DIABETICMedicine

DOI: 10.1111/dme.13313

Invited Review

New horizons in the understanding of the causes and management of diabetic foot disease: report from the 2017 Diabetes UK Annual Professional Conference Symposium

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Accepted 22 December 2016

Abstract

Diabetes-related foot disease remains a common problem. For wounds, classic teaching recommends the treatment of any infection, offloading the wound and ensuring a good blood supply, as well as ensuring that the other modifiable risk factors are addressed and optimized. There remain, however, several questions about these and other aspects of the care of diabetes-related foot disease. Some of these questions are addressed in the present report; in particular, the impact of newer technologies in the identification of any organisms present in a wound, as well as the use of novel approaches to treat infections. The use of new remote sensing technology to identify people at risk of developing foot ulceration is also considered, in an attempt to allow early intervention and prevention of foot ulcers. The psychological impact of foot disease is often overlooked, but with an increasing number of publications on the subject, the cause-and-effect role that psychology plays in foot disease, such as ulcers and Charcot neuroarthropathy, is considered. Finally, because of heterogeneity in diabetic foot studies, comparing results is difficult. A recently published document focusing on ensuring a standardized way of reporting foot disease trials is discussed.

Diabet. Med. 34, 305–315 (2017)

Introduction

Incident and prevalent diabetes-related foot disease remains common [1,2]. People with diabetes have a 25% chance of developing a foot ulcer in their lifetime [3], and it has been estimated that ~2.5% of the 415 million adults worldwide who have diabetes also have diabetic foot ulcers [4]. This translates to ~86,000 people in the UK having diabetic foot ulcers at any given time. The combination of neuropathy, with or without peripheral vascular disease, increases the risk of ulceration, and subsequent infection. Around a quarter of all diabetes-related hospital admissions within Europe and the USA stem from diabetic foot infections [5]. As a result, up to 85% of lower extremity amputations are preceded by ulcers, most of which were infected by difficult-to-treat polymicrobial communities. In the UK, diabetes-related foot disease accounts for approximately £1 in every £150 spent in the National Health Service [1].

For many years, it has been standard practice to treat diabetic foot ulcers with a combination of any of the following: appropriate wound dressing; offloading; antibiotics; and improving the blood supply. The best way of offloading the foot is, however, uncertain. In addition, whilst there are widely respected guidelines available on treating infection [6], the choice of antibiotics is also hotly debated, and relies on local sensitivities, the availability of antimicrobial agents and frequently, local microbiologist preferences. Revascularization is dependent on local availability; non-invasive techniques such as angioplasty are often only available in specialist centres, meaning that many units in low-resource environments do not have access to this procedure, let alone a vascular surgeon. Even after effective treatment, relapse probability is ~70% [7], which frequently leads to amputation.

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What's new?

- Foot disease is relatively common in people with diabetes. Newer technologies for the management of wound infections are on the horizon.
- Remote sensing technologies are being developed to allow identification of at-risk tissues at an early stage, allowing timely intervention and prevention of foot wounds.
- The psychological impact of foot disease is often underappreciated but has a potentially significant role in cause and effect on ulcers and Charcot neuroarthopathy.
- Comparing outcomes of published trials in foot disease has been difficult because of the lack of standardization. A framework for reporting standards has recently been published to help overcome this.

With this background, newer aspects of the care and management of the diabetic foot are emerging. Martha Clokie and Alice Greenway discuss the impact of newer technologies on the identification of the organisms present in an ulcer, as well as novel approaches to treating infections. Keith Harding and Nia Jones also discuss newer technologies, in particular, various uses of remote sensing, that may help in the early detection of tissue damage, thus allowing more timely intervention to prevent ulceration developing.

Recent data suggest that only a small proportion of diabetes-related research funding goes into psychosocial studies [8]. This is despite the psychological burden of people with foot disease being larger than in the population without diabetes, or in those with diabetes, but without diabetic foot ulcers. Kavita Vedhara discusses the relationship between the psychological aspects of foot disease, and its relationship to cause or effect of the condition.

Despite the increasing prevalence, diabetes-related foot disease research has received little investment over recent years [9]. As a result, many studies have been of relatively poor quality with a great deal of heterogeneity, even when addressing the same issues, making direct comparison between studies difficult. Fran Game discusses her recent commentary, which outlines a set of reporting standards for foot-related research [10].

New horizons in understanding the microbiology of foot disease

Diabetic foot ulcers need to be treated with effective antimicrobials. As with many chronic diseases, persistent antibiotic treatment often fails because wounds are colonized by antibiotic-resistant bacteria, or because resistance *in situ* is selected for during treatment. Identifying the causative agents and selecting effective antimicrobials would improve patient treatment. The purpose of this section is to highlight: (1) the composition of foot ulcer polymicrobial bacterial communities; (2) current diabetic foot ulcer diagnosis; (3) culture-independent methods to characterize infection; and (4) novel antimicrobials that could be effectively exploited.

Microbiology and current diagnosis of diabetic foot ulcers

Effective diabetic foot infection treatment requires an understanding of the formation and composition of the diabetic foot ulcer microbiota (bacteria associated with infection). Our knowledge of this is largely based on culture-based studies that have revealed that bacterial colonization evolves from precursor bacteria into complex polymicrobial communities. Ulcer duration and depth are positively correlated with microbial diversity and are associated with specific pathogens [11]. Figure 1 shows how species number and composition change with disease state and severity [12]. In brief, foot ulcers are associated with a complex polymicrobial community, in which *Staphylcoccus aureus* is a dominant early colonizer of wounds, together with *Enterococcus* spp., *Corynebacterium* spp. and coagulase-negative *staphylococci*. These species are then followed in succession by *Pseudomonas* and various members of the Enterobacteriacea, followed by a set of strict anaerobes during severe infection.

Sampling and diagnosis of bacteria

The diagnosis of most diabetic foot ulcers is based on the presence of clinical signs and symptoms [13]. Most

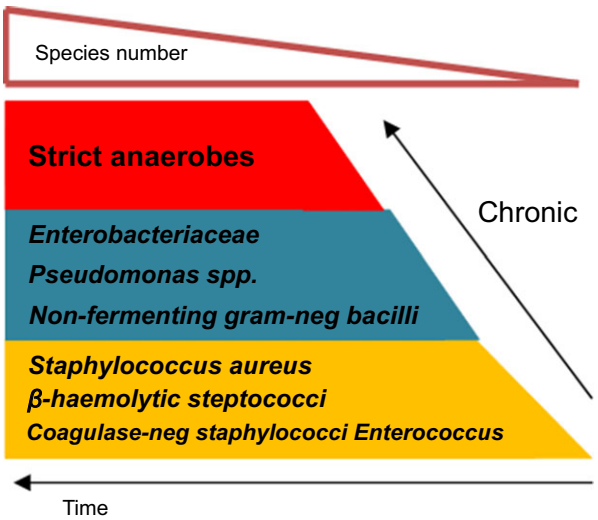

FIGURE 1 Schematic diagram showing how the microbiology of the diabetic foot ulcer develops over time. The colonizing bacterial species are dependent on the chronicity of the ulcer and the age of wound. Species number increases resulting in the evolution from a monomicrobial to a polymicrobial community. Adapted from Gardner *et al.* [11].

frequently, tissue biopsy and ulcer fluid aspirates are sent for culture-based identification [14]. Less invasive swabbing from the base of the ulcer is also used to detect surface-associated bacteria, but does not detect bacteria associated with deeper structures [15].

Insights from 16S 'bar coding'

The use of non-culture-based molecular microbiological techniques to characterize foot infection microbiota could significantly enhance our understanding of the composition and abundance of the infection and guide effective antimicrobial selection. These techniques have the advantage over culture-based approaches because they are not dependent on the culturability of the bacteria. This is particularly pertinent for diabetic foot ulcers, which are typically colonized by anaerobes that are notoriously difficult to isolate. The most commonly used culture-independent approach is to extract total DNA from the whole bacterial community and use universal polymerase chain reaction primers to amplify and sequence the 16S RNA gene. After further analysis ('deep sequencing'), the sequence data are then compared with reference databases to establish the type and diversity of species [16]. Because all bacteria encode ribosomes, the use of 16S ribosomal RNA as a 'bar code' has revolutionized our ability to describe bacterial communities and is now well established in environmental and medical microbiology, and recently provided fascinating insights into the bacteria associated with diabetic foot ulcers [17].

16S ribosomal RNA analysis has shown that chronic infections possess a far wider array of micro-organisms than was identified from standard culture-based approaches [11]. This raises concerns about the use of culture as a diagnostic tool in a clinical setting. Even though 16S sequencing is limited to the detection of bacteria; the approach could be modified to unravel the contributions from protozoa, virus and fungi.

Although 16S sequencing gives a powerful resolution on the components and structure of the diabetic foot ulcers' microbiota, it does not provide mechanistic information on bacterial physiology or other useful traits such as antibiotic resistance profiling. This requires full metagenomic analysis techniques from whole-genome sequencing or potentially transcriptome profiling to see which genes are expressed and when. In addition, antibiotic resistance targeting could also be carried out by amplifying known genes that encode for the 'resistome' (all known genes that encode for antibiotic resistance).

Problems associated with antibiotic resistance and antibiotic penetration

Multi-drug resistant bacteria ('superbugs') are becoming a major health concern; treatment can be difficult, expensive and sometimes impossible. The exponential rise in antibiotic-resistant bacteria has negatively impacted diabetic foot ulcer treatment strategy. One of the key factors that promotes antibiotic resistance is wound chronicity [18]. Unfortunately, most patients undergo extensive drawn out wound care treatment, with intermittent periods of antibiotic treatment, aimed at the putative causative agent. These essentially prophylactic treatments can lead to infection within previously unaffected ulcers. Furthermore, without proper diagnosis of the infection with deep tissue swabs, selection of the wrong antibiotic can lead to chronic 'superbug' infections [19].

Bacteriophages

One of the key problems associated with diabetes is peripheral vascular disease and wound ischaemia [20]. Poor antibiotic penetration into tissues because of a lack of blood flow is another reason why antibiotics are so unsuccessful. Both the lack of effective penetration of antibiotics, and problems with antibiotic resistance mean that novel approaches to treating infection are needed. One promising alternative to standard antibiotics is the use of bacteriophages, or phages, which are viruses that target and kill bacteria.

The use of bacteriophages is justifiable when one considers that, as with all bacterial systems, they are already a natural component of the diabetic foot ulcer microbiota; however, by altering the balance and composition of viruses present they could be used to manipulate the bacterial part of the microbiota and remove conditions that facilitate disease progression. Unlike conventional antibiotics, these phages have several traits that can overcome difficulties associated with resistance and penetration, and thus could be useful in removing or reducing the bacteria associated with infection.

Bacteriophages and foot ulcers

Phages have a long history of use in Georgia, Russia, Poland and France but fell out of favour after the discovery of antibiotics. Their use as a therapy, however, is undergoing a resurgence of interest in the Western world because of: (1) their exquisite specificity; (2) their ability to self-replicate and therefore 'auto dose' *in situ* to clear infection; and (3) their ability to penetrate biofilms. They can be used as an alternative, or an adjunct to conventional antibiotics. Phages have access to two main life cycles, one where they integrate and reside within bacterial cells and a second where they infect and kill the bacteria. It is those phages that access this secondary lytic cycle that are suitable for therapeutic use. In contrast to when bacteriophages were first isolated, we now have a vast array of tools such as genome sequencing and advance proteomics, and a much better understanding of bacteria–phage relationships, that can be used to inform their successful development.

Phages that target *S. aureus* and *Pseudomonas* spp.

Because complex polymicrobial communities are associated with foot ulcers, conceptually a phage mixture could be developed that targets and removes each bacterial pathogen. Alternatively, a mixture could be developed that removes one or a few key bacterial members to prevent further bacterial colonization, and thus 'reset' the microbial succession associated with disease. Either approach relies on a better understanding of the foot ulcer microbiota, which could come from 16S profiling described above, or personalized phage therapy (testing diabetic foot infection samples for susceptibility to different phages and selection of the most effective). An obvious place to start in terms of removing bacteria is by using *S. aureus* phages because this pathogen is the dominant early colonizer (Fig. 1) [11]. Treatment of *S. aureus* could prevent colonization and thus chronic infection. A beneficial property of anti-*Staphylococcus* phages is their relatively broad host range, which means that only two to three phages are needed to target and kill the most representative *S. aureus* strains. By contrast, in Gram-negative infections, relatively high phage numbers (>10) are often required to target the causative agent [21].

Current usage, safety and efficacy trials of *S. aureus* and *Pseudomonas* spp. phages

In Georgia and Russia, these phage products are available over the counter at pharmacies [22]. Methicillin-resistant *S. aureus* (MRSA) strains do not affect phage efficacy, and these strains are targeted by phage cocktails such as 'Pyophage' which contains phages active against *S. aureus, Pseudomonas* spp. and *Streptococcus spp*. [23]. This Pyophage formula and other phage mixtures are commonly used to treat diabetic foot ulcers in Georgia, but in the Western world phage therapy is still awaiting general acceptance. To ensure that phages are used effectively and sustainably in the UK, investigation of well-characterized bacteriophage sets with optimum host ranges and physiological properties is needed, in the context of current practices and regulation. This research has not received adequate funding and therefore has largely not been performed. There needs to be a closer connection between microbiologists and clinical practitioners to develop products and ultimately collect clinical trial data.

Further evidence of efficacy can be seen in Poland where *S. aureus* and *Pseudomonas* phages were used over many years to treat wound infections. One study reported the treatment of 550 people with phages between 1981 and 1986, 518 of whom had failed to respond to antibiotics. The phages targeted various bacteria including *S. aureus* and *Pseudomonas aeruginosa*. Positive results were obtained in 92.4% of cases, and 6.9% demonstrated transient improvement [24].

In the USA, a phase I safety trial on phages suitable for wound infection was conducted in the Wound Care Centre in Lubbock, Texas [25]. The trial used a fully sequenced well-defined phage cocktail (WPP-201) imported from the Eliava institute in Georgia, containing phages against *S. aureus*, *P. aeruginosa* and *Escherishia coli*. In that trial, 39 people with chronic leg ulcerations were successfully treated without any observed side effects.

Currently, smaller phase I safely trials have shown success, and phase II efficacy trials appear to show promise. It is hoped that these will set the groundwork for further large-scale work to assess the efficacy of *Staphylococcus* phages to treat diabetic foot ulcers; however, to test *Staphylococcus* phages in larger-scale clinical trials and determine the impact of adding phages that target the other pathogens would require some fundamental research because many pathogens involved in foot infections do not have well characterized phages. There also needs to be a greater synergy between microbiologists and foot specialists.

Remote sensing in the assessment of diabetic foot disease

It is generally accepted that early diagnosis of risk factors associated with diabetic foot ulcers is a prerequisite for maintenance of lower limb health [26]. In comparison to current clinical assessment methods, the evolution of innovative technologies provides new opportunities for remotely detecting and monitoring diabetic neuropathy and angiopathy earlier in the disease progression. The following section explores the role of remote sensing in the assessment and monitoring of diabetic foot disease.

International best practice guidelines recommend that people with diabetes are assessed on an annual basis for peripheral neuropathy and peripheral arterial disease using a range of simple screening tests [27]. However, a recent systematic review reported that the quality of evidence demonstrating the efficacy of this intervention was relatively low [28]. This was attributed to a paucity of high-quality randomized controlled trials involving the screening, prevention and treatment of diabetic foot ulcers (discussed below).

Measuring skin temperature is considered one of the most reliable indicators of cutaneous perfusion, and evidence suggests that infrared thermographic monitoring may be an effective method of predicting tissue viability complications in the diabetic foot [28,29]. Dermal thermography is currently used in routine clinical practice to detect temperature differences between the ipsilateral and contralateral foot in Charcot neuroarthropathy, but emerging evidence suggests that this technology could be adopted to support self-monitoring of diabetic foot disease [28].

There is a marked increase in temperature associated with tissue stress and sub-clinical inflammation, which may develop 7 days before the onset of foot ulceration [30,31]. This suggests that performing daily foot temperatures could prevent lower limb-threatening foot ulceration in this high-risk population. One of the documented drawbacks with the use of these self-monitoring devices (TempTouch®,

TempStat™ and Thermoscale®), however, is the lack of standardized reference criteria. Partly, this is because foot temperatures are known to vary in people with diabetes because of the adverse effects of microangiopathy, levels of physical activity and changes in ambient temperature. Despite acknowledging these intrinsic and extrinsic limitations, the literature recommends using the corresponding area on the contralateral foot as a reference point [30–32], and a temperature difference > 2.2°C being regarded as a precursor of tissue stress and sub-clinical inflammation [32].

Hyperspectral imaging is currently a laboratory-based assessment method used to determine oxygen saturation in human tissue and to detect early microcirculatory changes in the diabetic foot [33,34]. Yudovsky *et al.* [35] investigated the validity of hyperspectral tissue oximetry imaging in predicting foot ulcer risk in people with Type 1 and Type 2 diabetes. They established that hyperspectral tissue oximetry had the ability to detect (with a sensitivity of 95% and specificity of 80%) ischaemic changes and inflammatory complications, on average, 58 days prior to cutaneous pre-ulcerative changes becoming clinically evident. Hyperspectral imaging technology has also been evaluated as a tool for predicting the healing potential of a foot ulcer with a reported sensitivity and specificity of 80% and 74%, respectively [36]. This technology has the potential for miniaturization, as do many other current laboratory-based devices and, as such, develop greater utility in the patients' own environment for monitoring and detection of foot complications.

Skin perfusion pressure, in contrast to hyperspectral imaging, is a portable tool used in routine clinical practice to diagnose small vessel disease in high-risk populations and assess the healing potential of chronic wounds in the lower limb. Skin perfusion pressure is not affected by diffuse vascular calcification and was superior in the diagnosis of peripheral arterial disease in people with diabetes when compared with ankle and toe brachial pressure indices and transcutaneous partial pressure of oxygen ($TcPO_2$) [37,38]. Hyperspectral tissue oximetry and skin perfusion pressure (Sensilase PAD-IQ®) may therefore provide opportunities for earlier detection of peripheral arterial disease in people with diabetes, but the one major drawback is that the application of these technologies is driven by the clinician and not the person with diabetes.

The presence and severity of infection is regarded as the single greatest threat to lower limb survival. In routine clinical practice, features of infection are established after visual inspection and microbiological sampling, but these methods do not accurately represent the overall bacterial load within the wound bed [6]. MolecuLight™ is a novel handheld fluorescence imaging device that identifies bacterial presence and distribution in and around the wound (Fig. 2). This remote sensing device provides instant and precise detection of potentially harmful bacteria to guide clinicians at the point of care. A recent pilot study reported that this device can be used to guide wound treatment and monitor treatment response by tracking wound size and changes in bacterial bioburden within the wound bed [39]. Further high-quality studies are needed to compare the clinical effectiveness of systemic therapy vs topical treatments to eliminate harmful bacteria, but the introduction of autofluorescence imaging in individuals with wounds may have the potential to provide novel solutions in the ever-increasing battle against antibiotic resistance and support improved antibiotic stewardship.

FIGURE 2 MolecuLight™ hand-held fluorescence imaging device.

Wearable technology is another evolving field in the monitoring and treatment of diabetic foot disease because sensory and motor complications associated with peripheral neuropathy often result in altered proprioception and ataxic gait patterns. Human exoskeleton robots are in early development, but some of these devices have remote body sensors which consist of shoe-embedded force sensors and walking canes to aid with gait difficulties and alert people to the risk of falls when standing from a sitting position [40]. One simple and inexpensive method of adopting wearable technology into practice would be to encourage patients to wear pedometers to monitor their physical activity levels and visually inspect their feet daily for evidence of tissue trauma. This intervention would enable the person to recognize when they need to limit their activity levels and seek advice from their podiatrist. PulseFlowDF™ is an offloading device which has taken the concept of monitoring physical activity to another level (Fig. 3). It has built-in monitoring software that enables the clinician to capture data on the use of the offloading device. Previous work has suggested that people with ulceration may be more active than they admit to their treating clinician [41].

The opportunities to expand on the role of remote sensing technology in patient-centred care are limitless and this technology can play an important role in the assessment of diabetic foot disease, despite the limitations and paucity of empirical evidence. Dermal thermography and hyperspectral imaging have the capacity to diagnose tissue viability complications associated with pressure injury and ischaemia earlier in the natural course of the disease, whilst autofluorescence imaging may have the potential to change the landscape of standard care in the treatment of diabetic foot infections.

FIGURE 3 PulseFlowDF™ offloading device.

The transition of incorporating remote sensing technology for self-monitoring diabetic foot disease in routine clinical practice may be challenging for both people with diabetes and clinicians. With the ever-increasing socio-economic burden of foot complications on global healthcare resources we need to find novel solutions that encourage this patient population to engage in their care; a theme that is continued in the next section.

Psychological and behavioural aspects of foot disease and its management: cause vs consequence

There can be little doubt that diabetic foot disease has psychological and behavioural consequences. In terms of the former, data suggest that over a third of individuals are anxious or depressed [42]. The rates of psychological morbidity may be even higher in people with Charcot foot [43]. Health-related quality of life is significantly impaired in people with both healed and unhealed ulcers, compared with the general population and individuals with diabetes but no history of ulceration [44], and, perhaps not surprisingly, significant deteriorations in quality of life are evident in those with non-healing ulcers [45].

The behavioural consequences of foot disease are far-reaching. For example, the International Working Group on the Diabetic Foot made a number of recommendations in 2016 on footwear and offloading interventions aimed at preventing ulceration or promoting healing [46]. With the exception of surgical recommendations, all of the suggested approaches require the individual to engage with treatments they may be unable or unwilling to tolerate. Furthermore, it is of interest that nine out of 13 recommendations were based on low-quality evidence, with only one (offloading with a non-removable device) being derived from high-quality evidence. This juxtaposition of potentially unwelcome behavioural demands, advocated on the basis of a weak evidence base, leads to people reporting low knowledge of, and exhibiting poor adherence with, foot care behaviours [47,48].

The emotional and behavioural consequences of diabetic foot disease are evidently far-reaching; however, of potentially greater interest is evidence suggesting that these emotional and behavioural sequelae may influence clinical outcomes, i.e. have a causal role.

In terms of psychological determinants, several studies have explored the relationship between mood and related psychological constructs with ulcer risk, healing, amputation and mortality. For example, large cohort studies suggest that depression is associated with a two- to threefold increase in incident foot ulcers [49,50]. By contrast, the evidence regarding depression and recurrence is less clear, with Gonzalez *et al.* [51] reporting that depression predicts first ulcers, but not their recurrence, while Monami *et al.* [52] reported that ulcer recurrence over 12 months was significantly associated with depression. The evidence pertaining to ulcer healing appears to be equivocal. For example, depression predicted healing in the study by Monami *et al.* [52] but, in a more recent study, healing was predicted by coping style not depression, although depression was significantly associated with healing rate (as measured by change in ulcer area), accounting for >30% of the variance in this outcome [53]. Finally, a number of studies have examined the relationship between indices of psychological functioning and mortality. Depression, health-related quality of life and patient beliefs regarding their ulcers, all predict mortality [54–56].

People with diabetes are encouraged to engage in a variety of different behaviours to reduce their risk of ulceration and promote healing, although the underlying evidence for these behaviours is unclear. One behaviour often shrouded in uncertainty is physical activity. This is largely because its merits or otherwise vary according to the nature of the activity and the ulcer status. For example, several studies have shown that, in those at risk of ulceration but who are ulcer-free, moderate and regular physical activity may be protective [57,58]. In contrast, during active ulceration, weight-bearing activity can be detrimental and consequently minimal or non-weight bearing activity is recommended [59]. Other common behaviours include the use of prescribed footwear and monitoring foot temperature. The evidence base for these behaviours in primary prevention is unclear because, as a recent review has suggested (discussed in the next section), only a few low-quality studies in this area have been published [28]. In contrast, trial evidence provides stronger support for these behaviours influencing ulcer recurrence [28], but perhaps of greater import is the observation by Bus *et al.* [60] that, for behaviours with a stronger evidence base, it is clear that adherence is critical. They note that in all trials that have examined adherence, non-adherent individuals have significantly poorer outcomes

and that the size of the 'adherence effect' is large, ranging from 58 to 98%.

It is clear that more trial evidence is needed to address the areas of uncertainty, such as whether the effects of psychological and behavioural determinants are independent [51] and whether and why effects might vary between related clinical outcomes [53]. Notwithstanding these issues, it is clear that psychological and behavioural factors influence ulcer outcomes. Paradoxically, however, patient-centred interventions in the diabetic foot focus not on psychological and behavioural factors, but overwhelmingly on education. This is despite the fact that successive systematic reviews have not found that education improves clinical outcomes [61–65]. Even the small number of complex interventions that have been trialled to date ($n = 6$) have neglected psychological and behavioural factors. Instead, they too have focused predominantly on patient and/or healthcare professional education, combined with changes in healthcare structure or organization and, again, have failed to show effects on clinical outcomes [66].

The prevention and management of diabetic foot ulcers is a complex problem that requires complex solutions, but it is time, as recommended by the National Institute for Health and Care Excellence (NICE), for these complex solutions to target psychological and behavioural factors with a view to achieving effective and cost-effective improvements in clinical outcomes [67].

Diabetic foot disease: assessing the strengths and weaknesses of reported studies

High-quality evidence to support clinicians in providing best practice treatments for both the prevention and management of foot disease is sadly lacking. Repeated systematic reviews on the subject by the International Working Group of the Diabetic Foot have drawn attention to the paucity of quality research and the urgent need for more high-quality studies in this field [28,68–72].

There is no shortage of guidance available on the general principles of trial design and conduct (e.g. a CONSORT statement for randomized trials [73], STROBE for epidemiological studies [74], and PRISMA for systemic reviews/meta-analyses [75]). Systems already also exist for scoring studies of different design [76]; for example, the GRADE system [77].

Hitherto, it may have been considered unnecessary to produce any further guidance on the design and conduct of studies specifically to examine aspects of diabetic foot disease, but it is now evident that the complexity of the clinical area, including the number of diverse and overlapping processes involved in the development and presentation of foot ulcers, as well as their effect on healing, requires a more standardized approach. For example, there are a number of bedside tests available to clinicians to describe vascular disease [69], but as the majority of people presenting with diabetes and foot disease will also have peripheral neuropathy, these tests may be adversely affected, and the clinician misled as to the scale of vascular disease present unless all the patient clinical details are described. Additionally, the failure to address neuropathy by providing suitable offloading during a study of diabetes and vascular disease, particularly one which involves wound healing, could also undermine any conclusions drawn.

Recently a subgroup of the International Working Group of the Diabetic Foot published guidelines on the standards of reporting of studies on the diabetic foot and lays out some fundamental items to be considered when either setting up or assessing a study in either the prevention or management of the diabetic foot disease [10]. A summary of those recommendations is shown in Table 1.

Whilst the details will vary between studies of ulcer prevention and studies of ulcer management and between different aspects of wound healing and pathogenesis, there are a number of 'core' details which should be included in all studies. These include details of the populations (of the people, the limb *and* the foot), as well as the interventions and the outcomes. For example, studies focusing on prevention must give details of the baseline risk of the development of foot disease of the population (at least in terms of neuropathy, arterial disease and deformity) and the specific tests used to assess these.

Any intervention must be defined in sufficient detail to allow it to be reproduced in future studies, including who delivered the intervention and where it was delivered and, in comparative studies, usual care must be carefully described.

In a study of ulcer healing, baseline characteristics of both the limb and the ulcer must be defined with a description of tests used to define them. Features of ulcers that are known to affect healing outcome (e.g. depth, area, site, whether single or multiple ulcers and duration of the index ulcer) should also be defined. Ulcers are frequently described according to one of the many classification systems published [78]. Care must be taken, however, not to use these systems outside the purpose for which they are designed. For example the Megitt–Wagner system contains too little detail to establish the necessary baseline features of a population of ulcers [79], whilst the University of Texas system does not include neuropathy [80].

The primary outcome of the study must be clearly stated. For example, if healing is the main outcome, the definition of healing, who assessed it, and whether the assessment was blind to the intervention needs to be stated. Often complete epithelialization without drainage is used as a definition, with or without maintenance of healing over a stated period of time. However, some studies, particularly those on a surgical intervention, may include wounds closed primarily surgically. If so, this needs to be stated. Obviously, in an open-label study, surgical closure may introduce a source of

Table 1 Core details that should be reported for an intervention study of diabetic foot disease

Population	Intervention	Outcome(s)
Relating to the person • Age, gender, ethnicity • Diabetes type and duration • Comorbidities (renal failure, heart failure, impaired vision)	For each intervention sufficient information must be provided to define: • its nature (including source); • route, frequency and duration of delivery; • delivery by whom: professional, non-professional carer, self; • place of delivery: domiciliary, community clinic or surgery, hospital, specialist centre.	Relating to the person • Survival • Being ulcer-free and/or amputation-free at a fixed time after presentation • Ulcer-free survival days • Adverse events and/or adverse device effects • Health-related quality of life
Relating to the limb • PAD: minimal assessment by palpation of pulses and ABPI • Neuropathy: minimal assessment by loss of sensation (e.g. 10-g monofilament or vibration perception) • Foot deformity • History of previous foot ulceration and amputation		Relating to the ulcer and limb Direct • Ulcer healing (defined); time to healing • Healing after local surgery, including operative debridement • Failure to heal by a fixed time; ulcer persistent • Amputation (with exact level defined)Possible surrogates
Relating to the ulcer • Number of active ulcers • Site of index ulcer • Duration of index ulcer • Type or classification of index ulcer (where appropriate) • Area, depth • Presence or absence of infection		• Change in ulcer area by a given period of time • Change in ulcer appearance, biochemistry, histology or other laboratory measure of wound bed status

ABPI, ankle brachial pressure index; PAD, peripheral arterial disease.
Adapted from Jeffcoate *et al.* [10].

bias if the decision to surgically close a wound is carried out in the knowledge of the intervention.

Of particular importance in a controlled trial is the description of usual care, which must include all aspects according to best practice guidance, including the management of infection, the provision of pressure relieving offloading devices and revascularization where appropriate [81].

As discussed earlier, infection is a particular problem when designing and evaluating clinical trials, particularly with the advent of new methods of evaluating infection and new novel treatments. One challenge when a study about ulcer infection is being designed, is to decide whether the eradication of infection or ulcer healing is the correct outcome measure. In most instances this should be the eradication of infection, as ulcer healing may be influenced by many different pathological processes. This in itself brings challenges, however, as deciding when infection has been eradicated is not straightforward. This may be defined as the disappearance of, or sufficient improvement in, signs and symptoms related to the infection such that it does not require further treatment, a clinical definition that necessarily has a degree of subjectivity. At present there are no microbiological tests to assess whether an infection has been eradicated, despite the more recent description of newer techniques including molecular microbiological testing [82].

Finally, an objective measure of the quality of published papers is required. The systematic reviews performed by the International Working Group of the Diabetic Foot have, as with other systematic reviews, applied standard grading to the papers they have evaluated. Nevertheless some papers score highly. This happens particularly when there is a lack of clarity. This means that experts in the field have inadequate clinical details upon which to base their understanding about whether an intervention could be useful above and beyond usual care. For this reason, a 21-point checklist has been defined which, it is hoped, will allow

investigators, readers and journal editors alike to assess the quality of work in this area [10]. The higher the score achieved, the greater the chance that the reported study is free from bias and is relevant to clinical practice.

Funding sources

None.

Competing interests

None declared.

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