Diabetes: foot ulcers and amputations

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ABSTRACT

INTRODUCTION: Diabetic foot ulceration is full-thickness penetration of the dermis of the foot in a person with diabetes. Severity is classified using the Wagner system, which grades it from 1 to 5. The annual incidence of ulcers among people with diabetes is 2.5–10.7% in resource-rich countries, and the annual incidence of amputation for any reason is 0.25–1.8%. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent foot ulcers and amputations in people with diabetes? What are the effects of treatments in people with diabetes with foot ulceration? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 41 systematic reviews and RCTs that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: debridement, human cultured dermis, human skin equivalent, patient education, pressure off-loading with felted foam or pressure-relief half-shoe, pressure off-loading with total-contact or non-removable casts, screening and referral to foot care clinics, systemic hyperbaric oxygen for non-infected ulcers, systemic hyperbaric oxygen in infected ulcers, therapeutic footwear, topical growth factors, and wound dressings.

QUESTIONS

INTERVENTIONS

Key points

- Diabetic foot ulceration is full-thickness penetration of the dermis of the foot in a person with diabetes. Severity is classified using the Wagner system, which grades it from 1 to 5.

  The annual incidence of ulcers among people with diabetes is 2.5–10.7% in resource-rich countries, and the annual incidence of amputation for any reason is 0.25–1.8%.

  For people with healed diabetic foot ulcers, the 5-year cumulative rate of ulcer recurrence is 66% and of amputation is 12%.

- The most effective preventive measure for major amputation seems to be screening and referral to a foot care clinic if high-risk features are present.

  Other interventions for reducing the risk of foot ulcers include wearing therapeutic footware, and increasing patient education for prevention, but we found no sufficient evidence to ascertain the effectiveness of these treatments.

- Pressure off-loading with total-contact casting or non-removable fibreglass casts successfully improves healing of ulcers.

  Removable-cast walkers rendered irremovable seem equally effective, but have the added benefit of requiring less technical expertise for fitting.

  We don't know whether pressure off-loading with felted foam or pressure-relief half-shoe is effective in treating diabetic foot ulcers.

- Human skin equivalent (applied weekly for a maximum of 5 weeks) seems better at promoting ulcer healing than saline moistened gauze.

  Human cultured dermis does not seem effective at promoting healing.

- Topical growth factors seem to increase healing rates, but there has been little long-term follow-up of people treated with these factors.
- Systemic hyperbaric oxygen seems to be effective in treating people with severely infected ulcers, although it is unclear whether it is useful in people with non-infected, non-ischaemic ulcers.
- We don't know whether debridement or wound dressings are effective in healing ulcers.

  However, debridement with hydrogel and dimethyl sulfoxide wound dressings does seem to help ulcer healing.

  Debridement and wound dressings have been included together because the exact mechanism of the treatment can be unclear (e.g. hydrogel).

DEFINITION

Diabetic foot ulceration is full-thickness penetration of the dermis of the foot in a person with diabetes. Ulcer severity is often classified using the Wagner system. [1] **Grade 1** ulcers are superficial ulcers involving the full skin thickness but no underlying tissues. **Grade 2** ulcers are deeper, penetrating down to ligaments and muscle, but not involving bone or abscess formation. **Grade 3** ulcers are deep ulcers with cellulitis or abscess formation, often complicated with osteomyelitis. Ulcers with localised gangrene are classified as **Grade 4**, and those with extensive gangrene involving the entire foot are classified as **Grade 5**.

INCIDENCE/ PREVALENCE

Studies conducted in Australia, Finland, the UK, and the USA have reported the annual incidence of foot ulcers among people with diabetes as 2.5–10.7%, and the annual incidence of amputation for any reason as 0.25–1.8%. [2] [3] [4] [5] [6] [7] [8] [9] [10] [11]

AETIOLOGY/ RISK FACTORS

Long-term risk factors for foot ulcers and amputation include duration of diabetes, poor glycaemic control, microvascular complications (retinopathy, nephropathy, and neuropathy), peripheral vascular disease, foot deformities, and previous foot ulceration or amputation. [1] [2] [3] [4] [5] [6] [7] [8] [9] [11] Strong predictors of foot ulceration are altered foot sensation, foot deformities, and previous foot ulcer or amputation of the other foot (altered sensation: RR 2.2, 95% CI 1.5 to 3.1; foot deformity: RR 3.5, 95% CI 1.2 to 9.9; previous foot ulcer: RR 1.6, 95% CI 1.2 to 2.3; previous amputation: RR 2.8, 95% CI 1.8 to 4.3). [10]

PROGNOSIS

In people with diabetes, foot ulcers frequently co-exist with vascular insufficiency (although foot ulcers can occur in people with no vascular insufficiency) and may be complicated by infection. Amputation is indicated if disease is severe or does not improve with conservative treatment. As well as affecting quality of life, these complications of diabetes account for a large proportion of the healthcare costs of dealing with diabetes. For people with healed diabetic foot ulcers, the 5-year cumulative rate of ulcer recurrence is 66%, and of amputation is 12%. [12] Severe infected foot ulcers are associated with an increased risk of mortality.

AIMS OF INTERVENTION

To prevent diabetic foot complications, including ulcers and amputations; and to improve ulcer healing and prevent amputations where ulcers already exist, with minimum adverse effects.

OUTCOMES

Rates of development or recurrence of foot ulcers or major foot lesions; rate of amputation (surgical removal of all or part of the lower extremity); major amputation or minor amputation; time ulcers take to heal, or the proportion healed in a given period; rates of hospital admission; rates of foot infection; adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal November 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2007, Embase 1980 to November 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 people of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs.

We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14).

QUESTION **What are the effects of interventions to prevent foot ulcers and amputations in people with diabetes?**

OPTION SCREENING AND REFERRAL TO FOOT CARE CLINIC

Amputation rates
Compared with usual care A diabetes screening and referral programme is more effective at reducing the rate of major amputation over 2 years in people at high risk of foot ulcers (high-quality evidence).

Ulcer development
Compared with usual care A diabetes screening and referral programme is no more effective at reducing the incidence of foot ulcers over 2 years in high-risk people (high-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review (search date 1998, 1 RCT, 2001 people attending a general diabetes clinic). [13] The RCT compared a diabetes screening and protection programme (in high-risk people) with usual care (in people not screened for level of risk) over 2 years. [14] People in the diabetes screening and protection programme were screened for deficits in pedal pulses, light touch, and vibration sensation. People with persistent abnormal findings were referred to the diabetic foot clinic if they had a history of foot ulcer, were found to have a low ankle–brachial index (less than 0.75), or were noted to have foot deformities. The clinic provided podiatry and protective shoes as well as education regarding foot care. Usual care consisted of the normal follow-up for people in the clinic, who could be referred to the foot care clinic by a healthcare professional. The RCT found that the diabetes screening and protection programme significantly reduced major amputation compared with usual care (1001 people, AR: 1/1001 [0.1%] with the diabetes programme *v* 12/1001 [1.2%] with usual care; ARR 1.1%; P less than 0.01; NNT 91, 95% CI 53 to 250; P less than 0.04). However, it found no significant difference in the incidence of ulceration (AR: 24/1001 [2.4%] with the diabetes programme *v* 35/1001 [3.5%] with usual care; P less than 0.14).

Harms: The RCT gave no information on adverse effects. [14]

Comment: **Clinical guide:**
Identifying individuals at high risk of foot complications is universally recognised as a key part of optimal care of people with diabetes mellitus. Being aware of locally available foot care clinics is important to facilitate appropriate referrals of high-risk individuals. Foot care clinics are not available widely.

OPTION EDUCATION

Amputation rates
Compared with usual care We don't know whether patient education is more effective at reducing the risk of amputation (very low-quality evidence).

Ulcer development
Compared with usual care We don't know whether patient education is more effective at reducing the risk of developing foot ulcers (very low-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review (search date 2001, 3 RCTs, one quasi-randomised trial). [15] The first RCT in the review (352 people with diabetes attending 4 primary-care teams, randomised by primary-care team) compared structured care (a patient education session about foot care plus patient follow-up reminders plus prompts to healthcare providers to examine feet and provide education) versus usual care (not described). [16] It found that structured care reduced "serious foot lesions" (based on the Seattle Wound Classification Scale) [17] after 12 months compared with usual care (OR 0.41, 95% CI 0.16 to 1.00) but found no significant difference between groups on the composite outcome of all foot lesions (OR 0.65, 95% CI 0.36 to 1.17) or amputations (OR 0.32, 95% CI 0.05 to 1.86). [16] The second RCT in the review (266 people with diabetes attending primary care) compared foot care education (9 sessions on foot care and skin hygiene, diabetes, risk factors, diet, and weight management) versus usual care. [18] It found no significant difference in ulcer and amputation rates (combined) after 1.5 years (10/127 [8%] with foot care education *v* 16/139 [12%] with usual care; OR 0.66, 95% CI 0.30 to 1.49). The third RCT in the review (530

people with diabetes without any obvious need for foot care) compared education from a podiatrist (45-minute session covering footwear, hygiene, toenail cutting, emollient cream, avoiding risk, foot gymnastics, and preventive podiatric care) plus podiatric visits of 30–60 minutes' duration for 1 year (as many times as judged appropriate by the podiatrist) versus written foot care instructions. [19] [20] It also found no significant difference in amputation and ulcer rates after 7 years between foot education plus podiatric visits and written foot care instructions (amputation rate: 1/267 [0.4%] with education plus podiatric visits *v* 0/263 [0%] with written foot care instructions; P value not reported; ulcer rate: 0.6% with education plus podiatric visits *v* 0.6% with written foot care instructions; P = 1.0). The quasi-randomised trial in the review (227 people with diabetes, allocated according to social security number) compared a single 1-hour educational class about foot care with routine diabetes education. [21] It found that the educational session significantly reduced ulcer recurrences and major amputation after 2 years (ulcer recurrence: 5% with foot care education *v* 15% with routine education; RR 0.31, 95% CI 0.15 to 0.65; NNT 10, 95% CI 6 to 26; major amputation: 3% with foot care education *v* 10% with routine education; RR 0.28, 95% CI 0.11 to 0.70; NNT 14, 95% CI 8 to 50).

Harms: The systematic review gave no information on adverse effects. [15]

Comment: The trials included in the systematic review had weak methods. [15] The flaws included the following: only one trial had blinded outcome assessment; one trial made no comment on loss to follow-up; some trials offered no comment on concealment of randomisation; the trials did not use an intention-to-treat approach; and the eligibility criteria with respect to risk of ulceration were described adequately in only one trial.

Clinical guide:
Given the devastating nature of serious lower extremity complications, including a component of foot care education as part of general diabetes education would seem reasonable.

OPTION THERAPEUTIC FOOTWEAR

Ulcer development
Compared with usual footwear We don't know whether therapeutic footwear is more effective at reducing the incidence of foot ulcers after 1–2 years in people without severe foot deformity (low-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review (search date 1998), [13] which identified no RCTs, but found one non-randomised controlled trial. [22] The trial allocated treatment by alternate allocation, which can increase the possibility of confounding. The trial alternately allocated 69 people with a previous diabetic foot ulcer to either an intervention group (in which people received therapeutic shoes) or to a control group (in which people continued to wear their ordinary shoes). [22] Therapeutic shoes were manufactured according to the Towey guidelines (deep enough to fit customised insoles and toe deformities, and made with soft thermoformable leather along with semirocker soles). All participants received information on foot care and footwear. After 1 year, the trial found that wearing therapeutic shoes reduced ulcer recurrence compared with ordinary shoes (27% with therapeutic shoes *v* 58% with ordinary shoes; ARR 31%, 95% CI 7% to 55%; NNT 4, 95% CI 2 to 14). We found one subsequent RCT (400 people with diabetes mellitus and previous foot ulcer but without severe foot deformity, mean age 62 years) comparing three treatments over 2 years: extra-depth and extra-width therapeutic shoes fitted with customised cork inserts, therapeutic shoes fitted with polyurethane inserts, and usual footwear. [23] The RCT found no significant difference in foot ulceration rates between therapeutic footwear and usual footwear (AR for foot ulceration: 15% with cork insert *v* 14% with polyurethane insert *v* 17% with usual footwear; RR cork insert *v* usual footwear 0.88, 95% CI 0.51 to 1.52; RR polyurethane insert *v* usual footwear 0.85, 95% CI 0.48 to 1.48).

Harms: The systematic review and subsequent RCT gave no information on adverse effects. [13] [23]

Comment:

Clinical guide:
Individuals with significant foot deformities (such as hammer toes or a Charcot foot) should be considered for referral for assessment for customised shoes that can accommodate the altered foot anatomy. In the absence of significant deformities, high-quality well-fitting non-prescription footwear seems to be a reasonable option.

QUESTION What are the effects of treatments in people with diabetes with foot ulceration?

OPTION HUMAN SKIN EQUIVALENT

Amputation rates
Compared with saline-moistened gauze Human skin equivalent is more effective at reducing the risk of amputation after 12 weeks in people with chronic neuropathic non-infected foot ulcers (high-quality evidence).

Ulcer healing rates
Compared with saline-moistened gauze Human skin equivalent is more effective at increasing ulcer healing rates after 12 weeks in people with chronic neuropathic non-infected foot ulcers (high-quality evidence).

Infection rates
Compared with saline-moistened gauze Human skin equivalent is more effective at reducing the risk of osteomyelitis after 12 weeks in people with chronic neuropathic non-infected foot ulcers (high-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review (search date 2006), [24] which identified one RCT (208 people aged 18–80 years with diabetes mellitus and chronic neuropathic non-infected foot ulceration) comparing human skin equivalent (Graftskin applied weekly for a maximum of 5 weeks) versus saline-moistened gauze (applied weekly). [25] The RCT found that human skin equivalent significantly improved ulcer healing compared with saline-moistened gauze after 12 weeks (rate of wound closure: 63/112 [56%] with human skin equivalent *v* 36/92 [38%] with saline-moistened gauze; OR 2.14, 95% CI 1.23 to 3.74; P = 0.0042). At 6 months' follow-up, there was no significant difference in the rate of recurrence of completely healed ulcers (recurrence rates: 3/51 [6%] with human skin equivalent *v* 4/31 [13%] with saline-moistened gauze; P value not reported, reported as not significant). Osteomyelitis and amputations were significantly less frequent in people receiving human skin equivalent (osteomyelitis: 3/112 [3%] with human skin equivalent *v* 10/96 [10%] with saline-moistened gauze; P = 0.04; amputations: 7/112 [6%] with human skin equivalent *v* 15/96 [16%] with saline-moistened gauze; P = 0.028).

Harms: The RCT found no serious adverse effects. [25] Wound infections and cellulitis were equally frequent in both groups.

Comment: **Clinical guide:**
Human skin equivalent may not be widely available.

OPTION PRESSURE OFF-LOADING (TOTAL-CONTACT OR NON-REMOVABLE CAST)

Ulcer healing rates
Compared with traditional dressing changes Pressure off-loading with total-contact casting is more effective at increasing ulcer healing rates (high-quality evidence).

Compared with removable casts/shoes Pressure off-loading with total-contact casting is more effective at increasing ulcer healing after 12 weeks in people with non-infected neuropathic foot ulcers (moderate-quality evidence).

Compared with pressure off-loading using a removable-cast walker made non-removable Pressure off-loading using a removable-cast walker rendered non-removable and pressure off-loading using total-contact casting are equally effective at promoting ulcer healing. A removable-cast walker rendered non-removable is also easier to apply (moderate-quality evidence).

Infection rates
Compared with traditional dressing changes Pressure off-loading with total-contact casting is more effective at reducing infection rates (high-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review (search date 1998, 1 RCT, [26] 40 people with diabetes and plantar foot ulcers but no signs of infection or gangrene) [27] and five subsequent RCTs. [28] [29] [30] [31] [32]

Pressure off-loading versus traditional dressing changes:
The RCT identified by the review compared total-contact casting versus traditional dressing changes. [26] Casts were applied by an experienced physiotherapist, changed after 5–7 days, and then every 2–3 weeks until healing occurred. People in the control group were provided with accommodative

footwear and crutches or a walker, and were instructed to complete wet to dry dressing changes 2–3 times daily. The RCT found that total-contact casting significantly increased ulcer healing and reduced infection compared with traditional dressing changes (ulcer healing: 19/21 [91%] with total-contact casting [in a mean of 42 days] *v* 6/19 [32%] with traditional dressing [in a mean of 65 days]; ARR 59%; infection: 0/21 [0%] with total-contact casting *v* 5/19 [26%] with traditional dressing; P less than 0.05). [26]

Pressure off-loading versus removable casts/shoes:
The first subsequent RCT (63 people with diabetes mellitus and non-infected neuropathic plantar foot ulcers) compared three treatments: total-contact casting, removable-cast walker, and a half-shoe. [28] All participants had weekly visits for wound care and debridements. The RCT found that total-contact casting significantly increased ulcer healing compared with removable-cast walkers or half-shoes after 12 weeks (89% with total-contact casting *v* 61% with removable-cast walker or half-shoe; ARR 28%; P = 0.026, absolute numbers not reported). The second subsequent RCT (50 people with diabetes mellitus and non-infected neuropathic plantar foot ulcers) compared non-removable fibreglass casts versus specialised cloth shoes with rigid soles and off-loading insoles over 30 days. [29] All participants had dressing changes every 2 days. It found that non-removable fibreglass casts significantly improved ulcer healing compared with specialised cloth shoes (13/24 [50%] of ulcers healed with fibreglass casts *v* 5/26 [21%] with specialised cloth shoes; ARR 29%; P = 0.03). The third subsequent RCT (50 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers) compared a removable-cast walker versus a standard removable-cast walker wrapped in cohesive or plaster bandage to render it non-removable. [30] All participants had weekly visits for wound care and debridements. The RCT found that the non-removable-cast walker significantly increased ulcer healing at 12 weeks compared with the removable-cast walker (19/23 [83%] with the irremovable cast *v* 14/27 [52%] with the removable-cast walker; ARR 31%; P = 0.02). [30] The fourth subsequent RCT (41 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers) compared a standard total-contact cast versus a removable-cast walker rendered non-removable by wrapping it with a single layer of fibreglass casting material. [31] All participants had weekly visits for wound care and debridements. The RCT found no significant difference in ulcer healing rates at 12 weeks (74% with total-contact cast *v* 80% with non-removable-cast walker; ARR +6%; P = 0.65, absolute numbers not reported). The fifth subsequent RCT (40 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers) compared a fibreglass total-contact cast versus a removable-cast walker rendered non-removable by wrapping it with a plastic band. [32] All participants had weekly visits for wound care and debridements. The RCT found no significant difference in ulcer healing rates at 12 weeks (95% with total-contact cast *v* 85% with non-removable-cast walker; P = 0.2104, absolute numbers not reported).

Harms:

Pressure off-loading versus traditional dressing changes:
The RCT identified in the systematic review found that 3/21 (14%) of people treated with total-contact casting developed fungal infections requiring topical treatment. This did not prevent continued casting. [26]

Pressure off-loading versus removable casts/shoes:
The third subsequent RCT found no significant difference between groups in the percentage of people requiring antibiotics for an episode of infection (27% with non-removable-cast walker *v* 42% with removable-cast walker; P = 0.4). [30] It found that peri-wound skin maceration was significantly more common with the non-removable-cast walker compared with the removable-cast walker (68% with non-removable-cast walker *v* 38% with removable-cast walker; P = 0.04). [30] The fifth subsequent RCT found no significant differences in the number of people requiring antibiotics for local infections between fibreglass total-contact cast and a removable-cast walker rendered non-removable (absolute numbers not reported). [32] The other RCTs gave no information on adverse effects. [28] [29] [31]

Comment:

Clinical guide:
Soft-tissue infections and osteomyelitis are contraindications to total-contact casting. Pressure off-loading with the total-contact cast is the gold standard of care for chronic neuropathic non-infected, non-ischaemic plantar foot ulcers in individuals with diabetes mellitus. The recent trials of removable-cast walkers rendered irremovable suggest that this alternate approach may be preferable given that less technical expertise for fitting is required.

OPTION SYSTEMIC HYPERBARIC OXYGEN (FOR INFECTED ULCERS)

Amputation rates
Compared with usual care Systemic hyperbaric oxygen may be more effective after 2–10 weeks at reducing the risk of major amputations in people with severely infected diabetic foot ulcers (very low-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review (search date 2005), [33] which identified three systematic reviews evaluating hyperbaric oxygen therapy in the management of chronic diabetic foot ulcers.The first systematic review [34] included non-randomised trials and case series that did not meet our inclusion criteria and so is not discussed further. The second systematic review [35] identified five RCTs (175 people with diabetic ulcers) of which two RCTs were in people with infected diabetic ulcers. The third systematic review identified four RCTs of which two RCTs of interest were identified by the second systematic review). [36] The reviews did not pool results for the two RCTs of interest. The first RCT in the systematic review (70 people with severe infected diabetic foot ulcers with full-thickness gangrene or abscess, or a large infected ulcer that had not healed after 30 days) compared systemic hyperbaric oxygen (daily 90-minute sessions at 2.2–2.5 atmospheres) plus usual care (aggressive debridement, broad-spectrum iv antibiotics, revascularisation if indicated, and optimised glycaemic control) versus usual care alone. [37] It found that, after 10 weeks, systemic hyperbaric oxygen plus usual care significantly reduced rates of major amputation compared with usual care alone (3/35 [9%] with systemic hyperbaric oxygen *v* 11/33 [33%] with usual care alone; P = 0.016. The second RCT (30 people with chronic infected foot ulcers) compared usual care alone (including debridement, iv antibiotics, and optimised glycaemic control) versus usual care plus four treatments with systemic hyperbaric oxygen (4 x 45-minute sessions at 3 atmospheres) over 2 weeks. [38] It found that systemic hyperbaric oxygen significantly reduced the rates of major amputation compared with usual care but found no significant difference in the risk of minor amputations (major amputations: 2 with systemic hyperbaric oxygen *v* 7 with usual care; P less than 0.05; number of people in each group not reported; minor amputations: 4 with systemic hyperbaric oxygen *v* 2 with usual care; reported as not significant; P value and number of people in each group not reported). The third systematic review came to similar conclusions.

Harms: The first RCT identified by the systematic review reported that two people developed symptoms of barotraumata to the ear, but this did not interrupt treatment. [37] The second RCT gave no information on adverse effects. [38]

Comment: **Clinical guide:**
Systemic hyperbaric oxygen therapy may be considered in an individual with severe infected diabetic foot ulcers with full thickness gangrene or abscess, or with a large infected ulcer that has not healed in over 30 days. More widespread application of this technology cannot be recommended given the limited RCT data.

OPTION TOPICAL GROWTH FACTORS

Ulcer healing rates

Platelet-derived growth factors compared with placebo Platelet-derived growth factors are more effective at increasing ulcer healing rates. Autologous growth factors (platelet-rich plasma gel) are no more effective than saline gel at 12 weeks at increasing ulcer healing rates in people with diabetes mellitus and chronic full thickness non-ischaemic, non-infected foot ulceration (high-quality evidence).

Protein-based growth factors compared with placebo/control Arginine–glycine–aspartic acid matrix, and insulin may be more effective at increasing ulcer healing rates. Talactoferrin alpha may be no more effective than placebo gel at increasing ulcer-healing rates (low-quality evidence).

Epidermal growth factors compared with placebo/control We don't know whether epidermal growth factors are more effective at 4–12 weeks at increasing ulcer healing rates in people with diabetes mellitus and non-ischaemic foot ulceration (low-quality evidence).

Retinoids compared with saline Tretinoin seems more effective at 16 weeks at increasing ulcer healing rates in people with diabetes mellitus and non-ischaemic, non-infected foot ulceration (moderate-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review [27] and eight subsequent RCTs. [39] [40] [41] [42] [43] [44] [45] [46] The systematic review (search date 1998, 6 RCTs) compared four different topical growth factors versus placebo in people attending hospital outpatient clinics with diabetic foot ulcers, who were free of signs of infection or severe vascular compromise. All participants received wound debridement and were encouraged to avoid weight bearing on the affected limb. The systematic review did not pool the results from the RCTs. [27] Two of the identified RCTs include fewer than 10 people per treatment arm, and are therefore excluded from this summary.

Platelet-derived growth factors

The systematic review identified three RCTs. The first RCT (118 people) found that treatment with platelet-derived growth factor (30 micrograms/g once daily for up to 20 weeks) significantly increased healing rates compared with placebo (AR for non-healing: 32/61 [52%] with platelet-derived growth factor *v* 43/57 [75%] with placebo; ARR 23%; P = 0.01). [47] The second RCT (382 people) compared platelet-derived growth factors (100 micrograms/g, 30 micrograms/g) with placebo. It found that platelet-derived growth factor (100 micrograms/g once daily for up to 20 weeks) significantly increased healing rates compared with placebo (AR for non-healing: 62/123 [50%] with platelet-derived growth factor *v* 83/127 [65%] with placebo; ARR 15%; P = 0.007). There was no significant difference in healing rates between 30 micrograms/g compared with placebo. [48] The third RCT (81 people) compared different strengths of CT-102 (a platelet-derived growth factor) versus placebo. The RCT found that CT-102 0.01% significantly increased healing compared with placebo (non-healing rates: 3/15 [20%] with CT-102 0.01% *v* 15/21 [71%] with placebo; P = 0.01). [49] The second subsequent RCT (113 people with diabetes mellitus and non-ischaemic foot ulceration) compared daily application of 0.01% recombinant human platelet-derived growth factor versus placebo for up to 20 weeks. [41] The RCT found a significantly higher ulcer healing rate with the growth factor than with placebo at 20 weeks (47/55 [85%] healed with growth factor *v* 31/58 [53%] with placebo; P less than 0.05). The fifth subsequent RCT (146 people with diabetes mellitus and neuropathic non-infected, non-ischaemic plantar foot ulcers) compared daily application of a recombinant form of human platelet-derived growth factor (beclapermin 100 micrograms/g [0.01%]) plus Adaptic dressing versus Adaptic dressing alone. [40] All participants were instructed on daily dressing changes and optimal wound care and the importance of non-weight bearing, and were assessed on a weekly basis. The RCT found no significant difference in complete ulcer healing rates at 20 weeks (42% with beclapermin plus Adaptic dressing *v* 35% with Adaptic dressing alone; ARR +7%; P = 0.3, absolute numbers not reported). The sixth subsequent RCT (72 people with diabetes mellitus and chronic full-thickness, non-ischaemic, non-infected foot ulceration) compared twice-weekly application of platelet-rich plasma gel versus saline gel for 12 weeks. [43] There were no significant differences in ulcer healing rates (13/40 [33%] with platelet-rich plasma gel *v* 9/32 [28%] with saline gel; P = 0.79).

Protein-based growth factors

The systematic review identified one RCT (65 people) comparing arginine–glycine–aspartic acid matrix with placebo. It found that treatment with arginine–glycine–aspartic acid matrix twice weekly for up to 10 weeks significantly increased healing rates compared with placebo (AR for non-wound healing rates: 26/40 [65%] with matrix *v* 23/25 [92%] with placebo; ARR 27%; P = 0.02). [47] Although the arginine–glycine–aspartic acid matrix is not strictly a growth factor, the matrix is designed to facilitate the rapid and organised repopulation of the site by fibroblasts, endothelial cells, and keratinocytes. The fourth subsequent RCT (24 people with diabetes mellitus and severe foot complications including infected ulceration, abscess, or toe gangrene) compared daily wound dressing with a saline-soaked gauze impregnated with 5–10 units of insulin with daily wound dressing using 0.05% poviodine. [44] All patients initially received appropriate debridement, abscess drainage, and amputation of any gangrenous digits, along with antibiotic therapy. The RCT reported time to complete healing and found a significant benefit with topical insulin (12 people in each group, healing time: 19.6 days with insulin *v* 53.5 days with povidone; P less than 0.001). The eighth subsequent RCT (46 people with diabetes mellitus and non-ischaemic, non-infected foot ulcers) compared daily applications of lactoferrin (an iron-binding glycoprotein) as a 2.5% gel versus 8.5% gel versus placebo gel for 12 weeks. [46] The RCT found no significant difference in complete ulcer healing rates at 12 weeks (3/15 [20%] with 2.5% gel, *v* 3/15 [20%] with 8.5% gel *v* 3/16 [19%] with placebo gel; P value reported as not significant).

Epidermal growth factors

The first subsequent RCT (61 people with diabetes mellitus and non-ischaemic foot ulceration) compared human epidermal growth factor (0.02% or 0.04% applied daily) plus a control cream (containing a protein-free calf blood extract) versus control cream alone. [39] The RCT found that higher-dose human epidermal growth factor significantly increased ulcer healing rates compared with lower-dose human epidermal growth factor and control at 12 weeks (complete wound healing rates: 20/21 [95%] with 0.04% human epidermal growth factor *v* 12/21 [57%] with 0.02% human epidermal growth factor *v* 8/19 [42%] with control; P = 0.0003 for 0.04% human epidermal growth factor *v* other two treatments combined). The seventh subsequent RCT (50 people with diabetes mellitus and non-ischaemic foot ulceration) compared daily application of 0.1% recombinant human epidermal growth factor versus placebo for 28 days. [45] Compete ulcer healing rates did not differ significantly at 4 weeks (7/30 [23%] with epidermal growth factor *v* 2/20 [10%] with placebo; P = 0.3).

Retinoids

The third subsequent RCT (24 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration) compared daily topical application of a retinoid (0.05% tretinoin) versus a saline solution for 4 weeks. [42] At 16 weeks, complete ulcer healing was significantly higher with tretinoin than

with saline (6/13 [46%] of ulcers completely healed with tretinoin *v* 2/11 [18%] completely healed with placebo; P = 0.03).

Harms:

The systematic review [27] and first and fifth subsequent RCTs [39] [40] reported no growth factor-related adverse effects. The second subsequent RCT found no significant difference in adverse effects between 0.01% recombinant human platelet-derived growth factor versus placebo (13% with growth factor *v* 17% with placebo; P value not reported; nature of adverse effects not clear). [41] The third subsequent RCT found that one person with 0.05% tretinoin and one person with saline solution reported mild to moderate pain (no data analysis reported). [42] The fourth subsequent RCT gave no information on adverse effects. [44] The sixth subsequent RCT reported that there were 60 adverse events with platelet-rich plasma gel versus 62 with saline gel; however, only two of these (contact dermatitis and maceration) were related to treatment. [43] The seventh subsequent RCT reported that there were no topical or generalised adverse effects. [45] The eighth subsequent RCT reported no talactoferrin-related adverse effects. [46]

Drug safety alert:

A drug safety alert has been issued on the increased risk of cancer mortality associated with use of 3 or more tubes of becaplermin (http://www.fda.gov).

Comment:

Clinical guide:

No randomised trials have compared optimal pressure off-loading with topical growth factor application in terms of ulcer healing rates.

OPTION DEBRIDEMENT OR WOUND DRESSINGS

Ulcer healing rates

Debridement with hydrogel compared with standard care Debridement with hydrogel may be more effective at increasing ulcer healing rates after 12–20 weeks (very low-quality evidence).

Surgical debridement compared with usual care Surgical debridement may be no more effective at promoting ulcer healing (low-quality evidence).

Debridement with larvae compared with debridement with hydrogel We don't know whether debridement with larvae is more effective at promoting ulcer healing (very low-quality evidence).

Wound dressings compared with each other We don't know which wound dressing is more effective at 4–12 weeks at promoting ulcer healing (low-quality evidence).

Dimethyl sulfoxide dressing compared with conventional treatment Dimethyl sulfoxide seems to be more effective at 15 weeks at increasing ulcer healing rates (moderate-quality evidence).

Cadexomer iodine ointment compared with standard dressings We don't know whether cadexomer iodine ointment is more effective at 12 weeks at increasing ulcer healing rates in people with diabetes and cavity ulcers of the foot (low-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits:

Debridement:

We found one systematic review (search date 2005, 5 RCTs, 418 people). [50] The review found that debridement using hydrogel significantly increased healing at 12–20 weeks compared with gauze dressing or standard wound care (3 RCTs, 198 people; RR 1.84, 95% CI 1.30 to 2.61; ARI 23%, 95% CI 10% to 26%; NNT 5, 95% CI 2 to 10). The review also found no significant difference in complete healing between debridement with larvae compared with hydrogel (1 RCT, 140 people: 5/70 [7%] with larvae *v* 2/70 [3%] with hydrogel; RR 2.5, 95% CI 0.5 to 12.4; published in abstract form only; duration of follow-up unclear). The review also found no significant difference in ulcer healing between surgical debridement (surgical excision, eventual debridement or removal of bone segments underlying the lesion, and surgical closure) compared with conventional management (pressure relief and regular dressings; the type of dressing was not reported) (1 RCT, 42 people; 19/24 [79%] with conservative care *v* 21/22 [95%] with surgical debridement; RR 1.21, 95% CI 0.96 to 1.51; P = 0.1).

Wound dressings:

We found two systematic reviews [51] [52] and one subsequent RCT. [53] The first systematic review (search date 2006) found no RCTs on silver-based dressings for foot ulcers in people with diabetes. [51] The second systematic review (search date 1998, 9 RCTs, number of people unclear) did not perform a meta-analysis, but reported by specific wound dressing comparisons. [52] We have reported the comparisons here where the RCTs found fitted our inclusion critieria of greater than 20 people per study. The review found no significant difference between hydrocellular dressing com-

pared with alginate-based dressings in complete healing rates (2 RCTs, 40 people; OR 2.44, 95% CI 0.78 to 7.57). The review found no significant difference between an adhesive "hydroactive" polyurethane gel dressing compared with a hydrocellular dressing in time to healing or reduction in wound size at 4 weeks (1 RCT, 40 people with neuropathic foot ulceration; time to healing: WMD +4.76 days, 95% CI –7.41 days to +16.93 days; reduction in wound size: WMD –1.1 mm^2, 95% CI –41.7 mm^2 to +39.5 mm^2). The review found no significant difference between a collagen–alginate dressing versus saline-moistened gauze in either complete healing or mean time to complete healing (1 RCT, 75 people with non-ischaemic, non-infected diabetic foot ulcers; complete healing: OR 1.07, 95% CI 0.35 to 3.25; mean time to complete healing: WMD +2.80 days, 95% CI –8.8 days to +14.4 days). The review found significantly more ulcer healing at 15 weeks with dimethyl sulfoxide compared with conventional treatment (not described) (1 RCT, 40 people with diabetic foot ulceration; OR 11.44, 95% CI 3.28 to 39.92). The review found no significant difference in ulcer healing rates between cadexomer iodine ointment compared with standard dressings (not described) at 12 weeks (1 RCT, 35 people with diabetes and "cavity" ulcers of the foot; OR 3.04, 95% CI 0.59 to 15.56). One subsequent RCT (39 people) compared moist (calcium alginate) versus dry (fine mesh gauze) wound dressings applied daily for up to 4 weeks. [53] The RCT found no significant difference in healing between wet versus dry dressings (OR 1.2, 95% CI 0.3 to 4.9; P = 0.8).

Harms:

Debridement:
The systematic review found that there were significantly fewer adverse effects with hydrogel compared with good wound care (total of 22 events with hydrogel *v* 36 with good wound care; RR 0.60, 95% CI 0.38 to 0.95). [50] The review also found that significantly more people became infected with conservative treatment compared with surgical debridement (3/24 [13%] *v* 1/22 [5%]; RR 0.33, 95% CI 0.03 to 3.47).

Wound dressings:
The systematic review and subsequent RCT gave no information on adverse effects. [52] [53]

Comment:

In the systematic review on debridement, the trials were generally small and of poor methodological quality.

Clinical guide:
We have included debridement and wound dressings together in the same option as the exact mechanism of the treatment can be unclear (e.g. hydrogel). Hydrogel functions by increasing the moisture of the wound environment and that this effect may be more significant than its effect on debridement.

OPTION PRESSURE OFF-LOADING (WITH FELTED FOAM OR PRESSURE-RELIEF HALF-SHOE)

Ulcer healing rates
Pressure off-loading with felted foam dressings compared with pressure-relief half-shoe Pressure off-loading with felted foam dressings and pressure-relief half-shoe seem equally effective at 10 weeks at promoting ulcer healing (moderate-quality evidence).

Felted foam padding applied to the skin compared with being inserted into footwear Felted foam padding applied to the skin and padding inserted into footwear seem to be equally effective at promoting ulcer healing (moderate-quality evidence).

Compared with non-removable casts Removable half-shoes are less effective after 12 weeks than pressure off-loading with total-contact casting at promoting ulcer healing in people with non-infected neuropathic foot ulcers (moderate-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits:

Pressure off-loading felted foam dressings versus a pressure-relief half-shoe:
One RCT (61 people with diabetes mellitus and a neuropathic plantar forefoot ulcer) compared pressure off-loading felted foam dressings with a pressure-relief half-shoe over at least 10 weeks. [54] The RCT found no significant difference in time to ulcer healing (79.6 days with felted foam *v* 83.2 days with a half-shoe; P = 0.61).

Felted foam padding directly applied to the skin versus being inserted into footwear:
One RCT (32 people with diabetes mellitus and a Grade 1 or 2 neuropathic plantar forefoot ulcer) compared pressure off-loading felted foam dressings directly applied to the skin with felted foam dressings inserted into footwear over 4 weeks. [55] The RCT found no difference in ulcer healing rates at 4 weeks (number of people with wound closure: 73% with dressings to the skin *v* 74% with dressings in the footwear; P = 0.9).

Pressure relief half-shoe versus non-removable casts:
See pressure off-loading versus removable casts/shoes, p 5 .

Harms: The RCTs gave no information on adverse effects. [28] [54] [55]

Comment: See clinical guide under pressure off-loading (non-removable cast), p 5 .

OPTION SYSTEMIC HYPERBARIC OXYGEN (FOR NON-INFECTED, NON-ISCHAEMIC ULCERS)

Ulcer healing rates
Compared with usual care Hyperbaric oxygen plus usual care may be no more effective at promoting ulcer healing at 4 weeks in people with non-infected neuropathic foot ulcers (low-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review [33] which identified three systematic reviews. The first systematic review [34] included non-randomised trials and case series that did not meet our inclusion criteria and so is not discussed further. The second systematic review [35] identified five RCTs (175 people with diabetic ulcers) of which one RCT included people with non-infected diabetic ulcers. The RCT (28 people with neuropathic foot ulcers) compared systemic hyperbaric oxygen therapy (90-minute sessions at 2.5 atmospheres twice daily for 2 weeks) plus usual care versus usual care alone. [56] It found no significant difference in the proportion of completely healed ulcers or in reduction in ulcer size at 4 weeks (completely healed: 2/14 [14%] with hyperbaric treatment *v* 0/13 [0%] with control; reported as not significant; P value not reported; reduction of ulcer surface area: 62% with hyperbaric treatment *v* 22% with control; reported as not significant; P value not reported). This RCT may have lacked power to detect a clinically important effect. The third systematic review did not identify any RCTs in people with non-infected, non-ischaemic ulcers.

Harms: The RCT reported one case of mild barotraumata to the ear. [56]

Comment: None.

OPTION HUMAN CULTURED DERMIS

Ulcer healing rates
Compared with usual care Human cultured dermis substitute plus usual care is no more effective at 12 weeks at increasing ulcer healing rates (high-quality evidence).

Infection rates
Compared with usual care Human cultured dermis substitute plus usual care is no more effective at 12 weeks at reducing ulcer infection rates (high-quality evidence).

For GRADE evaluation of interventions for foot ulcers and amputations in diabetes, see table, p 14 .

Benefits: We found one systematic review (search date 1998, 2 RCTs, 331 people) comparing topical application of human cultured dermis substitute (weekly for 8 weeks) plus usual care versus usual care alone in people attending hospital outpatient clinics with diabetic foot ulcers with no signs of infection or severe vascular compromise. [27] All participants received wound debridement and were encouraged to avoid weight bearing on the affected limb. The review found no significant difference in ulcer healing at 12 weeks between human cultured dermis compared with usual care (+21% increase in ulcer healing with human cultured dermis compared with usual care at 12 weeks, 95% CI –13% to +36%). One RCT identified by the review found no significant difference between human cultured dermis and usual care in the rates of ulcer infections, and no effect on haematology or serum chemistry values or glycaemic control. [27] The other RCT found no significant difference in wound infection rates.

Harms: The systematic review gave no information on adverse effects. [27]

Comment: **Clinical guide:**
Human cultured dermis may not be widely available.

GLOSSARY

Ankle–brachial index is the ratio between the systolic pressure measured at the dorsalis pedis or posterior tibial artery and the highest systolic pressure at the brachial arteries. It is usually assessed with a blood pressure cuff and a high frequency continuous wave Doppler.

Human cultured dermis consists of neonatal fibroblasts cultured *in vitro* onto a bioabsorbable mesh to produce a living, metabolically active tissue containing normal dermal matrix proteins and cytokines.
Human skin equivalent consists of two allogenic layers containing human skin cells. One layer is formed by dermal cells (human fibroblasts) and the second layer is formed by epidermal cells. Human skin equivalent produces cytokines and growth factors involved in the skin healing process.
Major amputations are above or below knee amputations.
Minor amputations involve partial removal of a foot, including toe or forefoot resections.
Pressure off-loading refers to the use of different techniques designed to minimise the amount of force applied to the ulcer site.
Seattle Wound Classification Scale is used to standardise the description of diabetic foot ulcers. It has 10 categories, from superficial wound (category 1) to deep wound involving infection and tissue necrosis (category 10). [17]
Topical growth factors are synthetically produced factors specifically designed to promote cellular proliferation or matrix production at an ulcer site.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Systemic hyperbaric oxygen refers to exposing a person to a high oxygen, high-pressure environment designed to improve oxygen delivery to the ulcer site.
Total-contact casting is the application of a layer of plaster over the foot and lower leg, designed to distribute pressure evenly over the entire plantar aspect of the foot to reduce exposure of plantar ulcers to pressure, even when the person is walking.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Human skin equivalent: One systematic review [24] added which identified one RCT. [25] The RCT found that human skin equivalent increased ulcer healing rates and reduced the incidence of osteomyelitis and amputations compared with saline-moistened gauze. There was no significant difference in rate of recurrence of completely healed ulcers at 6 months. Categorisation unchanged (Likely to be beneficial).
Systemic hyperbaric oxygen (infected ulcers): One systematic review [33] identifying two systematic reviews [35] [36] for population of interest added. The second and third review identified the same RCTs and came to similar conclusions. One RCT [37] found systemic hyperbaric oxygen plus usual care reduced rates of major amputation in people with severely infected diabetic foot ulcers compared with usual care. One RCT [38] in people with chronic infected foot ulcers found systemic hyperbaric oxygen reduced the rates of major amputations but there was no significant diffference in reduction of minor amputations compared with usual care. Categorisation unchanged (Likely to be beneficial).
Systemic hyperbaric oxygen (non-infected ulcers): One systematic review [33] identifying one systematic review [35] in population of interest added. The systematic review identified one RCT [56] in people with neuropathic foot ulcers which found no significant difference in the proportion of completely healed ulcers between systematic hyperbaric oxygen therapy plus usual care compared with usual care alone. Categorisation unchanged (Unknown effectiveness).
Topical growth factors: One RCT [46] added. The RCT found no significant difference in complete ulcer healing rates at 12 weeks between lactoferrin gel (iron-binding glycoprotein) and placebo. Categorisation unchanged (Likely to be beneficial).
Pressure off-loading: One RCT added. [32] The RCT found no significant difference in healing rates at 12 weeks between total-contact cast and removable-cast walker rendered non-removeable. Categorisation changed from Beneficial to Likely to be beneficial.

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Disclaimer

TABLE GRADE evaluation of interventions for foot ulcers and amputations in diabetes

Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
Important outcomes	**Ulcer development, amputation rates, ulcer healing rates, infection rates, and adverse effects**								
What are the effects of interventions to prevent foot ulcers and amputations in people with diabetes?									
1 (2001) [27]	Amputation rates	Diabetes screening and protection programme *v* usual care	4	0	0	0	0	High	
1 (2001) [27]	Ulcer development	Diabetes screening and protection programme *v* usual care	4	0	0	0	0	High	
4 (1375) [16] [18] [19] [20]	Amputation rates	Patient education *v* usual care	4	–3	–1	–1	0	Very low	Quality points deducted for flaws with randomisation, blinding, follow-up, and statistical analysis. Consistency point deducted for conflicting results. Directness point deducted for composite outcomes
4 (1375) [16] [18] [19] [20]	Ulcer development	Patient education *v* usual care	4	–3	–1	–1	0	Very low	Quality points deducted for flaws with randomisation, blinding, follow-up, and statistical analysis. Consistency point deducted for conflicting results. Directness point deducted for composite outcomes
2 (469) [22] [23]	Ulcer development	Therapeutic footwear *v* usual footwear	4	–1	–1	0	0	Low	Quality point deducted for randomisation flaws. Consistency point deducted for conflicting results
What are the effects of treatments in people with diabetes with foot ulceration?									
1 (208) [25]	Ulcer healing rates	Human skin equivalent *v* saline-moistened gauze	4	0	0	0	0	High	
1 (208) [25]	Amputation rates	Human skin equivalent *v* saline-moistened gauze	4	0	0	0	0	High	
1 (208) [25]	Infection rates	Human skin equivalent *v* saline-moistened gauze	4	0	0	0	0	High	
1 (40) [26]	Ulcer healing rates	Pressure off-loading (total-contact casting) *v* traditional dressing changes	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for RR greater than 2
1 (40) [26]	Infection rates	Pressure off-loading (total-contact casting) *v* traditional dressing changes	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for RR greater than 2
3 (163) [28] [29] [30]	Ulcer healing rates	Pressure off-loading *v* removable casts/shoes	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (81) [31] [32]	Ulcer healing rates	Pressure off-loading (total-contact cast) *v* removable-cast walker made non-removable	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (100) [27] [38]	Amputation rates	Systemic hyperbaric oxygen plus usual care *v* usual care alone	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results

Important outcomes	Ulcer development, amputation rates, ulcer healing rates, infection rates, and adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
6 (867) [47] [48] [49] [41] [40] [43]	Ulcer healing rates	Platelet-derived growth factors *v* placebo	4	0	0	0	0	High	
2 (112) [39] [45]	Ulcer healing rates	Epidermal growth factors *v* placebo/control	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
3 (135) [57] [44] [46]	Ulcer healing rates	Protein-based topical growth factors *v* placebo/control	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for lack of consistency in benefits with different types of topical growth factors
1 (24) [42]	Ulcer healing rates	Retinoids *v* saline	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (198) [50]	Ulcer healing rates	Debridement (hydrogel) *v* usual care	4	–2	0	0	0	Low	Quality point deducted for sparse data and methodological flaws
1 (42) [50]	Ulcer healing rates	Surgical debridement *v* usual care	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about comparator (type of dressing)
1 (140) [50]	Ulcer healing rates	Debridement with larvae *v* debridement with hydrogel	4	–3	0	0	0	Very low	Quality points deducted for sparse data, uncertain follow-up, and incomplete reporting of results
6 (229) [52] [53]	Ulcer healing rates	Wound dressings compared with each other	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and for methodological flaws. Directness point deducted for large number of interventions compared
1 (40) [52]	Ulcer healing rates	Dimethyl sulfoxide *v* conventional treatment	4	–2	0	–1	+2	Moderate	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainity about comparator. Effect-size points added for OR greater than 5
1 (35) [52]	Ulcer healing rates	Cadexomer iodine ointment *v* standard dressings	4	–2	0	–1	+1	Low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainity about comparator. Effect-size point added for OR greater than 2
1 (61) [54]	Ulcer healing rates	Pressure off-loading with felted foam dressings *v* pressure-relief half-shoe	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (32) [55]	Ulcer healing rates	Felted foam padding applied to the skin *v* inserted into footwear	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (28) [56]	Ulcer healing rates	Hyperbaric oxygen plus usual care *v* usual care alone (non-infected ulcer)	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
2 (331) [27]	Ulcer healing rates	Human cultured dermis substitute plus usual care *v* usual care alone	4	0	0	0	0	High	
2 (331) [27]	Infection rates	Human cultured dermis substitute plus usual care *v* usual care alone	4	0	0	0	0	High	

Important outcomes	Ulcer development, amputation rates, ulcer healing rates, infection rates, and adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evi-dence	Quality	Consis-tency	Direct-ness	Effect size	GRADE	Comment

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio