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Prevention and treatment of diabetic foot ulcers

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Summary

The rising prevalence of diabetes estimated at 3.6 million people in the UK represents a major public health and socioeconomic burden to our National Health Service. Diabetes and its associated complications are of a growing concern. Diabetes-related foot complications have been identified as the single most common cause of morbidity among diabetic patients. The complicating factor of underlying peripheral vascular disease renders the majority of diabetic foot ulcers asymptomatic until latter evidence of non-healing ulcers become evident. Therefore, preventative strategies including annual diabetic foot screening and diabetic foot care interventions facilitated through a multidisciplinary team have been implemented to enable early identification of diabetic patients at high risk of diabetic foot complications. The National Diabetes Foot Care Audit reported significant variability and deficiencies of care throughout England and Wales, with emphasis on change in the structure of healthcare provision and commissioning, improvement of patient education and availability of healthcare access, and emphasis on preventative strategies to reduce morbidities and mortality of this debilitating disease. This review article aims to summarise major risk factors contributing to the development of diabetic foot ulcers. It also considers the key evidence-based strategies towards preventing diabetic foot ulcer. We discuss tools used in risk stratification and classifications of foot ulcer.

Keywords

diabetic foot ulcer, wound dressing, offloading, wound debridement, growth factor

Introduction

Diabetes mellitus represents a growing public health concern with an increasing prevalence of diabetes estimated at 3.6 million people in the UK with an expected further rise to 5 million in the coming 10 years (Diabetes UK 2015).[1] In the UK, diabetic foot complications constitute a major health burden amounting to the single largest reason for hospitalisation among diabetic patients. Up to 2–3% of patients with diabetes mellitus are thought to have an active foot ulcer with a lifetime risk of developing a foot ulcer as high as 25%.[2,3] An epidemiological survey across six districts of North-West England reported the cumulative two-year incidence of new diabetic foot ulcers at 2.2%.[4]

The management of diabetic foot ulcers therefore poses an increasing socioeconomic burden with an estimate cost of £580 million to the National Health Service in the UK in 2010–2011, more than half of which were spent on community care of foot ulcers.[5] The United Kingdom Department of Health Quality Improvement, Innovation and Prevention agenda[6] further highlights the need for better efforts on active chronic disease management to optimise the utilisation of healthcare resources.

Evidently, it is also increasingly recognised that latter stages of complications from foot ulcers are associated with serious morbidity and overall reduction in quality of life. It is estimated that more than two-thirds of non-traumatic lower limb amputations are preceded by an ulcer (84%), a pivotal event that opens the window for early intervention.[7] However, the complicating factor of underlying peripheral vascular disease renders majority of diabetic foot ulcers asymptomatic during the early stages of disease. In the latter more advanced stages, evidence of tissue loss becomes more evident, frequently occurring in the form of chronic non-healing foot ulcers.

This review article aims to summarise major risk factors contributing to the development of diabetic foot ulcers. It also considers more recent evidence on the significance of chronic disease monitoring, prevention and most importantly management of the diabetic foot ulcer.

Methods

We electronically searched PubMed, MEDLINE, OvidSP and the Cochrane Collaboration Database using a keyword search for ‘diabetic foot ulcer’, ‘diabetes foot care’, ‘neuropathy’, ‘management of diabetic foot ulcer’, ‘wound dressing’ and ‘multidisciplinary team’. We reviewed the current literature consisting mainly of prospective cohort studies,

randomised controlled trials and systematic reviews that were published up to 11 February 2016. We made specific reference to guidelines published by National Institute of Clinical Excellence and National Diabetes Foot Care Audit report.

Pathogenesis/Pathophysiology

Diabetes mellitus has been commonly associated with a series of micro- and macro-vascular changes that manifest as a wide range of complications. Diabetic foot ulcers are a devastating component of diabetes progression with an estimated 15% of diabetic patients developing foot ulcers during the course of their disease.[8,9] The commonly identified risk factors predisposing to the development of foot ulcers include poor glycaemic control, peripheral neuropathy, peripheral vascular disease and immunosuppression. Boulton[10] concluded that up to 85% of diabetic foot ulcers are attributable to underlying peripheral neuropathy altering foot pressures. The biochemical basis of ulceration is the result of a combination of components that together lead to tissue breakdown. Persistent hyperglycaemic states result in the complex formation of advanced glycation end products and cytokines which in turn induce an oxidative stress on nerve cell resulting in motor, autonomic and sensory neuropathy, and hence the term neuropathic foot ulcers.[11] In addition, skin insensitivity arising from autonomic changes which impair the function of sweat glands result in further callus formation. Damaged sensorimotor neurones inexplicably lead to reduced or altered sensation which further affects the mechanics of weight bearing and gait.

Assessment and diagnosis

The annual assessment of the diabetic foot as recommended by the National Institute of Clinical Excellence[12] guidelines requires that all diabetic patients have:

- Neurological foot testing: 10 g monofilament at four sites on each foot and one of the following: vibration using 128 Hz tuning fork, pinprick sensation, ankle reflexes and vibration perception threshold;
- Foot shape: prominent metatarsal heads/claw toes, hallux valgus, muscle wasting or Charcot deformity;
- Dermatological: callus, erythema and sweating;
- Vascular: foot pulses, ankle brachial index (if indicated) and Doppler wave forms.

A Turkish prospective cross-sectional study suggested the use of acute phase reactants (C-reactive protein, white cell count and erythrocyte sedimentation rate) along with the Wagner classification system to predict duration of hospital stay.[13] Tabur et al. demonstrated a rise in acute phase reactants along with increased Wagner grading (Table 1) positively predicted a longer duration of hospital stay.

Table 1. Wagner Ulcer Classification system.

• Grade 1 – superficial diabetic ulcer
• Grade 2 – ulcer extension involving ligament, tendon, joint capsule or fascia with no abscess or osteomyelitis
• Grade 3 – deep ulcer with abscess or osteomyelitis
• Grade 4 – extensive gangrene of the foot

Screening and prevention of foot ulceration

The mainstay therapy for intervention of diabetic lower limb complications is prevention. There has been increasing evidence promoting the use of podiatry services within the community to facilitate diabetic foot care with recent evidence demonstrating both a reduction in hospital admissions and the number of preventable amputations. Gibson et al.[14] utilised multivariate Cox proportional hazard models to estimate the hazard of amputation and hospitalisation in those who received podiatry care in the year prior to their diabetic foot ulcer. The study demonstrated that care by podiatrist for diabetic foot had been associated with a lower hazard of lower extremity amputation and reduced hospital admission rate.

The National Institute of Clinical Excellence, in their most recent guideline published in August 2015 on *Diabetic foot problems: prevention and management*, have devised a useful risk stratification strategy that can be used to assess patient's risk of developing diabetic foot problems or those needing an amputation (Table 2).[13]

In addition, patient education has also been shown to be an important element in delaying the onset or recurrence of diabetic foot ulcers. This includes providing information on basic foot care advice including advice on appropriate foot wear and wound care. Emphasis should also be made on the importance of foot care. A survey conducted to evaluate the efficacy of patient education on diabetic foot care has demonstrated a positive impact on patients' health beliefs as evident by a statistically significant positive change in weight, body mass index and blood pressure.[15] However, there have been data to suggest that

Table 2. Risk stratification for the assessment of risk of developing diabetic foot problems or risk of future amputation.

Low risk	Moderate risk	High risk
No risk factors present.	Deformity *or*	Previous ulceration *or*
Presence of callus formation alone.	Neuropathy *or*	Previous amputation *or*
	Non-critical limb ischaemia	On renal replacement therapy *or*
		Neuropathy and non-critical limb ischaemia *or*
		Neuropathy with callus and /or deformity *or*
		Non-critical limb ischaemia with callus and/or deformity

Adapted from the National Institute of Clinical Excellence.[12]

self-assessment of diabetes-related foot problems by patients to be unreliable.[16]

Annual diabetic foot assessments either in primary care or the podiatry clinic have been recommended by the National Institute of Clinical Excellence to enable early identification of debilitating diabetic foot complications. Appropriate clinical examination of the diabetic foot can diagnose diabetic peripheral neuropathy and reveal reduced sensation to large and small fibre stimuli in the feet and lower part of the limbs. Clinical examination is also useful in the classification and risk stratification of the disease for appropriate monitoring in diabetic foot clinic (Table 3).

Table 3. Clinical examination of the diabetic foot and risk stratification.

Examination of the patients' feet should include:
• Testing of foot sensation using a 10-g monofilament or vibration
• Palpation of foot pulses
• Inspection for any foot deformity and footwear
Based on this the foot should be classified as:
• At low current risk
• At increased risk
• High risk
• Acute foot / ulcerated foot / Charcot

Management of diabetic foot ulcers

Glycaemic control

Increasing evidence has shown that intensive glycaemic control delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in patients with insulin-dependent diabetes mellitus.[17,18] However, intensive glycaemic control must also be accompanied by cautious monitoring as tighter control of glycaemic state could lead to profound hypoglycaemia. Callaghan et al.[19] conducted a meta-analysis of the effect of intense glycaemic control on diabetic neuropathy and demonstrated a significantly reduced risk of developing clinical neuropathy with better glycaemic control, especially in Type 1 diabetes mellitus.

Despite challenges to measure distal sensorimotor neuropathy objectively, Ang collated evidence to suggest tight glycaemic control is the only significant tool, to date, in prevention or delay in development of neuropathy in patients with type 1 diabetes and to slow progression of neuropathy in some patients with type 2 diabetes.[20]

Pharmacological therapy

Individualised patient education, improved diabetes knowledge and self-management activities have improved medication adherence to oral diabetic medications in case-controlled trial.[21] Diabetic neuropathies resulting from chronic sensorimotor distal symmetrical polyneuropathy poses challenges for neuropathic pain. The National Institute of Clinical Excellence recommends use of first-line agent duloxetine and pregabalin for pain control.[22] Significant atherosclerotic risk factors should be addressed to reduce risk of development of concurrent peripheral vascular disease or critical limb ischaemia. Main key strategies include smoking cessation and use of pharmacological aids such as nicotine replacement and statins irrespective of cholesterol levels and antiplatelet medications.

In addition, diabetic foot ulcers with superadded infection have also been shown to benefit from a

Table 4. Overview of dressing types used in the treatment of diabetic foot infections.

Dressing type	Description	Suggestions for use
Alginates	Highly absorbent with bacteriostatic and haemostats properties.	Useful in cavitating lesions.
Foam dressing	Moderately absorbent with thermal insulation properties.	Used in light and heavy exudative wounds.
Hydrocolloids	Absorbent and aids rehydration and autolysis. Promotes granulation.	Useful for dry, sloughy, necrotic wounds. Avoid use on infected wounds.
Hydrogels	Absorbent, donates liquid and aids autolysis.	Useful for dry, sloughy, necrotic wounds. Avoid in concurrent/suspected infection.
Iodine preparations	Moderately absorbent with antiseptic properties.	Discolours wound. Avoid in case of iodine allergy, pregnancy or thyroid disease.
Low-adherence	Minimally absorbent with hypoallergenic properties.	Standard diabetic ulcer treatment. Often use in conjunction with anti-microbials.
Silver-impregnated	Absorbent with anti-septic properties.	Useful for infected diabetic foot ulcers. Avoid in known sensitivities to silver.

targeted antibiotic regimen based on wound culture results. Duration of treatment ranged from two weeks up to two months depending on the severity of the underlying infection.

Improving vascularisation

Revascularisation of critically ischaemic legs results in increased perfusion after the procedure which in turn is associated with a further reduced amputation rate.

Debridement

Repeated sheer pressure on the diabetic foot results in callus formation. The removal of necrotic and hyperkeratotic tissue either in the form of superficial ulcer debridement or selective sharp debridement thus promotes better wound healing. Deep wounds, specifically those with bone and soft tissue involvement, require more aggressive debridement with some involving surgery. A 10-year review on standardised wound care protocol and integrated multidisciplinary team found a decline in amputation rate in diabetic foot patients through efficient on-time debridement.[23]

Offloading

Further pressure reduction and redistribution of weight-bearing load over an increased area of the foot can be achieved through 'offloading' strategies. A randomised controlled trial of cast walkers over the diabetic foot has shown benefit and the 'total contact cast' stipulates the most effective offloading device.[24] Other devices to promote offloading include removable or non-removable casts, orthotic devices (patella-tendon weight-bearing orthosis) and custom fabricated shoes and insoles.

Wound dressings

Dressings offer an external protection and barrier to external forces and contaminants while promoting absorption of exudate around the ulcer site. There are a variety of dressing types available along with increasingly advanced methods of promoting wound healing (Table 4).[25] Despite further advancements in wound dressing, there has however been limited evidence to suggest that moist dressings are more effective than 'dry' dressings or vice versa.[26] Silver-impregnated dressings have not been shown to be more effective in treating diabetic foot ulcers in randomised controlled trials than dressings for treating any other wound.[27]

Negative pressure wound therapy

Targeted negative pressure wound therapy is another increasingly common method used in the management of diabetic foot ulcers primarily involving the removal of wound fluid through a sealed vacuum. This is aimed at improving tissue perfusion and in

the promotion of formation of granulation tissue, and often a shorter treatment in comparison with ulcers treated with traditional gauze dressing. However, a Canadian evidence-based study revealed no statistically significant difference ($p = 0.15$) between negative pressure wound therapy and the standard wound care in length of time to complete wound closure.[28]

Maggot therapy

Use of maggot therapy primarily functions by removing dead necrotic tissue leaving healthy granulation tissue on the wound bed. In a meta-analysis of four studies comparing maggot debridement therapy with standard therapy on 356 participants, Tian et al.[29] demonstrated a more rapid growth of granulation tissue and greater wound healing rate ($p = 0.0004$), and increase in number of antibiotic-free days (126.8 ± 30.3 days vs. 81.9 ± 42.1 days; $p = 0.001$) as compared to standard wound care.

Growth factors and skin substitutes

Additional evidence from research on biophysiological stimulants of wound healing have led to development of a variety of growth factors including platelet-derived growth factor, epidermal growth factor and transforming growth factor beta, all of which have been thought to have a major role in the wound-healing process. Becaplermin is a recombinant platelet-derived growth factor also currently used. A meta-analysis by Buchberger et al.[30] evaluating the evidence for the use of growth factors and active skin substitutes for the treatment of diabetic foot ulcers showed the combination of such treatment did indeed result in a higher incidence and shorter duration to complete wound closure. There has also been recent evidence which has demonstrated promising results in the use of granulocyte colony-stimulating factor in reducing the need for surgical interventions as shown by an overall reduction in amputation rates from diabetic foot ulcers.[31] Granulocyte colony-stimulating factor functions by increasing release of neutrophil progenitor cells from the bone marrow resulting in improved neutrophil functions. However, more work is still required to substantiate these findings and in identifying patient groups who will most benefit from this therapy.

Multidisciplinary team input

The management of complex diabetic foot complications requires the integration of various members comprising the specialist team in order to provide a comprehensive management of multiple aspects of diabetes care. Evidently, optimisation of clinical outcomes and a reduction in the risk of progression to amputation has been seen in patients with diabetic foot ulcers who have been cared for by a specialist diabetes foot care team. This specialist team frequently but not invariably comprises a diabetologist, podiatrist, microbiologist, tissue viability nurse, orthopaedic surgeon and vascular surgeon with a thorough understanding of foot function. This is due to the fact that factors including glycaemic and blood pressure control, baseline renal function and diabetic retinopathy have all been increasingly highlighted as aspects that considerably influence prognosis. In addition, the delivery of an effective service facilitated by input from the multidisciplinary team has demonstrated significant benefit in reducing incidence of both minor and major amputations.[32]

Conclusion

Diabetic foot ulcers are a devastating component of diabetes progression affecting about 15% of patients with diabetes. The underlying pathophysiology of diabetic foot ulcers is a complex interplay between the body's persistent hyperglycaemic state and that of neuropathic, vascular and immune system components. Preventative strategies in the form of patient education and regular foot assessments for peripheral vascular disease and neuropathy along with risk stratification form the basis of the management of diabetic foot disease. However, a combination of a number of treatment modalities can also be facilitated by the multidisciplinary team for those with more complex diabetic foot complications.

Declarations

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