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SUPPLEMENT ARTICLE

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

Prashanth Vas[1] | Gerry Rayman[2] | Ketan Dhatariya[3] | Vickie Driver[4] | Agnes Hartemann[5] | Magnus Londahl[6,7] | Alberto Piaggesi[8] | Jan Apelqvist[9] | Chris Attinger[10] | Fran Game[11]

[1]Diabetes Foot Clinic, King's College Hospital, London, UK

[2]Diabetes Centre and Research Unit, East Suffolk and North East Essex Foundation Trust, Colchester, UK

[3]Department of Diabetes, Norfolk and Norwich University Hospitals NHS Foundation Trust, University of East Anglia, Norwich, UK

[4]School of Medicine, Brown University, Providence, RI

[5]Pitié-Salpêtrière Hospital, APHP, Paris 6 University, ICAN, Lyon, France

[6]Department of Endocrinology, Skane University Hospital, Lund, Lund University, Lund, Sweden

[7]Department of Clinical Sciences, Lund, Lund University, Lund, Sweden

[8]Diabetic Foot Section, Department of Medicine, University of Pisa, Pisa, Italy

[9]Department of Endocrinology, University Hospital of Malmö, Malmö, Sweden

[10]Department of Plastic Surgery, Medstar Georgetown University Hospital, Washington DC, WA

[11]Department of Diabetes and Endocrinology, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

Correspondence
Prashanth Vas, Diabetes Foot Clinic, King's College Hospital, London, UK.
Email: prashanth.vas@nhs.net

Abstract

The management of diabetic foot ulcers (DFU) remains a challenge, and there is continuing uncertainty concerning optimal approaches to wound healing. The International Working Group of the Diabetic Foot (IWGDF) working group on wound healing has previously published systematic reviews of the evidence in 2008, 2012 and 2016 to inform protocols for routine care and to highlight areas which should be considered for further study. The working group has now updated this review by considering papers on the interventions to improve the healing of DFU's published between June 2014 and August 2018. Methodological quality of selected studies was independently assessed by a minimum of two reviewers using the recently published 21-point questionnaire as recommended by IWGDF/European Wound Management Association, as well as the previously incorporated Scottish Intercollegiate Guidelines Network criteria. Of the 2275 papers identified, 97 were finally selected for grading following full text review. Overall, there has been an improvement in study design and a significant rise in the number of published studies. While previous systematic reviews did not find any evidence to justify the use of newer therapies, except for negative pressure wound therapy in post-surgical wounds, in this review we found additional evidence to support some interventions including a sucrose-octasulfate dressing, the combined leucocyte, fibrin and platelet patch as well as topical application of some placental membrane products, all when used in addition to usual best care. Nonetheless, the assessment and comparison of published trials remains difficult with marked clinical heterogeneity between studies: in patient selection, study duration, standard of usual care provision and the timing and description of the clinical endpoints.

KEYWORDS

debridement, diabetic foot, dressing, foot ulcer, guidelines, hyperbaric oxygen, negative pressure wound therapy, placental-derived products, topical oxygen, wound healing

Abbreviations: ADM, acellular dermal matrix; APG, autologous platelet gel; C, comparator or control; DFU, diabetic foot ulcer; dHACM, dehydrated human amniotic chorionic membrane; EGF, epidermal growth factor; FGF, fibroblast growth factor; G-CSF, granulocyte colony stimulating factor; HBOT, hyperbaric oxygen therapy; I, intervention; ITT, intention to treat; NPWT, negative pressure wound therapy; PAR, percentage area reduction; PDGF, platelet-derived growth factor; PP, per protocol; RCT, randomized control trial; rPDGF, recombinant platelet-derived growth factor; SOC, standard of care; TCPO2, transcutaneous oxygen pressure; WSA, wound surface area.

1 | INTRODUCTION

The management of foot disease in diabetes remains a major therapeutic and financial challenge throughout the world. The International Working Group of the Diabetic Foot (IWGDF) has issued guidelines on the management since 1999 and systematic reviews to underpin these 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 patients with diabetes in order both to inform protocols for routine care and to highlight areas, which should be considered for further study. The first review[1] included all articles published up to December 2006 and was published in 2008. Subsequently, updated systematic reviews were published in 2012[2] and 2016[3]; the latter included a review of articles until June 2014. The working group has now undertaken a further update by also considering articles published until August 2018.

2 | MATERIALS AND METHODS

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was in line with the consensus and checklist on updating systematic reviews.[4,5] As a start, the population of interest (P), interventions (I), and outcomes (O) was defined, and clinical questions (PICOs) were formulated accordingly. These definitions and PICOs were reviewed for their clinical relevance by the IWGDF Editorial Board and 10 external experts worldwide, from various geographical regions. 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 diabetes mellitus, were considered. Studies were included if they concerned agents or interventions that may accelerate the healing process and had at least one of the following primary outcomes: healing, time to healing, and/or reduction in ulcer area.

2.1 | Search

We used the same search strategies (Appendix S1) in this update review as in our 2008, 2012, and 2016 systematic reviews, which included selected search terms on study design, patient group, clinical problem, and interventions of interest by using Medline (June 2014 to August 2018) and Embase (June 2014 to August 2018). Randomized controlled trials (RCTs), 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 clinical trials registries using the search terms shown in Appendix S2, and attempts were made to contact investigators if there was no evidence of publication of relevant studies.

2.2 | Assessment and data extraction

Two reviewers (Vas and Rayman) independently assessed all identified references by title and abstract to determine possible eligibility. Full-article copies of identified articles were retrieved, and eligibility was confirmed or rejected by one of five 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).[6] Equal weighting was applied to each validity criterion. Findings on data extraction and methodological quality were discussed between coreviewers, and a final decision was 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[6]: (a) RCTs and (b) 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). In addition, all new studies identified in the current systematic review (2014-2018) underwent review using the 21-point criteria suggested by Jeffcoate et al[7] by a minimum of two members of the working group. These criteria provide a semiquantitative framework of assessing aspects of trial design, conduct, and reporting in order to minimize study bias and improve quality. Meta-analyses, other reviews, and studies reporting non-analytic case reports and case series were not included. Reviewers did not assess or discuss their own studies to avoid bias.

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. All studies included in our previous three reviews were incorporated in this updated review and entered into the evidence tables. The evidence tables were compiled following collective discussion by the working party, and conclusions were drawn. And subsequently, evidence statements were formulated according to the GRADE system.[8]

2.3 | Categorization of studies

The articles selected for scoring were divided into the same previous categories as in our previous reviews, but we added one additional category with several recent publications. The categories were debridement, larvae, and hydrotherapy; antiseptics, applications, and dressing products; resection of the chronic wound; negative pressure wound therapy (NPWT) or compression; products to correct aspects of wound biochemistry and cell biology; growth factor, cellular products, and cells; placental-derived products (new category); bioengineered skin and skin

grafts; oxygen and other gases; physical therapies; and other systemic therapies including medical and nutritional therapies.

3 | RESULTS

In our previous reviews, we identified a total of 4905 articles from Embase and Medline. An additional 13 articles were identified from other sources, including other systematic reviews. Of these, 507 were selected for full-text review, and 137 were included in the final review. In the current search, 2917 articles were identified: Medline 2001 and Embase 916, giving us 2275 after excluding duplicates. Of these, 116 were selected for full text of which 97 articles were graded and included in the final review (Figure 1).

4 | DEBRIDEMENT AND WOUND BED PREPARATION

4.1 | Sharp debridement

One study on sharp debridement was identified, a subgroup analysis of cases from an RCT of another intervention reporting that healing at 12 weeks was more likely following a more vigorous debridement (Table 1 in Appendix S3).[9] Sharp debridement also featured as a standard-of-care provision in a number of studies reviewed; however, we were unable to ascertain outcomes specifically related to this intervention.

4.2 | Hydrodebridement

One controlled study on hydrodebridement[10] that did not show benefit on healing at 12 weeks in a small study was previously reported. No further studies were identified in the current search.

4.3 | Enzymatic debridement

The use of clostridial collagenase ointment (CCO) used daily as a debriding agent has been examined in five RCTs, all of which were unblinded.[11-15] Only one study examined the complete ulcer healing as a primary outcome.[15] This study, at moderate risk of bias, compared daily application of CCO in comparison with daily application of hydrogel but found no statistical difference on ulcer healing at 12 weeks (I: 65% vs C: 60%, P = NS).[15] The other four studies reported on percentage change in ulcer area,[11-14] and one primarily

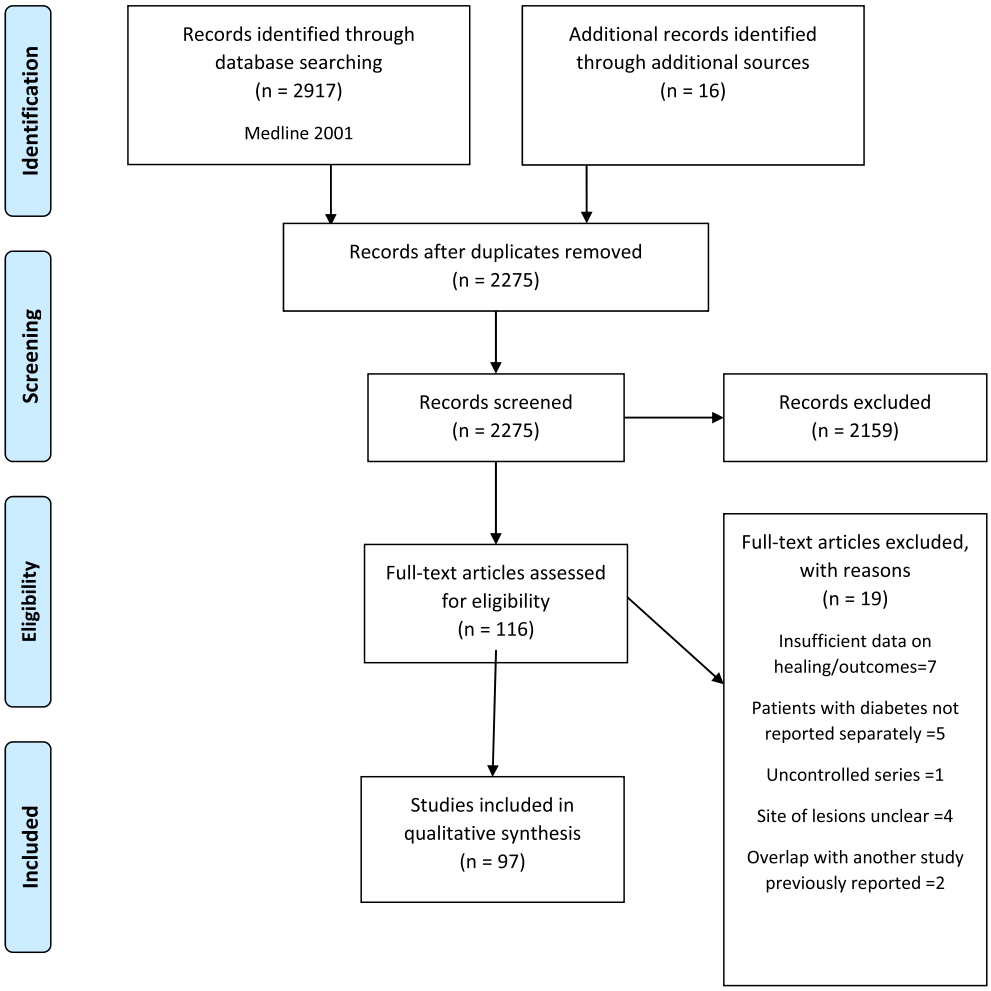

FIGURE 1 PRISMA statement

reported on analytes associated with resolution of inflammation.[12] In the studies using percentage change in ulcer area reduction, two did not have a statistical difference between intervention and control groups.[11,12] In the study, where CCO-based debridement suggested an apparent improvement in the percentage change in ulcer area (CCO: 72% vs C: 34%), only within group analysis was performed rather an estimation of between group differences.[13]

A study exploring the effect of proteolytic fraction from latex of vasconcellea versus hydrogel[16] utilized an unorthodox composite end point of complete ulcer healing and percentage area reduction, which made it difficult to interpret the findings.

4.4 | Larval therapy

Only one recent retrospective controlled cohort study at a high risk of bias[17] was found in addition to the four studies previously reported.[18-21] All four of the older studies were at high risk of bias, non-randomized, and unblinded. Any apparent effect of improved healing should therefore be treated with caution. Wilsarusmee described a retrospective cohort who received larval therapy versus standard care and reported a seven times greater likelihood of ulcer closure. However, there were significant limitations of study design and reporting, including key details of ulcer characteristics and how patients were selected for larval therapy. Furthermore, those treated with standard care alone, which was poorly defined, had healing rates lower than would be expected.[17]

4.5 | Evidence statement

Apart from sharp debridement, there is inadequate evidence to establish whether one debridement technique is superior to the another. Quality of evidence: low.

5 | ANTISEPTICS, APPLICATIONS, AND DRESSING PRODUCTS

5.1 | Antiseptics and antimicrobials

One study on cadexomer iodine did not demonstrate benefit in cavity wounds when compared with usual care.[22] Similarly, a subsequent large, observer-blinded, RCT of good quality reported no difference between three products in terms of healing by 24 weeks: carboxymethylcellulose hydrofibre, an iodine-impregnated dressing, and a nonadherent gauze product.[23] We also found evidence from a single small study from 1990 of possible benefit from the use of zinc oxide tape, but no subsequent reports have been found.[24]

A single-blind RCT evaluating potassium permanganate 5% solution in comparison with standard of care, which included offloading and daily cleansing, was identified.[25] The duration of follow-up was short (21 days), and the study did not report a significant benefit on the primary outcome of ulcer area reduction. Included, patients were admitted to the hospital, and a clear description of all aspects of standard care including the type of offloading provided was not provided.

A single nonblinded RCT on the use of superoxidized antiseptic solution was identified,[26] which compared the incidence of healing at 6 months after infected surgical wounds of the foot had been irrigated either with the superoxidized solution or with povidone/iodine. There was a high risk of bias, and results should be treated with caution (-Table 2 in Appendix S3).

5.2 | Alginate and collagen-alginate products

Two small studies of alginate-containing products were found; both identified previously. Neither showed evidence of improved ulcer healing in comparison with saline-moistened gauze[27] or Vaseline gauze.[28]

5.3 | Carboxymethylcellulose dressings

We previously identified an RCT, which reported improvement with the use of a carboxymethylcellulose hydrofibre dressing in the 2008 review.[29] In the 2012 review, however, a further larger RCT with a silver-impregnated dressing was reported, which showed no difference in healing at 8 weeks when compared with an alginate dressing.[30] Another large, observer-blinded, RCT of good quality reported no difference between three products: carboxymethylcellulose hydrofibre, an iodine-impregnated dressing, and a nonadherent gauze product, in terms of healing by 24 weeks.[23]

5.4 | Honey and bee-related products

In 2016, we had identified three studies. In this search, we have identified two further RCTs on honey and additional two new studies on bee-related products. Two nonblinded but randomized comparisons between the topical application of honey and povidone/iodine were found but were limited by the small sample sizes, short follow-up, and poor study design.[31,32] One did not report any benefit.[31] The other noted an apparent difference in ulcer area reduction at 15 days, but the lack of data on the baseline characteristics of the ulcers and the probable inappropriate use of parametric statistics make this result difficult to interpret.[32] One cohort study[33] compared honey dressings with iodine dressings and found no differences 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. There was poor description of baseline characteristics, and the patients were not randomized; therefore, this result should be treated with caution. A larger but poor scoring unblinded study randomized 338 subjects to either honey dressings or saline-soaked dressings reported a higher complete ulcer healing rate at 120 days (I: 76% vs C: 57%, P = .001) and a reduction in time to healing.[34] However, the unblinded study design, limited information on patient and ulcer characteristics, and reporting only the per-protocol analysis set this result at a

high risk of bias. Another smaller, equally poorly scoring cohort study investigated the effect of manuka-honey–impregnated dressings in comparison with saline-soaked dressings and reported that mean duration to complete ulcer healing was lower in the honey-treated group.[35] The incidence of complete ulcer healing was not reported, however.

More recently, a cohort study of the topical application of propolis, a resinous beehive product, was compared with historical controls.[36] This poorly scoring study reported no difference in the percentage area reduction but found an apparent higher rate of healing in those treated with the propolis. This result is at high risk of bias, and the healing rate in the control arm appears lower than expected. Another RCT, using Royal jelly, a worker bee product, did not find differences in complete ulcer healing at 12 weeks compared with placebo.[37]

Therefore, despite the widespread use of honey dressings in clinical practice and newer investigations into bee-related products, there remain insufficient data to support their use to enhance the healing of diabetic foot ulcers.

5.5 | Sucrose octasulfate

One recent large multicentre double-blind RCT with a high methodological quality and low risk of bias investigated the efficacy of sucrose octasulfate impregnated dressings in neuroischaemic (ABI < 0.9 or TBI < 0.7 but toe pressure > 50 mmHg) non-infected ulcers, of area[38] of 1 to 30 cm^2. Patients were excluded if they had a reduction in the ulcer area of more than 30% during a 2-week run-in period of usual care, which was well defined including the use of approved offloading devices. At 20 weeks (140 days), there were a significant increase in the proportion of healed ulcers (I: 48% vs C: 30%, $P = .002$) and faster estimated median time to healing (120 vs 180 days) by Kaplan-Meier analysis. Of note, however, the actual time to healing of those ulcers that healed was not reported.

5.6 | Topical phenytoin

We did not find any new studies on phenytoin in the current search. In the previous systematic review, we reported on one cohort[39] and three RCTs on the use of topical phenytoin.[40-42] The cohort study and two RCTs, which were poorly scoring, reported a positive benefit in terms of ulcer area reduction but with a high risk of bias. The other RCT, which was slightly larger, higher scoring, double-blind study, compared topical phenytoin with an alginate dressing.[42] 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.

5.7 | Hydrogels

Three previously identified controlled trials have suggested that hydrogels may hasten healing. One nonblind RCT reported a significant benefit in terms of healing of nonischaemic foot ulcers when a hydrogel was compared with saline-moistened gauze.[43] Two cohort studies were identified, but neither reported any specific data on ulcer healing, and one used no statistical analysis.[44,45] No further studies on hydrogels were identified, and the place of these products in routine care is still not clear.

5.8 | Topical application of antibiotic products

The use of topical antimicrobials (tobramycin beads) on the wound at the time of forefoot amputation was shown in a non-randomized cohort study to have a significant beneficial effect on the need for later surgical revision[46] but no difference in healing times or later transtibial amputation. While we are aware of a number of case series, no further controlled studies on antibiotic-impregnated beads or cement have been identified, and so the place of these agents in ulcer healing is yet to be determined. In some countries, the use of applications impregnated with antibiotics is disallowed.

5.9 | Herb/bark extracts

One 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.[47] Another small, nonblinded, and poorly scoring study of a polyherbal cream compared with application of a silver sulphadiazine cream was identified.[48] There was no difference in the time to healing between the two groups. A small, poorly scoring multicentre RCT of a Chinese polyherbal preparation[49] 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.

5.10 | Other topical products

A further small, poorly scoring, nonblinded RCT of bismuth subgallate/borneol with patients randomized in a 2:1 ratio to topical application either of this or of intrasite gel found no difference in healing at 12 weeks.[50] 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 NorLeu3-A^{1-7} (an analogue of angiotensin 1-7) 0.01% or 0.03% versus placebo.[51] There was no difference in the proportion of patients healed in either of the two treatment groups or in reduction in ulcer area at 12 weeks compared with placebo. At 24 weeks, there was a reported significant increase in the proportion of patients healed in the NorLeu3-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 randomized study in uninfected DFU with a crossover design at 8 weeks was found investigating topical pirfenidone (PFD) against standard care.[52] While there was an apparent significant benefit of PFD in the complete ulcer healing at the end of 8 weeks, the report suffered from significant methodological flaws and therefore scored poorly. In addition to the small sample size, there was a high dropout rate, leading to per-protocol analysis only. Another RCT explored the use of Kitocell-Q (gel that combines PFD 8% and M-DDO 0.016%) versus another active comparator, Ketanserin gel, in a small cohort of neuropathic uninfected DFU.[53] It reported superior reduction in ulcer volume with Kitocell-Q at 3 months (primary outcome), but rates of complete ulcer healing were not different. For a neuropathic DFU cohort, the offloading provided was not described, and rate of healing in both arms was lower than expected.[53]

A randomized multicentre study evaluating the efficacy and safety of a peptide mimetic of the C-terminus of Cx43, alpha connexin carboxy-terminal (ACT1), was identified.[54] This study received a high Cochrane score but was moderately scoring on the 21-point assessment. The intention-to-treat (ITT) analysis reported that the 12-week percentage area reduction from baseline (primary outcome) was superior in the intervention arm along with a higher rate of complete ulcer closure. Firm conclusions could not be drawn as there was a high dropout rate in the intervention, protocol non-compliance along with errors in the statistical analysis.

One small open-label cohort study of a microbial cellulose membrane compared with xeroform gauze was identified.[55] The two groups were not well matched at baseline in terms of the presence of peripheral arterial 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 has been reported.[56] 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, and the clinical baseline characteristics of the patients were not reported, rendering these results difficult to interpret.

5.10.1 | Evidence statement

There is inadequate evidence to establish whether dressings/applications containing surface antimicrobial agents and honey or bee-related products accelerate ulcer healing. Quality of evidence: low.

5.10.2 | Evidence statement

Sucrose octasulfate impregnated dressings probably accelerate ulcer healing in non-infected neuroischaemic ulcers when used in addition to best standard of care. Quality of evidence: moderate.

5.10.3 | Evidence statement

There is no evidence to support the superiority of any other dressing product or over another to achieve ulcer healing. Quality of evidence: low.

6 | RESECTION OF THE CHRONIC ULCER

Three studies relating to excision of plantar ulcers with or without removal of underlying bone were found, all noted in previous reviews. 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.[57] Two retrospective cohort studies looking at the effect of either excising the fifth metatarsal head underlying a chronic ulcer[58] or excising ulcers under the interphalangeal joint of the hallux or first metatarsophalangeal joint[59] combined with arthroplasty reported benefit in terms of healing. No further publications on this topic have been found during the course of this update (Table 3 in Appendix S3).

In summary, surgical resection of the chronic ulcer 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.

6.1 | Evidence statement

Surgical resection of a chronic ulcer, combined when indicated, with removal of underlying bone may reduce time to healing. Quality of evidence: low.

7 | NEGATIVE PRESSURE WOUND THERAPY OR COMPRESSION

7.1 | Negative pressure wound therapy

There are two distinct clinical scenarios in which NPWT has been studied in the management of DFUs—the postsurgical wound and the chronic non-surgical ulcer (Table 4 in Appendix S3).

7.1.1 | Postsurgical wounds

In one relatively large study of 162 patients with postamputation wounds, there was a small but significant benefit ($P = .04$) in the proportion of wounds healed.[60] The dropout rate was high, and the outcome definition was unusual as it included those healed by secondary intention as well as those unhealed but rendered suitable for surgical wound closure. In the other relatively large study of 342 postoperative wounds, a greater proportion of foot ulcers achieved complete ulcer closure with NPWT than with advanced wound therapy within 112-day active treatment phase (I: 43.2% vs C: 28.9%, $P = .007$), but the study was nonblind, and there was a relatively high

(30%) dropout rate.[61] Another small RCT on postsurgical wounds following transmetatarsal amputation or resection of toes reported benefit from NPWT application, but the end point of 90% granulation may be interpreted as subjective, and there was variability in the standard of care provided.[62] A further low scoring study suggested that split skin grafting (SSG)[63] was more successful with the application of concomitant NPWT but was limited by the lack of wound characteristics and clarity on the dropout rate. The same study described a second small nonblind RCT of infected or surface-contaminated chronic wounds and compared the use of NPWT after debridement with other advanced wound care products.[63] The definition of healing was a composite, including those wounds that were surgically closed as well as those 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 dropout rate, and the lack of blinding make the results difficult to interpret. The most recent RCT[64] was a small study with only 80% of participants having diabetes. NPWT was applied for the first 2 weeks, followed by topical dressings. There was no significant change in the primary outcome of wound volume reported. Of note, the significant reduction in wound depth was a secondary outcome. The study was found to high risk of bias with only a per-protocol analysis and a high dropout rate and scored poorly in our assessments. Indeed, its primary aim was to explore tissue oxygen response in acute wounds.[64] We also found a small cohort study,[65] which did not report a benefit in wound area reduction when photon therapy was added to NPWT, but the study lacked a true control group comprising standard wound care. Additionally, the ulcer areas appear large (5-100 cm^2) for diabetic foot wounds, and it was unclear how patients were allocated to each group.[65]

7.1.2 | Chronic non-surgical ulcers

In total four RCTs, three cohort studies and one case control were found comparing the use of NPWT with standard of care, all of which were at high risk of bias.[66-73]

Two early RCTs were very small and poorly scoring but reported significant benefits in both healing rate and healing time.[66,67] One larger RCT also suggested benefit of NPWT over "advanced moist wound therapy" in terms of reduced ulcer area in an outpatient cohort but did not provide a clear description of the statistical basis of the conclusion.[70] The follow-up duration was only 2 weeks, and the baseline characteristics lacked key between group characteristics such as renal function and vascular indices or vascular intervention rates.[70] A cohort study attempted to confirm the effectiveness of NPWT versus traditional wound therapies through analysis of reimbursement claims, but the results could potentially be explained (in part) by confounding factors.[68] The findings from two other cohort-controlled studies,[71,74] while indicating apparent benefit, could not be easily interpreted due to unclear statistical analysis, and both were considered at high risk of bias. A recent prospective observational cohort[73] did not report a difference in ulcer healing outcomes at 1 year, but allocation to NPWT if ulcer area was more than 1 cm^2 or to a comparator if less than 1 cm^2 would have introduced significant bias. Moreover, adequate description of the comparator was not provided.

The previous systematic review concluded that further high-quality evidence was needed to substantiate the place of NPWT in routine clinical practice, while noting apparent benefit in acute postsurgical wounds.[3] The findings from the current review do not change these conclusions.

7.2 | Compression (vacuum or compressed air massage)

We found four RCTs and one cohort study, of which one was newly identified in this search. One RCT suggested a benefit from pneumatic compression therapy of infected post-operative wounds.[75] Another RCT reported an apparent reduction in ulcer area following the use of vacuum compression but was of poor methodological quality.[76] The third RCT investigated the impact of compressed air massage 5 d/wk on large post-operative ulcers, and although the results indicated a reduction in time to healing in the intervention group, the study was unblinded.[77] One recent small RCT reported a significant improvement in the percentage change in ulcer area over 16 weeks (P = .043) with high-pressure, intermittent pneumatic compression for 16 weeks versus an unsupervised exercise regimen in those with no-option ischaemia.[78] However, the study included those with intermittent claudication, did not provide details on how the decision of no-option ischaemia was achieved, and was therefore considered to be at a high risk of bias. One cohort study from 2008 with an 18-month follow-up showed an apparent significant increase in the number of patients who healed with limbs with intermittent pneumatic compression but was potentially biassed given its retrospective nature and the fact that as patients could choose whether to have the intervention or not.[79]

7.2.1 | Evidence statement

Negative pressure wound therapy in postsurgical wounds may reduce the time to healing when provided in addition to best standard of care. Quality of evidence: low.

7.2.2 | Evidence statement

There is insufficient evidence to establish whether NPWT reduces time to healing in chronic ulcers when provided in addition to best standard of care. Quality of evidence: low.

8 | PRODUCTS TO CORRECT ASPECTS OF ULCER BIOCHEMISTRY AND CELL BIOLOGY

8.1 | Collagen/oxidized regenerated cellulose

Previous reviews found one large RCT of a collagen/oxidized regenerated cellulose (ORC) dressing product, but this failed to

confirm an effect on healing,[80] and a small nonblind RCT reported a significant benefit when a collagen/ORC dressing was compared with standard care[81] but was compromised by the use of per-protocol analysis only. This report included details of a second study, which suggested that there may be an additional benefit of combining this dressing with an autologous platelet supernatant when compared with either treatment alone, but the data were not fully presented, and the conclusions are therefore difficult to interpret.[82]

The current search identified two further RCTs comparing collagen/ORC dressings with usual care. The first, which also contained silver in the dressing, was at risk of bias and found no difference compared with the control group.[83] The second was also very small and at high risk of bias and reported an apparent improvement in ulcer healing at 8 weeks even though there was a difference in the baseline area of the two groups, which would have favoured the intervention.[84]

8.2 | Acellular dermal matrices

In one older study, an acellular dermal matrix (ADM) derived from the small intestinal submucosa of pigs was compared with platelet-derived growth factor (PDGF), and no benefit was observed.[85]

Since then, a number of studies of human-derived ADMs have been published with different comparators. One, a small nonblinded RCT of poor quality, combined an acellular dermal regenerative tissue matrix with a mineral oil–soaked dressing.[86] A significant difference in healing and the final ulcer area was shown when compared with the control group, but no data were provided on area at baseline. Another study, also of at high risk of bias, compared a single application of an acellular dermal regenerative tissue matrix combined with a silver-impregnated dressing, with usual ulcer care.[87] A significant difference in healing at 12 weeks was found, but the study was not blinded, and this result should be viewed with caution.

We identified one large RCT on a human three-dimensional ADM with a temporary epidermal layer made of silicone compared with moist wound therapy.[88] This well-conducted study reported a higher rate of complete ulcer healing in the intervention arm at 16 weeks (I: 84% vs C: 34%, $P < .05$), but the primary outcome was not blinded. Another small RCT on a flowable matrix of type 1 collagen, glycosaminoglycans, and glycoproteins[89] allowing filling of cavities in acute postsurgical wounds reported per-protocol findings favouring the intervention at 6 weeks (complete wound closure; odds ratio [OR] 1.67, $P = .01$). One randomized open-label study had three treatment arms consisting of two different human ADM products and a "conventional care" arm. A significantly higher ulcer healing rate at weeks 16 and 24 was observed of the intervention ADM (I: 70.0% vs C: 49.3%; OR 1.589, $P = .044$), but this was a per-protocol analysis.[90] Another study of aseptically processed human reticular ADM (HR-ADM) of 80 patients assessed the proportion of ulcers closed at 6 weeks compared with a standard care group receiving daily collagen alginate dressing changes.[91] It reported a significantly higher rate of healing (I: 80% vs C: 30%) as well as lower mean time to heal with the intervention, but the study was not blinded and was considered to be at a moderate risk of bias[91] especially as an interim analysis of the same cohort had previously been published.[92]

8.2.1 | Evidence statement

There is insufficient evidence to establish whether acellular products designed to correct aspects of ulcer biochemistry and cell biology improve healing when compared with best standard of care (Table 5 in Appendix S3). Quality of evidence: low.

9 | GROWTH FACTORS, CELLULAR PRODUCTS, AND CELLS

9.1 | Fibroblast growth factor

One small early RCT of basic fibroblast growth factor (bFGF) suggested no benefit in healing by 12 weeks compared with controls.[93] A second partial dose ranging RCT of bFGF topical spray noted a significant difference in the proportion of ulcers achieving a 75% reduction in area at 8 weeks between the higher dose and placebo, but only a per-protocol analysis was available.[94] The authors are aware that the full results of another trial on bFGF topical spray are yet to be published. Results published in the clinical trial registry, last updated in August 2014, suggested that there was no difference between intervention and control arms regarding healing after 12 weeks of treatment.[95]

9.2 | Epidermal growth factor

Seven older studies of epidermal growth factor (EGF) were included. The first was a small partial dose-ranging, double-blind RCT of topical EGF cream,[96] which showed a significant improvement in healing at 12 weeks in the group randomized to the higher dose of EGF when compared with placebo. The second was less robust and included patients with leg ulcers,[97] but there was no difference in the numbers healed by 16 weeks. Another double-blind RCT of recombinant human EGF (rhEGF) gel showed no benefit overall,[98] but the actual dose used was unclear. In a further double-blind placebo-controlled study of rhEGF, 75 μg was applied three times per week; the proportion of ulcers healed was significantly higher ($P = .033$) in the intervention arm. However, the sample size was small (n = 34), the assessment of the primary outcome was at 8 weeks, and the offloading offered considered suboptimal.[99] A further study of intralesional injections of rhEGF with a low risk of bias[100] 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 the intervention arm after the first 2 weeks. In a large RCT of 167 patients, topical spray treatment with 0.005% rhEGF was found to significantly improve complete ulcer healing at 12 weeks (I: 73.2% vs C:

50.6%, $P = .001$) and the time required to achieve 50% ulcer area reduction.[101] We also found a small cohort study from 2012, deemed to be at a high risk of bias, which found no difference in healing at 8 weeks following weekly application of topical EGF compared with saline-moistened gauze.[102] One three-arm cohort study reported a higher wound closure index at 6 weeks with the use of EGF or platelet-derived growth factor when compared with placebo but was at a high risk of bias with incomplete reporting of results, and the duration of ulcers, at a mean of 8.9 days at inclusion, was relatively short.[103] There was no difference between the two intervention groups.

9.3 | Combination of epidermal and fibroblast growth factors

One four-arm RCT of 199 patients at a high risk of bias compared the combination of rhEGF and acidic FGF against treatment with rhEGF only or acidic FGF only or placebo only.[104] It reported that the time to 50% and 100% ulcer healing was faster in the combination group and rhEGF only group (but not acidic FGF group) compared with the placebo group. Complete ulcer healing rates were not reported however, and the definition of complete healing was ambiguous.

Importantly, all studies on the effect of FGF and EGF on ulcer healing were found to be at a high risk of bias with significant limitations in study methodology, description of intervention and/or control care, reporting of key ulcer characteristics such as vascular status and duration of ulceration, and unclear statistical methods. No recent controlled studies of EGF have been found, and so it remains unclear whether the use of FGF and/or EGF could improve ulcer healing when used in addition to more up-to-date standards of usual care.

9.4 | Granulocyte colony stimulating factor

Five studies of granulocyte colony stimulating factor (G-CSF) were included. While designed to determine its effect on infection, the five RCTs also assessed ulcer healing and reduction of amputation as secondary end points.[105-109] Only one of the five[109] was associated with any apparent benefit.

9.5 | Other growth factors

We found one small but well-designed double-blind RCT assessing the effect of intramuscular injections of a plasmid containing the gene for vascular endothelial growth factor, phVEGF165,[110] which showed that a significantly greater percentage of the intervention group achieved the primary outcome measure of more than 60% reduction in ulcer area than controls.

A single observer blind placebo-controlled RCT with a low risk of bias of autologous lipoaspirate cells reported a significantly higher incidence of healing at 8 weeks as well as a significantly reduced time to healing.[111] This pilot study was published in 2010 however, and the present search found no more recent controlled studies of this intervention.

A single nonblind, single-centre RCT comparing hyaluronic acid (HA) incorporated dressing material compared against conventional dressings was found, reporting a statistically significant complete ulcer healing rate at 12 weeks.[112] However, the study was limited by a high dropout rate and per-protocol analysis in addition to the small sample size of 34 patients.

9.6 | Platelet-derived factor and platelets

9.6.1 | Recombinant platelet-derived growth factor

Previously five controlled studies on PDGF were identified. The first RCT[113] in non-infected neuropathic ulcers indicated a significant effect on healing, and this was confirmed in the later definitive phase III study.[114] A further study[115] failed to complete recruitment, and so 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 preregistration era, could be identified. Two further studies published a few years later also were small and at high risk of bias. The first was a small three-way comparison between topical antiseptics, topical hyperbaric oxygen therapy (HBOT), and topical PDGF.[116] Although the authors suggested superiority of PDGF treatment in terms of healing at 10 weeks, the lack of baseline data and nonblinding of patients and outcomes means that the significance of any such effect is difficult to determine. The second was a poorly scoring, nonblind study, which showed no difference in outcome between the two treatment arms (PDGF versus a nonadherent gauze).[117]

In the current search, we identified two further RCTs. The first, a small but double-blind RCT with 16-week follow-up, did not report any benefit over standard care including offloading in neuropathic DFUs.[118] The second, although reporting a higher OR of complete ulcer healing at 24 weeks, was considered at high risk of bias as due to the small sample size, the inclusion of more than one ulcer per patient (29 patients, 35 ulcers) and an intention-to-treat analysis were lacking.[119]

Additional data are required in order to establish the effectiveness of topical PDGF when applied in addition to current best standards of usual care, and in particular, its cost-effectiveness needs to be established given the high cost of the product in most health care settings.

9.7 | Platelet-based applications

Five older studies of platelets were identified in previous searches, and this search identified two additional controlled studies. The oldest of these studies reported a benefit of autologous platelet factor on ulcer healing but included leg and foot ulcers and was conducted in both people with and without diabetes.[120] A later study using platelet concentrate reported an apparent improvement in ulcer healing but

was marred by there being high number of dropouts and the use of per-protocol analysis (61). Another RCT using platelet autogel reported a positive result for complete ulcer healing at 12 weeks; however, there was a very high exclusion rate, which necessitated the use of per-protocol analysis.[121] To overcome the problem of the volume of blood required from an individual for the preparation of autologous platelet gel or fluid, one study used blood bank–derived platelets.[122] Although a benefit on ulcer healing was reported, limited details of the inclusion criteria were provided. Of the two more recent studies, one large RCT of autologous platelet gel reported benefit in time to complete ulcer closure at 12 weeks in comparison with standard car. However, this study was confined to the hospital in-patients, and there was a moderate risk of bias.[123] Using povidone/iodine 10% ointment as comparator, another RCT also suggested a higher probability of ulcer healing with autologous platelet gel but did not report of DFU characteristics, any additional medical or vascular interventions provided, and was therefore regarded to be at a high risk of bias.[124] One large retrospective cohort study found that platelet releasate was more effective than standard therapy with more pronounced effect in ulcers of higher severity, but there were limitations of the study design and analysis including the use of propensity scoring.[125]

Overall, although the trial results of autologous platelets may suggest a potential benefit in ulcer healing the evidence is inconclusive, including the optimal frequency of applying such products as well which ulcers may benefit the most. In addition, cost-effectiveness analyses would be required before adoption into routine clinical care.

9.8 | Autologous combined leucocytes, platelets, and fibrin

The use of a multilayered patch of autologous leucocytes, platelets, and fibrin was recently assessed in patients with hard-to-heal ulcers defined as those with less than 50% reduction in ulcer size after a 4-week run-in period.[126] This well-designed outcome blind multicentre RCT reported significantly more ulcers achieving complete ulcer healing in the intervention group compared with the group receiving standard of care only (34% vs 22%). Although derived from the patients' own blood without additional reagent, only 18 mL of blood was required for a patch covering 5 cm^2, and the study reported no increase in anaemia compared with the control arm. A limitation of this study was that it was not possible to blind the patients or those delivering the therapy. In addition, the intervention involved weekly visits for preparation and application of the patch, which may have significant cost implications. Further studies would be needed together with cost-effectiveness to establish the routine place of this therapy in all health economies.

9.8.1 | Evidence statement

The use of growth factors, cellular products, and cells does not seem to be more effective in ulcer healing when compared with best standard of care. Quality of evidence: low.

9.8.2 | Evidence statement

Autologous combined leucocyte, platelet, and fibrin patch applied weekly probably accelerates ulcer healing when used in addition to best standard of care. Quality of evidence: moderate.

10 | PLACENTAL-DERIVED PRODUCTS

Human placental membranes contain a combination of growth factors, collagen-rich extracellular matrix, and cells including mesenchymal stem cells, neonatal fibroblasts, and epithelial cells that provide the necessary mechanisms for coordinated ulcer healing. A number of products derived from different components of the placental and umbilical cord have been developed to enhance healing; cryopreserved preparations contain living cells as well as growth factors, whereas dehydrated products, which are easier to store and handle, contain growth factors but no living cells (Table 7 in Appendix S3).

The previous review reported a single study of a cryopreserved amniotic membrane ulcer graft but commented that the study was at high risk of bias and the conclusions marred by the low rate of healing in the comparator group.[127] In the relatively short period of time since that study, interest in this type of therapy has developed rapidly with the publication of eight RCTs and a cohort registry study.[128-137]

The effect of weekly application of a cryopreserved amniotic membrane allograft was compared with standard care in a well-designed single-blind RCT.[128] The incidence of ulcer closure was greater (62% vs 21%, $P < .001$) after 12 weeks, as was median time to ulcer closure in those receiving the amniotic membrane allograft. It was unclear however whether the outcome was truly blinded as local investigators were the first to note healing only subsequently confirmed by blinded independent image analysis. A three-arm RCT compared weekly treatment with bioengineered skin substitute, with an amniotic membrane product and a collagen-alginate dressing.[136] The incidence of healing within 12 weeks was reported as being highest in those receiving the amniotic membrane product. Outcomes were unblinded however, and a planned interim analysis had been previously reported, leading to a moderate risk of bias.

Two other RCTs (one comparing the use of a bioimplant of amniotic membrane tissue with a wet dressing[131] and the other amniotic membrane allograft with usual care[132]) were found. Both reported improvements in healing with those treated with amniotic membrane products, although both studies were considered high risk of bias, and the significance of the findings is therefore uncertain.

A single-blind study of an umbilical cord product was recently reported to show a significant improvement in healing compared with good usual care.[135] Neither patient nor investigator was blind to treatment allocation however, and digital images assessed by a blinded outcome committee were used to assess the primary outcome of healing. These interesting early data therefore need confirming in a further blinded RCT. A further study designed to show noninferiority of a placental product compared with a human fibroblast-derived

dermal substitute was also found; however, the significance of this finding is unclear given the comparator.[133]

A cohort registry study compared the use of a dehydrated human amniotic membrane allograft with a commercially available bilayered "living cellular construct."[137] The median time to closure was significantly less in those receiving the amniotic membrane allograft. The significance of the finding is weakened by the high risk of bias of the study.[137] Of note, the complete ulcer healing rate and median time to healing of the ulcers treated with dehydrated human amniotic chorionic membrane were lower than suggested in previous trial settings.[130,134,138]

The available evidence from a number of studies suggests that placenta-derived products may have a beneficial effect on ulcer healing. However, the evidence is insufficient to support the superiority of one product above another, and the cost-effectiveness of these products needs to be determined in different health economies.

10.1 | Evidence statement

Placental-derived products may be more effective for ulcer healing when compared with best standard of care. Quality of evidence: low.

11 | BIOENGINEERED SKIN AND SKIN GRAFTS

11.1 | Dermal fibroblast culture

We identified three older studies of dermal fibroblast. One dose-ranging study[139] 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[140] found no difference between intervention and placebo. Although the third RCT[141] reported that healing by 12 weeks was significantly greater in the intervention arm than in controls, there was a high risk of bias, and the healing rate in the control arm of 18% was unexpectedly low.

11.2 | Cultured keratinocytes

We found three studies, all of which were identified in previous reviews. One RCT with a high risk of bias reported the use of keratinocytes alone, but few data were presented.[142] One reported the use of a novel keratinocyte delivery system was of very poor methodological quality, and the result was inconclusive.[143] Another small single-blind multicentre RCT was found, 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.[144]

11.3 | Fibroblast/keratinocyte co-culture

Three studies on fibroblast/keratinocyte co-culture were identified. One multicentre RCT of 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.[145] Another study of a bioengineered living cellular construct (BLCC) comprising human neonatal keratinocytes and fibroblasts in an extracellular matrix of bovine and human collagen and other extracellular matrix proteins, which was prematurely terminated when only 72 of 120 planned participants had been enrolled, reported an apparent significant improvement in healing at 12 weeks in the intervention group (51.5% vs 26.3%, $P = 0.049$).[146] Although well designed, the failure to complete recruitment casts doubt on the strength of the conclusion and the efficacy of the product. One recent study investigated the comparative effectiveness of BLCC with dHACM in a "real-world" setting through a retrospective analysis of a wound care database.[137] It reported that the proportion of ulcers healed was higher in the BLCC arm at 12 weeks (48% vs 28%) and 24 weeks (72% vs 47%) with a 50% less median time to healing. However, the study methodology and involvement of a significant number of centres (248 centres for 218 patients) meant that it was at a high risk of bias.

Two older studies using an HA scaffold to deliver cultured autologous fibroblasts and/or keratinocytes were found in previous searches. One was an open-label study of a two-stage procedure, cultured autologous fibroblasts and keratinocytes (HYAFF auto-graft), followed by engineered epidermal tissue autografts compared with paraffin gauze. There was no difference in the numbers of patients healed at 12 weeks, but the study was stopped before the planned target of 200 patients was reached because of the long duration of recruitment (>6 years).[147] Another unblinded study of cultured autologous fibroblasts plus HA in 63 patients reported significant benefit on complete ulcer healing at 12 weeks but only included dorsal ulcers and was considered to be at a high risk of bias.[148]

11.4 | Split skin grafts

One small case-control study of the use of SSG 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.[149] Another small cohort study of the use of artificial dermis replacement applied under an SSG[150] reported improvement in the rates of healing at 12 weeks compared with SSG alone. However, the study was non-randomized with inconsistencies in the data presented in the text as opposed to the tables, which make the significance of the observations difficult to determine. A cohort-controlled study of PRP gel plus SSG compared with SSG only did not report additional benefit,[151] but the extremely small sample size of 13 DFU out of 162 lower limb ulcers limits any conclusions. An RCT of 52 patients comparing the simultaneous application of SSG and ADM

versus SSG only in DFU larger than 3 cm^2 did not find a difference in ulcer healing at 2, 4, or 8 weeks.[152]

11.4.1 | Evidence statement

The use of bioengineered skin or split skin graft does not seem to be more effective in ulcer healing when compared with best standard of care (Table 8 in Appendix S3). Quality of evidence: low.

11.5 | Others

In the previous searches, a small partial dose-ranging study of talactoferrin was identified in Lyons et al.[153] 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,[154] 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[155] was also identified in the same review. No newer studies of any of these interventions were identified in the current search.

The previous searches also identified 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 usual care.[156]

12 | OXYGEN AND OTHER GASES

12.1 | Topical oxygen

We found six studies, four RCTs and two cohort studies, of which three were identified previously. One early randomized study reported no apparent reduction in the cross-sectional area of ulcers at either 7 or 14 days.[157] One early small cohort study[158] 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 health care professionals. The other cohort study reported an apparent benefit at 4 weeks.[159]

Among the three newer studies that we found, the first was a small (n = 20) poorly scoring RCT at high risk of bias, which explored the use of topical oxygen delivered through a portable oxygen concentrator in comparison with best practice, which included iodine dressing, regular debridement, and offloading.[160] It found a significantly higher healing rate from baseline within the intervention group in contrast to the control group. No sham treatment was provided however, and only the per-protocol analysis was available. Another double-blind RCT, with a low risk of bias, of 130 subjects,[161] explored transdermal continuous oxygen therapy along with moist wound therapy and optimal offloading in comparison with a control arm and found no significant difference in the proportion of patients whose ulcers had completely healed (I: 54% vs C: 49%).[161] By contrast, another double-blind RCT of 146 subjects compared continuously diffused topical oxygen therapy (CDO) versus usual care including the use of a sham device and reported an almost twofold significantly higher rate of complete ulcer closure at 12 weeks (I: 32% vs C: 15.7%).[162] Of note, the per-protocol analysis of the same cohort was published in the previous year and was therefore not included in this review.[163]

The authors of this review are aware of an imminent publication on topical oxygen therapy, which has been previously presented as an abstract.[164]

12.2 | Systemic oxygen

We identified nine RCTs and one large cohort study during the previous reviews.[116,165-174] In this review, we have identified a further four RCTs meeting our selection criteria.[175-178]

The earlier RCTs[45-48] 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.[165] One high-quality double-blind RCT demonstrated significantly improved outcomes in the intervention group, who were more likely to heal within 12 months.[170] 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[165] where only patients with unreconstructable critical limb ischaemia were included. The other RCTs identified during the previous systematic review reported apparent benefit[116,172] or noninferiority of HBOT[173] against the comparator arm but were either small,[116,172] had an extremely short duration of follow-up[172] and major methodological limitations,[116,172,173] or reported results that were difficult to interpret.[173]

A more recent, 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 United States according to the reimbursement guidelines from Centers for Medicare and Medicaid Services[174] was reported in 2013. 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 an ulcer would heal in a cohort of patients selected on the eligibility criteria for reimbursement.[174] These controversial conclusions have been criticized by several authors who have questioned the methodology.[56,57]

Two more recent smaller RCTs on HBOT exhibited significant methodological limitations and were considered at very high of bias.[176,178] Both had a short follow-up duration of 4 weeks and utilized unconventional statistical methods, making it difficult to draw firm conclusions. However, two larger RCTs were also found. One moderate scoring RCT of 120 patients did not find any difference in ulcer healing, a secondary outcome, in comparison with standard care and sham treatment.[175] However, the choice of a subjective primary outcome measure—meeting the criteria for amputation as assessed by a vascular surgeon on the basis of clinical history and images, although assessed blind to the treatment allocation—was considered unconventional and potentially introduced significant bias. The vascular phenotype of the patients was not clear, and despite randomization, there was a lower mean prior duration of ulceration (approximately 100 days) in the intervention group at baseline.

The second large but nonblinded RCT comparing HBOT with standard care in neuro-ischaemic DFUs older than 4 weeks showed no difference in ulcer healing at the end of 12 months.[177] During the recruitment period, the sample size was recalculated downwards due to budgetary constraints, and the eventual dropout rate was higher than the 10% initially anticipated. This meant that the study was probably underpowered to show a difference in the primary outcome. Of note, approximately 35% of the HBOT cohorts were unable to complete the full regime due to poor health.[177]

Overall, there was marked heterogeneity among the studies identified in terms of patient selection, including the severity of PAD, and the choice of study end points. The duration of follow-up ranged from 14 days to 12 months, and there was variability in the HBOT regimens used. The cost-effectiveness of this expensive therapy has also not been established in all health economies, and in addition, the ability of many patients to tolerate the recommended regimens may be in doubt.

Further blinded, appropriately powered, and randomized trials are therefore required to confirm the effectiveness and cost-effectiveness of systemic HBOT, as well as to identify the population most likely to benefit from its use and the most appropriate regimen.

12.3 | Ozone and helium

One small but high scoring study of topical ozone on healing by 24 weeks was identified. No difference was reported between the intervention and control groups.[179]

12.4 | Nitric oxide

A single RCT on topical nitric oxide compared against standard care was identified.[180] At the start of the study, DFUs of longer than 6 weeks duration with ABI more than 0.5 were recruited, but the study protocol was subsequently amended to include DFUs older than 14 days. The primary outcome of percentage area reduction at 12 weeks was reported as being significantly better in the intervention arm, but no difference in the rate of complete ulcer healing ($P = .07$) was noted. However, patients could have more than one ulcer, and some were rerandomized, resulting in inappropriate statistical analysis and a high risk of bias.[180]

12.4.1 | Evidence statement

In nonhealing ischaemic ulcers, the use of hyperbaric oxygen probably accelerates ulcer healing in addition to best standard of care, although the type of ulcers, which would most benefit, and the cost-effectiveness in all health economies are unknown. Quality of evidence: moderate.

12.4.2 | Evidence statement

The use of topical oxygen therapy or other gases does not seem to be more effective in ulcer healing when compared with best standard of care (Table 9 in Appendix S3). Quality of evidence: low.

13 | PHYSICAL THERAPIES

13.1 | Electrical stimulation

We found five studies, all randomized, which examined the effect of electrical stimulation on healing of DFUs. Two RCTs did not observe a benefit,[181,182] one reported a non-significant trend towards greater healing at 12 weeks,[183] and one reported significant benefit in ulcer area reduction at 4 weeks.[184] All the studies had significant methodological limitations, which made it difficult to interpret the observed outcomes. One recent small single-blinded RCT noted beneficial effect of low-intensity cathodal direct current in reducing ulcer area at 6 weeks compared with placebo, but the standard of care was not described, and the primary aim of the study was to assess changes in ulcer fluid biochemistry.[185]

13.2 | Shockwave therapy

Five trials of shockwave therapy were identified. One randomized 30 patients to receive either shockwave therapy to the perimeter of the ulcer or a sham intervention.[126] There was no difference in ulcer healing by 20 weeks. Two trials compared extracorporeal shockwave treatment (ESWT) with HBOT.[173,186] Both were at high risk of bias, and it was unclear if the second larger study was simply an update of the older study or was completely new. The two other RCTs compared twice weekly ESWT with standard care.[187,188] The first, a high scoring single-blinded study, reported superior complete healing time with ESWT at 8 weeks and at 20 weeks but used more than one ulcers per patient in the analysis.[187] The other, a very small study, reported only on ulcer area reduction at 7 weeks, which although

significant would have been impacted by the unusually low healing rate in the control group.[188]

13.3 | Laser therapy

Five small studies (four RCTs and one matched cohort) were identified. None of the RCTs were blinded and were all at high risk of bias. The stated results of the therapy on ulcer healing were either unclear,[189,190] did not show benefit,[191] or used a surrogate outcome for ulcer healing, ulcer area reduction at 2 weeks.[192] One small, exploratory matched cohort study using a class IV laser (emitting four wavelengths) device reported apparent benefit at 12 weeks, but the complete lack of healing in the control group was surprising.[193]

13.4 | Magnetic and therapeutic magnetic resonance therapies

One RCT on static magnetic therapy had a small sample size, randomization did not control for baseline differences between the two groups, and therefore, the results are difficult to interpret.[194] A multicentre double-blind RCT with a low risk of bias comparing twice daily application of therapeutic magnetic resonance for 4 weeks[195] to usual care did not find a difference in ulcer healing at 10 weeks of follow-up, in contrast to the findings from an earlier smaller, open observational pilot study.[196]

13.5 | Normothermic/infrared radiation/radiotherapy/electrostatic field therapies

The interim analysis of an otherwise unpublished study of noncontact normothermic therapy (ulcer warming by infrared radiation) reported greater percentage ulcer area reduction than saline-moistened gauze control,[197] although this result must be treated with caution given the high risk of bias. Two other studies were identified: one using infrared radiation via a tungsten generator[198] and another using thrice weekly pulsed radiofrequency treatment,[199] both of which reported apparent benefit, but the robustness of these results could not been ascertained as the study reports contained a number of methodological and statistical errors and were, therefore, at a high risk of bias.

One small poorly designed, "randomly assigned" study of pulsating electrostatic field reported benefit on ulcer area reduction in ischaemic refractory ulcers.[200] A nonblinded dose-ranging RCT on non-contact low-frequency ultrasound reported greater ulcer area reduction with thrice weekly applications, but there were only four patients in each of the three groups.[201]

In addition to the earlier discussed RCT, which studied adjuvant photon therapy with NPWT,[65] we also identified two controlled studies at a high risk of bias, exploring the effect of photodynamic therapy[202] and phototherapy.[203] In both, the robustness of the effect on ulcer healing could not be ascertained.

13.5.1 | Evidence statement

The use of electrical stimulation, shockwaves, lasers, and magnetic and radiation-based therapies does not seem to be more effective in ulcer healing when compared with best standard of care (Table 10 in Appendix S3). Quality of evidence: low.

14 | SYSTEMIC INCLUDING MEDICAL AND NUTRITIONAL THERAPIES

14.1 | Medical therapies

Seven trials were identified. In previous searches, one of low molecular weight heparin,[219] one of iloprost infusion,[220] and three of herbal preparations administered orally in two[221,222] and intravenously[223] in one were found.

A nonblinded study of oral vildagliptin[224] 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 conclusion. The article was also notable for the remarkably good matching of all the baseline clinical measures, especially for a relatively small population.

There was also a report of the use of oral pentoxyfilline in a small cohort study.[225] The only results included were the number of patients with a more than 10×10-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 article. All were at therefore at high risk of bias, and none showed any major improvement in outcome.

14.2 | Nutritional therapies

One well conducted study at a low risk of bias randomized patients to receive either an oral nutritional supplement with 1 kcal/mL or 400-mL placebo daily for 6 months.[226] Only 40 of the 52 patients completed the study, and at the end of 6 months, there was no difference in complete ulcer healing between the groups. Another double-blind RCT of 270 patients, at low risk of bias, compared twice daily protein drink (arginine, glutamine, and β-hydroxy-β-methylbutyrate) with a control drink for 16 weeks and did not find a difference in ulcer closure rates or time to healing.[227] We also found RCTs assessing the impact of supplementation with vitamin D,[228] magnesium,[229] zinc,[230] flax seed oil omega-3 fatty acids,[231] and probiotic capsules[232] on DFU healing. Although they all reported statistically significant benefit from the interventions, the studies contained major methodological inconsistencies including the quality of standard care, assessment of compliance during follow-up, reporting of baseline biochemistry, and discrepancies in analytical reporting. Therefore, it was difficult to be certain of the robustness of the findings. One small RCT on topical olive oil reported beneficial effect on complete healing rate ($P = .003$) at 4 weeks in a per-protocol analysis.[233] In addition

to the study where unsupervised exercise was investigated in no-option ischaemia, we also found another nonblinded study on foot exercise, which reported a benefit at 12 weeks in a per-protocol analysis.[234] Limited information was provided on the type of exercise however, compliance, and how offloading was managed during exercise.

14.2.1 | Evidence statement

The use of other systemic medical therapies and nutritional supplementation does not seem to be more effective in ulcer healing when compared with best standard of care (Table 11 in Appendix S3). Quality of evidence: low.

15 | DISCUSSION

The 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 are 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 review published in 2016, and the conclusion is similar in many aspects—that the evidence to support many of the therapies that are in routine use is poor. However, for some specific interventions, we have found evidence suggesting clinical effectiveness when compared with best standard of care.

15.1 | Quality of evidence

There has been an improvement in the quality of evidence published since the last review. The 21-point assessment criteria developed jointly by the IWGDF and the European Wound Management Association to guide improvements in trial design and presentation of study findings[7] were published in 2016. Following their introduction, more studies have been published with detailed study methodologies, independent randomization, blinding, and standardization of usual care in multicentre studies.[38,161,180,235] This is encouraging and supports the long-held notion that the delivery of high-quality studies in this field is indeed feasible.[236] Despite this, the majority of the new articles reviewed was still at a moderate to high risk of bias.[237]

15.2 | New evidence of effectiveness of tested interventions

The efficacy of sucrose octasulfate impregnated dressings[38] and the autologous combined leucocytes, platelets, and fibrin patch[235] has been shown in large, well-conducted randomized trials, both at low risk of bias. The choice of ulcers included was different although neither included infected ulcers at randomization. The run-in time after screening as well the percentage threshold for ulcer area reduction to define "hard to heal" was also different. Despite this, the unadjusted OR for healing at 20 weeks was similar.

Several recently published studies have reported apparent superior clinical effectiveness for healing of DFUs with the topical application of placental-derived products compared with standard care. However, some of the studies lacked detailed description of important baseline ulcer characteristics and were considered at high risk of bias. It is also unclear if there is any difference in outcomes between the dehydrated and cryopreserved products. Further high-quality studies are required before clinical effectiveness is unequivocally assured. Similarly, studies evaluating autologous platelet products have also suggested an apparent benefit; however, the optimal duration, volume of product, and type of ulcer that would clearly benefit remain to be established.

Despite its widespread use, there were no new high-quality studies on the use of NPWT identified during this search. Therefore, the evidence to support its effectiveness or cost-effectiveness in the healing of chronic diabetic foot ulcers—as opposed to postsurgical wounds—is not strong, a conclusion echoed in the two most recent Cochrane reviews.[237,238]

The use of HBOT therapy is advocated in the treatment of diabetic foot ulcers; however, the type of ulcer that would benefit and the optimal regimen remains uncertain. The two most recent large randomized studies used subjective end points or were underpowered to detect an effect on ulcer healing. Cost-effectiveness in all health economies is unknown. An effect on the reduction of the number of major amputations has been noted, confirmed by the findings of a Cochrane report.[239]

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

15.3 | Challenges surrounding trials in ulcer healing

This review further confirms findings of the previous IWGDF wound healing systematics reviews[2,3] and others[7,240] that there is a significant variation in the study design, size of ulcers included, criteria applied to denote difficult to heal, randomization procedure, duration of the treatment phase, and follow-up. Furthermore, the end points used varied significantly from subjective measures such an improvement to granulation and percentage change in ulcer size (area, depth, and length) to the more definite complete wound healing as defined by Jeffcoate et al.[7] We also note that there is limited evidence to support wound healing interventions in ulcers that penetrate deep to the bone or with coexistent osteomyelitis.

15.4 | Standard of care

Another important finding from these reviews is the difference in the reported standard of care, including offloading, between studies. This is a

challenge in understanding the impact of the intervention, if it were applied in addition to the best standard of usual care as described in the other IWGDF guidelines.[241] Thus, we were only able to formulate weak evidence statements based on limited supporting evidence.

15.5 | Timing of and choice of ulcer type for the introduction of advanced therapies

Although we have reported on the apparent benefit in healing of DFUs with some interventions, it remains unclear at exactly what time point these products should be introduced. Many studies included only non-infected ulcers without ischaemia. In addition, those studies that included ischaemic or neuro-ischaemic ulcers used different thresholds for the definition of ischaemia. The healing options for ulcers complicated by infection or ischaemia remain unclear.

15.6 | Strength and limitations

All articles identified in the most recent search were rigorously assessed against the 21-point criteria as well as the Cochrane and SIGN scores by a minimum of two reviewers and any disagreements resolved by consensus. The advantage of this approach was an equitable division of the work among the assessors and avoiding authors having to assess publications they (co-)authored, thereby minimizing bias. A limitation of the review was that a pooled analysis of the efficacy of intervention for products designed to improve the efficacy of ulcer healing was not undertaken.

16 | CONCLUSIONS

The evidence base to support the use of specific interventions to enhance healing of chronic ulcers of the foot in diabetes has improved substantially since the last review but is still limited. It is clear that despite the complexity of the disease, it is possible to undertake high-quality studies, although consensus on some key aspects of trial design and cost-effectiveness studies are still required.

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For completeness, studies that were previously reported in the 2016 systematic review that are not discussed in the present document have been included in the supplementary tables.[204-218]

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CONFLICT OF INTEREST

Full conflict of interest statements of all authors can be found online at www.iwgdfguidelines.org.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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