focusing on interactive communication and partnership with our patients, is one way forward.[125] This can be achieved by applying the skills of:

- Open-ended questions
- Reflective listening/making affirmations
- Summarizing/using reflections.

These skills will help to determine what the patient's motivations and goals are so that we can bring them toward a common goal with the clinician.[124,126] The acknowledgment and consideration of the patient's preferences and perspectives are essential in gaining the patient's buy in.[127]

Another important and emerging consideration, when exploring ways of engaging and motivating patients, is the use of Information Communication Technology (ICT). Interest in ICT is growing primarily because of its potential to improve facilitation of patient–provider communication, patient self-management, and the coordination of care across settings. Technology can be used to supplement care by providing both educational and motivational support.[128,129] Types of ICT that have been trialed and reviewed include mobile phones (for communication, education, and monitoring),

Internet-based education programs, and Internet-based self-management programs.[128,130] Along with the potential benefits, it is important to also note the challenges associated with the use and access to emerging technologies, namely, the presence of the "digital divide". In Australia, data suggest that a lack of access to computers, mobile phones, and the Internet, particularly in lower socioeconomic households, has the potential to exclude some people from information communicated through ICT.[131] Technological advancements will never replace the crucial face-to-face role clinicians play in DFU management, but there are certainly indications of their benefit when applied in conjunction with traditional care delivery.

In some instances, we do not have the skills, resources, or support to bring about behavior change interventions, or occasionally, the need for change is expedited and there is not enough time to address the underlying non-adherence issues. This is particularly the case for patients with mental illness and other mental health comorbidities, as discussed in the next section. In these situations, HPs can seek to make it as easy as possible for patients to follow the aspects of care that are of greatest importance and enlist the support of carers and family members and refer if indicated for treatment of mental health problems.

Just because behavior change and adherence initiatives are complex,[119] it does not mean we should give up. To achieve patient-centered care, we must strive to strike a balance between treatment that aligns with best clinical evidence and treatment that aligns with the patient's wishes.

Appointment nonattendance

Not keeping scheduled appointments is an important, readily identifiable form of non-adherence to care, and it is a well-recognized predictor of poor health outcomes in chronic diseases.[132] In diabetes and foot disease, appointment nonattendance has been documented as a predictor of repetitive foot ulceration.[133,134] Individual factors such as reduced mobility, lack of prioritizing appointments in a busy workday, and reduced motivation, as well as clinic organizational factors such as proximity, parking access, and timeliness of appointment provision, may contribute to reduced appointment attendance in diabetes.[135] These factors reflect the dynamic and complex nature of health care delivery and imply the need to customize care including in people with foot ulceration in diabetes, to support a patient in their clinic attendance.[136,137] More studies are needed to examine to what degree appointment nonattendance may be linked to foot ulcer development and healing rate in diabetes and related predictive factors; for example, a recent publication from the UK did not find that clinic access based on geographical factors affected foot ulceration development or amputation.[138]

Comorbid mental health problems: depression and stress

Mental illness, in particular depression, is strongly associated with chronic physical diseases including diabetes.[139] Depressive symptoms and reduced quality of life in people are frequent companions to DFU, with depression diagnosed in ~30% of people with DFU.[140,141] Patients with DFU in the presence of neuropathy have an increased risk of depression, which is associated with delayed healing.[141] With severe depression, comes a twofold increase in incidence of DFU and greater mortality risk.[142,143] Anecdotally, at least, healing of DFU in people with comorbid mental illness is harder.

The causal effect of depression on self-care behaviors, healing outcomes, and mortality is not clear, and there is likely a bidirectional relationship between DFU and depression. However, there is a link between depression, non-adherence, and worse healing outcomes for DFU, due to reduced adherence to prescribed treatments[144] potentially explained by the effect of depression on planning capacity, motivation, communication, and adherence to treatment. To become overwhelmed with the frequency of different appointments, conflicting medical advice and complexity of dressing, and antibiotic regimens, pressure offloading and diabetes medication management are common and understandable in the context of having both a physical and a mental health problem. Further to this, there is the propensity of neuropathic patients to treat foot problems as a low in priority in the absence of pain.

Healing may also be impacted by the effect of stress on health, reportedly due to the disruption of the neuroendocrine immune equilibrium.[145] The event of having a foot ulcer and the experience of treatment are plausible stressors given the threat of amputation, restrictions on mobility, and restrictions on activities of daily living.[146] How patients cope with this stress may also have a major influence on the healing process and overall well-being of the patient.

Management of DFU often focuses on physical interventions; however, the integration of specialists' services offered by multidisciplinary teams allows for a more holistic approach. The challenge is to integrate the silos that exist, particularly between the physical health and mental health areas, and remove system barriers and financial disincentives in order to realize more integrated and coordinated

treatment. In Australia, both mental health and diabetes are highlighted as national health priorities; yet, there is limited focus on their comorbidity with the majority of research and guidelines focusing on only the single disease states. Better identification of depression by those treating DFU and primary care and application of a more coordinated approach among HPs in order to achieve the individual patient's goals for both physical and mental wellness are likely to provide better outcomes.

Collaborative care models offer promise, and there is evidence of successful programs integrating physical and mental health management for some noncommunicable diseases.[147] In our local area, chronic care co-coordinators provide an additional layer of support to help patients who are struggling with the complexities of their treatment due to the burden of additional physical or mental problems. Anecdotally, this appeared to help these patients to follow treatment plans. Katon et al[148] represented examples where management of depression has improved depression outcomes for patients without increasing the net cost of treatment. While these programs have not necessarily shown a change in physical health outcomes, there can be little argument that improving the well-being of patients with physical and mental health burden and high mortality risk is a valuable and progressive approach to caring for people with DFU.

A summary of recommendations from these discussions is provided in Table 1.

Table 1 Summary of recommendations to address the issues related to hard-to-heal DFUs

1. Use wound grading and wound fluid analysis to guide treatment
2. Identify and mitigate barriers to and facilitate implementation of EBG
   a. Remove financial disincentives
   b. Provide point-of-care access to information
   c. Employ change management approach
   d. Use data and performance measures
   e. Target resources to EBG
3. Identify and mitigate causes of delayed referral to specialized multidisciplinary teams
   a. Publish and promote referral pathways and available services
4. Improve identification and management of infection
   a. Adopt EBG (as in 2)
   b. Research identification and management of pathogens implicated in infection
5. Improve primary prevention, identification, and management of ischemia
   a. Adopt EBG (as in 2)
6. Improve use of pressure offloading strategies
   a. Adopt EBG (as in 2)
   b. Research pressure offloading to address gap between EBG (clinical trials) and practice
7. Identify and mitigate barriers to patient adherence to treatment
   a. Consider health literacy in patient education
   b. Use techniques that focus on patient behavior and motivators
   c. Use Information Communication Technology in supporting positive behavior
   d. Improve patient access to care
8. Integrate mental health care for clients identified as having mental illness

Abbreviations: DFUs, diabetes-related foot ulcers; EBG, evidence-based practice guidelines.

Conclusion

Research into effective prevention and treatment of diabetic foot complications is important and ongoing work. Already, there are gains in healing outcomes in many areas, but there is still considerable variation in outcomes and ~25% of foot ulcers do not heal readily. Grading systems and data on predicting outcomes are of value in planning and implementing treatment and in communication and performance monitoring. It is clear that the main risk factors for non-healing, such as size, duration, infection, and ischemia, need to be mitigated if we are to continue to improve on the healing outcomes for people with DFUs. To achieve this, focus on achieving better adherence to treatment guidelines and translating evidence into practice is needed and addressing patients' mental health and supporting adherence to treatment will be important. Future prospects for improved care include the coordinated implementation and monitoring of services, collaborative care models integrating management of comorbid mental health, better strategies to manage patient adherence through patient-centered care, methods for early identification of hard-to-heal wounds, and therapies to address factors such as infection, ischemia, inflammation, and pressure.

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Disclosure

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