Review

@ Diabetic foot ulcers

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Ulceration of the foot in diabetes is common and disabling and frequently leads to amputation of the leg. Mortality is high and healed ulcers often recur. The pathogenesis of foot ulceration is complex, clinical presentation variable, and management requires early expert assessment. Interventions should be directed at infection, peripheral ischaemia, and abnormal pressure loading caused by peripheral neuropathy and limited joint mobility. Despite treatment, ulcers readily become chronic wounds. Diabetic foot ulcers have been neglected in health-care research and planning, and clinical practice is based more on opinion than scientific fact. Furthermore, the pathological processes are poorly understood and poorly taught and communication between the many specialties involved is disjointed and insensitive to the needs of patients.

In this review, we describe the epidemiology, pathogenesis, and management of diabetic foot ulceration, and its effect on patients and society. The condition deserves more attention, both from those who provide care and those who fund research.

Epidemiology

Incidence and prevalence

Although accurate figures are difficult to obtain for the prevalence or incidence of foot ulcers, the results of cross-sectional community surveys in the UK showed that 5·3% (type 2)[1] and 7·4% (type 1 and 2 combined)[2] of people with diabetes had a history of active or previous foot ulcer. The lifetime risk for any diabetic patient is up to 15%.[3] Ramsey and colleagues[4] noted a cumulative 3-year incidence of 5·8% in diabetic patients in the USA, but this value was based on hospital discharge data; community surveys have produced slightly higher figures. An annual incidence of 3·6% was reported in a randomly selected diabetic population in Sweden,[5] and a survey in the Netherlands found a mean incidence of new ulceration (in type 2 diabetes alone) of 2·1%.[6] This value was 2·2% in a large community survey in UK,[7] and up to 7·2% in patients with neuropathy.[8]

Amputation

In the absence of accurate data on foot ulceration, amputation rates are often used as a crude measure. Indeed, a 50% reduction in amputation was the target for improved foot care set by the St Vincent Declaration.[9] However, information on amputation can also be misleading,[10–12] and the definitions unclear. The terms amputation or lower extremity amputation, can be used to apply to all surgery, or restricted to amputation at or about the knee. Major amputation can mean either operations above the ankle or those proximal to the tarsometatarsal joint, and a multinational WHO survey on lower extremity amputation also included cases of unoperated gangrene.[13]

Moreover, amputation is a marker not just of disease but also of disease management. The decision to operate is determined by many factors, which vary between centres and patients. A high amputation rate might result from high disease prevalence, late presentation, and inadequate resources, but could also reflect a particular approach by local surgeons. In many cases, major amputation is not a mutilating admission of failure but the most appropriate way of ensuring an early return to a relatively independent existence. Conversely, a low rate of amputation might reflect better care, but might also conceal the effects of an inappropriately conservative approach—namely, protracted incapacity, suffering, and death with ulcers unhealed.

15–27% of all ulcers result in surgical removal of bone,[4,11–14] but rates vary between countries.[10,12] The annual incidence of all amputations in age-matched populations is significantly higher in the USA than in the Netherlands (5·0 per 1000 people with diabetes *vs* 3·6).[15]

Major amputation

The incidence of major amputation is 0·5–5·0 per 1000 people with diabetes.[16–18] In total populations, rates vary between countries, racial groups, and within countries and can exceed 20 per 100 000.[12,19–23] Some variation is due to race and real differences in incidence and severity,[24] but much will result from unequal access to care and differing opinion on best practice.[12]

Survival after amputation

Ulceration has a poor prognosis.[25,26] For amputation, perioperative mortality is 9% in the Netherlands[27] and

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Search strategy and selection criteria

The authors based the review on personal knowledge of the subject, supplemented by information derived from comprehensive reviews of the different aspects of the subject area. This information was crosschecked with repeated searches on PubMed for articles recently published using the following index terms: diabetes, foot ulcer, amputation, vascular surgery, neuropathy, osteomyelitis, Charcot.

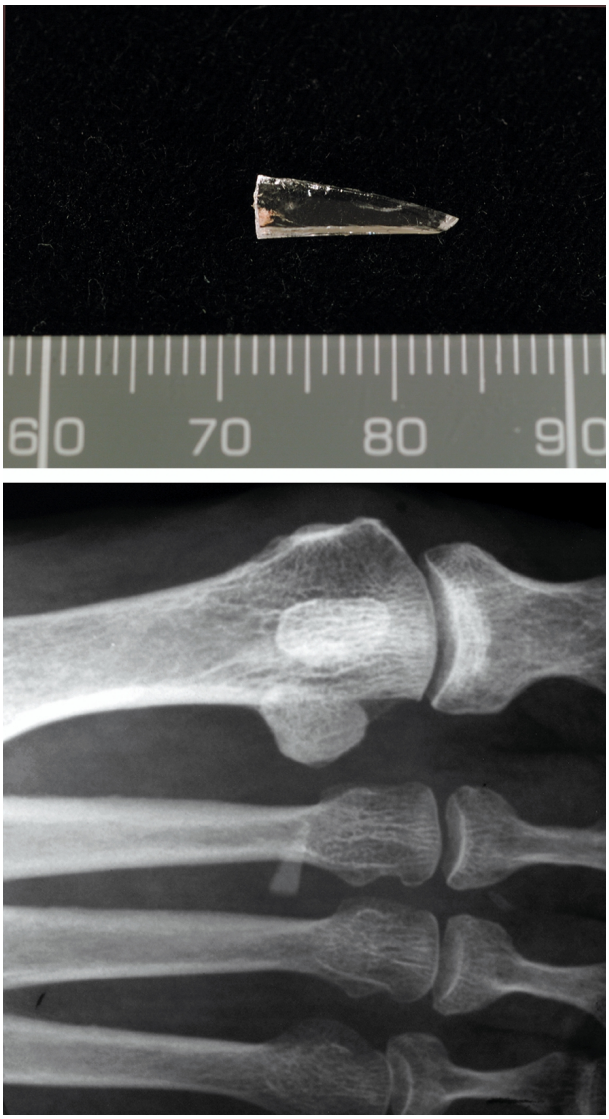

Figure 1: **Shard of glass (A) removed from sole of a patient's foot and (B) radiograph of foot showing shard before removal**

10–15% in the UK.[28] In Sweden and Italy, 3-year survival rates are 59% and 50%, respectively.[13,29] The high mortality reflects the old age, widespread vascular disease, and other complications of diabetes common to many amputation patients. Women tend to be almost 10 years older and have worse survival rates than men at the time of first amputation.[29] The USA has a better survival rate than Europe,[4,30] which could reflect faster access to specialised care, or a greater readiness to do amputations in young and otherwise fit people.

Predisposing and precipitating factors

Many overlapping factors lead to foot ulceration;[31–35] they put the foot at risk, precipitate a break in the skin, or impair healing. The peripheral neuropathy of diabetes results in abnormal forces being applied to the foot, which diabetic ischaemia renders the skin less able to withstand. Other complications contributing to the onset of ulceration include poor vision, limited joint mobility, and the consequences of cardiovascular and cerebrovascular disease. However, the most common precipitant is accidental trauma, especially from ill-fitting footwear.[32,36] Once the skin is broken, many processes contribute to defective healing.

Neuropathies

In diabetes, nerve damage results from interacting metabolic abnormalities, worsened by disease of the vasa nervorum.[37,38] The damage affects peripheral sensation, innervation of the small muscles of the foot, and fine vasomotor control of the pedal circulation. In sensory neuropathy, loss of protective sensation leads to lack of awareness of incipient or actual ulceration (figure 1). Motor neuropathy affects the muscles required for normal foot movement, altering the distribution of forces during walking and causing reactive thickening of skin (callus) at sites of abnormal load. Next, ischaemic necrosis of tissues beneath the callus leads to breakdown of skin and subcutaneous tissue, resulting in a neuropathic ulcer with a punched-out appearance (figure 2).

Arteriolar-venular shunting causes dysfunction of the microcirculation with reduced distribution of blood to areas of need. Thus, tissue ischaemia can occur in a foot with palpable pedal pulses. Vasomotor (autonomic) neuropathy affects the peripheral nerve function, which controls the distribution of blood through arteriolar vessels.[39,40] Indeed, pulses may be readily palpable and the veins on the dorsum of the foot distended.

The Charcot foot of diabetes, like that of syphilis, is manifest by dislocation or collapse of one or more joints or bones of the foot, occurring either spontaneously or after slight trauma. It is not simply the result of loss of pain sensation, and in fact is often painful in acute stages. The principal defect is osteopenia, with loss of structural integrity of the bone, which is thought to result from arteriolar-venular shunting of vasomotor neuropathy.[41,42] Slight trauma triggers fracture of a weakened bone, which increases the load on adjacent bones, leading to gross destruction. The process is self-limiting but the persisting deformity greatly increases the risk of secondary ulceration.

Ischaemia

Foot tissues can become ischaemic because of macrovascular disease (atherosclerosis), notably in the calf with relative sparing of proximal vessels and those in the foot. Ischaemia also results from microvascular disease—both structural (thickened basement membrane, capillary wall fragility, and thrombosis) and functional (vasomotor neuropathy with defective microcirculation and abnormal endothelial function).[43–45] Protective sweating is lost and the skin of the ischaemic foot is red, dry, thin with dystrophic nails, and susceptible to the pressure from a shoe or even an adjacent toe.

Figure 2: **Neuropathic ulcer in typical position under second metatarsal head and surrounded by callus**

Failure to heal

Bacterial infection, tissue ischaemia, continuing trauma, and poor management cause diabetic foot ulcers to heal slowly and transform readily into chronic wounds.

Infection

Infection is usually the consequence rather than the cause of foot ulceration, but can cause substantial deterioration and delay in healing, and clinicians should consider early use of antibiotics. Infection can be divided into three categories: superficial and local, soft tissue and spreading (cellulitis), and osteomyelitis. The contribution of yeasts and dermatophytes in chronic ulceration is uncertain.

Bacteria will be present irrespective of whether a wound seems clean or is covered by slough and debris. It can be difficult to determine whether these are harmless or the extent to which they impair healing by releasing locally acting substances. Therefore, a surface swab is insufficient to establish whether a wound is infected; microbiological results should be interpreted in relation to clinical circumstances. Without other evidence of infection, systemic antibiotics are not beneficial.[46]

With the more serious categories (cellulitis and osteomyelitis) diagnosis is mainly clinical, with imaging assistance in osteomyelitis. Soft-tissue infection is characterised by obvious inflammation if the foot is well perfused, but can be difficult to identify if the foot is ischaemic. It may be marked by an increase in exudate or by localised pain, and can trigger thrombosis of smaller end-arteries and arterioles: infection is the usual precipitant of localised digital gangrene (figure 3).

Clinical diagnosis of cellulitis and osteomyelitis can be supplemented by microbiology. Typically, more than one organism is involved, including gram-positive, gram-negative, aerobic, and anaerobic species[47]—though *Staphylococcus aureus* is the most common pathogen in osteomyelitis.[48] Sampling requires vigorous curettage, aspiration, scrubbing, and/or biopsy of deeper tissue with saline-moistened swabs, and material should be cultured quickly, both aerobically and anaerobically. However, at best there is poor correspondence between isolates from bone in osteomyelitis and from adjacent soft tissue.[48] In the real world, sampling may be limited to excluding particular organisms, such as meticillin-resistant *S aureus*, and it may be cost effective to choose the initial antibiotic regimen empirically.[49]

Ischaemia and distal sensory neuropathy

Since ischaemia can delay healing, revascularisation needs to be considered at an early stage. Distal symmetrical neuropathy leads to reduced protective behaviour: the patient is more likely to use the affected foot and the repair process will be compromised by continuing trauma.

Delays

Deterioration in a wound is more likely if assessment is delayed. In one specialist clinic, the median delay between onset of ulceration and first referral was 15 days.[36] The patient might be unaware of the ulcer or might avoid seeking advice for fear of being a nuisance or in the hope that the ulcer will heal on its own. However, delays are more likely to be caused by lack of speedy access to an informed opinion and by poor communication between specialist departments.[36]

Biology of the chronic wound

Wound healing involves a cascade of interacting phases of haemostasis, inflammation, proliferation, epithelialisation, and scar maturation, which can be affected by diabetes and its complications.[50–52] Impairment of leucocyte function and proliferation occur in hyperglycaemia,[53,54] but the overall effect of the disease on healing is complex. The benefit of good blood glucose control has not been assessed, but is likely to be important, even though the rate of healing of neuropathic ulcers does not differ between people with and without diabetes.[55]

Figure 3: **Digital gangrene**

Classification of foot ulcers

There is no widely accepted method for classifying or even describing foot ulcers.[56,57] Non-specialists commonly refer to all ulcers as diabetic foot. Two international working parties are trying to define a system of describing individual ulcers to improve communication and develop a classification for audit and research.[14,58] Without classification, selection of comparable populations for urgently needed multicentre trials will be impossible.

Principles of management

The first principle is to treat any infection; the second is to establish whether any associated ischaemia is amenable to revascularisation; the third is to keep forces applied to the ulcerated part to a minimum; and the fourth is to improve the condition of the wound or ulcer by wound-bed preparation, topical applications, and removal of callus. Once the wound has healed, attention can be turned to the prevention of ulcer recurrence.

Eradication of infection

The antibiotic regimen chosen should be based on the anticipated spectrum of infecting organisms. The combination of an aminopenicillin and a penicillinase inhibitor has the required activity, but other options include a quinolone plus either metronidazole or clindamycin.[47,59] Intravenous options for soft-tissue infection include imipenem and gentamicin. Vancomycin, teicoplanin, rifampicin, or linezolid should be used for meticillin-resistant *S aureus*.[60,61]

The same broad-spectrum antibiotics are appropriate for osteomyelitis. Beta-lactams and quinolones are concentrated intracellularly at the site of infection, and clindamycin penetrates bones well. It has always been taught that infected bone should be removed,[33,62] but a non-surgical approach might be effective.[63–65] The relative benefits of parenteral versus oral antibiotics are not known, but the parenteral route is preferred if the foot is severely ischaemic or in cases of systemic illness. Nor is the optimum duration of treatment known, though most clinicians opt for prolonged courses despite risks of inducing antibiotic resistance.

Remediable macrovascular disease

Clinical evidence and positive non-invasive tests for macrovascular disease, such as an ankle/brachial pressure index below 0·8, toe systolic pressure of less than 30 mm Hg, reduced transcutaneous oxygen tension, and abnormal duplex waveform on ultrasonography, indicate the need for assessment by a vascular surgical team. Options for revascularisation include angioplasty, thrombolysis, and bypass surgery. Distal bypass to the pedal vessels is increasingly common,[45,66–69] though with regional variations.[28] Despite a huge increase in revascularisation procedures in the past 20 years, the effect on the rate of major amputation has been disappointing.[70] The potential benefit is clear,[71,72] but the place of revascularisation has yet to be precisely defined.[73]

Off-loading

It is unrealistic to tell a patient to immobilise the foot for the time required for healing, and immobilisation carries the risk of thrombosis, muscle wasting, depression, and secondary ulceration elsewhere. Instead, custom-made orthotic devices and plaster or fibreglass casts are used to off-load the wound while allowing the patient to remain partly active. These devices can greatly lower plantar pressures,[74] but patients dislike and may choose not to wear them, especially in the home.[75,76] Devices that cannot be taken off are more effective.[77,78] Off-loading devices might be impractical for patients who are frail or susceptible to falls, and a disadvantage of devices that cannot be removed is interference with bathing and showering.

Ulcer management

Wound bed preparation removes many specific impediments to healing, including necrotic tissue, exudate, bacteria, and abnormal cells.[79] Ulcers heal more quickly if their surface is clean and if sinuses are laid open. Vigorous and repeated sharp debridement of the wound is recommended, although evidence for efficacy is slim.[80] Complete excision of neuropathic ulcers did lead to healing in a mean of 31[81] and 47[82] days, as opposed to 129 days in non-randomised controls managed more conservatively.[82]

Necrotic material can also be removed with debriding agents (enzymes, hydrogels, and hydrocolloids) although evidence to justify their use is not available.[83] Larval therapy (maggots) to clean the wound bed,[84] though not immediately appealing, does merit further study. Antiseptics containing iodine and silver have also been promoted but once again, the evidence base for their use is slight.[85]

Attention has also focused on controlling oedema, and significant benefit from a foot-compression device has been shown after debridement.[86] No reliable evidence supports the use of hyperbaric oxygen.[85]

Although dressings also help protect the ulcer from injury and secondary infection, their principal use is to provide a warm, moist environment to promote tissue repair.[87] Such products include hydrogels, hydrocolloids, films, foams, and alginates and there are no scientific grounds for preferring any one of them.[83,85,88,89] Nevertheless, theoretical criteria for making a choice do exist[89–91] and these criteria need to be formally assessed.

There is considerable interest in the therapeutic potential of growth factors.[92–94] Two trials have shown significant, but small, benefit from recombinant platelet-derived growth factor (becaplermin).[95,96] Granulocyte-colony stimulating factor accelerated the resolution of infection in a pilot study,[97] and results from a randomised trial suggested a reduction in amputation done for osteomyelitis[98] that has yet to be substantiated.[99]

Some of the effects of allografts might result from their capacity to release growth factors, but promotion of angiogenesis might be another explanation.[100] Unblinded clinical studies showed a significant improvement in healing.[101,102] This approach is expensive, but a case can be made for its use in selected patients.[103]

Prevention

Primary prevention is the aim of diabetes management, but secondary prevention is the goal of good foot-ulcer care. The recurrence rate is high[13] and ulcer healing should be followed by a well coordinated programme of secondary prevention. Sadly, this approach is beyond the capacity of health services in most countries. Surgery to correct deformities and abnormalities of posture, gait, and load-bearing[74] (eg, lengthening the achilles tendon) has a place in both primary and secondary prevention, but is probably underused.

Primary prevention

Improved blood-glucose control will reduce microvascular complications, and reduction in cardiovascular risk factors will render the foot less susceptible to ischaemia from macrovascular disease. Routine surveillance will detect patients whose feet are at risk, and they should receive targeted care. Modelling indicates that this approach would be cost effective,[104] but primary prevention programmes have not always been beneficial.[105–08] The case for primary prevention might seem self-evident, but is not yet evidence based.[109]

Secondary prevention

A previous lesion is strongly predictive for new ulceration.[7,110] Efforts should be made to reduce abnormal pressure loading,[74] which might involve cushioning in frail and immobile people and individually fitted footwear in those who are mobile, but such interventions need to be properly targeted.[111]

Education should focus on foot care, regular podiatry, self-examination,[29] and provision of emergency contacts. Education improves knowledge and illness-related behaviour,[112] and led in one trial to a three-fold reduction in re-ulceration and amputation within 13 months,[113] whereas McCabe and colleagues[114] showed reduction in amputation but not in new ulceration. These findings require confirmation.[115] Educational effort might be more effective if aimed mainly at professionals.[36]

Structure of care

Successful management of diabetic foot ulcers requires close collaboration between many different groups in primary care and in the hospital service, and this collaboration might not be easy to establish while traditional barriers between health-care professionals remain in place. Supervision is also made difficult by the frequent coincidence of both social and medical problems, when the patient may be looked after by independent teams of professional carers. The needs and wishes of the patient (or his or her family) in influencing management choices are critical, and informed decisions by the patient should be an essential part of the process. Patients and carers should be counselled by trained health-care professionals at every stage, and should have ready access to a second opinion. The four-fold regional variation in incidence of major amputation reported both in the Netherlands and in the UK[22,23] suggests that patients are not always as informed and influential as they should be.

Assessing effectiveness of care

The effectivenesss of recommended practice needs rigorous assessment, and for that more meaningful measurements have to be available. A reduction in major amputations has been reported by some specialist units,[29,71,116–118] including those serving an entire community where altered referral practice is not an issue. In some cases, however, the initial rate was rather high.[71,116] Other studies record no change in incidence of amputation,[119–121] or even an increase.[122,123] However, as discussed earlier, the amputation rate may not be a good marker of the quality of clinical care and better endpoints are required.

Effectiveness can be judged in terms of outcomes relating to the ulcer, the limb, and the patient, and all three should be considered together. It would be absurd, for example, to emphasise the healing of one ulcer when another ulcer on the same foot results in loss of the leg. The most appropriate end point is complete healing without amputation, but this is often not achieved.

Ulcer outcome

In a cohort of 558 people, only 345 (62%) healed after primary treatment; 123 (22%) healed after surgery and 90 (16%) died unhealed.[13] In deep infections, the rate of healing without surgery can drop to 40%,[124] with a median healing time of 24 weeks; with surgery this rate increases to 52 (minor amputation) and 38 weeks (major amputation). Of 389 ulcers (in 179 people, newly referred) only 33% healed without surgery within 3 months. Of those followed up for 6 months, 48% healed without surgery, while 40% were unhealed; six patients lost a lower limb; and ten died (unpublished data from Nottingham City Hospital, 2000).

Rates and speed of healing are best in ulcers that are mainly a result of neuropathy. In trials of off-loading techniques, 21–50% of patients healed within 30 days,[77] and 58–90% within 12 weeks.[76] Piaggesi and colleagues[82] reported 79% healing at 25 weeks in neuropathic ulcers after conventional treatment, compared with 96% after excision of the ulcer and adjacent bone.[82] However, despite good management, healing rates in large multicentre trials were 24% at 12 weeks and 31% at 20 weeks.[125]

Patients' outcome

Since perioperative and postoperative mortality rates are high, crude data for amputation incidence are insufficient; survival, functional outcomes, and quality of life should be assessed by measures such as the SF-36 health survey, Barthel index, walking and walking stairs questionnaire, and Euroqol-5D.[126–128] Using the psychological adjustment to illness scale and hospital anxiety and depression scale, Carrington and colleagues showed worse adjustment to illness and significantly more depression in patients with active ulcers than in diabetic controls.[129] In addition to these generic measures, one disease-specific scale has recently been developed and validated and its use considered for future clinical studies.[130]

Outpatient dressings and nursing time contribute most to the cost of care for ulcer patients in Europe.[91,124] These costs are met by various care agencies and could be difficult to collate. In the USA, the principal identified costs are those of inpatient care.[131]

Conclusions

Investment is urgently needed for basic research into the pathophysiology of chronic wounds. Clinical management lacks a scientific basis and is determined by personal preference and the availability of local expertise and facilities. Therefore, clinicians should identify differences between centres, and undertake robust clinical trials of management, using appropriate end-points. Speedy and effective care will be possible only with effective communication and collaboration between all relevant professionals. Many foot-care teams are described as multidisciplinary, but might still be restricted by traditional working practices. Specialist subregional centres should be established as in the USA and Denmark.[132,133]

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References

1 Kumar S, Ashe HA, Parnell LN et al. The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. *Diabet Med* 1994; **11:** 480–84.
2 Walters DP, Gatling W, Mullee MA, et al. The distribution and severity of diabetic foot disease: a community study with comparison to non-diabetic group. *Diabet Med* 1992; **9:** 354–58.
3 Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. *Am J Surg* 1998; **176:** 5S–10S.
4 Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diab Care* 1999; **22:** 382–87.
5 Henriksson F, Agardh C-D, Berne C, et al. Direct medical costs for patients with type 2 diabetes in Sweden. *J Intern Med* 2000; **248:** 387–96.
6 Muller IS, de Grauw WJC, van Gerwen WHEM, et al. Foot amputation and lower limb amputation in type 2 diabetic patients in Dutch primary health care. *Diab Care* 2002; **25:** 570–74.
7 Abbott CA, Carrington AL, Ashe H, et al. The NorthWest Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based cohort. *Diabet Med* 2002; **19:** 377–84.
8 Abbott CA, Vileikyte L, Williamson S, et al. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diab Care* 1998; **21:** 1071–75.
9 World Health Organization (Europe) and International Diabetes Federation (Europe). Diabetes care and research in Europe: the Saint Vincent Declaration. *Diabet Med* 1990; **7:** 360.
10 Chaturvedi N, Stevens LK, Fuller JH, et al. Risk factors, ethnic differences and mortality associated with lower-extremity gangrene and amputation in diabetes: the WHO multinational study of vascular disease in diabetes. *Diabetologia* 2001; **44** (suppl 2)**:** S65–71.
11 Oyibo SO, Jude EB, Tarawneh I, et al. The effects of ulcer size, patient's age, gender and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med* 2001; **18:** 133–38.
12 Group TG. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia: the global lower extremity amputation study group. *Br J Surg* 2000; **87:** 328–37.
13 Apelqvist J, Larsson J, Agardh C-D. Long-term prognosis for diabetic patients with foot ulcers. *J Intern Med* 1993; **233:** 485–91.
14 Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. *Diab Care* 1998; **21:** 855–59.
15 Van Houtum WH, Lavery LA. Outcomes associated with diabetes-related amputations in The Netherlands and in the state of California, USA. *J Intern Med* 1996; **240:** 227–31.
16 Van Houtum WH, Lavery LA, Harkless LB. The impact of diabetes-related lower-extremity amputations in The Netherlands. *J Diabetes Comp* 1996; **10:** 325–30.
17 Witsø E, Rønningen H. Lower limb amputations: registration of all

lower limb amputations performed at the University Hospital of Trondheim, Norway, 1994–1997. *Prosthet Orthop Int* 2001; **25:** 181–85.
18 Calle-Pascual AL, Redondo MJ, Ballesteros M, et al. Nontraumatic lower extremity amputations in diabetic and non-diabetic subjects in Madrid, Spain. *Diabets Metab* 1997; **23:** 519–23.
19 Spichler ERS, Spichler D, Lessa I, et al. Capture-recapture method to estimate lower extremity amputation rates in Rio de Janeiro, Brazil. *Pan Am J Public Health* 2001; **19:** 334–40.
20 Trautner C, Giani G, Haastert B, et al. Unchanged incidence of lower-limb amputations in a German city, 1990–1998. *Diab Care* 2001; **24:** 855–59.
21 Wrobel JS, Mayfield JA, Reiber GE. Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. *Diab Care* 2001; **24:** 860–64.
22 Van Houtum WH, Lavery LA. Regional variation in the incidence of diabetes-related amputation in The Netherlands. *Diabetes Res Clin Pract* 1996; **31:** 125–32.
23 Canavan R, Connolly V, Airey CM, et al. A population based study of lower extremity amputations among four UK centres *Diabet Med* 2002; **19** (suppl 2)**:** A23.
24 Chaturvedi N, Abbott CA, Whalley A, et al. Risk of diabetes-related amputation in South Asians vs Europeans in the UK. *Diabet Med* 2002; **19:** 99–104.
25 Boyko EJ, Ahroni JH, Smith DG, et al. Increased mortality associated with diabetic foot ulcer. *Diabet Med* 1996; **13:** 967–72.
26 Moulik P, Gill G. Mortality in diabetic patients with foot ulcers. *Diabet Foot* 2002; **5:** 51–53.
27 Lavery LA, van Houtum WH, Harkless LB. In-hospital mortality and disposition of the diabetic amputees in The Netherlands. *Diabet Med* 1996; **13:** 192–97.
28 da Silva AF, Desgranges P, Holdsworth J, et al. The management and outcome of critical limb ischaemia in diabetic patients: results of a national survey. Audit Committee of the Vascular Surgical Society of Great Britain and Ireland. *Diabet Med* 1996; **13:** 726–28.
29 Faglia E, Favales F, Morabito A. New ulceration, new major amputation, and survival rats in diabetic subjects hospitalised for foot ulceration from 1990 to 1993: a 6·5 year follow-up. *Diab Care* 2001; **24:** 78–83.
30 Lee JS, Lu M, Lee VS, et al. Lower-extremity amputation: incidence, risk factors, and mortality in the Oklahoma Indian diabetes study. *Diabetes* 1993; **42:** 876–82.
31 Boulton AJM. The pathway to ulceration: aetiopathogenesis. In: Boulton AJM, Connor H, Cavanagh PR, eds. The foot in diabetes. Chichester: John Wiley and Sons, **2000:** 19–31.
32 Reiber GE, Vileikyte L, Boyko EJ, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diab Care* 1999; **22:** 157–62.
33 American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care. *Diab Care* 1999; **22:** 1354–60.
34 International Consensus on the Diabetic Foot. Amsterdam: International Working Group on the Diabetic Foot, 1999.
35 Adler EI, Boyko EJ, Ahroni JH, et al. Lower-extremity amputation in diabetes: the independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. *Diab Care* 1999; **22:** 1029–35.
36 Macfarlane RM, Jeffcoate WJ. Factors contributing to the presentation of diabetic foot ulcers. *Diabet Med* 1997; **14:** 867–70.
37 Greene DA, Stevens MJ, Feldman EL. Diabetic neuropathy: scope of the syndrome. *Am J Med* 1999; **107:** 2S–8S.
38 Vinik AI. Diabetic neuropathy: pathogenesis and therapy. *Am J Med* 1999; **107:** 17S–26S.
39 Vinik AI, Erbas T, Park TS, et al. Dermal neurovascular dysfunction in type 2 diabetes. *Diab Care* 2001; **24:** 1468–75.
40 Nabuurs-Franssen MH, Houben AJHM, Tooke JE, Schaper NC. The effect of polyneuropathy on foot microcirculation in type II diabetes. *Diabetologia* 2002; **45:** 1164–71.
41 Jeffcoate W, Lima J, Nobrega L. The Charcot foot. *Diabet Med* 2000; **17:** 253–58.
42 Rajbandhari SM, Jenkins RC, Davies C, Tesfaye S. Charcot neuroarthropathy in diabetes mellitus. *Diabetologia* 2002; **45:** 1085–96.
43 Strandness DE, Priest RE, Gibbons GE. Combined clinical and pathological study of diabetic and non diabetic peripheral arterial disease. *Diabetes* 1964; **13:** 366–72.
44 LoGerfo FW, Coffman JD. Vascular and microvascular disease of the foot in diabetes. *N Engl J Med* 1984; **311:** 1615–19.
45 Akbari CM, LoGerfo FW. Diabetes and peripheral vascular disease. *J Vasc Surg* 1999; **30:** 373–84.
46 Chantelau E, Tanudjaja T, Altenhofer F, et al. Antibiotic treatment for uncomplicated neuropathic forefoot ulcers in diabetes: a controlled trial. *Diabet Med* 1996; **13:** 156–59.
47 Lipsky BA, Berendt AR. Principles and practice of antibiotic therapy of diabetic foot infections. *Diabet Metab Res Rev* 2000; **16** (suppl)**:** 42–46.
48 Lipsky BA. Osteomyelitis of the foot in diabetic patients. *Clin Infect Dis* 1997; **25:** 1318–26.
49 Eckman MH, Greenfield S, Mackey WC, et al. Foot infections in diabetic patients. *JAMA* 1995; **273:** 712–20.
50 Hamilton AI, Blackwood HJ. Insulin deficiency and cell proliferation in oral mucosal epitheliam of the rat. *J Anat* 1977; **124:** 757–63.
51 Yue DK, Swanson B, McLellan S, et al. Abnormalities of granulation tissue and collagen formation in experimental diabetes, uraemia and malnutrition. *Diabet Med* 1986; **3:** 221–25.
52 Tengrup L, Hallmans G, Agren MS. Granulation tissue formation and metabolism of zinc and copper in alloxan—diabetic rats. *Sanc J Plast Reconstr Surg Hand Surg* 1998; **22:** 41–45.
53 Delamaire M, Maugendre D, Moreno M, et al. Impaired leucocyte function in diabetic patients. *Diabet Med* 1997; **14:** 29–34.
54 Loots MA, Lamme EN, Zeegelgar J, et al. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous leg ulcers versus acute wounds. *J Invest Dermatol* 1998; **111:** 850–57.
55 Birke JA, Novick A, Patout CA, et al. Healing rates of plantar ulcers in leprosy and diabetes. *Lepr Rev* 1992; **63:** 365–74.
56 Jeffcoate WJ, Macfarlane RM, Fletcher EM. The description and classification of foot ulcers. *Diabet Med* 1993; **10:** 676–79.
57 Armstrong DG, Peters EJG. Classification of wounds of the diabetic foot. *Current Diab Reports* 2001; **1:** 233–38.
58 Macfarlane RM, Jeffcoate WJ. Classification of diabetic foot ulcers: the S(AD) SAD system. *Diabet Foot* 1999; **2:** 123–31.
59 Lipsky BA. A current approach to diabetic foot infections. *Curr Infect Dis Rep* 1999; **1:** 253–60.
60 Tentolouris N, Jude EB, Smirnof I, et al. Methicillin-resistant *Staphylococcus aureus*: an increasing problem in a diabetic foot clinic. *Diabet Med* 1996; **16:** 767–71.
61 Wagner A, Reike H, Angelkort B, et al. Highly resistant pathogens in patients with diabetic foot syndrome with special reference to methicillin-resistant *Staphylococcus aureus* infections. *Dtsch Med Wochenschr* 2001; **126:** 1353–56.
62 Norden CW. Acute and chronic osteomyelitis. In: Armstrong D, Cohen J, eds. Infectious diseases. London: Mosby Wolfe 1999; **2:** 1–9.
63 Venkatesan P, Lawn S, Macfarlane RM, et al. Conservative management of osetomyelitis in the feet of diabetic patients. *Diabet Med* 1997; **14:** 487–90.
64 Pittet D, Wyssa B, Herter-Clavel C, et al. Outcome of diabetic foot ulcerations treated conservatively: a retrospective cohort study with long-term follow-up. *Arch Intern Med* 1999; **159:** 851–56.
65 Embil J. The management of diabetic foot osteomyelitis. *Diabet Foot* 2000; **3:** 76–83.
66 McGee SR, Boyko EJ. Physical examination, chronic lower-extremity ischemia: a critical review. *Arch Intern Med* 1998; **158:** 1357–64.
67 Holstein PE, Sorensen S. Limb salvage experience in a multidisciplinary diabetic foot clinic. *Diab Care* 1999; **22** (suppl 2)**:** B97–103.
68 Taylor RS, Belli AM, Jacob S. Distal venous arterialisation for salvage of critically ischaemic inoperable limbs. *Lancet* 1999; **354:** 1962–65.
69 Akbari CM, Pomposelli FB Jr, Gibbons GW, et al. Lower extremity revascularisation in diabetes: late observations. *Arch Surg* 2000; **135:** 452–56.
70 Tunis SR, Bass EB, Steinberg EP. The use of angioplasty, bypass surgery and amputation in the management of peripheral vascular disease. *N Engl J Med* 1991; **325:** 556–62.
71 Holstein P, Ellitsgaard N, Olsen BB, et al. Decreasing incidence of major amputations in people with diabetes. *Diabetologia* 2000; **43:** 844–47.
72 Isaksson L, Lundgren F. Vein bypass surgery to the foot in patients with diabetes and critical ischaemia. *Br J Surg* 1994; **81:** 517–20.
73 Bradbury AW, Ruckley CV. Angioplasty for lower-limb ischaemia: time for randomised controlled trials. *Lancet* 1996; **347:** 277–78.
74 Cavanagh PR, Ulbrecht JS, Caputo GM. What the practising physician should know about diabetic foot mechanics. In: Boulton AJM, Connor H, Cavanagh PR, eds. The foot in diabetes. Chichester: John Wiley and Sons, **2000:** 33–59.
75 Chantelau E, Haage P. An audit of cushioned diabetic footwear: relation to patient compliance. *Diabet Med* 1994 **11:** 114–16.
76 Armstrong DG, Abu-Rumman PL, Nixon BP, et al. Continuous activity monitoring in persons at high risk for diabetes-related lower-extremity amputation. *J Am Podiat Med Assoc* 2001; **9:** 451–55.
77 Caravaggi C, Faglia E, De Giglio R, et al. Effectiveness and safety of a non-removable fibreglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomised study. *Diab Care* 2000; **23:** 1746–51.

78 Armstrong DG, Nguyen HC, Lavery LA, et al. Off-loading the diabetic foot wound. *Diab Care* 2001; **24:** 1019–22.

79 Falanga V. Classification for wound bed preparation of chronic wounds. *Wound Rep Regen* 2000; **8:** 347–52.

80 Bradley M, Cullum N, Sheldon T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1999; **3:** no 17, part 1.

81 Blume PA, Paragas LK, Sumpio BE, et al. Single-stage surgical treatment of noninfected diabetic foot ulcers. *Plast Reconstr Surg* 2002; **109:** 601–09.

82 Piaggesi A, Schipani E, Campi F, et al. Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomised trial. *Diabet Med* 1998; **15:** 412–17.

83 O'Meara S, Cullum, N, Majid M, Sheldon T. Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. *Health Technol Assess* 2000; **4:** no 21.

84 Mumcuoglu KY. Clinical applications for maggots in wound care. *Am J Clin Dermatol* 2000; **2:** 219–27.

85 Mason J, O'Keffe C, Hutchinson A, et al. A systematic review of foot ulcer in patients with type 2 diabetes mellitus: II—treatment. *Diabet Med* 1999; **16:** 889–909.

86 Armstrong DG, Nguyen HC. Improvement in healing with aggressive edema reduction after debridement of foot infection in persons with diabetes. *Arch Surg* 2000; **135:** 1405–09.

87 Harding KG, Morris HL, Patel GK. Healing chronic wounds. *BMJ* 2002; **324:** 160–63.

88 De P, Scarpello JHB. What is the evidence for effective treatment of diabetic foot ulceration? *Pract Diabetes Int* 1999; **16:** 179–84.

89 Bradley M, Cullum N, Nelson EA, et al. Systematic reviews of wound care management: (2) dressings and topical agents used in the healing of chronic wounds. *Health Technol Assess* 1999; **3:** no 17, part 2.

90 Harding KG, Jones VJ, Price P. Topical treatment: which dressing to choose. *Diabet Metab Res Rev* 2000; **16** (suppl 1)**:** 547–50.

91 Harding K, Cutting K, Price P. The cost-effectiveness of wound management protocols of care. *Brit J Nurs* 2000; **19:** S6–S24.

92 Cooper DM, Yu E Z, Hennesey P, et al. Determination of endogonous cytokines in chronic wounds. *Ann Surg* 1994; **219:** 668–92.

93 Ross R. Platelet-derived growth factor. *Lancet* 1989; **1:** 1179–82.

94 Margolis D J, Kantor J, Santanna J, et al. Effectiveness of platelet releasate for the treatment of diabetic neuropathic fott ulcers. *Diab Care* 2001; **24:** 483–88.

95 Steed DL. Clinical evaluation of recombinant human platelet derived growth factors for the treatment of lower extremity diabetic ulcers. *J Vasc Surg* 1995: **21:** 71–81.

96 Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet derived growth factor BB (Becaplermin) in platelets with chronic neuropathic diabetic foot ulcers: a phase III randomised placebo controlled double blind study. *Diab Care* 1998; **21:** 822–27.

97 Gough A, Clapperton M, Rolando N, et al. Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot ulceration. *Lancet* 1997; **350:** 855–59.

98 de Lalla F, Pellizer G, Strazzabosco M, et al. Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection. *Antimicrob Agents Chemother* 2000; **45:** 1094–98.

99 Yonem A, Cakir B, Guler S, et al. Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. *Diabetes Obes Metab* 2001; **3:** 332–37.

100 Martin T, Harding KG, Jiang WG. Regulation of angiogenesis and endothelial cell motility by matrix-bound fibroblasts. *Angiogenesis* 1999; **3:** 69–76.

101 Pollak RA, Edington H, Jensen JL, et al. A human dermal replacement for the treatment of diabetic foot ulcers. *Wounds* 1997; **9:** 175–83.

102 Veves A, Flanaga V, Armstrong DG, et al. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomised multicenter trial. *Diab Care* 2001; **24:** 290–95.

103 Allenet B, Paree F, Lebrun T, et al. Cost-effectiveness modelling of Dermagraft for the treatment of diabetic foot ulcers in the French context. *Diabet Metab* 2000; **26:** 125–32.

104 Ragnarsson Tennvall G, Apelqvist J. Prevention of diabetes-related foot ulcers and amputations: a cost-utility analysis based on Markov model simulations. *Diabetologia* 2001; **44:** 2077–81.

105 Patout CA, Birke JA, Horswell R, et al. Effectiveness of a comprehensive diabetes lower-extremity amputation prevention program in a predominantly low-income African-American population. *Diab Care* 2000; **23:** 1339–42.

106 Rith-Najarian S, Branchard C, Beaulieu O, et al. Reducing lower-extremity amputations due to diabetes: application of the staged diabetes management approach in a primary care setting. *J Fam Pract* 1998; **47:** 127–32.

107 Mayfield JA, Reiber GE, Nelson RG, et al. Do foot examinations reduce the risk of diabetic amputation ? *J Fam Pract* 2000; **49:** 505–06.

108 Bruckner M, Mangan M, Godin S, et al. Project LEAP of New Jersey: lower extremity amputation prevention in persons with type 2 diabetes. *Am J Manag Care* 1999; **5:** 609–16.

109 Valk GD, Kriegsman DMW, Assendelft WJ. Patient education for preventing diabetic foot ulceration: a systematic review. *Endocrinol Metab Clin N Am* 2002; **31:** 633–58.

110 Litzelman DK, Marriott DJ, Vinicor F. Independent physiological predictors of foot lesions in patients with NIDDM. *Diab Care* 1997; **20:** 1273–78.

111 Reiber GE, Smith DG, Wallace C, et al. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomised controlled trial. *JAMA* 2002; **287:** 2552–58.

112 Barth R, Campbell LV, Allen S, et al. Intensive education improves knowledge, compliance, and foot problems in type 2 diabetes. *Diabet Med* 1991; **8:** 111–17.

113 Malone JM, Snyder M, Anderson G, et al. Prevention of amputation by diabetic education. *Am J Surg* 1989; **158:** 520–24.

114 McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. *Diabet Med* 1998; **15:** 80–84.

115 Valk GD, Kriegsman DM, Assendelft WJ. Patient education for preventing diabetic foot ulceration. *Cochrane Database Syst Rev* 2001; **4:** CD001488.

116 Larsson J, Apelqvist J, Agardh C-D, et al. Decreasing incidence of lower limb amputations in diabetic patients: a consequence of a multidisciplinary foot care team approach? *Diabet Med*; 1995; **12:** 770–76.

117 Calle-Pascual AL, Garcia-Torre N, Moraga I, et al. Epidemiology of nontraumatic lower-extremity amputations in Area 7, Madrid, between 1989 and 1999. *Diab Care* **24:** 1686–89.

118 Faglia E, Favales F, Aldeghi A, et al. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. *J Diabet Comp* 1998; **12:** 96–102.

119 Trautner C, Haastert B, Spraul M, et al. Unchanged incidence of lower-limb amputation in a German City 1990–1998. *Diab Care* 2001; **24:** 855–59.

120 Mayfield JA, Reiber GE, Maynard C, et al. Trends in lower limb amputation in the Veterans Health Administration, 1989–1998. *J Rehab Res Devel* 2000; **37:** 23–30.

121 Stiegler H, Standl E, Frank S, et al. Failure of reducing lower extremity amputations in diabetic patients: results of two subsequent population based surveys 1990 and 1995 in Germany. *Vasa* 1998; **27:** 10–14.

122 Feinglass J, Brown JL, LoSasso A, et al. Rates of lower-extremity amputation and arterial reconstruction in the United States, 1979 to 1996.

123 Anon. Hospital discharge rates for nontraumatic lower extremity amputation by diabetes status—United States, 1997. *MMWR Morb Mortal Wkly Rep* 2001; **50:** 954–58.

124 Tennvall GR, Apelqvist J, Eneroth M. Costs of deep foot infections in patients with diabetes mellitus. *Pharmacoeconomics* 2000; **18:** 225–38.

125 Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment: a meta-analysis. *Diab Care* 1999; **22:** 692–95.

126 Vileikyte L. Diabetic foot ulcers: a quality of life issue. *Diabetes Metab Res Rev* 2001; **17:** 246–49.

127 Meijer JW, Trip J, Jaegers SM, et al. Quality of life in patients with diabetic foot ulcers. *Disabil Rehabil* 2001; **20:** 336–40.

128 Ragnarsson Tennvall G, Apelqvist J. Health-related quality of life in patients with diabetes mellitus and foot ulcers. *J Diabet Compl* 2000; **14:** 235–41.

129 Carrington AL, Mawdsley SK, Morley M, et al. Psychological status of diabetic people with or without lower limb disability. *Diabetes Res Clin Pract* 1996; **32:** 19–25.

130 Abetz L, Sutton M, Brady L, McNulty P, Gagnon DD. The diabetic foot ulcer scale (DFS): a quality of life instrument for use in clinical trials. *Pract Diab Int* 2002; **19:** 167–75.

131 Harrington C, Zagari MJ, Corea J, et al. A cost analysis of diabetic lower-extremity ulcers. *Diab Care* 2000; **23:** 1333–38.

132 Steed DL, Edington H, Mossa HH, et al. Organisation and development of a university multidisciplinary wound care clinic. *Surgery* 1993; **114:** 775–79.

133 Gottrup F, Holstein P, Jørgensen B, Lohmann M, Karlsmar T. A new concept of a multidisciplinary wound healing center and a national expert function of wound healing. *Arch Surg* 2001; **136:** 765–72.