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SUPPLEMENT ARTICLE

Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review

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Abstract

The outcome of management of diabetic foot ulcers remains a challenge, and there remains continuing uncertainty concerning optimal approaches to management. It is for these reasons that in 2008 and 2012, the International Working Group of the Diabetic Foot (IWGDF) working group on wound healing published systematic reviews of the evidence to inform protocols for routine care and to highlight areas, which should be considered for further study. The same working group has now updated this review by considering papers on the interventions to improve the healing of chronic ulcers published between June 2010 and June 2014. Methodological quality of selected studies was independently assessed by two reviewers using Scottish Intercollegiate Guidelines Network criteria. Selected studies fell into the following ten categories: sharp debridement and wound bed preparation with larvae or hydrotherapy; wound bed preparation using antiseptics, applications and dressing products; resection of the chronic wound; oxygen and other gases, compression or negative pressure therapy; products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing; application of cells, including platelets and stem cells; bioengineered skin and skin grafts; electrical, electromagnetic, lasers, shockwaves and ultrasound and other systemic therapies, which did not fit in the aforementioned categories. Heterogeneity of studies prevented pooled analysis of results. Of the 2161 papers identified, 30 were selected for grading following full text review. The present report is an update of the earlier IWGDF systematic reviews, and the conclusion is similar: that with the possible exception of negative pressure wound therapy in post-operative wounds, there is little published evidence to justify the use of newer therapies. Analysis of the evidence continues to present difficulties in this field as controlled studies remain few and the majority continue to be of poor methodological quality. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords diabetes; diabetic foot; ulcer; wound healing; dressing

Abbreviations bFGF, – basic fibroblast growth factor; EGF, – epidermal growth factor; HBOT, – hyperbaric oxygen therapy; NPWT, – negative pressure wound therapy; PDGF, – platelet-derived growth factor; RCT, – randomized controlled trial; SIGN, – Scottish Intercollegiate Guidelines Network

Introduction

The management of foot disease in diabetes remains a major financial and therapeutic challenge throughout the world. The International Working Group of the Diabetic Foot (IWGDF) has issued guidelines on management since 1999 and systematic reviews to underpin those from 2005. In 2006, the IWGDF Editorial Board invited the IWGDF working group on wound healing to undertake a systematic review of the evidence supporting interventions to enhance the healing of chronic ulcers of the foot in diabetes in order both to inform protocols for routine care and to highlight areas, which should be considered for further study. The first review included all papers published up to December 2006 [1], and this was later updated to include all subsequent papers up until June 2010 [2]. The working group has now undertaken a further update by considering papers on the interventions to improve the healing of chronic ulcers of the foot in diabetes published between June 2010 and June 2014.

Materials and methods

Controlled studies, which were either prospective or retrospective, published in any language, and which evaluated interventions for the treatment of chronic foot ulcers in people aged 18 years or older with either type 1 or type 2 diabetes mellitus were considered. Studies were included if they concerned agents or interventions that may accelerate the healing process, and the primary outcomes used were clinical: healing, time to healing, and/or reduction in ulcer area. Search strategies (Appendix A) included selected search terms on study design, patient group, clinical problem and interventions of interest by using Medline (June 2010 to June 2014) and Embase (June 2010 to June 2014). Randomized controlled trials (RCT), case–control studies, prospective and retrospective cohort studies, control before-and-after and interrupted time series designs were included. Bibliography tracking of identified articles was not performed. Previously performed high-quality systematic reviews and Cochrane reviews on the topics of interest were searched to determine the need for an extension to the literature search. A later search was made of the following clinical trials registries; the search terms used were Foot Ulcer; Diabetes Mellitus; Diabetic Foot Ulcer; and Diabetic Foot: http://www.controlled-trials.com/, www.clinicaltrials.gov, www.who.int/trialsearch, clinicalstudies.info.nih.gov/, cordis.europa.eu/en/home.html, www.clinicaltrialsregister.eu/, www.pactr.org/, www.anzctr.org.au/, www.canadiancancertrials.ca/, www.fmhs.auckland.ac.nz/sms/oncology/ctnz/default.aspx, www.chictr.org/Default.aspx, cris.nih.go.kr/cris/en/search/basic_search.jsp, registroclinico.sld.cu/, drks-neu.uniklinik-freiburg.de/drks_web/, www.hkclinicaltrials.com/, www.irct.ir/, www.umin.ac.jp/ctr/ www.kctr.se/, clinicaltrials.health.nz/, www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx, www.slctr.lk/ www.clinicaltrials.in.th/, public.ukcrn.org.uk/search/ and www.controlled-trials.com/ukctr/, and attempts were made to contact investigators if there was no evidence of publication of relevant studies.

Two reviewers (FLG and WJJ) independently assessed all identified references by title and abstract to determine possible eligibility. Full-paper copies of identified articles were retrieved, and eligibility was confirmed or rejected by one of four pairs of independent reviewers. Each study was scored for methodological quality using scoring lists specific for each study design and based on checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN) [3]. Equal weighting was applied to each validity criterion. Findings on data extraction and methodological quality were discussed between co-reviewers and a final decision endorsed by the entire group. Quality items were rated as 'done', 'not done' or 'not reported', and only those rated as 'done' contributed to methodological quality score. This quality score was translated into a level of evidence according to the SIGN instrument [3]: (1) RCTs and (2) studies with case–control, cohort, control before and after or interrupted time series design. Studies were also rated as ++ (well conducted with very low risk of bias), + (well conducted with low risk of bias) and − (low quality with higher risk of bias). Meta-analyses, other reviews and studies reporting non-analytic case reports and case series were not included. Reviewers did not assess their own work because of potential conflicts of interest.

Extracted data were summarized in evidence tables on a study-by-study narrative basis. Because of the heterogeneity of study designs, including interventions, follow-up and outcomes, no attempt was made to pool the results. The evidence tables were compiled following collective discussion by the working party, and conclusions were drawn. The papers selected for scoring were divided into the same ten categories as the 2012 review, except that the articles on the use of platelet-derived growth factors have now been included in the section on cell therapy (in contrast to the previous allocation to the section on wound biochemistry); the section on oxygen has been expanded to include other gases.

Results

In 2008, a total of 2155 articles were identified from EMBASE and Medline. Of these, 372 were selected for full text review, and 61 were included in the review. In 2012,

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a total of 802 articles were identified from EMBASE and 507 from Medline. Seventy-two of these were selected for full text review. An additional 13 articles were identified from other sources, including other systematic reviews. Of the total 85 articles, 43 were included.

In the current update, a total of 2161 articles were identified in total: 1501 from Medline and 660 from EMBASE. Forty-three of these were selected for full text review. An additional seven articles were identified from other sources, either other systematic reviews or clinical trial databases. Of the total 50 articles, 33 that fulfilled the inclusion criteria as mentioned previously were included in the review (Figure 1). The selected papers were grouped into ten categories.

Sharp debridement and wound bed preparation with larvae or hydrotherapy (online Tables 1–3)

Sharp debridement

In the 2008 review, one study on sharp debridement was identified, which was a subgroup analysis of cases from an RCT of another intervention; it reported that healing at 12 weeks was more likely following a more vigorous debridement [4]. One further study was identified but lack of detail meant that it was not included [5].

Larval therapy

In 2008, we selected two studies on the use of larvae. One small, complex non-randomized cohort study reported an apparent significant effect on the appearance of the wound (but not healing) at 2 weeks [6]. The second, a case–control study in elderly, non-ambulant people with peripheral artery disease, reported an apparent significant decreased time to healing and amputation rates in those patients for whom 6-month follow-up data were available [7]. The 2012 review added one further low-scoring paper [8], which reported no difference in either healing or amputation rates between those treated with larval therapy and a control group.

The present search selected only one new paper to add to the three previously reported [9]. This study was a non-blind, low-scoring cohort design subject to further bias as patients were allowed to choose whether to have treatment with larvae or not. The lack of baseline data on the type of wounds makes the apparent benefit of larval therapy on healing uninterpretable.

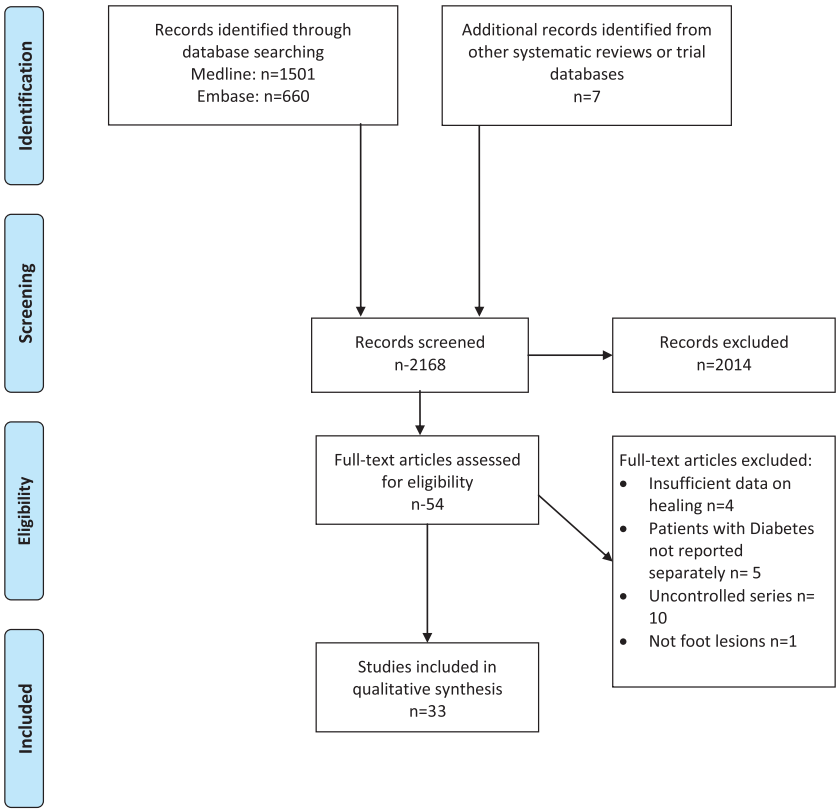

Figure 1. PRISMA flow diagram 2015 review

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Hydrotherapy

No further studies were identified to add to the one paper in the previous on hydrotherapy (Versajet®) [10], which showed no benefit to healing at 12 weeks in a small study.

Clostridial collagenase

The use of Clostridial collagenase ointment used daily as a debriding agent was examined in one small study [11]. This small, moderate scoring but unblinded study of non-ischaemic wounds showed an apparent improvement in area reduction from baseline in the treated group after 4 weeks, whereas there was no improvement seen in the control group. There were no between group comparisons made, however, and the finding that there was an average increase in the area of the wounds in the control group compared with baseline at 4 and 12 weeks suggests that the control group may not have received usual best practice.

Wound bed preparation using antiseptics, applications and dressing products (online Tables 4–6)

Antiseptics and antimicrobials

In 2008, one study was identified, which demonstrated that cadexomer-iodine showed no benefit in cavity wounds when compared with usual care [12]. A subsequent large, observer-blinded, RCT of good quality identified in the 2012 review reported no difference between three products: carboxymethylcellulose hydrofibre, a surface antiseptic (Inadine®) and a non-adherent product gauze in terms of healing by 24 weeks [13]. The 2008 review also found evidence from a single small study of possible benefit from the use of zinc oxide tape, but no subsequent reports have been found [14].

Only one study of the use of honey was identified in the 2012 review, and this was a small, non-blinded and poorly designed controlled study, which reported no difference in outcome between the use of honey and povidone/iodine [15]. In the current review, we identified two further studies. The first [16] was a very small, poorly scoring, non-blinded RCT of honey-soaked dressings compared with povidone/iodine dressings. Although there was an apparent difference in area reduction at 15 days between the two groups, this result is uninterpretable given the lack of data on the baseline characteristics of the ulcers in the two groups and the probable inappropriate use of parametric statistics. In a second small cohort, study [17] comparing honey dressings with iodine dressings, no differences were found in either the incidence of healing or of amputation at 10 weeks although there was an apparent reduction in time to outcome (healing or amputation) in the honey group. This result is difficult to interpret, and the study was of poor methodological quality with few data on the baseline characteristics of the patients. Despite the widespread use of honey dressings in clinical practice, there are no robust data to support their use to enhance the healing of diabetic foot wounds, and this reinforces the conclusions of a recent Cochrane review [18].

A single non-blinded RCT on the use of superoxidized solution (DermacynW) was identified in the 2012 review [19], which compared the incidence of healing at 6 months after infected surgical wounds of the foot had been irrigated with either the superoxidized solution or with povidone/iodine. The results of this trial were of doubtful quality given the methodological flaws in the study, and no further studies have been identified in this review.

The use of topical antimicrobials (tobramycin beads) on the wound at the time of forefoot amputation was shown in a non-randomized cohort study reported in the 2012 review to have a significant beneficial effect on the need for later surgical revision [20], but no difference in healing times or later transtibial amputation. No further studies on antibiotic-impregnated beads or cement have been identified, and so the place of these agents in wound healing is yet to be determined.

Alginate and collagen-alginate products

Two small studies of alginate-containing products were identified in the 2008 review. Neither showed evidence of improved wound healing either in comparison with saline-moistened gauze [21] or Vaseline gauze [22].

Carboxymethylcellulose dressings

We previously identified an RCT, which reported improvement with the use of a carboxymethylcellulose hydrofibre dressing in the 2008 review [23]. In the 2012 review, however, a further larger RCT with a silver-impregnated dressing [24] showed no difference in healing at 8 weeks when compared with an alginate dressing. Another large, observer-blinded, RCT of good quality reported no difference between three products: carboxymethylcellulose hydrofibre, a surface antiseptic (Inadine®) and a non-adherent product gauze in terms of healing by 24 weeks [13]. No relevant new studies were identified in the present search.

Topical phenytoin

The 2008 review found one cohort [25] and one small poorly scoring RCT on the use of topical phenytoin [26], both of which reported a positive benefit in terms of ulcer area reduction, but with a high risk of bias. The current search identified two further studies. The first was a small, poorly scoring, open-label RCT, which reported a significant apparent improvement in ulcer area at 8 weeks when compared with a control group who had just Vaseline gauze applied to their ulcers [27]. The lack of baseline data on the patients or ulcers and the lack of blinding make this finding difficult to interpret. The second study was a slightly larger, high scoring, double-blind study comparing topical phenytoin with an alginate dressing [28]. There was no difference between the two groups in terms of healing at 16 weeks. However, recruitment was incomplete, and so the study was ultimately not powered to show any differences between the two groups.

Hydrogels

We found evidence in the previous reviews from three controlled trials suggesting that hydrogels may hasten healing. One non-blind RCT reported a significant benefit in terms of healing of non-ischaemic foot ulcers when a hydrogel was compared with saline-moistened gauze [29]. Two cohort studies were identified, but neither reported any hard data on wound healing, and one used no statistical analysis [30,31]. No further studies on hydrogels were identified, and the place of these products in routine care is still not substantiated.

Herb/bark extracts

In the 2012 review, a small study of the use of QRB7 (oak bark extract) in Bensal HP compared with silver sulphadiazine for 6 weeks showed a significant benefit in terms of healing, but the quality of the study was difficult to assess because of missing details [32].

In the present search, a small, non-blinded and poorly scoring study of a polyherbal cream compared with application of a silver sulphadiazine cream was identified [33]. There was no difference in the time to healing between the two groups. A small, poorly scoring multicentre RCT of a Chinese polyherbal preparation [34] was also identified. Even though the only analysis was *per protocol*, no significant differences were observed between the intervention and control groups in terms of healing or ulcer area reduction up to 24 weeks.

Other

A further small, poorly scoring, non-blinded RCT of bismuth subgallate/borneol with patients randomized in a 2 : 1 ratio to either topical application of this or of intrasite gel, found no difference in healing at 12 weeks [35]. There was, however, a surprisingly high rate of healing in both groups (100%).

There was a single, small but well-designed double-blind RCT of NorLeu^3-A [1–7] (an analogue of angiotensin [1–7]), 0.01% or 0.03% *versus* placebo [36]. There was no difference in the proportion of patients healed in either of the two treatment groups, or in reduction in wound area at 12 weeks compared with placebo. At 24 weeks, there was a reported significant increase in the proportion of patients healed in the NorLeu^3-A 0.03% group compared with controls, but there were a high number of dropouts and only a *per protocol* analysis was reported. Hence, the efficacy of this treatment remains unproven.

One small open-label cohort study of a microbial cellulose membrane compared with xeroform gauze was identified [37]. The two groups were not well matched at baseline in terms of the presence of peripheral artery disease (PAD), gender, age ulcer size and duration, and so the positive results (an apparent significant improvement in time to healing and area reduction per week) reported should be interpreted with caution.

A small, double-blind, placebo-controlled RCT of the daily application of topical insulin cream was found in the current search [38]. Although mainly an animal/biochemical study, there appeared to be a significant improvement in the length, width and depth of the ulcers in the intervention group when compared with the control group. The analysis was *per protocol*, however, and both this and the lack of clinical baseline characteristics of the patients make the result difficult to interpret.

In summary, there is still little evidence to support the choice of any one dressing or wound application in preference to any other in attempts to promote healing of ulcers of the foot in diabetes.

Resection of the chronic wound (online Table 7)

The 2008 review included three studies relating to excision of plantar ulcers with or without removal of underlying bone. Wide excision of chronic plantar ulcers – combined when indicated with removal of underlying bone – reduced time to healing but had no effect on eventual healing rate [39]. Two retrospective cohort studies looking at either the effect of excising the fifth metatarsal head underlying a chronic ulcer [40] or excising

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wounds under the interphalangeal joint of the hallux or first metatarsophalangeal joint [41], combined with arthroplasty reported benefit in terms of healing. No further publications on this have been found in either the 2012 or this review.

In summary, surgical resection of the chronic wound particularly when combined with underlying bone may have a place in reducing time to healing, although this has not been tested in rigorous randomized and blinded trials of appropriate statistical power.

Oxygen and other gases (online Tables 8–10)

Topical Oxygen

Two studies were identified in the 2008 review, which evaluated the use of topical hyperbaric oxygen therapy (HBOT). One was randomized and reported no apparent reduction in the cross-sectional area of ulcers at either 7 or 14 days [42]. The other was only partially randomized but reported an apparent benefit at 4 weeks [43].

The present search identified one further study of topical HBOT. This was a small cohort study [44] and reported an apparent improvement in healing at 90 days in the intervention group, but it was marred by the fact that patients chose the intervention, and there were differences between groups in the number of contacts with healthcare professionals. At present, therefore, the evidence from these three studies does not support the use of topical oxygen therapy to enhance the healing of diabetic foot ulcers.

Systemic Oxygen

The 2008 review included four RCTs [45–48], which provided some evidence to suggest that systemic HBOT may reduce the rate of major amputation. The strongest data came from a high scoring but rather small, RCT of patients with unreconstructable PAD [48].

Two further RCTs were included in the 2012 review [49,50], only one of which was methodically sound [50]. This high-quality double-blind RCT demonstrated significantly improved outcomes in the intervention group, who were more likely to heal within 12 months. Of note, the intervention group included patients who either had no evidence of PAD or who were deemed unsuitable for vascular reconstruction, unlike the previous RCT identified in 2008 [48] where only patients with unreconstructable critical limb ischemia were included.

This review identified four more studies in this group: three RCTs and a large cohort study. The first was a small, non-blinded, randomized study of poor quality [51]. Although apparently showing an improvement in the intervention group at 10 weeks, the lack of blinding and incomplete data on important baseline variables makes this difficult to interpret. The second RCT [52] was an equally small, non-blinded study, which appeared to be designed mainly as a biochemical study. The apparent improvement in the group of patients allocated to systemic HBOT compared with either silver-impregnated or gauze dressings is surprising given the extremely short follow-up period of 2 weeks. The third was another small and non-blinded RCT that apparently showed inferiority of HBOT over shockwave treatment [53]. The results are difficult to interpret as the analysis was *per protocol* throughout, and the patients were able to choose a second course of either therapy at the end of 6 weeks. In addition, this study is very similar to the one included in the 2012 review by the same authors [54], albeit with slightly higher numbers in the two study arms. It is unclear whether the later paper is an update of the previously reported study or is completely new.

A single, very large, retrospective cohort study of the use of HBOT in a population of patients treated in 83 centres located in 31 states of the USA was reported [55]. Patient data were included if patients had poorly healing ulcers and had been treated according to reimbursement guidelines from Centers for Medicare and Medicaid Services, which included the need for adequate peripheral perfusion, as defined by the clinician. Using propensity score-adjusted models to adjust for differences in baseline variables compared with a cohort of patients who were not exposed to HBOT, the authors concluded that HBOT did not appear to be useful for the prevention of amputation and did not improve the likelihood that a wound would heal in a cohort of patients selected by the eligibility criteria for reimbursement. This paper has proved controversial with a number of authors criticizing the methodology [56,57]. Nevertheless, this report echoes the concerns of other authors that it is not yet possible to define the particular patient group in which this therapy would be effective and cost effective.

The authors of the present review are aware of another large blinded RCT of HBOT, which has been completed, but is yet to report its findings [58].

Ozone

One small but high-scoring study of topical ozone on healing by 24 weeks was identified in the current search. No difference was reported between the intervention and control groups [59].

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Compression or negative pressure wound therapy (online Tables 11–13)

Compression

The 2008 review reported a single RCT, which suggested a benefit from compression therapy on post-operative wounds [60]. In 2012, however, three further studies (two RCTs and a cohort study) were identified. The first RCT, which excluded patients with neuropathy, reported an apparent reduction in wound area following the use of vacuum compression, but was of poor methodological quality [61]. The second investigated large post-operative wounds and, although the results showed a reduction in time to healing in the intervention group, the study was un-blinded [62]. The cohort study, which showed an apparent significant increase in the number of patients who healed with limbs intact, was potentially biased as patients were allowed to choose whether to have the intervention or not [63].

There were no new studies identified in the current search.

Topical negative pressure wound therapy

The 2008 review also identified three RCTs of topical negative pressure wound therapy (NPWT). Two of the three RCTs were very small but reported significant benefits in both healing rate and healing time [64,65]. A third, much larger study reported a significant benefit of NPWT in both time to, and proportion of persons, healing in those who had recently undergone foot surgery [66] even though the definition of 'healing' used included those who healed after repeat surgery, and this weakens the conclusions to be drawn from the results.

The 2012 review included three studies of NPWT, two RCTs and a cohort study. One of the RCTs was too small to draw any firm conclusions [67]. The second however methodologically sound study involving the randomization of 342 patients [68] showed a reduced time to wound closure, an increased incidence of healing by 16 weeks, a greater reduction in cross-sectional area by 8 weeks and reduced incidence of minor amputation. The ulcers had been present for much longer than in other studies (mean 200 days), but it was not stated how many of them had originally been post-operative wounds. A cohort study (also identified in the 2012 review) attempted to confirm the effectiveness of NPWT through analysis of reimbursement claims, but the results could potentially be explained (in part) by confounding factors [69].

The present search identified only three more small studies, but none of these was of good methodological quality. The first, a small non-blind RCT, showed no difference between the two groups in terms of healing at 8 weeks, and although there was an apparent reduction in wound area, the lack of information on the baseline areas of the two groups makes this finding uninterpretable [70]. The second also included few patients, was non-blinded and compared NPWT with standard wound care. The size of the wounds was quite large at baseline (NPWT group mean 35.7 cm^2 and control group 29.7 cm^2), and it is therefore surprising that the apparent time to healing was less than 4.5 weeks in each group. Although the text of the paper states that the healing rate was faster in the intervention group, this result was not supported by the data given in the table, which suggests that the intervention group took on average 0.6 weeks longer to heal [71]. The third paper [72] contained two studies; the first was a small, low-scoring, non-blinded RCT comparing the use of NPWT after split skin graft with a non-adherent dressing over the graft, which suggested that the proportion of the split skin grafts, which took successfully, was significantly higher in those who had the NPWT. The lack of blinding and information on baseline wound characteristics makes this result difficult to interpret. This novel use of NPWT is, however of interest, even though the study needs confirmation. The second part of this paper describes a small non-blind RCT of infected or surface-contaminated chronic wounds and compared the use of NPWT with other advanced wound care products. The definition of healing included those wounds that were surgically closed as well as those which were allowed to heal by secondary intention. Although there was an apparent reduction in the time to healing in the intervention group, the lack of data on the baseline area of the ulcers, the uncertain drop-out rate and the lack of blinding (which could have influenced the decision to surgically close the wound) makes this result difficult to interpret.

In 2012, it was concluded that further high-quality evidence was needed to substantiate the place of NPWT in routine clinical practice, but no such evidence has been identified in this latest search.

This section included growth factors in the earlier reviews, but these have been included in the following section in this update.

Products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing (online Tables 14–16)

Collagen/oxidized regenerated cellulose

In 2008, the search found one large RCT of a collagen/oxidized regenerated cellulose (ORC) dressing product, but

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this failed to confirm an effect on healing [73]. In 2012, a small non-blind RCT reported a significant benefit when a collagen/ORC dressing was compared with usual care [74] but was compromised by using *per protocol* analysis. This report included details of a second study, which suggested that there may be an additional benefit of combining this dressing with autologous platelet supernatant when compared with either treatment alone, but the data were not fully presented, and the conclusions are therefore difficult to interpret [75].

The current search identified two further RCTs comparing collagen/ORC dressings with usual care. The first, which also contained silver in the dressing, was of poor quality but found no difference compared with the control group [76]. The second was also very small and of poor quality and reported an apparent improvement in wound healing at 8 weeks even though there was a difference in the baseline area of the two groups, which would have favoured the intervention [77].

Acellular bioproducts

A single study of an acellular bioproduct derived from the small intestinal submucosa of pigs was identified in the 2008 review [78]. When compared with platelet-derived growth factor (PDGF), no benefit was observed.

In 2012, a further two RCTs of an acellular dermal regenerative tissue matrix were identified. The first, a small non-blinded RCT of poor quality combined an acellular dermal regenerative tissue matrix with a mineral oil-soaked dressing [79]. A significant difference in healing and the final wound area was shown when compared with the control group, but no data were provided on area at baseline. The second was also of poor methodological quality and compared a single application of an acellular dermal regenerative tissue matrix combined with a silver-impregnated dressing, with usual wound care [80]. A significant difference in healing at 12 weeks was found, but the study was not blinded.

Others

In the 2012 review, a small partial dose-ranging study of talactoferrin was identified in [81]. The study design was poor, however, and no difference was observed between groups. Topical Chrysalin, a ligand for thrombin-binding sites, was studied in a small double-blind placebo-controlled, partial dose-ranging trial [82], and although no statistical analysis was presented, the outcomes appeared similar in the three groups. A small RCT of an extract of the plant *Tinospora cordifolia*, applied as an immunomodulator reported a non-significant change in the rate of healing [83] was also identified in the same review. No studies of any of these interventions were identified in the current review.

The current search did however identify a high-scoring, double-blind RCT of daily intramuscular injections of polydeoxyribonucleotide (a DNA product that is thought to stimulate cellular proliferation) for 5 days a week with additional perilesional injections 2 days a week for 8 weeks, compared with placebo injections. The study reported a significant improvement in the proportion of ulcers healed at 8 weeks as well as the time to healing in those that healed, although the healing rate in the control arm appeared quite low for this type of ulcer, and there was little information about offloading [84]. This interesting finding therefore needs to be confirmed.

Application of cells, including platelets and stem cells and growth factors (online Tables 17–19)

Growth factors

One small RCT of basic fibroblast growth factor (bFGF) was identified in the 2008 review, showing no benefit in healing by 12 weeks compared with controls [85]. A second high-quality, partial dose-ranging RCT of bFGF administered in spray form for 8 weeks was identified in the 2012 review. Although a significant difference between the higher dose and placebo in the proportion of ulcers having a reduction in area by $>75\%$ was reported, this was only on *per protocol* analysis [86]. The authors are aware of another trial of bFGF, the results of which are yet to be published. Preliminary results published in the clinical trial registry suggest there is no difference between intervention and control arms of the study in terms of healing after 12 weeks of treatment [87]. No further published studies on bFGF were identified in the current search.

In the 2008 review, two studies of epidermal growth factor (EGF) were included. The first was a small but high-scoring partial dose-ranging, double-blind RCT of topical EGF cream [88], which showed a significant improvement in healing of the group randomized to the higher dose EGF when compared with placebo at 12 weeks. Another study was less robust and included patients with leg ulcers [89], but there was no difference in the numbers healed by 16 weeks.

In the 2012 review, it was concluded that the preliminary findings of two more studies of EGF were interesting. One double-blind RCT showed no benefit overall [90], although a second [91], high-scoring RCT of intralesional injection of EGF reported a highly significant difference between groups in the prevalence of granulation tissue after just 2 weeks. Unfortunately, this latter study was marred by switching those in the control group to an intervention arm after the first two weeks. One further small, poor scoring cohort study was identified in the

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current search. No difference in healing was identified in healing at 8 weeks following weekly application of topical EGF compared with saline-moistened gauze [92].

In the 2012 review, a small but well-designed double-blind RCT [93] assessed the effect of intramuscular injections of a plasmid containing the gene for vascular endothelial growth factor, phVEGF$_{165,}$ and showed that a significantly greater percentage of the intervention group achieved the primary outcome measure of >60% reduction in ulcer area than controls. No further studies on this type of intervention have been identified.

In the 2008 review, five studies of granulocyte-colony stimulating factor granulocyte-colony stimulating factor were included. Whilst designed to determine its effect on infection, the five RCTs also assessed wound healing and reduction of amputation as secondary endpoints [94–98]. Only one of the five [96] was associated with any apparent benefit. No further studies were identified in either the 2012 or this review.

In 2008, three studies on PDGF were identified. The initial RCT [99] in non-infected neuropathic ulcers indicated a significant effect on healing, and this was confirmed in the later definitive phase III study [100]. A further study [101] failed to recruit sufficient numbers, and no differences were observed. It is also known to the authors that an equally large but allegedly negative study was never published; despite extensive efforts, no reference to this study, which started in the pre-registration era, could be identified. No studies were identified on PDGF in the 2012 search, but two studies were identified in this review. Both were small and of poor methodological quality. The first was a small three-way comparison between a group of patients treated with topical antiseptics, a group treated with topical HBOT and a group treated with PDGF. Although supposedly showing superiority of PDGF treatment in terms of healing at 10 weeks, the lack of baseline data and the open-label design means that the significance of any such effect is difficult to determine [44]. The second was a poorly scoring, open-label multicentre study, which showed no difference in outcome between the two treatment arms (PDGF *versus* TheraGauze®) [102].

The 2008 review identified five papers reporting the use of platelet-derived products, but all were limited by methodological problems, and no firm conclusion could be drawn, although there were data to suggest possible benefit [103–107].

It was noted in the 2012 review that products of platelet and platelet-derived products are expensive because of the cost of harvesting autologous platelets. A single study was identified that assessed the use of platelets from ABO and rhesus-matched blood bank samples in a single-blind RCT, reporting a significant improvement in the healing of the intervention group at 12 weeks [108]. No further studies of this type were found in the present search.

In the 2012 review, we found a single observer-blind, good quality, placebo-controlled RCT of autologous lipoaspirate cells, which reported a significantly higher incidence of healing at 8 weeks as well as a significantly reduced time to healing [109]. No further studies of this type of intervention have been found.

In summary, the evidence from studies of cell therapy including platelets and stem cells and growth factors to support their use in wound healing is not robust, and further rigorously designed blinded trials are needed.

Bioengineered skin and skin grafts (online Tables 20–22)

Dermal fibroblast culture

The 2008 review identified three studies of dermal fibroblast culture. One dose-ranging study [110] reported that weekly applications of dermal fibroblast culture improved healing of plantar neuropathic ulcers by 12 weeks, compared with saline-moistened gauze, but the results should be viewed with caution given the very low healing rate in the control group (8% at 12 weeks). Another study [111] found no difference between intervention and placebo. Although the third RCT [112] reported that healing by 12 weeks was significantly greater in the intervention arm than in controls, again the healing rate of the control arm was unexpectedly low at 18%.

No further studies of dermal fibroblast culture have been identified.

Fibroblast/keratinocyte co-culture

A single multicentre RCT of fibroblast/keratinocyte co-culture was identified in the 2008 review, which showed a significant improvement in both the proportion of ulcers healed at 12 weeks and time to healing in those treated for 4 weeks in the intervention arm compared with a control group treated with saline-moistened gauze [113].

One further study was included in the 2012 review. Although well designed, the trial was stopped prematurely when only 72 of 120 planned participants had been enrolled. Although there was an apparent significant improvement in healing at 12 weeks in the intervention group (51.5% *vs* 26.3%; $p = 0.049$), the failure to complete recruitment casts doubt on the strength of the conclusion that can be drawn and the efficacy of the product [114].

The current review found a single open-label study of a two-stage procedure, cultured autologous fibroblasts and keratinocytes on a hyaluronic acid scaffold (HYAFF autograft) followed by epidermal tissue engineered autografts

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compared with paraffin gauze. The study was stopped before the planned target of 200 patients was reached because of the long duration of recruitment (>6 years). Although there appeared to be a reduction in the time to 50% area reduction, there was no difference in the numbers of patients healed at 12 weeks [115].

Cultured Keratinocytes

In 2008, a single low-scoring RCT reported the use of keratinocytes alone, but few data were presented [116]. In the 2012 review, a small RCT reported the use of a novel keratinocyte delivery system but was of very poor methodological quality, and the result was inconclusive [117]. One small single-blind multicentre RCT was found in this search, which compared cultured allogenic keratinocytes on paraffin gauze with paraffin gauze alone. A significant improvement in the intervention group was noted at 12 weeks although many participants were lost to follow-up [118].

Split skin grafts

In the 2012 review, a small case–control study of the use of split skin grafting reported a positive outcome, but the study was of poor methodological quality and susceptible to bias because the patients had the option to select their treatment group [119]. In the present search, a small cohort study of the use of artificial dermis replacement applied under a split thickness skin graft was identified [120]. Although there appeared to be an improvement in the rates of healing at 12 weeks compared with split skin grafting alone, the study was non-randomized. There were also differences in the data presented in the text as opposed to the tables, which make the significance of the observations difficult to determine.

Amniotic membrane

There has also been a recent small and poor scoring, open-label RCT of the use of an amniotic membrane wound graft [121], which reported a significant improvement in healing at 6 weeks. However, the very low healing rate of the ulcers in the control group casts doubt on the significance of this finding.

Electrical, electromagnetic, lasers, shockwaves and ultrasound (online Tables 23–25)

Electrical stimulation

Two RCTs identified in the 2008 review examined electrical stimulation of the feet. The first was methodologically weak, and no benefit was observed [122]. In contrast, the second reported a non-significant trend towards a greater proportion healing at 12 weeks [123]. The 2012 review also identified two studies on electrical therapy. The first, a methodologically weak, cohort study showed no difference in ulcer area reduction at 60 days [124]. The second, a small low-scoring study [125] compared the use of electrical stimulation with a placebo comprising local warming of the skin. The lack of blinding and other methodological weaknesses cast doubt on the positive finding of a significant reduction in wound area at 4 weeks.

Shockwave therapy

Two trials of shockwave therapy were identified in the 2012 review. The first randomized 30 patients to receive either shockwave therapy to the perimeter of the ulcer each 72 h or a sham intervention [126]. There was no difference in ulcer healing by 20 weeks. The second compared extracorporeal shockwave treatment with hyperbaric oxygen [54]. Again methodologically weak, the reporting of a significant difference between the superiority of shockwave therapy over HBOT was based on a curious composite end point of the proportion of ulcers healed, or 'greater than 50% improved'.

The present search found only one new study on physical methods. This was a randomized trial comparing shockwave therapy with hyperbaric oxygen [53]. As noted previously, this study was very similar to the one included in the 2012 review by the same authors [54] albeit with slightly higher numbers in the two study arms and again shows an apparent superiority of shock wave therapy in terms of healing. It is unclear whether the later paper is an update of the previously reported study or is completely new.

Normothermic therapy/magnets/laser therapy

Small studies of the normothermic [127], magnetic [128] and laser therapy [129] were also identified in the 2008 review, but none reported any convincing evidence of benefit.

Other systemic therapies (online Tables 26, 27)

Five trials were identified in the 2012 review; one of low molecular weight heparin [130], one of iloprost infusion [131], and three of herbal preparations – administered orally in two [132,133] and intravenously [134] in one. None of the five were of good quality, and none showed any major improvement in outcome.

The current search found only two more papers in this category. One, a poor scoring non-blinded study of oral

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vildagliptin [135], showed an apparent improvement in healing at 12 weeks (31% *vs* 15%) but the very low incidence of healing in the control group is surprising for the type of ulcer selected for study, and this casts doubt on the likely clinical benefit of this product in routine clinical practice. The paper was also notable for the remarkably good matching of all the baseline clinical measures, especially for a relatively small population.

The second paper reported the use of oral pentoxyfilline in a small cohort study [136]. The only results included were the number of patients with a $>10 \times 10$ mm reduction in ulcer area at 30 days, with no data on the incidence of healing. In addition, no information was provided on adverse events in this paper.

Discussion

The outcome of treatment of ulcers of the foot in patients with diabetes remains a challenge. It is, however, important that the effectiveness and cost effectiveness of new treatments is rigorously assessed, and that the introduction of treatments that lack evidence of effectiveness should be avoided. The present report is an update of the earlier IWGDF systematic reviews in 2007 (published in 2008) and 2011 (published in 2012) [1,2], and the conclusion is similar in that the evidence to support many of the therapies that are in routine use is poor. A systematic review in 2012 [137] as well as that undertaken by the National Institute for Health and Clinical Excellence Guidelines Committee in the UK [138] came to similar conclusions, and these have not yet been updated.

There has been little change in the quality of the evidence since the last review. Once again, many of the papers selected as abstracts were not included as they were not controlled, and even those included were generally of poor methodological quality (online see Tables) with, in particular, a general lack of blinded assessments and hence weakened by potential bias. The lack of detail on baseline characteristics made a number of papers difficult to assess and makes it difficult to extrapolate the conclusions drawn from any positive findings difficult to a general clinical population.

New evidence of effectiveness of tested interventions

When the results of this updated review are taken together with those of the earlier report, they provide limited evidence to justify change in routine clinical practice. There are still no good studies to support the use of topical applications or dressing products, a finding supported by Cochrane reviews [18,139–142].

The previous earlier positive reports from randomized studies of hyperbaric oxygen have now been countered by a large cohort study [55], which showed little evidence of improvement when used in the patient cohort that qualifies for reimbursement in the USA, which is different from those patients recruited into the RCTs. Consequently, the question of which patient group would most benefit from this type of intervention remains unanswered.

Despite widespread use, there have been no further good studies on the use of NPWT, and at present, the evidence to support its effectiveness or cost effectiveness in the healing of chronic ulcers of the foot in diabetes – as opposed to post-operative wounds – is not strong, a conclusion echoed in the recent Cochrane review [143].

In the 2012 review, we reported on some interesting early studies on EGF. It is disappointing that no further randomized controlled studies were found in the current search, and although a number of uncontrolled cohort studies have been published, there has been no advancement of knowledge on the effectiveness or cost effectiveness of this therapy.

There have been no good quality studies, which advance our knowledge of the efficacy of any other growth factors, skin or skin substitutes or any other physical therapies.

Conflict of interest

F. G., J. A., A. H., R. H., M. L., P. P., W. J. declared none conflicting interest relating to the interventions reviewed.

C.A. is the consultant of Acelity, Integra and Smith & Nephew.

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Supporting information

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