Topical therapies for diabetic foot ulcers: standard treatments

This paper is the first in a two-part series reviewing the evidence on standard and advanced treatments for diabetic foot ulcers. Both clinical studies and economic models are evaluated. The first part concentrates on standard topical therapies

aetiology; prevalence; wound dressings; economic impact

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The mainstay of treatment for diabetes-related foot ulceration is a multidisciplinary team (MDT) approach that includes metabolic control, debridement, offloading/pressure redistribution, vascular control, infection control and seamless integrated wound care. This is supplemented by the use of topical therapies. While a wide range of therapies — both standard and advanced — are available, there is a dearth of scientific evidence to support the use of one product over another. This can make the selection difficult.

This paper is the first in a two-part series on the treatment of diabetic foot ulcers. The first article proposes that some hard-to-heal diabetic foot ulcers cannot be treated by standard topical treatments alone. The second article will review the literature on advanced therapies and the implications for their associated cost.

Literature search

An extensive literature search was undertaken to identify published articles in which reference is made to diabetic foot ulcers, with particular focus on the following search terms:

- Aetiology
- Prevalence
- Cost
- Treatment (includes both topical therapies and wound dressings).

The time frame for the literature search was 1980–2008. Inclusion criteria were peer-reviewed research studies that stated a clearly defined question, with a sound methodology and valid results. Systematic reviews, randomised controlled trials, cohort studies, economic evaluation studies and case-control studies were included.

Electronic searches were conducted of the following databases and internet sites:

- Medline
- Embase
- Cochrane Library
- Worldwidewounds.

These were supplemented with manual searches of conference proceedings and journals of relevance to wound management and diabetes.

Aetiology

A diabetic foot ulcer (DFU) is defined as 'a full thickness wound below the ankle in a diabetic patient, irrespective of duration'.[1] It is characterised by a loss of epithelium extending into or through the dermis and into deeper tissues.[2] Chronic ulcers fail to progress through an orderly and timely sequence of repair, and so are slow to heal.[3] They commonly develop at pressure points on the plantar surfaces, over the metatarsal heads, on the big toe, and on the heels.[2,4]

The major aetiologies of DFUs are neuropathy (nerve damage), peripheral vascular (arterial) disease and neuroischaemia.[3,4] Some 40–70% of DFUs are caused by neuropathy, 15–24% by peripheral vascular disease and 15–45% by neuroischaemia.[3-5]

The neuropathic foot is typically warm to touch with good perfusion and palpable pulses. The skin may be anyhdrotic (dry) and prone to fissuring and callosities. Ulcers often occur on the plantar surface, principally under the metatarsal heads in the forefoot.[6] They are round and surrounded by callus.[7,8]

The neuroischaemic foot is typically cool to touch and has poor perfusion, characterised by diminished or absent foot pulses. The skin is usually atrophic, anyhdrotic and shiny. Hair growth is often minimal and atrophy of the subcutaneous tissues is apparent. Ischaemic ulcers often occur on the digits and heels, and are usually dry with vertical walls. Necrotic tissue may be present.[9]

Neuropathy can give rise to foot deformity, plantar callus and soft-tissue damage (trauma) that can lead to foot ulceration.[10-12] While neuropathy can lead to an 'insensate' foot, it is not always painless and pain associated with neuropathy has been described as

Table 1. Systems used to classify and assess diabetic foot ulcers

Wagner
Grade 1: Superficial
Grade 2: Ulcer extension to ligament, tendon, joint capsule, or fascia, but without osteomyelitis
Grade 3: Deep ulcer with infection or osteomyelitis
Grade 4: Localised gangrene
Grade 5: Extensive gangrene
Texas
0: Pre- or post-ulcer with epithelialisation
1: Superficial and not involving tendon, bone or capsule
2: Ulcer penetrates through to tendon or capsule
3: Penetrating to bone or joint
Secondary classification
A: Non-infected/non-ischaemic
B: Infection
C: Ischaemia
D: Infection and Ischaemia[15]
PEDIS[65]
Perfusion
Extent/size
Depth/tissue loss
Infection
Sensation
S(AD)SAD[66]
Size
Area
Depth
Sepsis
Arteriopathy
Denervation

'burning', 'shooting' or 'stabbing'. Allodynia (pain or an unpleasant sensation from normal stimulus) may be experienced in the surrounding tissue including the peri-wound tissues, which may be at the site of callus, or in the skin surrounding the callus. Generally, however, the patient only notices an ulcer when blood or pus exudes from the wound.

Loss of sensation in conjunction with mechanical, thermal or chemical injury are the key predisposing factors for diabetic foot ulceration.[7,13] Inappropriate and/or ill-fitting footwear is another significant causative factor.[1] Additional risk factors include foot deformities, pressure and infection. Fungal infection, resulting in a breech in the skin integrity, can predispose to ulceration and secondary bacterial infection, and result in poor or delayed wound healing.

The many cellular and molecular aberrations associated with diabetic foot ulcers can make them recalcitrant to treatment. Increasing evidence suggests that there is a causal link between hyperglycaemia and oxidative stress, which can result in cellular damage.[14] Other factors, aside from an innate physiological state, that can cause chronicity in DFUs are:

- Delayed referral
- Lack of provision of good standard care
- Inadequate offloading
- Infection.

Ulcer classification

Approaches used to classify DFUs are the Wagner grading system, the Texas Wound Classification System, PEDIS and S(AD)SAD (Table 1). The Texas system is the most comprehensive grading system currently in use.[15]

Incidence and prevalence

It is predicted that the number of people with diabetes will rise from an estimated 171 million in 2000 to 366 million in 2030.[16]

Foot ulcers represent a severe complication of diabetes and are the most common cause of diabetes-associated hospital admissions.[17]

In people with diabetes the prevalence of foot ulcers in diabetes is 4–10%, the annual population-based incidence is 1.0–4.1% and the lifetime incidence may be as high as 25%.[18]

Furthermore, the condition precedes 85% of major amputations.[5] Data from the US has highlighted that amputation is associated with a significant increase in mortality at follow-up, ranging from 13–40% at one year to 39–80% at five years.[18]

Approximately half of all foot wounds become infected over the course of therapy.[17] Diabetic foot ulceration and its sequelae (infection, gangrene and amputation) are associated with a reduced quality of life, high morbidity and premature mortality.[19]

Compared with diabetic patients who do not have foot ulcers, those with DFUs have a 2.4-fold increased risk of death.[20]

Economic impact

In the UK the Department of Health estimated that caring for patients with diabetes (2–3% of the general population) consumes 5% of NHS resources.[21] It is likely that the treatment of diabetic peripheral neuropathy and its complications accounts for a high proportion of this total expenditure as the treatment is resource-intensive and long-term.[22] However, given that the prevalence of diabetes is increasing in the UK and globally, these figures could be an underestimation.

Lithner reported that, as DFUs are responsible for 47% of all diabetes-related hospital admissions, the economic impact is high.[23] An estimated 7–20% of total expenditure on diabetes is thought to be attributable to diabetic foot disease.[24]

The costs associated with diabetes are rising. The International Diabetes Federation stated that, in 2007, the world spent approximately US$232 billion on the treatment and prevention of diabetes and its complications.[25] This lower-bound estimate is predicted to exceed US$302.5 billion by 2025. Furthermore, in western countries the economic cost of a diabetic foot ulcer is thought to be between US$7000 and US$10,000. This may increase to approximately US$65,000 per person when healing is complicated and amputation is required.[26]

Total annual health-care costs in the UK for diabetic foot disease were last estimated as £13 million (1997 currency values) or £3600 for every ulcer treated.[27] However, these costs did not take into account amputation and subsequent rehabilitation, which in conjunction with inpatient care represent the highest proportion of DFU treatment costs.[26]

It has been estimated that lower limb amputation costs £10,600 per patient,[28] with a total annual burden of over £38 million.[27] Apelqvist et al. estimated that the cost of amputation was US$16,488–66,215 (1988 currency values).[29] The lower costs were based on studies that focused on inpatient hospital costs alone; studies that factored in total direct costs found that the expense of nursing and institutional care was considerably higher than that of the surgery itself.[30] For a minor lower extremity amputation at foot level, costs were US$43800; for a major lower extremity amputation above the ankle, they were US$ $66215, of which 77% was incurred after amputation.[29]

In another study Apelqvist et al. reported that amputation of one limb increases the risk of loss of the other limb and is associated with a 50% five-year mortality.[31]

It has been reported that amputation rates increase threefold in patients aged 45–74 years and sevenfold in those over 75.[32] In an audit of lower extremity complications in octogenarian patients with diabetes,[33] Reed showed, using data from the 1996–2002 National Hospital Discharge Survey, that the presence of diabetes increases the risk of complications in this patient population. Patients over 80 had a twofold risk of developing an ulcer, a threefold risk of developing a foot abscess and a fourfold risk of developing osteomyelitis. They were almost twice as likely to undergo debridement and three to five times more likely to have lower leg amputation, toe amputation, or any amputation.[33]

Diabetic foot ulcers place a heavy burden on community health services, especially nursing time. In a local UK population study, 85% of patients with diabetes were being cared for in the community, with district nurses making an average of three visits per week per patient.[34,35]

In diabetic patients with a lower extremity ulcer the hospital stay can be up to 50% longer than for patients without an ulcer.[36]

No published costs associated with podiatry exist, despite the fact that patients with diabetic foot disease require regular podiatric treatment.

Stokl et al. evaluated variations in treatment costs (2001 currency values) according to Wagner grade. Ulceration costs increased with severity and ranged from US$1892 (grade 1) to US$27,721 (grades 4 and 5).[37] These observations emphasise the value of intensive outpatient interventions to prevent ulcer progression.

Effect on quality of life

Diabetic foot ulcers are associated with decreased mobility, and qualitative studies support clinical observations of their negative psychological and social effect, including increased family tensions, reduced social activities, limited employment and financial hardship.[38] Furthermore, it has been reported that clinical depression is prevalent in people with diabetes. Indeed, it is reported to be as high as 15% which is associated with a high level of medical symptoms and poor self-care.[39]

In summary, DFUs represent a significant health and socioeconomic problem and are a major cause of morbidity — due to pain, incapacitation and limb loss[40] — and mortality.[41]

Standard treatment

The International Diabetes Federation (IDF) advises that the risk of amputation can be decreased by 49–85% by implementing a care strategy combining prevention, multidisciplinary treatment, appropriate organisation, close monitoring and the education of practitioners and patients.[41]

Cornerstones of treating full-thickness ulcers are:

- Debridement
- Offloading with orthotics, casting or non-weight

References

1 International Working Group on the Diabetic Foot. International Consensus on the Diabetic Foot. IWG, 1999.

2 Reiber, G.E., Lipsky, B.A., Gibbons, G.W. The burden of diabetic foot ulcers. Am J Surg 1998; 176: (2A Suppl), 5S-10S.

3 Lazarus, G.S., Cooper, D.M., Knighton, D.R. et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol 1994; 130: 4, 489-493.

4 Levin, M. Diabetic foot wounds: pathogenesis and management. Adv Wound Care 1997; 10: 2, 24-30.

5 Frykberg, R.G., Armstrong, D.G., Giurini, J. et al. Diabetic foot disorders: a clinical practice guideline. For the American College of Foot and Ankle Surgeons and the American College of Foot and Ankle Orthopedics and Medicine. J Foot Ankle Surg 2000; 45: Suppl 5, S1-60.

6 Abouaesha, F., Carine, H.M., Griffiths, G.D. et al. Plantar tissue thickness is related to peak plantar pressure in the high-risk diabetic foot. Diabetes Care 2001; 24: 7, 1270-1274.

7 Delbridge, L., Ctercteko, G., Fowler, C. et al. The aetiology of diabetic neuropathic ulceration of the foot. Br J Surg 1985; 72: 1, 1-6.

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bearing regimens
- Treatment of infections
- Local wound-care comprising cleansing with saline and the use of modern wound dressings that promote a moist environment.[42,43]

Consideration should be given to revascularisation where necessary and control of serum glucose levels and arterial risk factors such as hypertension and dyslipidaemia

Wound dressings

Although topical treatment is an important aspect of wound care, it should always be considered secondary to surgical and systemic care.[44] Generally, the choice of dressing is guided by the ulcer characteristics, patient requirements and costs.[45] While it is accepted that a moist wound environment promotes healing, less than 50% of chronic wounds are treated with a moist wound dressing.[46] Moist wound healing is associated with faster healing, better tissue quality with less scarring, and less pain.[47,48]

However, overhydration can cause maceration.[44] In creating a moist environment, dressings sooth exposed nerve endings by bathing them in wound secretions, thereby minimising or eliminating pain and allowing healing to progress more naturally.[42] Dressings that promote a moist wound environment include films, foams, alginates, hydrocolloids, Hydrofiber and hydrogels.[42,44]

However, some films not only use aggressive adhesives that can cause skin trauma but also lack absorbency which results in leakage channels breaking the seal, thereby facilitating bacterial proliferation and infection.

Hydrocolloids achieve a moist wound environment by gelling with wound fluid above the wound bed, but these also rely on aggressive adhesives which can cause wound trauma if removed inappropriately. Foams have a greater absorbency capacity than films and hydrocolloids; however, where wound exudation is low or has decreased through treatment, some foams, with the exception of those deemed 'atraumatic', have the disadvantage of sticking to the wound bed.

Alginates, when in contact with wound fluid, transform from fibres into a gel which provides non-adherent wound contact and a moist environment for healing. Hydrogels have a high water content in a lattice gel, so not only are they non-adherent but they also provide the wound with adequate moisture.[42] However, hydrogels require a secondary dressing. If used inappropriately or not changed when needed, alginates are at risk of super-saturation, which may macerate the surrounding skin, or they may dry out and adhere to the wound tissue.

Hydrofiber dressings have been evaluated in DFUs and found to be effective in exudate management and the promotion of healing.[49]

Although pain was once considered an insignificant problem in patients with neuropathic diabetic foot ulcers, recent work has demonstrated that up to 48% of such patients do suffer from wound-associated pain (Apelqvist et al. personal communication). Atraumatic dressings, such as those that utilise soft silicone technology, avoid pain and trauma at dressing removal.[50]

Clinical studies have highlighted the benefits of dressings utilising soft silicone technology in a diabetic application. These include ease of application and the provision of a moist layer over the wound that does not adhere or cause trauma to the wound bed or surrounding tissues on removal.[50]

Management of bacterial burden

Infected wounds normally have a high level of exudate which needs to be controlled through regular and appropriate dressing change to prevent maceration.[45] As they are highly absorbent, foams and alginates are well suited for this.

Management of infection can be further complicated in patients with dysvascularity as the reduced peripheral perfusion impairs the delivery of antibiotic to the infection site.[51] Antimicrobial dressings containing silver, honey or iodine may have a role to play, in conjunction with systemic antibiotic therapy, in the management of infection in the diabetic foot.

However, a systematic review of antimicrobial treatments for DFUs found that the current evidence base is too weak to recommend any particular antimicrobial agent and further studies of their effectiveness and cost-effectiveness are needed.[52]

A recent randomised controlled trial found that Aquacel Ag (ConvaTec) was associated with favourable clinical outcomes when compared with plain calcium alginate dressings.[53] In addition, hydrogels facilitate autolysis, which may be beneficial in the management of necrotic ulcers as it helps to control infection.[45]

The prevalence of meticillin-resistant *Staphylococcus aureus* (MRSA) is increasing in diabetic foot ulcers.[25] It delays healing and possibly increases treatment costs.[54] Strategies are needed to address this mounting problem.

Costs of topical treatment

These can be divided into those for drugs and materials and those for nursing or podiatry time, medical costs and travelling expenses. Total dressing costs depend on a variety of factors, including the dressing regimen used, cost per dressing, dressing change frequency and total time to healing.[55,56] When estimating the costs of treating DFUs, the long-term costs should also be considered due to the need for increased home care and likelihood of recurrent ulcers and amputations.[36,55]

Apelqvist et al. conducted a retrospective economic analysis of 274 patients whose ulcers healed following topical treatment.[56] All patients were treated by a multidisciplinary foot care team both as in- and outpatients. Data collected for each patient included total time to healing, treatment time for each type of dressing, and number of dressing changes. Material costs for dressings, labour and travelling were also considered.

Average weekly cost per patient for topical treatment ranged from £40.3 to £385 (at 1990 currency values). The dominant costs were for staff expenses and transport.

The authors concluded that the most important factor in reducing costs is the frequency of dressing changes. They proposed that novel treatment strategies will not increase total costs, despite their high unit costs, if they can be applied less frequently.[56] Indeed, many diabetes centres regard daily/alternate-daily dressing changes as best practice, which will have high cost implications.

This particular economic evaluation is dated. However, there is limited current published data on the health economics of topical interventions for diabetic foot ulcers. Further research is required to determine both the cost-effectiveness and clinical-effectiveness of topical therapies for diabetic foot ulceration.

Hard-to-heal DFUs

Normal wound healing is a finely controlled balance of repair processes leading to the formation of new tissue and destructive processes necessary for the removal of damaged tissue and remodelling of new tissue.

Within this complex environment a number of points of regulation precisely control the biological processes required to achieve normal wound healing.[3] Alterations to any of these processes may lead to a non-healing state and a chronic wound.[57,58] While chronic wounds such as diabetic and venous ulcers result from a different underlying pathology, biochemically they are considered similar in that they are characterised by persistent inflammatory stimuli.[59]

Persistent inflammatory stimuli can stimulate cytokine inflammatory mediators, in turn elevating protease levels, which degrade proteins, including growth factors, that promote cell proliferation and granulation tissue formation.

In this way, a shift in the wound equilibrium towards destructive processes occurs, effectively suspending the wound in the inflammatory phase of healing.[60] Hence, increased proteolytic activity and subsequent degradation of important growth factors, such as platelet-derived growth factor (PDGF), leads to the development of 'non-healing' or 'hard-to-heal' wounds.[61]

Healing rates for chronic DFUs are slow, with standard treatments averaging 12–20 weeks in clinical trials. In a meta-analysis of five prospective DFU trials, Margolis et al. reported an aggregated healing rate of 24% after 12 weeks and 31% after 20 weeks of standard treatment.[62] This means that after 20 weeks of 'standard treatment' approximately 70% of DFUs remain unhealed.

To gain the maximum advantage from advanced therapies in the treatment of hard-to-heal DFUs, it is important to identify potentially non-healing ulcers as early as possible.

Margolis et al. developed a simple prognostic model, assigning points according to ulcer duration, size and depth, to stratify the risk that patients would not respond to standard good wound care (defined as debridement, moist wound dressings and offloading).[63]

The model, which was derived from a retrospective study of 27,630 patients with diabetic neuropathic ulcers from a wound-care database spanning 18 years and encompassing 150 treatment centres, counts 1 point each for wounds over two months old, wounds larger than 2cm^2, or grade ≥3 on a six-point scale (penetrating through skin to expose tendon, ligament or joint, or worse). Wounds displaying none of these factors had a 66% probability of healing by 20 weeks, compared with only 22% for those with all three criteria.

Diabetic foot ulcer healing rates and times depend on the aetiology, with the shortest healing time occurring in neuropathic ulcers and longer healing time in those neuroischaemic and ischaemic ulcers.[64] Neuropathic ulcers treated with standard good wound care had an average healing time of 77.7 days, compared with 123.4 and 133 days for neuroischaemic and ischaemic ulcers respectively. These findings suggest that healing time is primarily determined by aetiological factors, rather than the size of the wound.

Discussion and conclusion

Management of DFUs poses many challenges to practitioners. Treatment is often costly and resource intensive, yet many ulcers remain recalcitrant to even standard wound care. Further research is needed on the role of advanced topical treatments to determine whether they can expedite healing and reduce the incidence of amputations.

A variety of advanced treatments, both in development and in clinical use — have been designed to achieve the successful management of hard-to-heal ulcers. The technology behind these treatments and the rationale for their use will be considered in the second article in this series. This will consider the efficacy data from clinical studies, along with cost-effectiveness findings of economic models and case scenarios. ■

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8 McInnes, A., White, R.J. The Diabetic Foot.
In: Lindsay, E., White, R.J. (eds). Leg Ulcers and Problems of the Lower Limb: An holistic approach. Health Comm, 2007.

9 Watkins, P.J. ABC of diabetes: The diabetic foot. Br Med J 2003; 326: 977-979.

10 Pecoraro, R.E., Reiber, G.E., Burgess, E.M. Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care 1990; 13: 5, 513-521.

11 Boulton, A.J., Hardisty, C.A., Betts, R.P. et al. Dynamic foot pressure and other studies as diagnostic and management aids in diabetic neuropathy. Diabetes Care 1983; 6: 1, 26-33.

12 Leese, G.P., Reid, F., Green, V. Stratification of foot ulcer risk in patients with diabetes. Int J Clin Pract 2006; 60: 5, 541-545.

13 Edmonds, M.E. The diabetic foot: pathophysiology and treatment. Clin Endocrinol Metab 1986; 15: 4, 889-916.

14 Sibbald, R.G., Woo, K.Y. The biology of chronic foot ulcers in persons with diabetes. Diabetes/Metabolism Res Rev 2008; 24: (Suppl. 1), S25-S30.

15 Armstrong, D.G., Lavery, L.A., Harkless, L.B. Validation of a diabetic wound classification system: the contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998; 21: 5, 855-859.

16 Wild, S., Roglic, G., Green, A. et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 5, 1047-1053.

17 Lavery, L.A., Armstrong, D.G., Murdoch, D.P. et al. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis 2007; 44: 4, 562-565.

18 Singh, N., Armstrong, D.G., Lipsky, B.A. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293: 2, 217-228.

19 International Diabetes Federation. Time to Act: Diabetes and foot care. IDF, 2005.

20 Boyko, E.J., Ahroni, J.H., Smith, D.G., Davignon, D. Increased mortality associated with diabetic foot ulcer. Diabet Med 1996; 13: 11, 967-972.

21 Department of Health. National Service Framework for Diabetes. DH, 2001.

22 Gordois, A., Scuffham, P., Shearer, A., Oglesby, A. The health care costs of diabetic peripheral neuropathy in the UK: cost-of-illness study. The Diabetic Foot, 2003.
http://findarticles.com/p/articles/mi_m0MDQ/is_2_6/ai_107836467/pg_2.

23 Lithner, F. The diabetic foot: epidemiology and economic impact. IDF Bulletin 1992; 39: 7-9.

24 British Diabetic Association. Foot problems in patients with diabetes mellitus. In: Pickup, J., Williams, G. (eds). Textbook of Diabetes (2nd edn). British Diabetic Association, 1997.

25 Dang, C.N., Prasad, Y.D., Boulton, A.J., Jude, E.B. Methicillin-resistant *Staphylococcus aureus* in the diabetic foot clinic: a worsening problem. Diabet Med 2003; 20: 2, 159-161.

26 Edmonds, M., Boulton, A., Buckenham, T. et al. Report of the Diabetic Foot and Amputation Group. Diabet Med 1996; 13; 9 (Suppl 4), S27-42.

27 Connor, H. The St Vincent amputation target: the cost of achieving it and the cost of failure. Pract Diabetes Int 1997; 14: 152-153.

28 McInnes, A., Booth, J., Birch, I. Multidisciplinary diabetic foot care teams: professional education. The Diabetic Foot 1998; 1: 3, 109-115.

29 Apelqvist, J., Ragnarson-Tennvall, G., Persson, U., Larsson, J. Diabetic foot ulcers in a multidisciplinary setting: an economic analysis of primary healing and healing with amputation. J Intern Med 1994; 235: 5, 463-471.

30 Boulton, A.J., Vileikyte, L., Ragnarson-Tennvall, G., Apelqvist, J. The global burden of diabetic foot disease. Lancet 2005; 366: 9498, 1719-1724.

31 Apelqvist, J., Larsson, J., Agardh, C.D. Long-term prognosis for diabetic patients with foot ulcers. J Intern Med 1993; 233: 6, 485-491.

32 Reiber, G. Epidemiology of the diabetic foot. In: Levin, M.E., O'Neal, L.W., Bowker, J.H. (eds). The Diabetic Foot (5th edn). Mosby Year Book, 1993.

33 Reed, J.F. 3rd. An audit of lower extremity complications in octogenarian patients with diabetes mellitus. Int J Low Extrem Wounds 2004; 3: 3, 161-164.

34 Peacock, I., Fletcher, E., Jeffcoate, W.J. The prevalence of foot lesions: a community survey. Diabet Med 1985; 2: 509A.

35 Complications of diabetes: screening for retinopathy. Management of foot ulcers. Effective Healthcare 1999; 5: 4.

36 Reiber, G.E., Boyko, E.J., Smith, D.G. Lower extremity foot ulcers and amputations in diabetes. In: Diabetes in America (2nd edn). National Institute of Health, 1995.

37 Stockl, K., Vanderplas, A., Tafesse, E., Chang, E. Costs of lower-extremity ulcers among patients with diabetes. Diabetes Care 2004; 27: 9, 2129-2134.

38 Goodridge, D., Trepman, E., Embil, J.M. Health-related quality of life in diabetic patients with foot ulcers: literature review. J Wound Ostomy Continence Nurs 2005; 32: 6, 368-377.

39 Wang, M., Pei-Shan, T., Kuei-Ru, C. et al. A systematic review of the efficacy of non-pharmacological treatments for depression on glycaemic control in type 2 diabetics. J Clin Nurs 2008; 17: 2524-2530.

40 Anichini, R., Zecchini, F., Cerretini, I. et al. Improvement of diabetic foot care after the implementation of the International Consensus on the Diabetic Foot (ICDF): results of a 5-year prospective study. Diabetes Res Clin Pract 2007; 75: 2, 153-158.

41 International Diabetes Federation. Costs of Diabetes. IDF, 2006. http://www.eatlas.idf.org/Costs_of_diabetes.

42 Queen, D., Orsted, H., Sanada, H., Sussman, G. A dressing history. Int Wound J 2004; 1: 1, 59-77.

43 Sibbald, R.G., Torrance, G., Hux, M., et al. Cost-effectiveness of becaplermin for nonhealing neuropathic diabetic foot ulcers. Ostomy Wound Manage 2003; 49: 11, 76-84.

44 Higgins, K.R., Ashry, H.R. Wound dressings and topical agents. Clin Podiatr Med Surg 1995; 12: 1, 31-40.

45 Hilton, J.R., Williams, D.T., Beuker, B. et al. Wound dressings in diabetic foot disease. Clin Infect Dis 2004; 39: Suppl 2, S100-103.

46 Eaglstein, W.H. Moist wound healing with occlusive dressings: a clinical focus. Dermatol Surg 2001; 27: 2, 175-181.

7 Nemeth, A.J., Eaglstein, W.H., Taylor, J.R. et al. Faster healing and less pain in skin biopsy sites treated with an occlusive dressing. Arch Dermatol 1991; 127: 11, 1679-1683.

48 Foertsch, C.E., O'Hara, M.W., Stoddard, F.J., Kealey, G.P. Treatment-resistant pain and distress during pediatric burn-dressing changes. J Burn Care Rehabil 1998; 19: 3, 219-224.

49 Piaggesi, A., Baccetti, F., Rizzo, L. Sodium carboxymethylcellulose dressings in the management of deep ulcerations of the diabetic foot. Diabet Med 2001; 18: 4, 320-324.

50 White, R. A multinational survey of the assessment of pain when removing dressings. Wounds UK 2008; 4: 1, 58-69.

51 Sheppard, S.J. Antibiotic treatment of infected diabetic foot ulcers. J Wound Care 2005; 14: 6, 260-263.

52 Nelson, E.A., O'Meara, S., Golder, S. et al. Systematic review of antimicrobial treatments for diabetic foot ulcers. Diabet Med 2006; 23: 348-359

53 Jude, E.B., Apelqvist, J., Spraul, M., Martini, J. Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. Diabet Med 2007; 24: 3, 280-288.

54 Tentolouris, N., Jude, E.B., Smirnof, I. et al. Methicillin-resistant *Staphylococcus aureus*: an increasing problem in a diabetic foot clinic. Diabet Med 1999; 16: 9, 767-771.

55 Apelqvist, J., Ragnarson-Tennvall, G., Larsson, J. Topical treatment of diabetic foot ulcers: an economic analysis of treatment alternatives and strategies. Diabet Med 1995; 12: 2, 123-128.

56 Apelqvist, J., Ragnarson-Tennvall, G., Larsson, J., Persson, U. Long-term costs for foot ulcers in diabetic patients in a multidisciplinary setting. Foot Ankle Int 1995; 16: 7, 388-394.

57 Nwomeh, B.C., Yager, D.R., Cohen, I.K. Physiology of the chronic wound. Clin Plast Surg 1998; 25: 3, 341-356.

58 Yager, D.R., Nwomeh, B.C. The proteolytic environment of chronic wounds. Wound Repair Regen 1999; 7: 6, 433-441.

59 Mast, B.A., Schultz, G.S. Interactions of cytokines, growth factors and proteases in acute and chronic wounds. Wound Repair Regen 1996; 4: 411-420.

60 Harris, I.R., Yee, K.C., Walters, C.E. et al. Cytokine and protease levels in healing and non-healing chronic venous leg ulcers. Exp Dermatol 1995; 4: 6, 342-349.

61 Palolahti, M., Lauharanta, J., Stephens, R.W. et al. Proteolytic activity in leg ulcer exudate. Exp Dermatol 1993; 2: 1, 29-37.

62 Margolis, D.J., Kantor, J., Santanna, J. et al. Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. Arch Dermatol 2000; 136: 12, 1531-1535. **63** Margolis, D.J., Allen-Taylor, L., Hoffstad, O., Berlin, J.A. Diabetic neuropathic foot ulcers: predicting which ones will not heal. Am J Med 2003; 115: 8, 627-631.

64 Zimny, S., Schatz, H., Pfohl, M. Determinants and estimation of healing times in diabetic foot ulcers. J Diabetes Complications 2002; 16: 5, 327-332.

65 Schaper, N.C. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab Res Rev 2004; 20: (Suppl. 1), S90-95.

66 Treece, K.A., Macfarlane, R.M., Pound, N. et al. Validation of a system of foot ulcer classification in diabetes mellitus. Diabetic Med 2004; 21: 9, 987-991.