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Review

Evidence-based management of diabetic foot problems☆

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ABSTRACT

At present we are experiencing a rapid rise in the global prevalence of diabetes and unfortunately, this is associated with an increase in many of the late complications of diabetes, particularly diabetic foot ulcers which have a significant impairment on quality of life as well as being associated with increased morbidity and mortality. The potential for preventing first and recurrent foot ulcers is reviewed particularly related to recent developments in smart technology and remote monitoring of foot temperature and pressures under high-risk feet. Recent trials on both these areas are reviewed and show promise for the future. Pharmacological approaches to reduce the incidence of foot ulcers are then considered and the small section on the potential role of fibrates which certainly demands further investigation. With respect to treatment of complex foot ulcers, a number of recent evidence-based therapies are described including sucrose octasulfate dressings, negative pressure wound therapy and topical wound oxygen therapy. Lastly, appropriate care and management of infected DFUs is considered particularly focusing on the area of osteomyelitis. A number of excellent recent Guidelines and related reviews are then listed to help readers further understand this rapidly developing and complex area.

1. Introduction

There has been much progress in a number of areas of diabetic foot care over the last 25 years including, firstly, in the prevention of first and recurrent ulcers, not only pharmacological approaches but also appropriate education, the team approach and now with smart technology in the prevention of recurrent ulcers using temperature and/or pressure sensing of the feet.

Secondly, in terms of the treatment of diabetic foot ulcers (DFUs), some of the strongest evidence is for the offloading of plantar neuropathic foot ulcers and more recently, evidence-based therapies for the management of complex hard to heal DFUs have been reported and all these areas will be reviewed in this paper. Lastly, useful comprehensive reviews and guidelines will be briefly presented with appropriate references to the full text which will be helpful for additional reading.

2. Prevention

2.1. Patient education

Despite the widely held belief that appropriate patient education in preventative foot care prevents both first and recurrent diabetic foot ulcers from occurring, there are no randomised controlled trials (RCTs) to confirm that this is actually the case [1,2]. A systematic review looking at primary prevention was published from the Netherlands in 2012 [3] and an RCT for the prevention of recurrent ulcers had similarly reported negative results in 2008 [4]. With respect to the recurrence of DFUs, which may be as high as 50 % per annum [2], it seems likely that those with a foot ulcer history have predominant physical abnormalities such that education alone in self-foot care is insufficient to prevent recurrent ulceration. However, education as part of a team approach to diabetic foot care has been shown to be useful in a number of studies, one of the earliest examples being from Ipswich, UK, which showed in a 10-year observational study, that the implementation of a team approach which included not only regular patient education, but also regular podiatry, regular foot checks and ability to contact the

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healthcare professionals, resulted in a highly significant fall in foot ulceration and amputations. Expressed as incidence per 10,000 people with diabetes, total amputations fell 70 % over this 10-year period [5].

2.2. Remote monitoring of feet using smart technology

One of the impacts of the Covid-19 pandemic has been an explosion in the use of remote monitoring in the care of the diabetic foot [6]. However, many years before that, Lavery and colleagues in the USA showed that adding a patient intervention, that is self-monitoring foot temperatures, could help to prevent recurrent ulcers. In a small RCT, they confirmed that those patients with a history of neuropathic ulcers who monitored their foot temperatures on a daily basis, and if one foot was consistently higher in temperature than the other for two or three readings, they were advised to rest and seek help from their podiatrist. This intervention led to a reduction from 30 % recurrent ulcers in the control groups to only 8 % in those who were self-temperature monitoring [7]. Moving forward to the era of smart technology, in one of the first studies, Frykberg et al studied patients who were remotely (at home) monitoring plantar temperatures although results were not given to the subjects, but rather monitored centrally. This was a preliminary observational study and a large number of these high-risk patients with a long history of recurrent ulceration developed ulcers. It was confirmed that a temperature differential of 2.2 °C between the feet using this remote home monitoring was a very strong predictor of ulcer development [8]. Ongoing RCTs will soon report as to whether such interventions may help in the reduction of recurrent neuropathic foot ulcers. In parallel, other groups have been developing and assessing intelligent pressure-sensing insole systems and the last RCT reported in 2019 showed that those with active feedback such that if the pressure was too high during walking, there was a feedback to a smart wristwatch, which led to the subjects either resting or altering their gait. This simple intervention led to a highly significant reduction of recurrent ulceration of about 70 % [9]. At the time of writing, there are many ongoing RCTs using remote temperature and pressure sensing with more advanced techniques which will potentially help in the reduction of recurrent DFUs.

2.3. Pharmacological

It has always been believed that improving glycaemic control to near normal levels from or soon after the diagnosis of diabetes might reduce the late complications. As noted in the Introduction, the longstanding type 1 diabetes trials from the USA, that is the DCCT/EDIC studies, have produced pivotal information confirming that indeed early glycaemic control does decrease the long-term diabetic foot ulcer risk [10]. As many patients with type 2 diabetes present late in the natural history of the condition and may even have late complications at diagnosis, the importance of glycaemic control from diagnosis or early on in the known history of the disease is less clear with respect to its influence on foot ulcer development.

Cardiovascular risk factors, including smoking, elevated cholesterol and lipids, hypertension and ischaemic heart disease, have been shown to be predictors of diabetic neuropathy and peripheral arterial disease [1,2]. The potential impact of these risk factors and their risk management was reported in patients with a history of diabetic foot ulcers and this strategy of aggressive cardiovascular risk management not only in those with a history of cardiovascular events, should be introduced in diabetic foot clinics with all those with a history of foot ulcers as this may improve survival in this patient group who are known to have a high mortality risk [1,11].

2.4. Might the fibrates have a role?

For some time, there has been a suggestion that the fibrate group of drugs, PPAR-alpha activators (peroxisome proliferator-activated receptor alpha) might have a place in reducing the incidence of neuroischaemic or ischaemic foot ulceration and/or amputation. This group of drugs has mainly been used in the treatment of hyperlipidaemia as they help reduce high triglyceride levels and might possibly also raise HDL. The large FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes), in a secondary analysis, showed that this drug which is a weak PPAR-alpha activator, reduced the incidence of major amputations [12]. A very recent study of Pemafibrate, the PROMINENT study (Pemafibrate to Reduce cardiovascular OutcoMes by reducINing trIglycErides in participaNTs with diabetes) showed that this selective PPAR-alpha modulator only had neutral effects on myocardial infarction, stroke and other large vessel outcomes including peripheral arterial disease [13]. However, in an exploratory analysis of this recent trial, Pemafibrate was shown to reduce diabetes lower extremity amputations and gangrene by 37 % [14]. As a result of these results, two RCTs are anticipated to further explore the hypothesis that these fibrate therapies might accelerate healing of existing diabetic foot ulcers and whether they can prevent recurrent ulceration in those with a history of ulcers [14]. Important data will be produced should these trials actually occur in future years.

3. Treatment of complex diabetic foot wounds

At the beginning of the 21st Century, there were few evidence-based therapies available to treat the hard-to-heal diabetic foot ulcers. Recommendation of most treatments was based upon either case reports, case series or expert opinion. A good example of this is the use of wound dressings in that there is little evidence to support the use of any particular dressing in treating DFUs. This is because until recently, there have been very few if any well-designed RCTs in this area and indeed, of other topical treatments. In an editorial published in 2018, Edmonds [15] reported on a renaissance in diabetic foot care following the publications of several well-designed RCTs. Prior to this, a review by Jeffcoate et al had identified aspects of trial design that should be included in studies in order to improve quality [16]. In a subsequent paper Jeffcoate et al outlined the challenges and opportunities in the prevention and management of diabetic foot ulcers [17]. These reviews emphasise the importance of taking into account confounding variables in any studies in putative new therapies for DFUs: the most important of which is probably offloading the plantar foot ulcer. The only properly designed RCTs prior to these reviews/guidelines being published was indeed in the area of offloading.

3.1. Offloading

It was the late Dr Paul Brand who worked in leprosy and later in diabetes in South India who emphasised how people with peripheral nerve damage due to either conditions, had “lost the gift of pain” and therefore would happily walk on an active plantar ulcer without any discomfort whatsoever because they had no feedback to alert them to do otherwise [18]. One of the earliest well-designed RCTs that confirmed the efficacy of irremovable below-knee casts in improving healing rates of plantar diabetic foot ulcers was published by Armstrong et al. [19]. In this study, patients were randomised to a below-knee irremovable cast, a removable cast Walker or a half shoe. The proportion of patients healing within 12 weeks was 90 % in the below-knee cast vs 65 % in the removable cast Walker and 58 % in the half shoe. As the removable cast Walker and below-knee cast offload equally well in the gait laboratory, further trials were performed to see if a removable cast Walker rendered irremovable (by some scotchcast wrapped around the top of the removable cast Walker) would have equal efficacy to the irremovable below-knee cast. Unsurprisingly, the results showed that both had equal healing rates in an RCT [20]. Thus, if worn, the removable cast Walker is a very good method of offloading neuropathic foot ulcers.

4. Evidence-based topical therapies

As stated above, well designed RCTs from 2018 onwards have shown that a number of therapies speed up the healing of hard-to-heal ulcers, normally defined as ulcers that fail to heal after six to eight weeks of standard of care. Selective studies will be described, and for a full review of efficacious therapies, the reader is referred to the 2022 American Diabetes Association (ADA) Compendium on this very topic [21].

4.1. Sucrose octasulfate-impregnated dressings

The expression of matrix metallo proteinases (MMPs) is exaggerated in chronic wounds resulting in tissue breakdown and delayed healing. The sucrose octasulfate dressing has been shown to inhibit MMP's action and possibly therefore impact on wound healing rates. A multi-national double-blinded RCT reported that healing was more rapid using these dressings compared to standard of care [22]. The design of this study followed those recommended by the International Guidelines [16]. This well-designed and positive trial [22] was approved by the National Institute of Clinical Excellence in the UK and subsequently by many other countries which have approved this dressing to treat hard-to-heal predominantly neuropathic and neuroischaemic diabetic foot ulcers. This particular product however, is not available in the United States at present.

4.2. Other topical treatments

The topical fibrin and leucocyte platelet patch (previously known as "LeucoPatch" or "3C-Patch") comprises a disc of autologous leucocytes, platelets and fibrin that is made by bedside centrifugation of patients' blood which can then be applied to the DFU. This too was assessed in a well-designed large multi-national outcome blinded RCT [23]. After 20 weeks of randomisation either to the active (patch) or standard of care, significantly more patients had complete ulcer healing in the active group. This simple bedside treatment can be used with the minimal amount of equipment and is widely available.

There are a number of other topical therapies that are of interest and more recent clinical trials have been promising although earlier clinical trials have not been well designed. These include a number of placenta-derived products which when applied, provide mechanisms for wound healing. Although these recent trials are indeed encouraging [21], cost-effectiveness in many healthcare settings remains to be confirmed and are mainly used in western countries.

4.3. Negative pressure wound therapy (NPWT)

NPWT has been used for many years in the treatment of post-surgical wounds but also complex hard-to-heal DFU wounds. Although this is a misnomer, as pressure is a positive quantity, the abbreviation NPWT is still widely used. It is thought to accelerate healing through reduction of oedema, removal of exudate, increasing perfusion and the formation of granulation tissue [24]. Several different systems of NPWT therapy are now available and are widely used across the world [21]. Two well-designed RCTs support its use: the first was in post-operative diabetic foot wounds where NPWT was compared with standard of care (standard moist wound care) in a large number of patients after partial amputations of the foot. Healing rates were significantly faster in the NPWT group [25]. The second well-designed RCT was of complex diabetic foot wounds that again were hard-to-heal but were not post-surgical. Similar results were shown at 16 weeks with a higher number of patients healed on the active treatment vs standard of care [26].

4.4. Oxygen therapies

Hyperbaric oxygen (HBO) has been promoted as a helpful treatment for DFUs for many years [27] although many of the RCTs have been criticised because of small numbers of subjects, methodological and reporting inadequacies: similar criticism was reported in a Cochrane review [28]. However, there was a positive well-designed and blinded RCT from Sweden showing benefit in those patients with chronic neuro-ischaemic infected wound ulcers with no possibility of revascularisation [29]. More recently, however, there have been three negative studies that showed no benefits of HBO in complex hard-to-heal diabetic foot wounds [21,28]. Thus, the use of this approach which of course is expensive and time consuming, is still unclear although it may be helpful in the group described in the study by Londahl et al. [29].

Topical oxygen therapy (TOT) has received increasing interest over the last decade with some strong evidence to support its use. There are a number of different systems available each of which has support from RCTs [21], the strongest evidence appears to be for higher cyclical pressurised and humidified delivery in a contained chamber (boot) which can fit over the lower limb and foot [30]. In this well-designed multinational RCT, topical wound oxygen was applied using continuous delivery of oxygen for 90 min a day, five days a week, for a 12-week period and was compared against the sham group who received topical air rather than topical oxygen. A highly significant reduction in time to wound healing was reported in those receiving the topical oxygen and also importantly, the number who remained healed at 12 months was significantly greater than those who received topical air [30]. A subsequent real-world and outcome report using the same modality of oxygen delivery also suggested that those with DFUs treated with topical wound oxygen had significant reductions in hospitalisations and amputations [31].

Finally, in this section on new evidence-based therapies for the diabetic foot, there are a number of interesting products in the research and development pipeline and readers are directed to the excellent section by Kramer and Gurtner in the 2022 American Diabetes Association Compendium on this topic [21].

5. Infections

It is generally agreed that a diabetic foot ulcer will heal if the arterial circulation is adequate, pressure is removed from the wound and its surroundings and lastly, infection is appropriately and aggressively treated [2]. However, there are several problems with giving specific advice on which antibiotic to use. It can safely be said that there is no evidence that clinically non-infected neuropathic ulcers warrant treatment with antibiotics [2]. With respect to the choice of antibiotic therapy for infected DFUs, as the common isolated organisms vary across different parts of the world, no direct advice will be given in this review. For more detailed discussion, the reader is referred to the recently published joint Guidelines on the management of the diabetic foot infections published by the International Working Group on the Diabetic Foot and the Infectious Diseases Society of America [32]. At about the same time as this Guideline was published, a multidisciplinary group also published a very useful state of the art review on the question of the evaluation and management of diabetic foot infections [33]. Additionally, a review of all aspects of diagnosis and management of diabetic foot infections, can be found in the second ADA Compendium on the diabetic foot [34].

5.1. Osteomyelitis

There have been interesting developments in the management of osteomyelitis complicating diabetic foot ulcers in recent years. Despite the fact that literature has focused on the use of computerised tomography (CT) scanning and magnetic resonance (MR) scanning and other nuclear medicine studies to diagnose diabetic foot osteomyelitis, the plain x-ray of a foot remains a most useful diagnostic tool, remembering that there may be up to two weeks of delay before changes of osteomyelitis are visible on a plain x-ray [2]. Controversies in management have included whether osteomyelitis should be treated by antibiotics or

surgically, and also if the former, by which route the antibiotics should be administered. For localised osteomyelitis in the diabetic foot, there is now evidence this may be successfully treated by antibiotics alone. A case series published by Game and Jeffcoate in 2008 in a relatively large number of patients, suggested the benefit of antibiotics alone [35]. However, it was Lázaro-Martinez et al who conducted a randomised comparative trial of conservative surgery vs antibiotics in the management of osteomyelitis: this study showed no superiority of either delivery modality suggesting that localised osteomyelitis can be successfully treated by oral antibiotics [36]. There has been much debate as to the duration of antibiotic therapy that is required to treat these lesions: it is generally agreed that six to eight weeks is sufficient and that a previously recommended 12 weeks is no longer necessary [37].

The most interesting development in recent years was the OVIVA (Oral Vs IntraVenous Antiobiotics) study [38] that randomised patients with osteomyelitis in a large multicentre study to oral vs intravenous delivery [38]. Surprisingly, this report could not confirm superiority of either delivery mode. It is therefore agreed that most cases of osteomyelitis, especially those treated on an outpatient basis, can be treated by oral antibiotics alone for a period of at least six weeks. Those who require hospital admission because of osteomyelitis with systemic features, abscesses, positive blood cultures, etc., clearly need to be started on intravenous antibiotics, but the use of home intravenous management for such patients after discharge from hospital is now controversial. It is generally agreed that home IV antibiotics for osteomyelitis of the diabetic foot are only required for those individuals who have positive bacterial cultures of organisms that are not sensitive to any oral antibiotic either alone or usually in combination [34].

6. Conclusions: Guidelines and recent reviews

In this review we have tried to provide an updated discussion on potential new therapies for both prevention and treatment of hard-to-heal diabetic foot ulcers. There are a number of helpful publications which can be downloaded without charge to which the reader is referred to for up-to-date discussion and evidence-based Guidelines for management of diabetic foot problems: many of these have already been referred to in various sections of the text.

For screening for diabetic foot ulcers, Guidelines were published by an ADA expert group on the Comprehensive Diabetic Foot Examination [39], but the most recent advice comes from the International Working Group on the Diabetic Foot and was published in 2023 [40]. The International Working Group Guidelines on Infection Control [32] and Wound Healing [41] are also available and were recently updated and cover aspects discussed in the review.

The two ADA Compendia have already been referred to and provided detailed discussion by multiple experts on aspects of management of infection and also new evidence-based therapies for complex diabetic foot wounds [21,34]. Finally, the ADA publishes its Standards of Care every year and those for 2025 are available and can be downloaded from either the ADA website or that of *Diabetes Care* [42]. These Guidelines recommend, that for chronic hard-to-heal diabetic foot ulcers, that considerations might be given to NPWT, certain placental membranes or bioengineered skin substitutes, the autologous fibrin and leucocyte platelet patches and topical oxygen therapy [42]. The sucrose octasulfate dressing was not considered by this panel as it is not available in the United States.

CRediT authorship contribution statement

Andrew James Michael Boulton: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **V Viswanathan:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

AJMB reports on the current advisory board/speakers and/or speakers bureau for Nevro Inc, AOT Inc, Urgo Pharma, France, Worwag Pharmaceuticals, Germany, Averitas, Diabetis JSC, Lithuania.

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