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RESEARCH ARTICLE

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

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Abstract

Background: It is critical that interventions used to enhance the healing of chronic foot ulcers in diabetes are backed by high-quality evidence and cost-effectiveness. In previous years, the systematic review accompanying guidelines published by the International Working Group of the Diabetic Foot performed 4-yearly updates of previous searches, including trials of prospective, cross-sectional and case-control design.

Aims: Due to a need to re-evaluate older studies against newer standards of reporting and assessment of risk of bias, we performed a whole new search from conception, but limiting studies to randomised control trials only.

Materials and Methods: For this systematic review, we searched PubMed, Scopus and Web of Science databases for published studies on randomised control trials of interventions to enhance healing of diabetes-related foot ulcers. We only included trials comparing interventions to standard of care. Two independent reviewers selected articles for inclusion and assessed relevant outcomes as well as methodological quality.

Results: The literature search identified 22,250 articles, of which 262 were selected for full text review across 10 categories of interventions. Overall, the certainty of evidence for a majority of wound healing interventions was low or very low, with moderate evidence existing for two interventions (sucrose-octasulfate and leucocyte, platelet and fibrin patch) and low quality evidence for a further four (hyperbaric oxygen, topical oxygen, placental derived products and negative pressure wound therapy). The majority of interventions had insufficient evidence.

Conclusion: Overall, the evidence to support any other intervention to enhance wound healing is lacking and further high-quality randomised control trials are encouraged.

KEYWORDS
diabetic foot, systematic review, wound healing

1 | INTRODUCTION

Diabetes-related foot ulceration (DFU) has a significant burden on healthcare systems and individuals alike due to its high financial costs and impacts on morbidity and mortality. Since 1999, the International Working Group of the Diabetic Foot (IWGDF) has commissioned and published guidelines every four years encompassing numerous aspects of the interdisciplinary management of diabetic foot disease. In 2008, the first edition focusing specifically on interventions to enhance healing of chronic foot ulcers in people with diabetes was published.[1] Subsequent systematic reviews and guidelines published in 2011,[2] 2015[3] and 2019[4] were updates of the original, considering and evaluating articles published in the preceding four years only.

During this time, recommendations for numerous aspects of diabetic foot management, such as offloading, were published. Similarly, introduction of the IWGDF/EWMA 21-point checklist in 2016[5] of reporting standards of studies and papers representing markers of good quality in DFU research marked a new yardstick against which new research should be evaluated. There is thus a pressing need for a re-evaluation of older published articles which at the time of previous assessment may have been considered of good quality but may not meet newer stringent requirements.

This systematic review and accompanying guidelines are a timely re-evaluation of evidence relating to interventions to enhance healing of chronic foot ulcers in patients with diabetes. Unlike previous guidelines, it examines and re-evaluates all randomised controlled trials (RCTs) from conception to October 2022.

2 | MATERIALS AND METHODS

A protocol for this systematic review was registered with PROSPERO (CRD42022309184).

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To begin with, a list of Interventions relevant to wound healing (I) and key outcomes (O) critical to wound healing in diabetes-related foot disease were identified by the Working Group. The population (P) of interest were patients with a diabetes-related foot ulcer (as defined previously by the IWGDF),[6] and comparators (C) defined to be "standard care" unless otherwise stated. Standard care has previously been defined as sharp debridement of the wound base of necrotic tissue unless contraindicated, treatment of infection, appropriate offloading where indicated and optimisation of peripheral artery disease by a multi-disciplinary team, and the use of basic dressings on the principles of comfort, exudate management and cost.[6] Where usual care in the control arm of studies deviated from what may be considered a "basic" dressing, where this would be considered usual care in that healthcare setting, these studies were included. The list of PICO questions was then reviewed by two patient representatives, 15 external experts and the IWGDF Editorial Board.

Groups of interventions and comparators are available in Table 1. Outcomes were selected by authors following the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) process,[7] based on outcomes identified in a recent systematic review.[8] All identified outcomes were scored independently by each member of the working group, external experts and patient representatives. All outcomes were rated as being "not important for decision-making", "important but not critical for decision making" or "critically important for decision-making".[7,9] Group means and medians were calculated and discussed with all working group members until consensus was reached.

Through this process, there were 10 outcomes identified as critical to decision making in wound healing, which were: (i) Complete wound healing; (ii) Time to healing; (iii) Sustained healing; (iv) Reduction in ulcer area; (v) Amputation (major or minor); (vi) Quality of life; (vii) Maintenance of function and ability to perform activities of daily living; (vii) New infection; (ix) Resource utilisation; and (x) Death/mortality.

2.1 | Search

A search was performed in MEDLINE (PubMed), Scopus and Web of Science in January 2022, and repeated in November 2022 to identify all studies published up to November 2022 (inclusive) with no restrictions placed on the search.

Search queries are available in Table S1. A validation set of 10 papers included in previous systematic reviews was used to check the accuracy of search terms. The initial search identified all ten (100%) of the validation set.

Additionally, reference lists of selected articles and previous systematic reviews were checked to identify potentially relevant articles.

2.2 | Assessment of risk of bias and data extraction

Screening of all titles and abstracts against the inclusion criteria was performed independently by two reviewers (Game and Chen) to determine possible eligibility. We used EndNote 20® to manage references and identify duplicates. Subsequently, Rayyan QCRI was used for blind and independent screening process.

References screened in were retrieved as full text, and assessed by one of six pairs of reviewers independently. Studies were included in the systematic review if they met all of the following criteria: (i) Randomized Control Trial (RCT) in design; (ii) >80% of the study population had DFUs or DFU outcomes were analysed and reported separately; (iii) Reported on any of the interventions or outcomes of interest listed above; (iv) Had a minimum of $n = 5$ in each arm of the trial. Where an earlier interim analysis of an individual trial was identified, only the main trial results were assessed.

Studies meeting the inclusion criteria were scored for methodological quality using the 21-point criteria suggested by Jeffcoate et al[5] as well as the Cochrane Risk of Bias 2 tool.[10] Items were rated as "done", "not done"; or "unclear" and only those scored as "done" contributed to the methodological quality score. This score was subsequently translated to a level of evidence according

TABLE 1 Wound healing intervention categories and comparators.

Category of intervention	List of interventions within the category	Comparator
Debridement	Enzymatic debridement	Sharp debridement
	Autolytic debridement	
	Biosurgical debridement	
	Hydrosurgical debridement	
	Ultrasonic debridement	
	Chemical debridement	
	Laser debridement	
	Surgical debridement	
	Frequency of debridement	
Dressings	Simple dressings	Basic dressings
	Dressings containing surface antimicrobial properties	
	Honey and bee products	
	Dressings that influence chronic wound biology	
	Collagen/alginates	
Negative pressure wound therapy	Negative pressure wound therapy	Standard care
Oxygen and other gases	Hyperbaric oxygen	Standard care
	Topical oxygen	
	Ozone	
	Cold atmospheric plasma	
	Nitric oxide	
	Gaseous carbon dioxide	
Physical therapies	Lasers	Standard care
	Shockwave	
	Therapeutic magnetic resonance	
	Ultrasound	
	Electric currents	
	Compression	
	Light	
Skin substitutes	Cellular skin substitutes	Standard care
	Acellular skin substitutes	
	Autologous skin	
Human tissue	Placental derived products	Standard care
	Amnion	
	Chorion	
Autologous products	Platelet based applications	Standard care
	Recombinant platelet-derived growth factors	
	Stem cells	
	Dermal derived growth factors	
	Autologous combined leucocytes, platelet and fibrin	

(Continues)

TABLE 1 (Continued)

Category of intervention	List of interventions within the category	Comparator
Pharmacological interventions	Supplementation of vitamins and trace elements	Standard care
	Agents promoting perfusion and angiogenesis	
	Stimulation of red cell production and protein supplementation	
	Others	
Metabolic management	Management of glycaemic control	Standard care
	Dipeptidyl peptidase iVs (PP-4s)	
	Statins	
	Sodium glucose transport protein 2 (SGLT-2) inhibitors	
	Glucagon-like peptide 1 (GLP-1) agonists	
Other	Bariatric surgery	Standard care
	Psychological interventions	
	Educational interventions	

to the Scottish Intercollegiate Guidelines Network (SIGN) instrument; being level 1 evidence (as all included studies were RCTs), ++ (well conducted with low risk of bias), + (well conducted with acceptable risk of bias), and–(low quality with high risk of bias).[7]

Data were extracted from each included study on prepared worksheets. Data included: (i) article identification (authors, year of publication, countries were the study was conducted), (ii) methods (study design, inclusion criteria, sample size, baseline participant and wound characteristics, description of potential confounders such as offloading and standard of care, participant attrition rate, length of follow-up and context of the study), (iii) wound healing intervention and detailed descriptions, (iv) outcomes of interest and respective effect sizes, and whether analyses were done per-protocol or intention to treat. Due to the clinical heterogeneity of the included studies, particularly the baseline characteristics of the included participants, and the variable length of intervention and follow-up, no formal meta-analysis was attempted.

All data and scoring were obtained in pairs, with one reviewer extracting data and the second confirming accuracy. All conflicts were resolved by consensus, and if necessary, by the involvement of a third reviewer. All reviewers did not assess papers they declared a conflict of interest on (i.e. if they were an author, were a study site for the trial or had previously worked with one of the authors on the study).

2.3 | Evidence statements

Based on the risk of bias assessments and data extracted, each pair of working group members drew conclusions of available evidence and formulated evidence statements and accompanying assessment of the certainty of evidence using the process proposed by GRADE to answer each clinical (PICO) question. Certainty of evidence was rated as "high", "moderate", "low" or "very low" based on level of evidence and risk of bias, according to SIGN, taking into account inconsistency of results, potential publication bias and effect size. GRADE definitions are "further research is unlikely to change our confidence in our evidence statement" for "high", "further research is likely to have an impact on our confidence in our evidence statement" for "moderate", "further research is very likely to have an impact on our confidence in our evidence statement" for "low", and "we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect" for "very low".[7]

All working group members discussed each evidence statement until consensus was achieved, with voting conducted on both certainty of evidence and strength of recommendation. All working group members who had conflicts of interest on a particular topic or paper were excluded from the decision making process for the relevant evidence statement.

3 | RESULTS

Overall, we assessed 532 full text articles from both our original search and search update and 262 studies that fulfilled our criteria were included in this systematic review (Figure 1, PRISMA flow diagram). Results were tabulated in an Evidence Table by outcome (see Supporting Information S1).

3.1 | Intervention 1: Debridement

We identified 27 titles related to debridement as a treatment for diabetic foot ulcers to support healing. Of these, we excluded 17 as not fulfilling the protocol criteria (see PRISMA diagram). We included 10 full papers describing randomised trials of debridement versus standard of care (sharp debridement).

Of these 10 papers, 5 were on enzymatic debridement,[11–15] 3 on ultrasound debridement,[16–18] 1 on surgical debridement (defined as

debridement performed in an aseptic environment, e.g. an operating theatre as opposed to clinic/office debridement),[19] and 1 investigating the frequency of sharp debridement.[20]

3.1.1 | Enzymatic debridement

Outcome: Complete wound healing

One study which included 215 participants investigated the use of enzymatic debridement using clostridial collagenase. It showed no difference in absolute healing at 12 weeks compared to sharp debridement as the standard of care. It was assessed to be at a high risk of bias.[11]

Outcome: Time to healing

Only one study, with no blinding of participants or outcome measures, investigated the outcome of time to healing when comparing enzymatic debridement to standard of care in a RCT[14] that compared daily application of clostridial collagenase ointment (CCO) to sharp debridement for 6 weeks, with follow-up for 12 weeks.

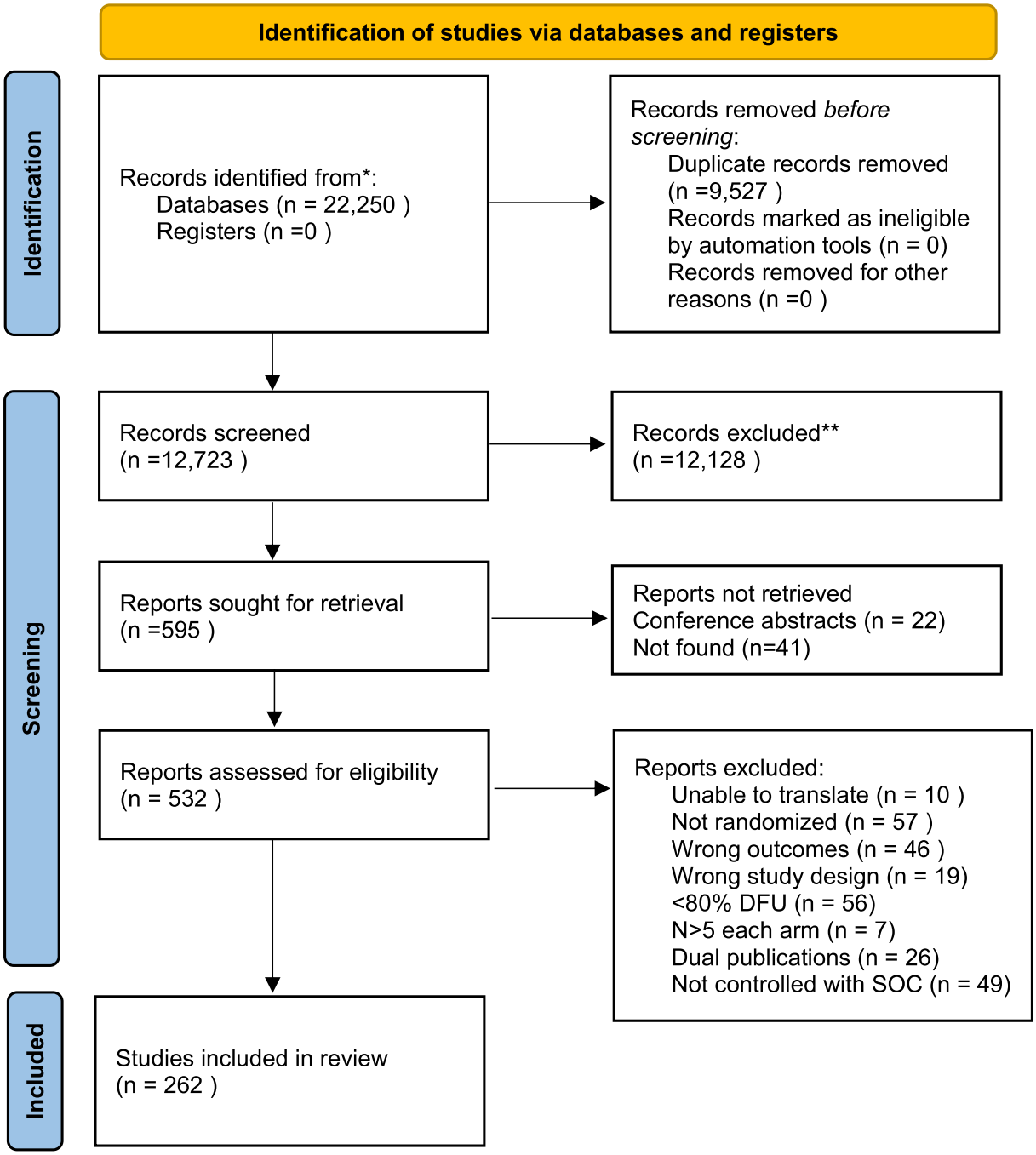

FIGURE 1 PRISMA flow diagram.

Although there was a 2-week difference in time to healing between the 2 groups, no between group statistical analyses were performed.

Outcome: Reduction in ulcer area

Five studies,[11–15] all at high risk of bias, investigated the outcome of reduction of ulcer area in comparing enzymatic debridement with clostridial collagenase to standard of care (sharp debridement). One study,[11] compared daily application of clostridial collagenase ointment (CCO) to daily application of hydrogel. Whilst the mean percent reductions for the CCO group were reportedly greater than those in the control group at each of the 12 time points, the difference between the groups was not statistically significant. A second study[12] evaluated and compared CCO debridement with saline moistened gauze and selective sharp debridement. Again, although there was an apparent reduction in mean percent change from baseline at the end of the treatment visit and at study exit in the intervention group, between group differences were not reported. A third study,[13] in a study primarily designed to evaluate the effects of CCO on markers of inflammation in cell culture and wound fluid, found that the percentage change in wound area was not statistically significantly different between the two groups at any of the assessment time points. In the fourth study,[14] an RCT with no blinding of participants or outcome measures that compared daily application of CCO to sharp debridement for 6 weeks with follow-up for 12 weeks, found no statistically significant difference in change in wound size between groups. The final study,[15] compared CCO to a 'vehicle' and compared reduction in ulcer area at 4 and 12 weeks. Only 12-week outcomes were reported and although there was an apparent increase in percentage wound reduction from baseline in the intervention arm, no between group analyses were offered.

No studies were found for the outcomes of sustained healing, amputation, quality of life, maintenance of function, new infection, resource utilisation, or mortality.

Evidence statement: *We found five RCTs comprising a total 392 participants investigating clostridial collagenase ointment compared to standard of care (i.e. sharp debridement). All were exploratory RCTs that were designed to generate hypotheses and were not designed to provide a statistically significant outcome. All had significant methodological limitations, were mainly unblinded and at high risk of bias. Different time points, between 4 and 6 weeks, with limited follow-up and different definitions of healing make comparisons between studies difficult.*

3.1.2 | Ultrasonic debridement

Outcome: Complete wound healing

Three studies, comprising a total of 101 participants and all at high risk of bias, investigated ultrasound assisted wound debridement (UAW).[16–18] The first,[16] was a non-blind trial comparing surgical debridement with ultrasound assisted wound debridement. Wounds in both groups had similar rates of healing after 6 months of follow-up. The second,[17] compared debridement with low frequency ultrasound waves plus standard wound care with standard wound care treatment alone. The complete healing rate at 6 months was not statistically significant between the groups. The third[18] compared the use of weekly low frequency ultrasound versus nonsurgical sharp debridement and reported that in the intervention arm 5/7 ulcers healed versus 5/5 in the control arm although no between group statistical analyses were presented.

Outcome: Time to healing

Two RCTs compared weekly ultrasonic debridement to either surgical debridement over 6 weeks[16] or the use of weekly low frequency ultrasound versus nonsurgical sharp debridement.[18] The first[16] reported time to healing was significantly lower in the ultrasonic debridement group compared to the surgical group; however, in this study, neither patients nor assessors were blind to the intervention and thus was at high risk of bias. The other,[18] reported that time to healing in the intervention arm was almost twice as long in those treated with ultrasound debridement as sharp debridement No between arm statistical analysis was done however.

Outcome: Sustained healing

The same study[16] described above found no differences in sustained healing of wounds that had healed after 6 months of follow-up.

Outcome: Reduction in ulcer area

Only one RCT where neither participants nor outcome assessors were blind to the intervention and which was at high risk of bias[17] compared debridement with low frequency ultrasound waves plus standard wound care with standard wound care treatment. Per protocol analysis only was offered, suggesting that the mean wound size reduction percentage was significantly higher in the UAW group only in the second and third months of follow up, but not at 6 months.

One study,[18] also at high risk of bias reported that quality of life in both arms of the study comparing non-surgical sharp debridement and low frequency ultrasound 'showed an improving trend as the ulcers healed'. No further data or statistical analysis was reported.

No studies were found for the outcomes of amputation, new infection, maintenance of function, resource use or mortality that met the inclusion criteria.

Evidence statement: *We found three RCTs comprising a total of 101 participants of low frequency ultrasonic debridement compared to standard of care (i.e. sharp debridement). All three studies were at high risk of bias with none having either blinding of participants, investigators, or outcomes. Only one suggested any differences between groups in time to healing, but this result should be treated with caution given the high risk of bias of the study. None showed any differences in absolute healing in the timescales of the follow-up of the studies. The other two studies presented either no difference between the two groups or did not present any difference between group analyses.*

3.1.3 | Surgical debridement

A single RCT with no blinding of participants, investigators, or outcome assessments and at high risk of bias was found comparing the efficacy of surgical treatment of non-infected neuropathic foot ulcers to conventional non-surgical management. Two outcomes were reported: time to healing, in which the surgical group apparently healed in a mean time almost 80 days shorter than the control arm,[19] and improved sustained healing at 6 months follow up. Although both outcomes were apparently in favour of the intervention, these results should be treated with caution given the unblinded nature of the study and the high risk of bias.

No studies were found for the outcome of complete wound healing, sustained healing, reduction in ulcer area, amputation, quality of life, maintenance of function, new infection, resource utilisation, or mortality.

Evidence statement: *We identified one RCT of surgical debridement comprising 41 participants which compared this intervention to standard of care (i.e. sharp debridement). Although there was an apparent improvement in time to healing and sustained healing, the study was at high risk of bias and assessments were not done by blinded assessors. These results should therefore be treated with caution.*

3.1.4 | Frequency of sharp debridement

One non-blinded RCT was found investigating the effects of frequency of sharp debridement (comparing second weekly to weekly debridement as standard of care).[20] Only one outcome of interest was reported, and at 12 weeks there was no difference in complete wound healing between both arms, although the study was rated at high risk of bias.

No studies were found reporting on the outcomes of time to healing, sustained healing, reduction in ulcer area, amputation, quality of life, maintenance of function, new infection, resource utilisation, or mortality.

Evidence statement: *We found one RCT that investigated the frequency of sharp debridement, weekly versus fortnightly. This one study, involving 61 participants per group, reported no statistically significant difference in wound healing outcomes; wound closure and healing times at 12 weeks between groups, although the level of certainty for this outcome is low.*

3.2 | Intervention 2: Dressings

We identified 70 studies of dressings or topical applications that met the inclusion criteria for the systematic review. Of the 70, some trials compared dressings from more than one category (below) to standard of care.

3.2.1 | Agents with antiseptic/antimicrobial effects

We identified 12 studies which investigated the use of either antiseptics or antimicrobials and reported our chosen outcomes. Five of these used silver containing dressings or applications,[21–25] three iodine containing dressings/applications,[26–28] a single study of Diperoxochloric acid (DPOCL),[29] a single study of a super-oxidised solution[30] and two studies of gentamicin impregnated sponges.[31,32]

Outcome: Complete wound healing

Silver (or silver impregnated). We identified 4 RCTs of topical silver containing applications/dressings which fulfilled our inclusion criteria[21–24] and reported total wound healing. The largest of these studies comprising 134 participants reported in a study with no blinding of participants or outcome measures that the use of an ionic silver hydrofibre dressing did not heal significantly more ulcers at 8 weeks when compared to a calcium alginate dressing.[23] Two much smaller, also non-blinded studies found that a nano-crystalline silver impregnated dressing was not superior to a paraffin tulle in terms of complete wound healing at 12 weeks[22] and a collagen/silver dressing did not heal significantly more ulcers than a control foam dressing at 14 weeks follow-up.[24]

The final study compared a silver ointment to a 'control treatment', the full details of which were not given, showed an apparent higher rate of complete wound healing at 4 weeks. However, this study had no blinding of participants or outcome measures and was assessed as being at high risk of bias and, as such, this result should be treated with caution.[21]

Iodine. Three studies were identified. The largest of these[26] comprising 317 participants was outcome assessor blind but assessed as being at moderate risk of bias and showed no difference in healing at 24 weeks between an iodine impregnated dressing and the other two arms consisting of carboxymethylcellulose hydrofibre and a non-adherent gauze. The second study compared an iodine foam dressing against a simple foam dressing, was unblinded, and at high risk of bias but did not report significant difference in complete wound healing at 8 weeks.[27] The last, a much older study at high risk of bias[28] showed no difference in healing between ulcers treated with iodosorb and those treated with usual care alone.

Diperoxochloric acid. We found one study comprising 324 participants, which was assessed as being at moderate risk of bias, which evaluated the efficacy of diperoxochloric acid as a topical solution compared with isotonic sodium chloride solution in diabetic foot ulcers.[29] It reported a significantly greater proportion achieving complete wound healing at 10 weeks, but offloading was not standardised and the results of the a per protocol analysis were reported only. Participants were mainly hospitalised and thus the generalisability of this result is unclear.

Gentamicin sponge. We identified a single study, comprising 22 participants, of a gentamicin sponge.[31] Although primarily designed as a study of infection in people with diabetes and ulcers which were complicated by mild infection, this study showed no difference in the proportion of healed wounds at 24 days.

Superoxidised solutions. We identified a single study which included 50 participants investigating a superoxidised solution in addition to standard of care, compared to standard of care alone.[30] This study had no blinding of participants or assessments, few details on baseline participants or wound characteristics, and was at a high risk of bias. No difference in complete healing was reported at 6 months compared to standard of care.

Outcome: Time to healing

Four of the above studies also reported time to healing[23,26,27,29] with a further study[32] investigating time to healing using a gentamicin sponge.

Silver (or silver impregnated). Only one of the studies reported time to healing,[23] and showed no difference between the two groups.

Iodine. Two of the above studies also reported time to healing,[26,27] and neither showed a difference in time to healing.

Diperoxochloric acid. One study identified of this intervention[29] reported time to healing. Although a shorter time to healing was reported compared to the control arm, no between group statistical analyses were reported and only results of the per-protocol analysis were reported.

Gentamicin. One study, comprising 50 participants, investigated the use of a gentamicin sponge in post-operative wounds.[32] This small study was unblinded, usual care was not well defined, and was assessed as being at high risk of bias. Thus, the apparent significant finding of a 1.9-week improvement in time to healing in the intervention group compared to the usual care group should be treated with caution.

Superoxidised solutions. A study comparing a superoxidised solution to standard of care also reported on time to healing.[30] Despite there being no difference in complete wound healing overall at 6 months, time to healing was apparently significantly shorter by a mean of 82 days in the intervention arm compared to the control. Due to the high risk of bias of this study, however, we have low confidence in this result.

Outcome: Sustained healing

Iodine. Only the largest of the studies described above[26] reported sustained healing, showing no difference between the groups.

Outcome: Reduction in ulcer area

Silver. Four of the studies[21–23,25] reported changes in ulcer area at time scales between 3 and 12 weeks; however, none reported a significant difference between the two groups.

Diperoxochloric acid. The single study of this intervention presented absolute differences in wound area change between the 2 groups, but provided no statistical analysis of between group differences in area reduction.[29]

Outcome: Amputation

Three of the above studies reported amputation, one investigating iodine,[26] one of Diperoxochloric Acid[29] and one of gentamicin sponge.[32] None reported any difference in either major or minor amputations between the interventions and standard of care.

Outcome: Quality of life

Only a single study of iodine[26] reported this outcome, showing no difference between the 2 groups.

Outcome: Maintenance of function and ability to perform activities of daily living

We identified no studies reporting this outcome.

Outcome: New infection

Four of the above studies reported this outcome. Of the two investigating the use of Iodine, the largest[26] showed an apparent increase in the numbers of secondary infections in the Iodine group. The other[27] showed no difference between the 2 groups.

A single study of a silver based dressing[23] that reported this outcome also showed an increase in the number of infections in the intervention group although no between group statistical analysis was presented with this result. A single study comparing superoxidised solution to a control[30] reported significantly lower rates of reinfection in the intervention arm, but this study was at high risk of bias.

Outcome: Resource use

Two studies reported this outcome, one of iodine and one of a gentamicin sponge.[32]

The study of an Iodine impregnated dressing[26] showed no difference in the overall costs when the costs of dressings were added to the cost of the professionals time to change the dressing between the intervention dressings and the control arm.

A study of post-operative wounds[32] showed an apparent improvement in the number of days in hospital post operatively. However, this was an unblinded study, and no between group analyses were reported.

Outcome: Mortality

Only one study[26] reported this outcome, showing no difference between the groups at 24 weeks.

Evidence statement: *The evidence from 12 RCTs comprising 1205 participants to support the use of antimicrobial dressings or topical antiseptic applications for wound healing, and/or new infection, when compared to standard of care of diabetes-related foot ulcers is of low certainty, and positive results should be treated with caution.*

3.2.2 | Honey and bee related products

We identified 6 studies[22,33–37] comprising 621 participants of honey or bee related products that reported our chosen outcomes.

Outcome: Complete wound healing

We identified 4 studies[22,33–35] which fulfilled our inclusion criteria. All were assessed as being at a high risk of bias with outcomes assessed at different times ranging between 4 and 17 weeks. The largest study of 375 participants[33], which compared honey dressings to saline soaked dressings, reported an apparent greater proportion of healed wounds at 120 days, but this was analysed per-protocol and there was no blinding of the participants, investigators or outcome measures. Baseline characteristics were also poorly reported; therefore, it is unclear whether baseline differences in ulcers could have accounted for the reported difference. A small study of 25 participants (64 ulcers) comparing manuka honey to paraffin tulle and nano-crystalline silver dressings (3-arm study) did not report any difference in complete wound healing at 12 weeks, an outcome also found in a double blind trial of a royal jelly product (a product of worker bees), even though this was analysed per protocol only.[34] The final study using a mixture of natural royal jelly and panthenol and compared this with the panthenol carrier alone but did not report any difference in complete wound at 12 weeks.[35]

Outcome: Time to healing

Two of the above studies also reported time to healing. Although the largest study[33] reported a significantly different median time to healing of 11 days, there was no blinding of participants or outcome measures and the analysis was per protocol. There is uncertainty about baseline differences in ulcer characteristics, and this result should therefore be treated with caution. The second study[34] reported no difference in time to healing between the 2 groups.

Outcome: Reduction in ulcer area

Three studies reported on this outcome. First, a three way study of 31 participants comparing manuka honey, a topical sliver preparation and a Vaseline gauze control arm,[22] reported no difference in wound area reduction between the manuka honey arm and the control arm at 12 weeks. Two studies reported on the use of a topical bee-produced product, propolis. The first[36] reported no difference in area reduction at 4 weeks, although the second[37] reported a greater ulcer area reduction at 8 weeks in the intervention arm. All three studies were at high risk of bias however and thus any positive results should be treated with caution.

We found no studies reporting any of our other outcomes.

Evidence statement: *The evidence from 6 studies of 621 participants to support the use of honey or bee-related products for wound healing when compared to standard of care in diabetes-related foot ulcers is of low certainty and any positive results should be treated with caution.*

3.2.3 | Collagen or alginates

We found 12 RCTs[24,38–48] comprising 986 participants comparing collagen/alginate dressings to a standard of care and which fulfilled our inclusion criteria. None of the studies were double-blind; three[38,39,41] were outcome blind, one[44] patient blind, and one had uncertain blinding.[48] All were at moderate or high risk of bias.

Outcome: Complete wound healing

Seven studies[24,38–41,43,45] reported on absolute wound healing at time frames ranging from 28 days[43] to 24 weeks.[39] Only two[39,41] reported statistically significant improvements in absolute wound healing with use of collagen dressings compared to a control dressing, but both studies were small (<70 participants), lacked details on baseline ulcer and participant characteristics and other aspects of usual care; thus, any positive findings should be interpreted with caution.

Outcome: Time to healing

Four of the studies reporting on absolute wound healing also reported on time to healing.[39–41,45] The only study where this reached statistical significance[41] was small with only 30 participants and was at a high risk of bias.

Outcome: Reduction in ulcer area

Eleven studies reported on reduction in ulcer area.[24,39–48] Only two[41,46] reported this being significantly improved in the intervention arm compared to a control dressing. The former was performed in a primarily inpatient population, and, as outcomes were assessed at only 9 days, generalisability is limited. The latter study[41] reported on 12-week outcomes but, as mentioned above, this study was small with only 39 participants and at high risk of bias. The remaining studies reported no difference in outcome, but all were small and at high risk of bias.

Outcome: Quality of life

Only one study reported on the quality of life. This study[42] reported a statistically significant reduction in pain (measured on a pain scale) at 4 weeks with the use of calcium alginate compared to Vaseline. However, this was a study with no blinding of participants or outcome measures, with a high attrition rate and a high risk of bias.

Outcome: New infection

Two studies[24,45] reported on new infections. The first study[24] reported four withdrawals due to infection in the control arm compared to none in the collagen arm. The second[45] reported no

difference in infection between a collagen/ORC dressing compared to standard wound care.

3.2.4 | Outcome: Resource utilisation

Two studies[42,45] reported on resource utilisation. In the first,[42] significantly fewer dressing changes were required in-trial with the use of calcium alginate compared to Vaseline gauze, although the study had no blinding of either participants or outcome measures. The second reported fewer dressings per week per patient with use of a collagen/ORC dressing compared to standard wound care,[45] but no between group statistics were offered. Both were at a high risk of bias.

Evidence statement: *The evidence from 12 RCTs comprising 986 participants to support the use of collagen or alginate dressings to improve healing or resource use when compared with usual care is of low certainty. Of the 12 studies, none were at low risk of bias and many were too small to have any certainty about reported outcomes.*

3.2.5 | Carboxymethylcellulose

We identified 2 studies investigating the use of a carboxymethylcellulose dressing comprising a total of 337 participants.[26,49]

Outcome: Complete healing

One of the 2 studies[26] reported complete healing but showed no difference at 24 weeks in an outcome blinded study with 317 participants, where a carboxymethylcellulose dressing was compared to an iodine containing dressing and an inert control dressing. This study was considered at acceptable risk of bias.

Outcome: Time to healing

Both studies of carboxymethylcellulose reported this outcome. The earlier smaller of the two comprising just 20 participants who compared carboxycellulose to saline gauze reported a significantly shorter time to healing[49] but was considered at high risk of bias. The much larger study[26] reported no such difference.

Outcome: Sustained healing

Only the largest study[26] reported on this outcome, showing no difference in the incidence of ulcer recurrence between the use of carboxymethylcellulose, an iodine containing dressing and a control (neutral) dressing.

Outcome: Amputation

Both studies on carboxymethylcellulose reported amputations. Neither reported on any difference in amputations major or minor between the groups at either 8[49] or 24[26] weeks.

Outcome: Quality of life

Just one of the 2 studies[26] reported on quality of life showing no difference between the 3 groups at 24 weeks.

Outcome: New infection

Both studies reported on new infections. The three arm study with carboxymethylcellulose, an iodine - containing dressing and a neutral dressing[26] showed no difference in new infection between the carboxymethylcellulose arm and the neutral dressing arm at 24 weeks. Similarly, the second study on carboxycellulose found no difference in new infection at 8 weeks.[49]

We found no other studies reporting on our other chosen outcomes.

Evidence statement: *The evidence from 2 RCTs comprising 327 participants to support the use of carboxymethylcellulose dressings when compared to inert or saline moistened gauze to improve wound healing in diabetes related foot ulcers is limited, with one study reporting no benefit and the other being very small and at high risk of bias. Thus, the certainty of any reported improvement is low.*

3.2.6 | Sucrose-octasulfate

We found one RCT[50] comparing the use of sucrose-octasulfate to a control dressing (identical but without the impregnated sucrose-octasulfate). This was a multicentre, double blind trial across 43 hospitals in Europe and included 240 participants with neuro-ischaemic foot ulcers that failed to improve by at least 30% after a 2-week run-in period. The study reported superiority of the intervention dressing for complete wound healing at week 20 (absolute difference in healing of 18%), a shorter median estimated time to healing of 60 days and greater absolute wound area reduction. There were no differences in the quality of life between the two groups. The study additionally reported on adverse events of local infection of the target wound, amputation of the target limb and mortality, with no difference between the intervention and control arms of the study. The study was assessed to be at a low risk of bias.

Evidence statement: *In non-infected, neuroischaemic ulcers that are hard to heal, the use of topical sucrose-octasulfate has been shown in one study with 240 participants, considered to be at low risk of bias, to benefit complete wound healing, percentage area reduction and estimated time to healing. As this is a single study, and has not been replicated elsewhere, the level of certainty in these reported outcomes is moderate.*

3.2.7 | Hydrogels

We found only one RCT[51] comparing a hydrogel wound dressing to saline gauze. This was a small study with just 31 participants, and reported on the outcomes of complete healing at 16 weeks, time to healing and resource utilisation. Although significant improvements in complete healing were reported and comparative costs of dressings in the hydrogel group were lower than the control arm, time to healing was not reported as differing between the two groups. Moreover, the study had a higher dropout rate in the control arm,

there was no blinding of participants or outcome measures and baseline characteristics of study participants, and details on usual care including offloading and other study processes were not described. Thus, any benefit of wound healing reported should be treated with caution.

Evidence statement: *The data reported in one RCT comprising 31 participants, considered at high risk of bias, does not support the use of hydrogels to improve wound healing of diabetes-related foot ulcers when compared to saline moistened gauze. Any positive reported outcomes are of low certainty.*

3.2.8 | Topical phenytoin

We found 12 RCTs,[52–63] including a total of 792 participants comparing topical phenytoin to a control intervention. The majority of studies were undertaken in low- and middle-income countries except one.[61] Two were double-blind; the first failing to recruit the prespecified number of participants[61] and the second being a small exploratory study with only 9 participants in each arm of the trial.[56] Despite the majority of studies reporting benefits in terms of shorter time to healing and reduction in ulcer area with topical phenytoin use, studies were generally at high risk of bias, having no blinding of participants, investigators or outcome measures,[52–55,57–60,62,63] small sample sizes with no power calculations, or lacked detail on baseline characteristics of limb and/or ulcer.[52–60,62,63] Thus, any positive results should be cautiously interpreted.

Outcome: Complete wound healing

Only one study[61] reported absolute healing when comparing a phenytoin impregnated hydrogel/alginate dressing to a placebo hydrogel/alginate dressing. Although a well-designed study comprising 65 participants and with blinding of participants and outcomes, the failure to recruit the required number of participants and 14% withdrawal rate meant that it was ultimately underpowered. The study reported no difference in absolute healing at 16 weeks.

Outcome: Time to healing

We identified 2 RCTs[53,57] investigating the use of topical phenytoin, which reported on time to healing. Both were small studies (100 and 60 participants, respectively) and at high risk of bias. Although there was a significantly different shorter time to healing reported with use of topical phenytoin when compared to normal saline dressing, as neither study had any blinding of participants or outcome measures, had poor description of participant characteristics, and did not report other aspects of usual care including offloading, any positive result should be interpreted with caution.

Outcome: Reduction in ulcer area

We identified 10 RCTs on topical phenytoin which evaluated reduction in ulcer area as an outcome[52,54–58,60–63] compared to usual care. Overall, they reported a greater reduction in ulcer area at 14 days,[54,60,62,63] 4 weeks[55,57] and 8 weeks[52,56] with only two studies showing no difference at 6 weeks[58] or 16 weeks.[61] However, the studies reporting a positive effect with topical phenytoin had no blinding of participants or outcome assessments, lacked detail of the baseline characteristics of the ulcers and limbs included and had poor description of usual care including offloading.

Outcome: Resource utilisation

A total 5 studies[54,59,60,62,63] reported on the length of hospital stay with phenytoin use. All reported shorter lengths of admission with phenytoin but lacked description of participant characteristics at baseline and it was unclear as to how data on hospital admission were collected. One study reported on the number of dressings used, which was significantly fewer in the phenytoin group,[63] but all studies had no blinding of participants or outcome measures and were at high risk of bias.

Evidence statement: *The evidence to support the use of topical phenytoin to improve healing of diabetes-related foot ulcers when compared to usual care is of low certainty. We identified 12 RCTs comprising 792 participants, of which only two had no blinding of participants or outcome measures. Only one of these was designed with a large enough sample size for adequate statistical power, but failure to recruit meant it was underpowered, and thus reported no difference in wound healing.*

3.2.9 | Traditional medicinal preparations

We found nine RCTs[64–72] comparing traditional medicinal preparations to standard of care. Only one[66] study of 70 participants comparing the use of *Teucrium polium* to normal saline dressings had blinding of participants and outcome measures. Two studies comparing the use of traditional Chinese medicines to standard of care[68,69] were outcome-assessor but not participant blinded. One study with only 5 participants with diabetes-related foot ulcers in each arm (as part of a larger study including pressure injuries and venous leg ulcers) was also outcome-assessor blind.[72] All were at acceptable to high risk of bias.

Outcome: Complete wound healing

Seven studies[64–70] reported on absolute wound healing. One[64] compared the use of *L. Plantarum* to a neutral dressing in a post-operative cohort of participants and reported higher rates of absolute wound healing in the intervention arm. This study with 22 participants was small and nonblinded, generalisability was limited and it was assessed as being at high risk of bias. Another[65] compared the use of *Quercus Infectoria* solution to normal saline dressings in 56 participants and although absolute wound healing was higher in the intervention arm at 12 weeks, the baseline characteristics of participants were uneven across both groups and neither participants nor outcome measures were blind; thus, they were rated at high risk of bias. A further study[66] of 70 participants, compared a 2% ointment of *Teucrium Polium* extract to moistened gauze and reported higher rates of complete healing at 4 weeks but, despite being participant and outcome blind, lacked detail on study conditions including offloading

and was considered at high risk of bias. A study comprising 50 participants[70] compared a proteolytic fraction from latex of *Vasconcellea cundinamarcensis* to a neutral collagen dressing and reported improved wound healing in the intervention arm at 16 weeks, but neither participants nor outcome measures were blinded and the study lacked details on how participants were randomized.

The remaining studies showed no difference in absolute wound healing with the use of oak bark in Bensal HP[67] or traditional Chinese medical preparations[68,69] when compared with standard care.

Outcome: Time to healing

Three studies reported on time to healing.[68,69,71] Only one[68] reported an improvement in time to healing with the use of Hongyou ointment and Shengji powder compared to "western medicine". This study was at a high risk of bias with poor description of study characteristics. Two further studies, comparing the use of Tangzu Yuyang[69] and a topical polyherbal ointment[71] to standard care, showed no difference in time to healing.

Outcome: Sustained healing

Two studies[68,71] reported on sustained healing, the former at 6 months and the latter 5 months. There were no differences between the use of traditional medical preparations when compared to standard care reported in either study.

Outcome: Reduction in ulcer area

Six studies reported on reduction in ulcer area.[64–66,69,70,72] The two studies reporting on a greater ulcer area reduction with *L. plantarum*[64] and *Teucrium polium*[66] ointment, respectively, were at high risk of bias due to unclear study characteristics and thus both positive results should be interpreted with caution.

Outcome: Amputation

Only one study reported on amputation[69] and found no difference in amputation rates with the use of Tangzu Yuyang ointment when compared with moist wound therapy at 24 weeks.

Outcome: Mortality

Only one study reported mortality. This study[69] found no difference in mortality from the use of Tangzu Yuyang ointment versus moist wound therapy at 24 weeks.

No studies have reported on quality of life, maintenance of function, new infection or resource utilisation.

Evidence statement: *The evidence to support the use of traditional medicinal preparations in wound healing of diabetes-related foot ulcers is of low certainty. In 9 studies of 407 participants, no studies were at low risk of bias.*

3.2.10 | Other dressings

We identified 16 studies of other types of topical applications and dressings which did not easily fit into the above categories. None of these were planned with a sufficiently large sample size to show efficacy, and none were at low risk of bias. None showed a benefit in terms of our outcomes of choice in which we had no level of confidence. The interventions were: a resorbable glass microfiber matrix,[73] NorLeu3-A (1–7) an analogue of the naturally occurring peptide, angiotensin 1–7,[74] a semi-permeable membrane,[75] Mepilex Lite,[76] a topical EPO-containing hydrogel formulation,[77] an Arginine - glycine aspartic acid peptide matrix,[78] a study of topical Chitosan and/or isosorbide dinitrate,[79] topical tretinoin[80], topical ENERGI-F703,[81] a soluble yeast b-1,3/1,6-glucan,[82] a kiwifruit extract[83] a zinc oxide tape,[84] a Venlafaxine and matrix metalloproteinase drug-loaded cellulose nanofiber sheet,[85] an alpha connexin carboxy-terminal,[86] topical pirfenidone[87] and a chloramine gel.[88]

Outcome: Complete wound healing

15 studies reported complete wound healing.[73–82,86–90] All but 3 of the studies[73,81,86] were considered at high risk of bias. One[73] investigated the use of a resorbable microfibre matrix in an outcome blind study of just 40 participants. Although planned according to a pre-specified sample size calculation, the protocol allowed participants whose ulcers had not decreased more than 50% in the first 6 weeks of the trial to be excluded from the study and allowed to pursue alternative treatments. This protocol meant that a large number of participants exited the protocol early and as such the reported improvement in healing of the intervention arm at 12 weeks is of low certainty. A single study of topical ENERGI-F703[81] was conducted in a mixed population of leg and foot ulcers. Although the foot ulcer population was reported separately in terms of absolute healing at 12 weeks, the mixed population meant other important details such as the usual care and offloading strategy were missing from the paper. As such, we cannot be confident in this positive result. The study of NorLeu3-A (1–7)[74] of 77 participants was published over a decade ago, and was intended to be a dose ranging study. Although there was an apparent increase in healing at 12 and 24 weeks at the highest dose tested, this study has, as far as we aware not been repeated, and as such, whether this agent would be more effective or cost-effective than more recent wound healing interventions remains unknown. The study comparing an alpha connexin carboxy-terminal (ACT-1) to a hydrogel as standard of care found a significant improvement in complete healing at 12 weeks in 92 participants, and although it was outcome blind, it had a high attrition rate.[86] The remaining studies reported complete wound healing were either too small to show any positive benefit or were at high risk of bias, such that any positive benefit in complete wound healing should be treated with caution.

Outcome: Time to healing

Three studies reported this outcome. The first[76] investigated the use of Mepilex lite. This was a small study, unblinded and thus at high risk of bias and the apparent improvement in healing time reported is of low certainty. The second study, a dose ranging study of NorLeu3-A (1–7)[74] showed no significant difference in the time to healing in the ITT population at the highest dose of intervention compared to placebo. The study on alpha connexin carboxy-terminal (ACT-1)[86] found

a significant improvement in median time to healing but was outcome blind only and had a high dropout rate, thus this positive result should be taken with caution.

Outcome: Reduction in ulcer area

Fifteen of the studies reported percentage wound area reduction.[73–77,79,80,82–85,87–90] All but the study of the resorbable microfibre matrix[73] were either at high risk of bias or showed no difference in percentage reduction ulcer area. This study,[73] although apparently showing a reduction in ulcer area, was marred by the small numbers ($n = 40$) and the protocol "exiting" participants after 6 weeks if they did not achieve 50% area reduction.

Outcome: Quality of life

Three studies reported on outcomes considered to be related to quality of life. A very small study of Venlafaxine and matrix metalloproteinase drug-loaded cellulose nanofiber sheet[85] showed an apparent improvement in pain free walking distance at 24 weeks, but the study was unblinded, and any positive result should be treated with caution. The small study of Mepliex lite[76] showed no difference between the 2 groups in terms of pain at 12 weeks. The study using chloramine gel[88] equally showed no difference in quality of life.

Outcome: New infection

Two studies reported on new infections as part of adverse event reporting.[73,77] Neither the use of resorbable glass microfiber matrix nor the topical EPO-containing hydrogel formulation was associated with any differences in new infection when compared to the control arm.[73,77]

We found no studies reporting on our other chosen outcomes.

Evidence statement: *The evidence to support the use of any other topical applications or dressings when compared to standard of care for wound healing of diabetes-related foot ulcers is of low certainty, with no studies at low risk of bias.*

3.3 | Intervention 3: Oxygen and other gases

We identified 18 studies which included a total of 906 participants who investigated the use of hyperbaric oxygen and 10 studies which included a total of 792 participants who investigated the use of topical oxygen. Of the 18 hyperbaric oxygen studies included in the systematic review, two were secondary analyses of primary trials.

3.3.1 | Hyperbaric oxygen

Outcome: Complete wound healing

We identified 10 studies comprising 629 participants on hyperbaric oxygen for the outcome of absolute wound healing.[91–100] Five studies[92,93,97,99,100] had no blinding of either participants, investigators, or outcome measures. Despite reporting some benefit towards healing in the intervention arm, these results should be interpreted cautiously as all these studies were at high risk of bias. One study[95] of 28 participants at high risk of bias was outcome blind and showed some improvement in absolute wound healing with hyperbaric oxygen compared to conventional treatment in the per-protocol analysis, but failed to provide statistical significance of this finding. A larger study of 120 participants[98] at unclear risk of bias recruited participants with Wagner Grade 2–4 ulcers with limb ischaemia, and was blinded for the outcome of complete wound healing only. The participants were not blinded. There was no difference in ITT or per-protocol analysis with the use of hyperbaric oxygen for complete wound healing, although the authors included wounds that healed after minor amputation in their definition of wound healing. The study recruited slowly and at interim analysis the sample size was changed to assume a greater difference between the groups. The study was therefore probably underpowered. This study was assessed as being at acceptable risk of bias.

Three studies had blinding of both participants and outcome measures. The first was a small single-centre, double blind RCT study comprising 18 participants, which reported some benefit of hyperbaric oxygen on healing of DFUs at 1 year but not at 6 weeks or 6 months.[91] However, this was in the per-protocol analysis only and therefore assessed as being at high risk of bias. The second,[96] considered to be at low risk of bias, was a single centre double-blind RCT of 94 participants with non-infected DFUs of Wagner grade 2–4. Sham treatment was with hyperbaric air and at 12 months there was a significant difference in the proportion of ulcers healed in favour of the intervention.

The final study was another single-centre double blind RCT of 107 participants assessed as being at low risk of bias, comparing the use of hyperbaric oxygen to hyperbaric air.[94] Wound healing was a secondary outcome, the primary outcome being the primary outcome of 'freedom from having or meeting the criteria for amputation by a single vascular surgeon (by digital photography and clinical imaging alone), and this outcome was blinded. No difference in healing was seen at 12 weeks in this study.

Due to the differing timepoints of the assessment of outcome (from 4 weeks to 12 months), the different baseline characteristics of participants included (where given) and the different protocols of treatments, no attempt to perform a meta-analysis on these outcome data was made.

Outcome: Time to healing

We identified one study on hyperbaric oxygen for the outcome of time to healing.[98] Whilst the median time to complete healing was shorter (202 vs. 217) days amongst participants who received hyperbaric oxygen therapy in the ITT analysis, no statistical significance was provided. The study was assessed as being at acceptable risk of bias.

Outcome: Sustained healing

Only one study was identified which investigated the effect of hyperbaric oxygen on sustained healing, and showed no benefit toward sustained healing.[98]

Outcome: Reduction in ulcer area

Nine studies comprising 418 participants were identified which investigated the use of hyperbaric oxygen on the reduction of ulcer area.[91,94,95,97,100–104] Only one study was at low risk of bias. This single-centre RCT[94] showed no difference in reduction of absolute wound surface area at 12 weeks in the ITT analysis when compared to the sham treatment.

One study[91] was a small double-blind study of 18 participants, and reported a statistically significant difference in relative reduction in ulcer area at 6 weeks but not 6 months; however, this was for the per-protocol analysis only. The second was a single-centre, outcome blind RCT[104] of 36 participants admitted to hospital with ulcers graded Wagner ≤3 and reported a statistically significant relative reduction in ulcer size at 14 days with use of hyperbaric oxygen. As the participants were treated as hospital inpatients, the generalisability of these findings may be limited. Of the remaining six studies, five were nonblinded,[97,100–103] and one outcome-assessor blinded[95] and all were assessed as being at high risk of bias.

Outcome: Amputation

Nine studies comprising 611 participants were identified which investigated the effect of hyperbaric oxygen on amputation (major or minor). Five studies[92,93,100,105,106] had no effect. Of the others, the first was a small double blind RCT[91] which reported no difference in amputation rate with hyperbaric oxygen compared to hyperbaric air even in the per protocol analysis presented. The time point at which this was evaluated was unclear. A second study assessed to be at low risk of bias,[96] a single centre double-blind RCT of 94 participants, reported no benefit of hyperbaric oxygen treatment as opposed to sham therapy with hyperbaric air on the amputation rate at 1 year.

One study[98], which was not blinded for the outcome of amputation and was assessed to be at high risk of bias, showed no difference in the outcome of being free from amputations at 12 months.

One single-centre double blind RCT, assessed to be at low risk of bias,[94] comprising 107 participants with Wagner 2–4 ulcers of at least 4 weeks duration showed no difference in "indications for amputation" (evaluated by a blinded vascular surgeon based on digital photographs and participant clinical data) with hyperbaric oxygen therapy compared to sham therapy after 12 weeks of treatment. Of note although the primary outcome was an adjudicated indication for major or minor amputation (51% in the intervention vs. 48% in the controls), only one minor amputation actually occurred during the 12 weeks of the study.

Outcome: Quality of life

Four studies were identified which reported the effect of hyperbaric oxygen on the quality of life. One study[92] was at high risk of bias and, although apparent improvements from baseline in both physical and mental capacity scores on the SF-36 in the intervention group were reported, no between group analyses were reported. Three studies[91,107,108] reported this outcome. The first, a prospective double-blind RCT,[91] comprised 18 participants and compared SF-36 scores between participants receiving hyperbaric oxygen therapy versus hyperbaric air (sham therapy) over 30 sessions, reporting significant improvements in general health and vitality in the treatment group but no significant improvement in other domains in both groups and no significant difference in quality of life scores between the two groups overall (per-protocol analysis only). The second study[108] was a secondary analysis of a double blind RCT[94] and showed no changes in EQ-5D scores or SF-36 6 or 12 weeks between individuals who completed 12 weeks of hyperbaric versus sham therapy.

The final study[107] was also a secondary analysis of patients who completed a double-blind RCT[96] comprised 75 participants and reported a significant difference in pre and post-treatment responses to mental summary scores and two of eight domains on the SF-36 in the hyperbaric oxygen group, whereas no significant improvements were seen in the control group. No between group analyses were reported; thus, the significance of these findings is uncertain.

Outcome: New infection

Only one study reported on new infections with the use of hyperbaric oxygen compared to the standard of care. This was a single centre, double blind RCT[94] of 107 participants. Two participants in the intervention arm developed new infections compared to none in the control arm. Statistical significance was not provided.

Outcome: Resource utilisation

Three studies were identified which investigated the effect of hyperbaric oxygen on resource utilisation. Two studies[98,105] were at high risk of bias. One study[91], which was a double blind RCT of 18 participants and assessed to be at unclear risk of bias, compared costs of visits for ulcer dressings to the total cost (including hyperbaric therapy), and the total cost of undergoing hyperbaric oxygen therapy was considerably less than the control group (£4972 vs. £7946) who underwent standard care.

Outcome: Mortality

Two studies[96,98] using hyperbaric oxygen looked at deaths. Neither study showed any difference in mortality at 12 months.

Evidence statement: *Of the 18 studies comprising 906 participants investigating the use of hyperbaric oxygen as an adjunctive therapy to improve the outcome of diabetes-related foot ulcers, only three had blinding of participants and outcome assessments and thus were considered at low risk of bias. Overall, the evidence is uncertain, but the studies with lowest risk of bias suggest that there may be some benefit for its use in improving absolute wound healing and reduction in ulcer area. However, good evidence of benefit in preventing amputation is lacking. Different time points (ranging between 30 days and 12 months), different degrees of ischaemia of the index limbs of included participants and definitions of healing make comparisons between studies difficult.*

3.3.2 | Topical oxygen

We identified 10 studies for topical oxygen that met criteria for inclusion in the systematic review.

Outcome: Complete wound healing

We identified six studies with a total of 636 participants which investigated the use of topical oxygen on the outcome of wound healing. The first was a comparison of a device providing continuous diffusion of oxygen to the wound surface to a sham device in 146 participants. Although double-blind, the study published an interim and per-protocol analysis before the final ITT analysis, which increases the risk of bias of the study. Thus, the reporting of a significant improvement in the relative risk (RR) of wound healing (RR 1.95) in favour of the intervention group after 12 weeks of therapy[109] should be interpreted with caution. In the second study,[110] another multicentre double blind RCT of 130 participants compared a device which provided a transdermal continuous oxygen therapy (TCOT) to a sham device for 12 weeks of therapy. This study, assessed at low risk of bias, showed no difference in complete wound healing at 12 weeks. Overall, the study was rated at a low risk of bias.

The third study was a multicentre participant and outcome blind RCT of 73 participants with nonischaemic, noninfected, hard-to-heal diabetes-related foot ulcers[111] who were randomised to receive cyclical oxygen diffused over the ulcer surface versus a sham device delivering no oxygen. Initially planned to randomise 220 participants, at the first planned interim analysis after 73 participants had been recruited, the study was stopped due to the active arm showing apparent superiority compared to the control arm. The consequent-wide confidence intervals around the effect size has led to uncertainty about the true effect size.[112] Baseline characteristics were not comparable for key prognostic indicators between the two groups, including inconsistencies in baseline infection between the groups. As such, the certainty of this positive result is low.

The remaining studies[113–115] were assessed to be at a high risk of bias and any positive results reported should be treated with caution.

Outcome: Time to healing

We included 3 studies which reported on time to healing with the use of topical oxygen. The first study[116] reported significantly shorter time to healing in a study of 58 participants; however, this was a nonblinded RCT, it was unclear if findings were from a per protocol or ITT analysis, and the study was thus rated as being at high risk of bias. The other two were both RCTs with blinding of both participants and outcome assessments[109,110] of 130 and 146 participants, respectively. One of these[110] reported no benefit in the outcome of time to healing using a device providing continuous topical oxygen diffused over the wound compared to a sham device in a per-protocol analysis. The other study[109] reported a significantly shorter mean number of days to healing with use of a topical oxygen delivering device; however, the actual mean days to closure were not provided.

Outcome: Sustained healing

Two studies were identified which reported on sustained DFU healing. The first was a participant and outcome blind, multicentre RCT of 73 participants, which showed some benefit with the use of topical oxygen compared to a sham device. The study however only reported on the per-protocol analysis, and thus was assessed as being of acceptable risk of bias.[111] The second study, also a double-blind sham-controlled RCT of 146 participants at low risk of bias showed no difference in the proportion of ulcers remaining healed 12 weeks after closure in an ITT analysis.[109]

Outcome: Reduction in ulcer area

We identified nine studies comprising 662 participants on the use of topical oxygen for the reduction of ulcer area. One multi-centre, participant and outcome blind RCT[111] at acceptable risk of bias investigated the use of a topical oxygen therapy device and showed benefit in ulcer area reduction at 12 weeks compared to sham therapy. The other, a participant and outcome blind RCT[109], which was assessed at low risk of bias, showed greater percentage wound closure in the topical oxygen group compared to sham therapy at 12 weeks. The remaining seven studies[113–119] were at high risk of bias as: neither participants nor outcome assessors were blind to the intervention allocation,[113–119] groups differed in baseline areas, studies reported no between group analysis,[115,117,118] or reported an absolute rather than relative area reduction[116] and thus any positive results reported were of low certainty.

Outcome: Amputation

Three studies were identified on the effect of topical oxygen on amputation. One study[114] was at a high risk of bias due to nonblinding. One study[110], which was a double blind RCT of 130 participants, showed no difference in amputation rate with the use of topical oxygen therapy compared to moist wound therapy; however, only one amputation was reported. A final study,[111] which was a multinational double blind RCT of 73 participants comparing topical oxygen therapy to a sham device, which was assessed to be at acceptable risk of bias, also reported no significant difference in amputation rate after 12 weeks.

Outcome: Quality of life

Two studies were identified using topical oxygen which reported on the quality of life. One study[117] was assessed as being at high risk of bias as the participants were not blinded, and no between group analyses were performed. Therefore, no conclusions can be drawn from an apparent improvement in QoL in the intervention arm. The other study[111] was a multinational double blind RCT of 73 participants, which reported a significant difference in the well-being component of the CWIS-QOL index from baseline to 12 weeks with use of topical oxygen. The study was assessed as being at acceptable risk of bias.

Outcome: New infection

Two studies were identified for topical oxygen, which reported new infections. Both studies, one[110] at low risk of bias and one at acceptable risk of bias [111] showed no significant differences in the development of new infection between intervention and control arms.

Outcome: Resource utilisation

We found no studies that fulfilled our inclusion criteria which reported on this outcome.

Outcome: Mortality

Two studies[113,118] using topical oxygen looked at death/mortality with high risk of bias but reported no difference between the 2 groups.

Evidence statement: *We found three double-blinded RCTs and seven non-blinded studies comprising a total of 792 participants which investigated the use of topical oxygen. Of the double-blinded studies, all using sham devices, one was terminated early at pre-planned interim analysis and had uneven baseline characteristics between control and intervention groups. It did, however, report a significant improvement in healing in the intervention group at 12 weeks. Of the other two double-blinded trials which were assessed at being low risk of bias and with almost twice as many participants randomized as the first study, only one reported a statistically significant improvement in complete wound healing in favour of topical oxygen at 12 weeks, with the other showing no difference between topical oxygen and standard care. Overall, there appears to be a positive effect on wound healing at 12 weeks with the use of topical oxygen, although there is uncertainty about the size of the effect. There was no benefit of topical oxygen on amputation, probably due to short duration of follow-up in most trials. We found no data on resource use, and few data on adverse events.*

3.3.3 | Other gases

We found one study on nitric oxide,[120] three on ozone therapy,[121–123] two on cold atmospheric plasma[124,125] and one on carbon dioxide (CO_2)[126]

Outcome: Complete wound healing

One study which investigated the use of topical nitric oxide was a multi-centre outcome blind RCT of 147 participants,[120] and described a higher rate of absolute wound healing at 12 weeks compared to a subjectively defined "best clinical practice at the time". There were however important differences in baseline characteristics of study participants regarding the most important prognostic indicators for DFU healing; therefore, the study was assessed as being at high risk of bias and results should be interpreted with caution.

One double-blind RCT of 51 participants comparing the use of ozone therapy plus oxygen versus a sham device showed some benefit in absolute wound healing in the per-protocol but not in the ITT analysis. Due to the high rate of attrition in this study, it was assessed as being at acceptable risk of bias[121] and these results should be treated with caution. A second study of 100 participants comparing ozone therapy with standard of care including systemic and topical antibiotics was nonblind and showed no difference in wound healing between the two arms of the study.[123]

Outcome: Time to healing

Only one study which included investigating the use of topical and systemic ozone[122] reported on time to healing. This was described as a "single blind trial", and although positive results were reported in the intervention group, it was unclear as to who was blinded and if the analysis was per-protocol or ITT.

Outcome: Sustained healing

Only the study on nitric oxide[120] reported sustained healing and no difference was reported between the intervention and control at 12 weeks.

Outcome: Reduction in ulcer area

One study on nitric oxide, one on CO_2 therapy, two on ozone therapy and two on cold atmospheric plasma reported on wound area reduction as an outcome.

The first study evaluating the effect of cold atmospheric plasma was a small double blind RCT of 44 participants at unclear risk of bias[124], which reported a positive effect of cold atmospheric plasma compared to standard care on reduction in ulcer size at 21 days. However, groups were not similar in all key baseline participants and DFU characteristics and it was unclear if it was an ITT or per-protocol analysis. The second was an outcome blind RCT[125] of 45 participants at acceptable risk of bias showed some benefit of cold atmospheric plasma on ulcer area reduction after 9 visits; however, it was unclear if this was in a per-protocol or ITT analysis.

The study on nitric oxide as previously described, and assessed as being at high risk of bias due to methodological flaws[120] reported statistically significant reductions in ulcer area in the intervention arm at 4 and 12 weeks.

The study investigating CO_2 therapy was a single-centre, double blind RCT of 57 wounds (43 participants)[126] which reported a significant improvement of CO_2 therapy on wound area reduction at 4 weeks. The actual results were not given though and no between group analyses were reported.

The first study[123] on ozone therapy was a single-centre RCT of 100 participants; however although a statistically significant reduction in wound area was reported after 20 days, this result should be interpreted with caution due to lack of comparable baseline characteristics and no blinding of participants or outcome measures. The second was a double-blind RCT[121] of 51 participants, assessed as acceptable risk of bias but which reported no benefit of ozone gas on reduction on wound area at 24 weeks.

Outcome: Amputation

ne study was identified using systemic ozone[122] on amputation showed benefit on amputation rate compared to standard of care, however it the study lacked detail on blinding, and it was also unclear if the results were from a per-protocol or ITT analysis; thus, it was rated at high risk of bias and the findings should be interpreted with caution.

Outcome: Quality of life

Only one study was identified; this was an outcome blind RCT[127] comparing the use of cold atmospheric plasma to placebo therapy. It was a small study of 45 participants and reported no difference in Euro-QoL-5D or SF-12 scores between the two groups. It was unclear if this was an ITT or PP analysis, and the study was rated as having an unclear risk of bias.

Outcome: New infection

Only one study on nitric oxide[120] reported new infection. 35% new infection was reported in both arms of the study. As previously detailed, this study was rated at a high risk of bias.

We found no studies reporting resource utilisation or mortality as outcomes.

Evidence statement: *The evidence to support the use of other gases such as nitric oxide, ozone, carbon dioxide and cold atmospheric plasma is poor, with no studies assessed to be at low risk of bias.*

3.4 | Intervention 4: Physical alteration of wound bed

We found 29 studies which investigated the use of physical therapies in the management of DFUs.

3.4.1 | Heat

We found three studies[128–130] investigating the use of heat application to DFU for wound management.

Outcome: Complete wound healing

Two studies investigated the use of local heat to the wound both using a device that heated the wound to 38^{O} C, the first for 8 weeks in 20 participants[129] and the second for 12 weeks in 36 participants.[128] Although both reported improvements in absolute wound healing, neither had any blinding of participants or outcome measures and were considered at high risk of bias; thus, these results should be treated with caution.

Outcome: Time to healing

One of the 2 studies above also reported time to healing[129] but, as above, the lack of blinding, and the high risk of bias mean that the certainty of this result is low.

Outcome: Reduction in ulcer area

The third study,[130] which was again an RCT with no blinding of participants or outcome measures, demonstrated a higher rate of area reduction in non-ischaemic DFU when electrical stimulation (ES) and heat was used compared to ES stimulation alone.

Evidence statement: *The evidence to support the use of heat application for DFU management is weak, depending on only 3 RCTs all considered at high risk of bias, none of which had any blinding of participants or outcome measures. Thus, the positive results reported in absolute wound healing or wound area reduction are of low certainty.*

3.4.2 | Therapeutic ultrasound

We found only two studies on the use of therapeutic ultrasound (US) in the treatment of DFUs that fulfilled our inclusion criteria.[131,132] Both studies evaluated the outcomes of complete wound healing and wound area reduction only.

Outcome: Complete wound healing

Both studies[131,132] showed improved complete wound healing at 4 and 12 weeks in 60 and 133 participants, respectively, with the use of low-frequency US in superficial DFUs in comparison to standard care. However, both were at high risk of bias with poor outcomes in the control group in the former and a high number of protocol violations in the latter, so this positive result should be interpreted with caution.

Outcome: Time to healing

Only one study reported on time to healing[132] and reported a shorter healing time with the use of therapeutic US. However, as there was a high attrition rate in the study and only the per-protocol analysis was reported, this study was assessed as being at a high risk of bias.

Outcome: Reduction in ulcer area

One study reported reduction in ulcer area. This study[131] reported a significant reduction in ulcer area after 4 weeks of treatment with low-frequency US when compared to standard care. Despite the sound methodology, the very low healing rate of controls makes it difficult to assess the effectiveness of the interventions in this study and may reflect bias.

Evidence statement: *The limited evidence available and the small number of studies limit the conclusions that can be drawn regarding the value of therapeutic ultrasound in the treatment of DFUs.*

3.4.3 | Compression

We found 3 RCTs reporting on the use of compression in the management of DFUs[133–135]

Outcome: Complete wound healing

Only one study on compression reported complete wound healing.[133] This study compared the use of a local pulsatile pneumatic foot compression system versus a sham device once a week for 3 months to standard care in plantar diabetes-related foot ulcers in 115 participants and reported higher rates of healing of lesions in the intervention group. The analysis was, however, per protocol and restricted to the "compliant patients" and there were some doubts about whether participants were truly blinded as it relied on their neuropathy being sufficiently severe that they could not ascertain the feeling of the compression. Thus, we could not be confident of this positive result.

Outcome: Time to healing

One study of 57 participants[134] compared compressed air massage to standard of care and demonstrated faster healing in the air massage arm, but only in those that completed the study. The study had no blinding of either participants or outcome measures, and was at a high risk of bias.

Outcome: Reduction in ulcer area

One study, also at high risk of bias, reported reduction in ulcer area. This study[135] reported a greater reduction in the wound area with the use of intermittent vacuum compression cycles for 3 weeks compared to controls treated with standard care. However, the study was small with only 18 participants, had short follow up and although wound acetate tracings were reported to have been done blind, the participants and investigators were not blind to the intervention administered. The high risk of bias thus reduces the certainty of the evidence produced in this study.

There were no studies reporting on the outcome of sustained healing, maintenance of function, minor or major amputation, new infection, resource utilisation or mortality.

Evidence statement: *On the basis of the few studies available, the evidence to support the use of compression as an adjunct to standard of care in the management of DFUs is of low certainty.*

3.4.4 | Electromagnetic and electrical stimulation

Six studies were identified that fulfilled our inclusion criteria, which focused on the use of electrical (ES) or electro-magnetic (EM) stimulation for the treatment of DFUs.[136–141]

Outcome: Complete wound healing

Two studies evaluated complete wound healing in patients treated with electrical stimulation in patients treated with electrical stimulation[136] and electromagnetic stimulation.[137] The first comprising 80 participants[136] used a sham device to ensure blinding of participants and outcome measures, the second comprising 40 participants[137] a 3-arm dosing regimen with the fourth group being standard of care alone. Neither reported superiority of electrical stimulation nor electromagnetic stimulation on complete wound healing compared to standard of care at 6[137] and 12 weeks, respectively.[136]

Outcome: Reduction in ulcer area

Four other studies reported on reduction in wound area in patients treated in trials with electromagnetic and electrical stimulation.

Three were double-blind. Two of these[139,141] reported no significant differences in reduction in ulcer area at 12 days and 4 weeks in 20 and 13 participants, respectively. The third study[140] reported a significant reduction in ES-treated patients with neuro-ischaemic DFUs compared with standard care at 4 weeks in 38 participants. However, the low wound area reduction in the control group and the interrupted recruitment resulting from the COVID-19 pandemic make it difficult to rely on the reported outcomes. Fourth, an outcome blind study of 15 participants[138] reported a significantly greater reduction in wound area in patients treated for 12 weeks with ES compared to standard care, but only a per-protocol analysis was reported.

Overall, the high variability of stimulation protocols in terms of intensity, frequency and time of application make it difficult to interpret and compare the results of these studies.

There were no studies meeting the inclusion criteria that reported on the outcomes of time to healing, sustained healing, maintenance of function, minor or major amputation, new infection, resource utilisation or mortality.

Evidence statement: *The evidence to support improvement in wound healing with the use of ES/EM stimulation based on the outcomes reported in the few available studies does not support the use of electrical or electromagnetic stimulation in the treatment of DFU in comparison with standard of care.*

3.4.5 | Light and laser therapies

We identified 8 RCTs[142–149] that explored the role of light and lasers in the management of DFUs.

Outcome: Complete wound healing

Three studies comparing light or laser therapies with standard care reported complete wound healing. The first[142] compared laser photobiomodulation to the standard of care in 21 participants and reported a higher healing rate at 12 weeks in patients with neuroischaemic foot ulcers. In contrast, the second[143] found no significant differences in complete healing at 20 weeks when comparing laser stimulation to standard care in 23 participants. The third study of 20 participants[144] reported a significantly higher wound healing rate at 12 weeks in patients treated with visible light compared to standard care. However, despite all studies being double-blind, all had small sample size and other methodological shortcomings including poor description of usual care including offloading, thus our certainty in any positive findings is reduced.

Outcome: Time to healing

Only one study reported on time to healing. This study of laser stimulation compared to standard of care reported no differences in time to healing over the 20-week study period.[143]

Outcome: Reduction in ulcer area

Six studies reported the outcome of wound area reduction following light and laser treatments in DFUs, of which three were double-blind. The first[142] showed no significant reduction in wound area after 12 weeks of treatment with laser when compared to standard care, whereas the second[147] reported superiority in wound area reduction but only had a 2-week follow up period. The third [146] compared laser-puncture treatment to standard care and reported a greater reduction in wound area in the treatment group at 4 weeks. All three were small studies and usual care including offloading was not well described; thus, these positive results should be interpreted with caution. The remaining three studies were nonblind. Despite reporting greater wound area reduction at 15 days,[148] 4 weeks[149] and up to 6 weeks,[145] these studies were at high risk of bias, and investigated very different protocols for electrical stimulation, thus reducing our certainty in these positive findings.

Outcome: New infection

Only one study[142] reported on new infection as part of adverse event reporting and no difference was reported between both arms of the study.

Outcome: Amputation

One study reported on amputation as part of adverse event reporting. No difference between control and intervention were noted[142]

Outcome: Mortality

Only one study reported no difference in mortality rates at 12 weeks.[142]

There were no studies meeting the inclusion criteria that reported on the outcomes of sustained healing, maintenance of function, or resource utilisation.

Evidence statement: *There was considerable heterogeneity of devices, treatment protocols and length of follow-up with individual studies being of small size. One study at lowest risk showed no difference in outcome in any of the outcome measures reported at 12 weeks. Thus, with all other studies at risk of bias it is difficult to have confidence in any positive outcomes reported in the remaining studies indicating effectiveness of light and laser treatments in the management of DFU when compared to standard of care.*

3.4.6 | Shockwaves

We identified four studies on the use of shockwave therapy for wound healing of DFUs[150–153]

Outcome: Complete wound healing

Three studies reported complete wound healing. None were at low risk of bias. The only patient and outcome blind double-blind trial[151] reported no difference in complete healing with the use of shockwave therapy compared to standard care at 12 weeks in 206 participants. Similarly, a single blind study of 38 participants[152] also reported no differences in complete healing with shockwave therapy at 4, 8 or 20 weeks. The only study reporting improved complete wound healing when compared to standard of care was a study of 30 participants,[150] where healing rates were compared after only 3 applications of ESWT with controls at 20 weeks. This study, however, had no blinding of participants or outcome measures.

There was considerable heterogeneity of treatment protocols between the 3 studies and two of the studies were considered at high risk of bias. Thus, any positive results should be interpreted with caution.

Outcome: Time to healing

Two of the studies which reported on complete wound healing also reported on time to healing. In both studies,[150,152] faster healing in shockwave-treated patients compared to controls was reported; however, both studies were at high risk of bias with the first having only 30 participants and having no blinding of participants or outcome measures[150] and the second being outcome blind but reporting only a per-protocol analysis.[152]

Outcome: Reduction in ulcer area

Three studies reported on reduction in the ulcer area, again with differing results. The first[152] reported a significant reduction in ulcer area at 8 and 20 weeks in patients treated with shockwave therapy for 4 weeks compared to controls treated with standard care, and was outcome blind but reported a per-protocol analysis only. The other two failed to show significant differences in wound area reduction at 7[153] and 20 weeks,[150] respectively.

There were no studies meeting the inclusion criteria that reported on the outcomes of sustained healing, maintenance of function, minor or major amputation, new infection, resource utilisation or mortality.

Evidence statement: *The small number of studies found had different protocols, devices and follow-up times. Only one study had blinding of outcome measures and participants and this showed no difference in outcome measures of healing. All 3 studies were at risk of bias and thus the evidence to suggest improvement in healing in diabetes-related foot ulcers when compared to standard of care is of low certainty.*

3.4.7 | Ischaemic preconditioning

We found one study evaluating ischaemic preconditioning in the treatment of non-ischaemic DFU.[154] This study investigated the application of intermittent compression to participants' upper limbs twice a week for 6 weeks in 40 participants and reported higher

healing rates when compared to standard of care. However, our confidence in this outcome was weakened by the unexpected poor healing rate in controls, the use of per protocol analysis, the fact that patients, but not outcome measures, were blind and poor description of baseline ulcers, including vascular status.

Evidence statement: *The evidence available from this single study is insufficient to support the use of ischaemic preconditioning in the management of DFU.*

3.4.8 | Connective tissue manipulation

We found one study[155] which studied the effects of manual manipulation of the skin of the lower limb (CTM) in the management of diabetes-related foot ulcers when compared to standard of care. This study, which was in 26 participants, failed to demonstrate significant differences in wound area reduction between patients with plantar superficial DFUs who were treated with proximal CTM for 6 weeks compared to standard care. The study did not report on any other outcomes critical to decision-making.

Evidence statement: *From the limited evidence derived from the only study published, there is little evidence to support the use of CTM in the management of DFU compared to standard of care.*

3.4.9 | Therapeutic magnetic resonance

We found only one study[156] which studied the effects of therapeutic magnetic resonance compared to standard of care in 157 participants. There was a high dropout rate and a per protocol analysis only was reported; nevertheless, no significant differences were found between the groups in healing rates at 10 weeks.

Evidence statement: *From the limited evidence derived from the only study published, there is no evidence to support the use of TMR in the management of DFU compared to standard of care.*

3.5 | Intervention 5: Skin substitutes

Skin substitutes are a grouping of wound care products that include cellular, acellular, and autologous skin graft subgroups. These products are applied to non-healing wounds to supply structural and/or biological support to the site via this externally derived product. They are generally secured with sutures, adhesive strips, and/or a secondary dressing. This heterogenous group of products are generally used to artificially deliver wound healing stimulation and seek to mimic the composition and function of human skin.

We found 26 RCTs across the broader category of skin substitutes. This body of research has greatly expanded over the last decade and now contains a significant number of enrolled people with diabetes-related foot ulcers, but presents a very complex review challenge given the non-uniformity of products, significant drop out rates, inconsistent blinding, and analysis that was often per protocol and not ITT. A helpful way to categorise and compare skin substitutes is to divide them into groups based on cellular (those products that contain cells), and acellular (those products that do not contain cells). An example of a cellular skin substitute would be a product containing human cells such as fibroblasts or keratinocytes. Some examples of acellular skin substitutes would be products such as human acellular dermal matrix and bovine collagen dermal matrix where the cells have been removed and the support structure or matrix is left in place. We also considered autologous skin grafts in this sub-category.

We found 10 RCTs which included a total of 947 participants which investigated the use of cellular products, 12 RCTs which included a total of 1112 participants which investigated the use of acellular products, and 5 RCTs which included a total of 458 participants which investigated the use of autologous skin graft products, some looking at more than one intervention.

3.5.1 | Cellular products

Outcome: Complete wound healing

We identified 9 RCTs[157–165] which reported complete healing. Although most studies demonstrated a positive effect of cellular products on complete wound healing after 8–12 weeks, all were rated at acceptable or high risk of bias.

Four studies comprising a total 390 participants used an allogenic bilayered cultured skin substitute (donated neonatal foreskin fibroblasts and keratinocytes) as the intervention and compared either with usual care[157,162,164] or in a 3-way study versus amniotic membrane product or usual care.[163] Two of these studies reported a significant improvement in the proportion of subjects in the intervention arm achieving complete wound closure compared with those in the standard care arm after 12 weeks.[157,162] However, neither study had blinding of either participants or outcome measures, both had a high dropout rate of over 20%, and were considered at high risk of bias. Thus, confidence in these two positive results is low. A smaller pilot study, also with no blinding of participants or outcome measures of the same product showed no difference in complete healing at 12 weeks.[164] The third study[163] judged at acceptable risk of bias, with outcomes adjudicated by blinded assessors, reported no difference in healing between the skin substitute group and controls treated with standard of care.

Four studies investigated the use of the same product comprising an absorbable polymer scaffold seeded with neonatal allogenic fibroblasts. All these studies were assessed at high risk of bias. In a dose-ranging study of 50 participants randomized into 4 arms[158], it was reported that ulcers treated with the highest dosage of the skin substitute (one piece weekly for 8 weeks) healed significantly more often than those treated with conventional wound closure methods. This study was reported to be single blind, but it was unclear if the patient or outcome was blind as no details of blinding were given. There were also differences in baseline characteristics of participants and the study report lacked detail on the usual care provided. Similarly a study of 46 participants[159] reported significantly more ulcers

healed in the intervention arm, but was only single (patient, not outcome) blind study, reported a per-protocol analysis only, and was thus considered to be at high risk of bias. The largest of this set of trials[160] comprising 245 participants compared the use of this cellular skin substitute to usual care and reported a significant improvement in healing at week 12. Although single (patient but not outcome) blind, it had a high dropout rate (19%), lacked detail on baseline vascular status and usual care, and in particular the use of offloading was not well described. Thus, being assessed at a high risk of bias, the positive result should be treated with caution. In a 3-way study of the cellular skin substitute intervention versus an acellular product versus usual care[161] no significant differences were reported at 12 weeks between the 3 arms even though only a per-protocol analysis was reported.

A single study of a microvascular tissue structural allograft[165] was identified. In an outcome blind multicentre study, 100 participants were randomised to either the allograft or a calcium alginate dressing with standardised offloading. Outcomes at 12 weeks suggested statistical differences in absolute healing, but the healing rate in the control arm, particularly after the fourth week, appeared low for the type of ulcers (Wagner Grade 1 and 2) included and there were differences in baseline characteristics of the ulcers.

Outcome: Time to healing

Six of the above studies also reported time to healing[157–159,162,163,165]; two with the bilayered skin substitute[157,163] and three with the polymer scaffold and neonatal fibroblast skin substitute.[158,159,162] All but one of the studies reported an apparent improvement in time to heal, but these were all studies at high risk of bias. Only one study[163] reported a similar time to healing between the intervention (bilayered skin substitute) compared to controls in the only outcome blind study, although this study was still assessed as being at moderate risk of bias due to the interim analysis having been previously published and differences in baseline characteristics of the participants.

The single trial of the microvascular tissue structural allograft also reported a time to healing[165] within 12 weeks and an apparent 10-day difference between the groups. Above the low healing rate in the control arm after 4 weeks of the study decreases our confidence in this result.

Outcome: Sustained healing

Two studies reported on sustained healing. The first[157] reported no difference between recurrences at 3 months compared to the control arm. The second study[158] reported no recurrences in either arm at 2 months of follow-up post healing.

Outcome: Reduction in ulcer area

Six studies on cellular skin substitutes reported on reduction in ulcer area, one[166] with the bilayered skin substitute, four with the polymer scaffold/fibroblast skin substitute,[158–161] and one with the microvascular tissue structural allograft.[165] All of the 4 studies with the polymer scaffold/fibroblast skin substitute[158–161] and the single study of the microvascular tissue structural allograft[165] demonstrated greater wound area reduction with the use of cellular skin substitutes compared to standard of care. All but one,[165] however, were at a high risk of bias and so positive results should be treated with caution. The single outcome blind study of a microvascular tissue allograft considered to be of uncertain bias[165] reported a significant difference between the intervention and control arms in terms of reduction in ulcer area although there was a marked lack of wound area reduction in the control arm after 4 weeks despite the type of ulcers included. The study which investigated the use of a bilayered skin substitute and usual care compared to usual care alone (which included NPWT),[166] but which had no blinding of either participants or outcome measures offered no between group analyses.

Outcome: Amputation

Only one study on cellular skin substitutes reported on amputation.[162] Amputation was reported only in safety reporting, with the study reporting a lower amputation rate in the intervention group. It was not clear however whether these were major or minor amputations , and with the high dropout rate and overall high risk of bias, the clinical significance of this result is uncertain.

Outcome: New infection

Only six studies reported on the outcome of new infection.[157–160,162,164] All 6 studies reported new infection as secondary outcomes and all were at high risk of bias. Any positive effects of new infection associated with the use of cellular skin grafts should therefore be interpreted with caution.

Outcome: Resource utilisation

Two studies reported on resource utilisation[167] The first a posthoc analysis on the resource of the 3-way study[163] comparing a bilayered skin substitute, a dehydrated amniotic membrane (dHAM) and usual care reported that the mean cost of the material per patient was approximately $8000 for the skin substitute and over $2000 for the dHAM. However, no other costs were provided. The second a study of a microvascular tissue structural allograft[165] reported hospitalizations (as adverse event reporting only). Although there were apparently fewer hospitalisations in the intervention group, no significance was attached to this result.

There were no studies reporting on quality of life, maintenance of function, or ability to perform activities of daily living or death/mortality.

Evidence Statement: *Although evidence from 10 RCTs suggests that cellular skin substitutes may improve the incidence of healing and reduce the time to healing in patients with diabetic foot ulcers when provided in addition to standard of care, all studies were at acceptable to high risk of bias and therefore this result is of low certainty. There is insufficient evidence to establish which if any particular cellular skin substitutes are superior and there is also insufficient evidence on cost effectiveness of this modality. There is some evidence to indicate that cellular skin substitutes are associated with a reduction in amputation rates, but this is of low certainty. No formal within-trial cost effectiveness data were found.*

3.5.2 | Acellular products

Outcome: Complete wound healing

Twelve RCTs[161,168–178] which investigated acellular skin substitute products reported complete healing. All were at high risk of bias, and therefore, any positive effects should be interpreted with caution. One study[168] compared the use of granulated cross-linked bovine tendon collagen and glycosaminoglycan, reporting a significant improvement in the proportion of wounds healed at 6 weeks; however, this was a small study of 46 participants, had no blinding of participants or outcome assessments and reported a per-protocol analysis only. A similar product but in a bilayered construction with a silicone outer layer was studied in a larger study of 307 participants but was not blinded for this outcome of absolute wound healing at 16 weeks nor were participants blind.[169] The authors reported a higher proportion of ulcers healed, but a high dropout rate was noted and overall the study was assessed as being at high risk of bias. In a three-way study[171] of two acellular human dermal matrices (Dermacell-ADM) versus Graftjacket ADM (the results of this arm were not reported for healing) versus usual care in 60 participants the D-ADM was reported to show significant improvement in healing rates, although a per-protocol analysis only was presented, and this study was assessed as being at high risk of bias. In another 3-way study of an acellular skin substitute versus a cellular skin substitute versus usual care in 56 participants[161] no difference was reported between the acellular skin substitute and usual care even though a per-protocol analysis only was presented. A small pilot study of 28 participants comparing the acellular skin substitute to usual care reported higher rates of complete closure at 16 weeks, but there was no blinding of participants or outcome measures and the study was assessed as being at high risk of bias.[175] Another small single-centre study of 30 participants[176] comparing a micronised acellular dermal matrix (ADM) product to standard care (which included negative pressure wound therapy) and reported improved healing at 42 days, 120 days and 6 months, but the study had no blinding of participants or outcome measures and was assessed at being at risk of bias.[176] The 2 final studies of acellular skin substitutes[163,170] reported apparent improvements in healing in the intervention arms. The first, comprising 80 participants, although outcome blind[163] was considered at high risk of bias as an interim analysis was published prior to the full report, ulcer characteristics at baseline were not well described and there was a difference in area at baseline between the 2 groups. The second study, which had no blinding of participants or outcome measures[170], was a study of 86 participants, but was also considered at high risk of bias. Thus, any positive results reported should be treated with caution.

Of the animal-based acellular products, 2 studies[172,177] reported that patients treated with foetal bovine ADM were found to be significantly more likely to achieve complete wound closure compared with standard of care alone, the first at 12 weeks in 207 participants[172] and the second at 6 months in 15 participants.[177] The larger of these[177] presented a modified ITT as the study was interrupted by the COVID-19 pandemic (study reported 207 of 226 participants randomized). Neither, however, had no blinding of outcome measures or participants and these positive results should be treated with caution. A porcine-derived, purified reconstituted bilayer wound matrix was investigated in one outcome blind RCT.[178] Although an apparent improvement in healing was reported at 12 weeks in 40 participants, the study was marred by the protocol specifying that participants who failed to heal after 6 weeks could seek alternative treatments. The healing rate in the control arm seemed unusually low after the first 4 weeks of the trial for the type of ulcers recruited; thus, this positive result should be treated with caution.

In the sole fish skin RCT identified,[173] a significantly higher proportion of ulcers were reported to heal at 12 weeks in 49 participants. However, this study was outcome but not patient blind and did not present an ITT analysis. Hence, these positive results should be treated with caution.

Outcome: Time to healing

Six studies in this category reported on time to healing.[169–172,175,178] All reported a significant improvement in time to healing although all were assessed as being at high risk of bias and, although two[171,178] were assessed blind for this outcome, other methodological problems mean that these results should be treated with caution.

Outcome: Sustained healing

Three studies reported sustained healing. Just one[174] showed an apparent difference in sustained healing at 4 weeks of the D-ADM versus control, but this was not sustained at 8 or 12 weeks. The other two studies[169,172] showed no significant difference. All 3 studies were at high risk of bias.

Outcome: Reduction in ulcer area

Seven RCTs[169–173,178,179] investigating acellular skin substitutes reported reduction in ulcer area compared to standard of care. An apparent significant reduction after 4 weeks was reported in a study of Collagen Laminin-Based Dermal Matrix combined with Resveratrol Microparticles[179] compared to standard wound care, but this study had no blinding of either participants or outcome measures and provided per-protocol analysis only. In one of the larger studies[169] the rate of wound size reduction was reported to be significantly better for the intervention-treated participants compared to the above. Although wound area reduction was assessed blindly in this study, there was a large drop-out rate, meaning that only a per-protocol analysis was reported; the study was assessed at high risk of bias and hence this result should be treated with caution. Two other studies were assessed at high risk of bias.[170,171] Although the latter reported an apparent improvement in wound area the high risk of bias means the confidence in this result is low.

Of the animal acellular skin substitutes, all three studies; the study of foetal bovine ADM,[172] the study of porcine purified reconstituted bilayer wound matrix,[178] and the study of fish skin substitutes[173], were associated with apparent improvements in wound area reduction at 12[172,178] and 6 weeks.[173] All studies were at high

risk of bias, and although the study of the porcine product was outcome blind, other aspects of the trial design, including the ability for participants to exit the trial at 6 weeks means that we have low confidence in the positive results reported.

Outcome: Amputation

Only two studies reported on amputation. The first[168] reported on major amputation at 6 weeks and reported a significant reduction compared to the control arm. The control arm, however, was reported to have had a 30% major amputation rate at 6 weeks, which seems high for the type of ulcers included. The second,[172] reported no statistically significant difference in amputation rates between the foetal bovine ADM treated participants compared to those in the control arm.

Outcome: Quality of life

Two studies reported on quality of life. The use of Dermal Regeneration Template treatment was reported to have improved components of quality of life, although these were not elaborated on in one RCT.[169] There was no significant difference seen in the 8 week quality of life between the 2 groups in the study of the porcine-derived bilayer wound matrix.[178]

Outcome: Maintenance of function and ability to perform activities of daily living

Only one study reported on this outcome. This study[169] reported a significant improvement in physical functioning and bodily pain with the use of Dermal Regeneration Template compared with standard of care but the high risk of bias and the unblinded assessment of this result means this should be treated with caution.

Outcome: New infection

Four studies on acellular skin substitutes reported new infections.[172,174,175,179] Only two of these[172,174] reported infection as planned secondary outcomes and not just adverse events. The first reported the rates of osteomyelitis to be similar in the DermaCell-ADM group and control groups but slightly higher in the GraftJacket-ADM group.[174] One[172] reported the rates of new infection to be similar in the foetal bovine ADM group and control groups, respectively. All four studies were at a high risk of bias.

Outcome: Resource utilisation

Two studies reported this outcome. The mean and median ADM product costs at 12 weeks were $1200 and $680, respectively, in one study.[171] The other study reported estimated costs to healing of those in the porcine reconstituted bilayer matrix arm was $1781.[178] However, no costs for the control arm receiving standrad care were given. Neither study reported full economic analyses.

Outcome: Mortality

We found no studies of acellular skin substitutes which reported this outcome.

Evidence Statement: *The evidence to support acellular skin substitutes being associated with improved healing, time to healing, or wound area reduction of diabetes-related foot ulcers when compared to standard of care is of low certainty. There is insufficient evidence to establish which, if any, particular acellular skin substitutes are superior and there are also few robust data on costs.*

3.5.3 | Autologous skin graft products

Five studies on autologous skin graft products met the inclusion criteria for the systematic review.[180–184] Three had no blinding of participants or outcome measures[180–182]; two studies were outcome blind.[183,184]

Outcome: Complete wound healing

All five studies reported complete healing. Two studies reported superiority in healing with the use of autologous skin graft products at 12 weeks compared with standard of care. The first[180] used an autologous heterogenous skin construct but had no blinding of participants, investigators, or outcome measures, and at the time of this review had only published an interim analysis of 50 participants.[180] The second,[184] compared a bioactive split thickness skin graft to a calcium alginate dressing in 100 participants. Although the study was outcome blind, participants were allowed to exit the study at 6 weeks if <50% wound area reduction was achieved, leading to a high attrition rate (19/50) in the control arm.[184] Both positive results should thus be interpreted with caution. Two studies investigating autologous skin grafts reported no difference in complete healing compared to a basic paraffin gauze dressing at 11[181] and 20 weeks[182] in 79 and 180 participants, respectively. The final study, comparing the use of a non-cultured autologous "spray-on skin" product to standard of care, found no difference in complete wound healing at 6 months in 49 participants.[183]

Outcome: Time to healing

Four of the studies which reported on complete healing[181–184] also reported on time to healing. Mean time to healing was reported as being shorter with use of an autologous tissue engineered graft[182] and a bioactive split thickness skin graft[184] compared to standard of care; however, as mentioned above, both studies were at risk of bias. No difference in time to healing was reported between an autologous "spray-on skin" product and standard of care.[183]

Outcome: Sustained healing

No studies on autologous skin substitutes have reported sustained healing.

Outcome: Reduction in ulcer area

Three studies reported on reduction in ulcer area. The first[180] compared the use of an autologous heterogenous skin construct with standard of care and although the treatment group was

reported to have achieved a greater percent area reduction compared to the control group at every prespecified timepoint of 4, 6, 8 and 12 weeks, statistical significance was not provided. The second study[184] reported a greater wound area reduction in the bioactive split thickness skin graft arm compared to standard of care including a calcium alginate dressing at 12 weeks. The final study[182] reported that a 50% reduction in ulcer area was achieved significantly faster with use of autologous skin graft compared with a paraffin gauze dressing. All three studies were at risk of bias however and these positive results should be interpreted with caution.

Outcome: Amputation

Only one study reported this outcome[183]; reporting no difference in amputation with use of a non-cultured autologous "spray-on skin" product.

Outcome: Quality of life

Three studies reported on quality of life[180,183,184] and no differences in quality of life were reported with use of autologous skin graft products.

Outcome: Maintenance of function and ability to perform activities of daily living

Only one study reported on this outcome[183] with no differences in changes in EQ-5D-5L domains of mobility, self-care, activities or anxiety/depression between the spray-on skin and control arms.

Outcome: New infection

Two studies[182,183] reported on new infections. Rates of new infection were slightly higher in both the "spray-on skin" group[183] and autologous skin graft groups[182] than in the control arms, although statistical significance was not provided in either.

Outcome: Resource utilisation

Only one study on autologous skin substitutes reported on resource utilisation,[183] and reported lower community nursing costs with the use of the autologous "spray-on skin" but did not include the actual cost of the device. Any overall cost-benefit with its use is thus uncertain.

Outcome: Mortality

Only one study, which was at high risk of bias, compared mortality with use of autologous skin substitutes; this was at high risk of bias (3 deaths in re-cell group vs. none in control).[183]

Evidence Statement: *There is very limited evidence on the use of Autologous Skin Graft Skin Substitutes for the treatment of diabetes-related foot ulcers when compared with standard of care. Any positive outcomes in the studies found should be treated with caution given the high risk of bias of the available evidence. There is insufficient evidence to establish their utility and effectiveness.*

3.6 | Intervention 6: Autologous products, growth factors and cellular therapies

We found 102 papers related to the use of cell therapies for the treatment of diabetic foot ulcers to support healing. Of these, we excluded 52 as not fulfilling the protocol criteria (see Figure 1). Fifty full papers describing randomised trials were included for review.

3.6.1 | Platelets

We included 15 trials on the use of platelet products for the management of diabetes related foot ulcers.[185–199] A number of our outcomes were critical to decision-making and are detailed below.

Outcome: Complete wound healing

We found 11 trials which described the outcome of complete wound healing[185–195] and in which the comparator was the standard of care. Comparisons between products and studies were difficult as the outcome was assessed at time points which varied between 4 and 20 weeks. Overall the studies were at high risk of bias, with only one being outcome blind[186] and one patient-, but not outcome-, blind.[191]

The first[186] reported an improvement in wound healing at 12 weeks using platelet autogel in a study of 72 participants; however, the high protocol deviation rate led to the authors reporting this positive outcome in a per protocol analysis, casting some doubt on the certainty of this result. Another relatively large RCT of platelet gel, which included 103 diabetes-related foot ulcers, with healing outcomes assessed at 12 weeks[190] was marred by non-blinded outcome assessments. The generalisability of this study may be of concern given that patients were recruited as hospital in-patients.

Platelet gel products may suffer from the problem of the volume of blood required from an individual for the preparation of autologous platelet gel or fluid, and so one study used blood bank–derived platelets.[191] Although a benefit on ulcer healing was reported in this study of 100 participants, limited details of the inclusion criteria were provided, and although patients were blind to the intervention arm, outcomes were not assessed blind.

The remainder of the studies were assessed to be at high risk of bias due to non-blinding of either participants or outcome assessors,[185,187–189,192–195] had outcomes assessed within a short times scale[189,192,194] or reported no significant difference in healing between the two arms.[189]

Outcome: Time to healing

A total 7 studies reported time to healing[186,190–192,195–197] of which 5 (see above) reported complete healing as well.

All but 2 were considered at a high risk of bias. The first,[186] in an outcome blind study, reported no difference in time to healing between the two groups. The other studies,[190,192,194–197] which reported improved time to healing were marred by significant

methodological problems including lack of blinding, poor description of usual care, or baseline characteristics including wound area. Any positive result should therefore be treated with caution. The study[191] described above, assessed at acceptable risk of bias, also reported a significant improvement in time to healing with the use of blood bank platelets. However, this is the only randomised study we have found using this type of intervention.

Outcome: Sustained healing

We found no studies of platelet products which described this outcome.

Outcome: Reduction in ulcer area

We identified 8 studies[187,189,191,193,194,197–199] which reported the outcome of wound area reduction at various time points, which varied between 4 and 20 weeks, making comparisons difficult. The majority of the studies were assessed as being at moderate to high risk of bias with the exception of the study of blood bank platelets.[191] This latter, patient-, but not outcome-, blind study, assessed the effect of blood bank derived platelet on wound area reduction at 20 weeks and reported a significant reduction in ulcer area at 12 weeks; however, as mentioned above, limited details on the inclusion criteria limit the generalisability of the data. In a much earlier study,[193] a double blind trial randomised only 13 participants, so our confidence in the reported apparent reduction in wound area is uncertain. A 3-way blinded study[198] did not report any raw data, although it was stated that there was no difference between the groups.

Outcome: Amputation

Only one study reported total lower extremity amputations (major and/or minor)[188] as an outcome. The high risk of bias and low numbers make the apparent improvement in amputations at 12 weeks of unclear certainty.

Outcome: New infection

We found only one study reporting new infections.[185] This study, which had no blinding of either participants or outcome measures, was judged to be at a high risk of bias; however, the apparent significant improvement in the number of ulcers which developed secondary infection needs to be interpreted with caution.

Outcome: Resource utilisation

We found only one study which reported resource utilisation including hospitalisation costs.[194] However, the detail of how the expenditure was captured and the unblinded nature of the study make the result difficult to interpret.

Outcome: Mortality

We found only one study[190] reporting mortality as a secondary outcome at 12 months. There was no statistical difference between the 2 groups, but the numbers were too small to draw any conclusions.

Evidence statement: *The evidence to support the use of autologous platelets in the management of diabetes-related foot ulcers when compared to standard of care is of low certainty. Across 15 studies, including a total of 950 participants, few studies were graded at low risk of bias. The different timescales, different products and different outcomes chosen make comparison of different interventions difficult.*

3.6.2 | Autologous leucocyte, platelet and fibrin patch

We found one RCT of this intervention.[200]

This multicentre outcome blind RCT, performed in 3 European countries was considered at low risk of bias and reported a significant improvement in the proportion of ulcers healed at 20 and 26 weeks, time to healing in those who healed at 20 weeks and wound area reduction at 20 and 26 weeks. Participants in the intervention arm had weekly visits for venesection to produce the patch, which was applied directly to the wound in addition to good standard of care. Patients were hard to heal in that they had a 4-week run-in period before randomisation, which may explain the low healing rates in the control arm despite good standard of care.[200]

There were no significant differences found in the outcomes of new infection, major or minor amputations, or mortality. Of note, although patients had 18–36 mls blood taken every week in the intervention arm, no difference was found in adverse events including new anaemia.[200]

Evidence statement: *One adequately powered multicentre outcome blind RCT at low risk of bias reported significant improvements in healing, time to healing and wound area reduction in patients with hard to heal ulcers of an autologous leucocyte, platelet and fibrin patch when used in addition to best standard of care compared to standard of care alone. As there is only one RCT reported of this intervention, we have only moderate certainty in this result.*

3.6.3 | Other cell therapies

We found 10 papers describing RCTs of other cell therapies for the promotion of healing of diabetes-related foot ulcers, including adipocytes,[201–205] Fibroblasts,[206] keratinocytes,[207,208] bone marrow derived stem cells,[209] allogeneic bone marrow mesenchymal stromal cells (allohBM MSC) and cultured allogeneic bone marrow mesenchymal stromal cell derivatives (cultured allohBM MSCs).[210]

Those describing our outcomes of critical interest are described below.

Outcome: Complete wound healing

Nine RCTs reported complete wound healing at timescales varying between 8 weeks and 6 months.

Of the studies investigating the use of autologous adipocytes, three[201–203] investigated abdominal lipo-aspirates. The first study[201] included 52 participants, assessed as being at low risk of bias, was

outcome blind and showed a significant increase in the proportion of ulcers healed at 8 weeks (100% vs. 60%) compared with usual care including offloading. Subsequently, two studies at higher risk of bias have been published.[202,203] Both had no blinding of either participants or outcome assessments and were marred by high dropout rates and per protocol analyses; as such, the reported improvement in healing at 12 weeks and 6 months should be treated with caution. The results of a study of 54 participants investigating the use of adipose stem cells[204] were described in a study which was patient but not assessor blind to the treatment allocation. A per protocol analysis only was presented, but there was no significant difference in wound healing compared to a silicon dressing at 8 or 12 weeks. A non-blind 3 arm feasibility study of fat grafting[205] showed no difference between the 3 groups (fat grafting vs. fat grafting plus PRP vs. usual care) in terms of healing at 12 weeks, but with only 18 participants the numbers were small.

Four further studies in this category were identified; one investigating the use of cultured keratinocytes from donated neonatal foreskin in 59 participants,[207] and the second investigating the use of fibroblasts cultured from autologous skin biopsy on the wound healing assessed at 12 weeks in 65 participants.[206] Neither had blinding of participants or outcome measures and were at high risk of bias. The third study[209] described the use of autologous bone marrow stem cells injected intramuscularly and peri-wound in 40 participants with critical limb ischaemia and with no apparent options for revascularisation. Although outcome blind there was a high loss to follow-up with a per-protocol analysis only presented. A three way study in 28 participants[210] of allogeneic bone marrow mesenchymal stromal cells (allohBM MSC) investigated allogeneic bone marrow mesenchymal stromal cell derivatives (cultured allohBM MSCs) versus controls. Hazard ratios for healing at 7 weeks were presented, but the actual numbers of ulcers healed were not given. This study also had no blinding of participants or outcome assessments , and with usual care also poorly described, any reported improvement in healing should be treated with caution.

Outcome: Time to healing

Five of the above studies also reported time to healing.[201,203,204,206,207] As above with the exception of one[201], all were at risk of bias. The study investigating abdominal lipoaspirates in 52 patients[201] was an outcome blind study and reported a significant 10-day reduction in mean time to healing, in those that healed, within 8 weeks.

Outcome: Sustained healing

Only one study,[207] in a study of autologous keratinocytes reported sustained healing with only one participant in each arm of the study reported to have re-ulcerated within 6 months of randomisation.

Outcome: Reduction in ulcer area

Five studies were identified which reported a reduction in wound area.[205–209] Two of these studies investigated the use of keratinocytes: allogenic keratinocytes[208] and cultured keratinocytes from donated neonatal foreskin.[207] Both studies were assessed as being at risk of bias, neither were outcome blind, and the reported improvements in wound area reduction, in 12 weeks[207] and 30 days[208] should therefore be treated with caution.

One study of cultured fibroblasts[206] also reported an apparent significant reduction in wound area at 12 weeks when compared with a foam dressing, but, as above, the study was at risk of bias, had no blinding of participants or outcome assessments, and this result should be treated with caution.

The 3-way feasibility trial[205] of fat grafting, although showing a reduction in both wound volume and wound area reduction in each group, did not report between group analyses.

There was a significant difference in absolute reduction in wound area in a study of autologous bone marrow-derived stem cells compared with usual care.[209] Although outcome blind there was a high dropout rate and the per protocol analysis means that this result should be treated with caution.

Outcome: Amputation

One study[209] reported no difference in major amputations at 12 weeks in a study of autologous bone marrow-derived stem cells in patients with critical limb ischaemia.

Outcome: Quality of life

Quality of Life (using the Diabetic Foot Ulcer Scale (DFS) score) was reported in a three arm feasibility study of fat grafting.[205] Although differences were reported between groups, it is unclear whether these were significantly different, and the trial was at high risk of bias having no blinding of participants or outcome measures. The main finding was a significant improvement in HRQoL between those who healed and those who did not. The pre-planned HRQoL assessment of a study of autologous lipoaspirates[203] was published in a separate report.[211] Using the SF36, they assessed HRQoL in the domains of physical component and mental component summaries. Per protocol analysis only was performed of this study with no blinding of participants or outcome measures and overall the study was assessed as being at high risk of bias. Thus, the reported between group improvement of the scores should be treated with caution. The study of autologous bone marrow derived stem cells in participants with critical limb ischaemia[209] reported quality of life by EQ5D scores, reporting improvement in QoL in the intervention but not the control arm. The study was not patient blinded, however, and there were no between group analyses presented.

Outcome: Resource utilisation

Only the non-blind feasibility study of fat grafting[205] reported resource utilisation, and reported a non-significant lower cost of "dressings" in the intervention groups compared with the control arm.

Outcome: Mortality

We found only one study which reported mortality in a study of autologous adipocytes.[203] Even though a per protocol analysis was

presented, there was no difference in the 6-month mortality between the 2 groups.

There were no studies reporting on the outcomes of new infection or maintenance of function.

Evidence statement for "other cells": *The evidence to support improved wound healing, wound area reduction or time to healing for the use of cultured keratinocytes, fibroblasts, adipocytes, either as fat grafting or following lipo-aspirates is currently of low certainty, with most studies being at acceptable or high risk of bias.*

3.6.4 | Growth factors

We identified 17 studies of growth factors fulfilling our inclusion criteria. Growth factors included were Platelet derived growth factor (PDGF),[212–218] Granulocyte colony-stimulating factor (GCSF),[219–221] Epidermal Growth Factor (EGF)[222–224] basic Fibroblast growth factor (bFGF),[225,226] and Vascular endothelial growth factor (VEGF).[227] One study[228] studied multiple growth factors (EGF and bFGF).

Platelet derived growth factor (PDGF)

Outcome: Complete wound healing. We identified 6 studies investigating the use of PDGF which reported absolute wound healing at variable time points between 12 and 24 weeks. The first was a patient and outcome blind placebo controlled trial involving over 300 participants in a multicentre study in the USA.[217] Partly a dose ranging study the highest dose of PGDF showed a significant improvement in absolute wound healing at 20 weeks compared with placebo. Usual care including offloading was not well described, however, and the study was thought to be at acceptable risk of bias overall. An outcome blind study published shortly after,[213] with the same higher dose of PGDF and which included 252 participants showed no difference in healing at 20 weeks compared to a placebo, although this study was thought to be at high risk of bias, and limited details of the methodology were available for review as the study was published only as part of another review.

Four other studies were much smaller and in total included fewer participants (n = 130) than the previous two. Two of these later studies were placebo controlled and both patients and outcome measures were performed blind.[214,215] One[215] group, which included 46 participants, was judged at low risk of bias, and showed no difference between the intervention and control arm in terms of healing at 16 weeks. The other, which included 32 participants (38 ulcers)[214] reported a per protocol analysis only and was judged at high risk of bias. The reported improvement in healing at 24 weeks in the intervention arm should therefore be treated with caution.

Outcome: Time to healing. Time to healing was reported in 2 studies. The first and largest (n = 382)[217] reported a significant improvement in time to healing between the highest doses of PDGF and control arm, although as mentioned above, the study was at moderate risk of bias. A low risk of bias study of 46 participants[215] found no difference in time to healing in their 24 week study.

Outcome: Reduction in ulcer area. Two studies reported this outcome, but both had no blinding of participants or outcome measures and were at high risk of bias. The first[212] study reported no difference in absolute wound area reduction at 20 weeks in 32 participants. The second, a larger study of 270 participants[216] reported a difference in percentage area reduction at 12 weeks in a 3-way randomised trial comparing PDGF with powdered amniotic membrane versus saline dressings. There was no blinding of participants or outcome measures, a per protocol analysis was reported, however, and usual care was not well described. It is also not clear whether comparisons were made between the amniotic membrane group and controls or between PDGF and controls.

Outcome: New infection. The largest of the studies[217] reported new infection only as adverse event reporting and found no difference between the 3 groups. No other study reported this outcome.

There were no studies reporting on the outcomes of sustained healing, amputation, resource utilisation, maintenance of function or mortality.

Evidence statement: *The evidence to support the use of PGDF is of low certainty with the majority of studies being assessed as being at high risk of bias. The studies at the lowest risk of bias showed no difference in terms of wound healing.*

Granulocyte colony-stimulating factor (G-CSF)

Outcome: Complete wound healing. Of the three studies fulfilling our inclusion criteria, two[219,220] reported wound healing at 7 and 21 days, respectively. Both studies were considered at low risk of bias, but neither reported a significant difference in wound healing. Both studies, however, were aimed primarily at the treatment of infection and thus were of short duration.

Outcome: Reduction in ulcer area. The third study[221], which did not report absolute healing, reported a reduction in ulcer volume at 10 days in an outcome blind study of G-CSF compared to a placebo. Primarily designed as an infection study, the trial was at acceptable risk of bias but reported no difference between the 2 groups.

Outcome: Amputation. Neither of the 2 studies which reported this outcome[219,220] reported a significant difference in amputation at 7 and 21 days respectively.

There were no studies reporting on the outcomes of time to healing, sustained healing, quality of life, new infection, resource utilisation, maintenance of function, or mortality.

Evidence statement: *The evidence to support GCSF as an agent to improve healing of diabetic foot ulcers is poor; however, the studies identified were mainly aimed at the treatment of infection and thus the short timescales of the studies may have precluded identification of any improved healing.*

Other growth factors: EGF/bFGF/VEGF and multiple GFs

Outcome: complete wound healing. We identified three studies fulfilling our inclusion criteria investigating the use of recombinant

human epidermal growth factor (rhEGF)[222–224] which reported wound healing of DFUs at 8[222] and 12[223,224] weeks.

The first,[224] was a dose ranging, participant and outcome blind study in 61 participants, which was judged at moderate risk of bias and reported healing at 12 weeks. In a post hoc analysis, a significant improvement in healing (level of significance not given) was reported when the highest dose was compared with low dose and control.

Subsequently, a small participant and outcome blind RCT[222] investigated EGF injected peri-wound in 31 participants. Wound healing was assessed at 8 weeks an apparent improvement in healing in the intervention arm was reported. However, baseline characteristics were not well reported and no participants in the control arm healed. The study was judged to be at acceptable risk of bias, and these results should be interpreted with caution.

However, the third study[223] investigated topical EGFR spray and reported healing outcomes at 12 weeks in 167 participants. This study was judged to be at a low risk of bias with blinding of participants and investigators and reported a significant improvement in healing at 12 weeks compared to a placebo.

Two studies investigating bFGF[225,226] also reported healing in RCTs which were participant- and outcome blind. The first was a pilot study and included only 17 patients, the second was marred by a per protocol analysis only, and as such, positive results reported should be treated with caution.

One study investigated the use of VEGF in a phase 1 pilot study[227] and reported no difference in wound healing at 12 weeks. As far as we are aware, this study has not been reported on a larger sample size.

Outcome: Time to healing. We identified 3 studies which reported times to healing as an outcome in RCTs.[223,224,228] The first investigating EGF,[224] was considered at high risk of bias, and reported improvement in time to healing with the highest EGF dose group although actual healing times were not given. The other study with topical EGF judged at low risk of bias[223], however, reported a reduction in estimated median time to healing of 14 days. The final study, with a combination of growth factors (EGF, AFGF) was judged to be at a high risk of bias but showed no difference in time to healing between the 4 groups.[228]

Outcome: Reduction in ulcer area. We identified 5 RCTs which reported changes in the ulcer area.[222,223,225–227] Of the 2 studies on the use of EGF,[222,223] only one[223] was considered at low risk of bias and reported a significant difference in percentage wound area reduction/week between the intervention and control arms.

The 2 studies of bFGF[225,226] were both considered to be at acceptable[226] or high risk[225] of bias, and so no conclusions can be drawn from any apparent reduction in ulcer area reported.

A single study of VEGF[227] showed no difference in wound area reduction over the 12 weeks of the study between the intervention and control arms. However, this was a small phase 1 study with only 55 participants included.

There were no studies reporting on the outcomes of sustained healing, amputation, quality of life, new infection, resource utilisation, or mortality.

Evidence statement: *With the exception of one large RCT[223] of EGF which was assessed as low risk of bias, the quality of the data to support the use of other GFs is of low certainty. This single RCT at low risk of bias investigating EGF suggests that EGF may be associated with improved absolute healing, and time to healing; however, we found no evidence of this intervention for the outcomes of reduction of amputation, quality of life, or resource use.*

Placental derived products

We identified 10 studies of placental-derived products,[163,216,229–236] which between them included a total of 886 participants.

Of these, one described the use of dehydrated amnion/chorion graft,[234] six the use of dehydrated human amniotic membrane (dHAM),[163,229,231,232,235,236] with one the use of cryopreserved placental membrane,[230] one the use of dehydrated human umbilical cord,[233] and one powdered dehydrated amniotic membrane.[216]

Outcome: complete wound healing. Nine studies described absolute wound healing at times points between 4 and 20 weeks. The most studied placental derived product, a human dehydrated amniotic membrane was investigated in 7 studies,[163,216,229,231,232,235,236] only two of which were assessed to be at low risk of bias.[232,236] None, apart from one small pilot study,[236] was patient and outcome blind. The first of these was an RCT with no blinding of either participants or outcome measures comparing dHAM with moist wound care (including silver based products at the treating clinicians discretion)[229], which reported superiority in wound healing in the intervention arm at 4 and 6 weeks. The total number of participants included was just 25 and the number of patients healed in the control arm was remarkably low (none healed at 4 weeks and 1 at 6 weeks). Subsequently, the same group published a further outcome blind RCT[163] of the same product, but in a 3 way RCT of 60 participants, judged at moderate risk of bias with patients randomised to either a skin substitute, dHAM or usual care. Outcomes were assessed at 4 and 6 weeks, and although there was a blinded adjudication assessment of images the initial assessment of healing was done by non-blinded clinicians at site. Although the dHAM was reported to significantly increase the number of participants healed compared to the other 2 arms, the poor performance of the control arm, particularly the active control of the skin substitute group, and methodological concerns reduced our certainty in this result.

The third study[232] using the same dehydrated human amnion and chorion allograft as the earlier studies[163,229] versus usual good care showed significant improvements in healing at 12 weeks in an outcome blind study. This study was considered at low risk of bias and included 126 participants. At 12 weeks an Odds Ratio of healing of 1.4 was reported when compared to standard of care.

The final two studies of dHAM[231,235] were judged at high risk of bias, both were non-blind and any positive results should be treated with caution.

One study,[230] investigated the use of a cryopreserved amniotic membrane product in an apparent outcome but not patient blind RCT of 97 participants. As with the studies described above although blinded adjudication of the primary outcome of healing was described, healing was assessed initially by the treating clinicians. Nevertheless, a significant improvement in the number of patients healed was seen at 12 weeks. The study did not finish recruitment as a pre-planned interim analysis, which apparently showed efficacy and the study was stopped with approximately half of the pre-planned sample size randomised. This reduces our certainty in the reported odds ratio (OR) of healing of 6.02 at 12 weeks.

The only patient and outcome blind study with a dHAM[236] was a small ($n = 31$) pilot study and hence, the numbers were too small to draw any conclusions.

We found one other outcome blind study of at low risk of bias[233] investigating the use of weekly application of a human dehydrated umbilical cord product versus usual care, again reporting an apparent improvement in healing at 12 and 16 weeks compared with standard of care.

Outcome: Time to healing. All the studies which reported absolute healing above also reported time to healing. Of those identified as being at low risk of bias, all reported a significant improvement in the median or mean time to healing (in days), although the actual times to healing were not given in the 2 largest studies at lowest risk of bias[232,233] and so comparison with other interventions is difficult.

Outcome: Sustained healing. We identified 2 studies which reported this outcome. One[235] reported fewer recurrences at 90 days in a very small study considered at high risk of bias, and the very high recurrence rate in the control arm (>80%) should be noted.

The other,[233] reported sustained healing rates that were higher in the intervention group treated with dehydrated umbilical cord product compared with usual care, but no comparative statistics were reported.

Outcome: Reduction in ulcer area. Five of the studies[216,229,230,234,236] reported percentage area reduction at various time points. The three studies of dHAM[216,234,236] all reported a significant difference in percentage wound area reduction between the intervention and control arms. However, only one of these was at low risk of bias but was too small (as a pilot trial) to draw any conclusions.[236] The study with a cryopreserved amniotic membrane product[230], which was considered at uncertain risk of bias, reported a significant difference in those ulcers achieving a 50% area reduction at 4 weeks (of a 12 weeks study). One 3-way study of an application of dried powdered amniotic membrane versus platelet derived growth factor versus usual care[216] only reported wound area reduction. However, the study was at high risk of bias, with no blinding of participants or outcome assessments and usual care was not well described. As such, any positive outcomes should be treated with caution.

Outcome: New infection. Only one study of dHAM reported new infection at 12 weeks post randomisation.[232] Although no comparative analyses were reported, the number of new target ulcer infections was numerically similar in both groups.

Outcome: Resource utilisation. Two papers reported the cost of the intervention per healed ulcer.[232,233] In neither case was there any assessment of the cost of the control interventions; however, the mean cost per healed ulcer was over $2000 for the dHAM, and over $3000 for the dehydrated umbilical cord product. In a post hoc analysis of the 3 way study of the bioengineered skin substitute, dHAM and usual care[163] described above a cost effectiveness analysis was subsequently published.[167] The analysis based on the cost of the material indicated that the mean cost per patient was over $8000 for the skin substitute and, similar to the only other paper we identified,[232] over $2000 for the dHAM.

There were no studies reporting on the outcomes of amputation, quality of life, or maintenance of function.

Evidence statement: *Although a number of the studies were considered at high risk of bias, and none of the largest studies were patient or care giver blind, those at low risk of bias suggest that the use of placental derived products particularly amniotic membrane are associated with improved absolute healing at times up to 20 weeks, and reduced time to healing. We found no evidence to suggest that there was an influence on new infections, and the short-term nature of the majority of studies and the lack of inclusion of patients with significant PAD means that we have no evidence of improvement in amputation rates. The resource use data suggest that the interventions may be less expensive for some providers compared to other skin substitutes.*

3.7 | Intervention 7: Pharmacological interventions

We identified 52 studies related to pharmacological interventions as a treatment for diabetic foot ulcers to support healing. Of these, we excluded 34 as not fulfilling the protocol criteria (see PRISMA diagram). We included 18 full studies which described randomised trials of pharmacological interventions and reported our outcomes of choice.

3.7.1 | Agents promoting angiogenesis

Outcome: Complete wound healing

We found 9 studies of these agents designed to promote perfusion and angiogenesis.[237–244] All were considered at acceptable or high risk of bias.

The studies comparing the use of resveratrol,[237] pentoxifylline,[244] low-dose erythropoietin (EPO),[238] subcutaneous injection dalteparin[239], insulin plus sulodexide to insulin plus placebo,[240] a

two herb Chinese medical formula[243] and intravenous native herbal extract, angipars,[241] contained too few patients to be certain of the results, and only the study of angipars performed an ITT analysis. As such, any apparent improvement in healing should be treated with caution.

A larger study[242] in 216 participants used a combination of intramuscular and perilesional injections of a DNA derivative, polydeoxyribonucleotide and reported an increase in the number of ulcers healed at 8 weeks. Although double blind and adequately powered, usual care including offloading was not well defined, and the study was considered at an unclear risk of bias. Another smaller study[245] using the same intervention included only 20 participants and hence was too small to show any difference between the 2 groups.

Outcome: Time to healing

Four of the above studies of agents designed to promote perfusion and angiogenesis[238,239,242,243] also reported on time to healing. All were considered at moderate or high risk of bias and any positive results on improvement in time to healing should be treated with caution.

Outcome: Reduction in ulcer area

Five of the above studies,[237–239,241,242] all of which were at moderate or high risk of bias, reported on the outcome of reduction in ulcer area.

Although all reported an improvement in ulcer area in those receiving the interventions over the course of the study in comparison with the control arms, these results, as with the other outcomes, should be treated with caution due to the high risk of bias of the studies.

Outcome: Amputation

We identified only one double blind study of subcutaneous dalteparin versus placebo injection graded at high risk of bias that documented amputation (major or minor) as an outcome.[239] Two patients were reported to have had an amputation in the intervention arm during follow-up compared with eight in the placebo group. No between group comparison was reported.

Outcome: Quality of life

We identified one study which documented quality of life as an outcome,[244] but was at high risk of bias. This study administered 400 mg pentoxifylline thrice daily versus placebo for 8 weeks. Those in the intervention arms showed statistically significant improvement in quality of life before and after treatment, whereas those on placebo did not, although no between group comparison was reported.

Outcome: Maintenance of function and ability to perform activities of daily living

We identified one unblinded study at high risk of bias which documented maintenance of function and ability to perform activities of daily living as an outcome.[244] The intervention was reported to improve the neuropathy disability score compared to placebo, although this result should be treated with caution given the risk of bias.

We identified no studies reporting on outcomes of sustained healing, resource utilisation, new infection, or mortality.

3.7.2 | Vitamins and trace elements

Outcome: Reduction in ulcer area

We identified four studies using supplementation of vitamins and trace elements that reported on the outcome of reduction in ulcer area[246–249] all at moderate or high risk of bias.

The interventions investigated were weekly doses of oral Vitamin D[246] for 12 weeks, platelet-rich plasma-fibrin glue (PRP-FG) dressing along with oral vitamins E and C,[249] a daily probiotic for 12 weeks,[247] and twice daily 1000 mg omega-3 fatty acids orally twice a day for 12 weeks.[248]

One study investigated the use of platelet-rich plasma-fibrin glue (PRP-FG) dressing along with oral vitamins E and C versus PRP-FG dressing plus placebo, with a reported improvement in healing at 8 weeks.[249] The study was at risk of bias however and with very few participants ($n = 25$) and so this result should be treated with caution. Moreover, although the latter 2 studies[247,248] were double blind, the outcome measure of absolute reductions in ulcer length and width, and the lack of detail of baseline ulcer characteristics and offloading means that the positive results in terms of reduction in ulcer area reported should also be treated with caution.

We found no studies reporting on outcomes of time to healing, sustained healing, amputation, quality of life, maintenance of function and ability to perform activities of daily living, new infection, resource utilisation and mortality.

3.7.3 | Red cell production and protein supplementation

Outcome: Complete wound healing

We found one study of 271 participants at moderate risk of bias investigating the use of protein supplementation.[250]

Participants in this study[250] were administered either arginine, glutamine and b-hydroxy-b-methylbutyrate or a placebo control drink for 16 weeks. There were no differences in healing or time to healing at week 16. Subgroup post hoc analysis suggested that those with low albumin or decreased limb perfusion in the supplementation group may have been more likely to benefit, but this result needs further investigation.

We found no studies reporting on outcomes of sustained healing, reduction in ulcer area, amputation, quality of life, maintenance of function and ability to perform activities of daily living, new infection, resource utilisation and mortality.

3.7.4 | Others including herbal treatments

We found four studies on other oral treatments including herbal remedies[251–254]

Outcome: Complete wound healing

We found two studies of other pharmacological interventions that reported complete wound healing.[251,252]

One study[251] administered 150 mg daily of systemic fluconazole to 75 participants with wounds with invasive fungal infection. They found no difference in the proportion of people achieving complete wound healing, but the study was at high risk of bias.

One study investigated[252] patients administered traditional Chinese herbal medicine orally. Eighty participants were initially randomized to blinded treatments, but were later allowed to be treated with the herbal preparation if not responding. The apparent differences in healing rates between the two groups should thus be treated with caution, especially as an ITT analysis was not performed.

A small phase 2 pilot study[254] investigated the use of a CXCR4 agonist designed to stimulate the release of bone marrow stem cells. This early study was stopped after 26 patients on the grounds of sufficient data to plan a future definitive study. Although at low risk of bias, the study was not powered to show a difference in healing.

Outcome: Time to healing

We identified one study reporting this outcome.[251] In this study,[251] 150 mg daily of systemic fluconazole was administered to those with wounds with invasive fungal infection together with standard of care versus standard of care alone. They found that the time to wound healing was significantly lower in those treated with fluconazole although this study was at high risk of bias and this result should be treated with caution.

Outcome: Reduction in ulcer area

We identified only one study reporting reduction in ulcer area. In this study, nanocurcumin supplements were administered to patients with Wagner 3 graded ulcers with deep abscess or osteomyelitis, and found no benefit over a placebo in reduction in ulcer area.[253]

Outcome: Amputation

Just one study[252] administered a traditional Chinese herbal oral medicine. Of the wounds that deteriorated, all of the limbs in the herbal treatment arm were preserved, compared to 50% in the placebo arm within the 24-week treatment period. No between group comparison was reported, however and this study is considered to be at high risk of bias.

We identified no studies reporting on outcomes of sustained healing, reduction in ulcer area, quality of life, maintenance of function and ability to perform activities of daily living, new infection resource utilisation and mortality.

Evidence statement: *The quality of data to support the use of any of these pharmacological interventions, including resveratrol, some plant extracts or Chinese herbal medicine, vitamins, or nutritional supplements for the improvement of healing of diabetic foot ulcers is too poor to draw any firm conclusions.*

3.8 | Intervention 8: Negative pressure wound therapy

We included 19 studies comparing negative-pressure wound therapy to standard of care,[46,166,255–271] which fitted our inclusion criteria, the majority of which were in post-surgical diabetes-related foot wounds. Two were in a mixed population comprising post-surgical and non-surgical wounds,[255,267] and only one in nonsurgical wounds alone.[261] All studies were either at acceptable or high risk of bias.

3.8.1 | Outcome: Complete wound healing

Ten studies reported on complete wound healing, six of which were at high risk of bias,[256,260–263,265] and a further four at acceptable risk of bias.[266–269]

Two studies in post-op wounds[266,268] reported complete healing. The first[268] compared NPWT to standard of care in non-ischaemic, partial foot amputation (up to the transmetatarsal level) wounds in 162 people with diabetes and reported a small but significant benefit in the proportion of wounds healed at 112 days. However, the dropout rate was high, the study had no blinding of patients, caregivers, or outcome measures and the definition of complete healing included wounds healed by secondary intention, as well as those unhealed but suitable for surgical wound closure. The lack of blinding of those making clinical decisions, including surgical closure, reduces our confidence in this result. The second[266] was a larger study with 342 participants comparing wound healing with NPWT to advanced moist wound healing therapy at 112 days. Although a greater proportion of foot ulcers achieved complete ulcer closure with NPWT, the study was similarly at acceptable risk of bias with patients and outcome measures being assessed non-blind and with a high (30%) dropout rate.

A further single centre study, again with no blinding of patients, caregivers, or outcome measures, included 150 participants[269] and compared NPWT delivered at 125 mmHg continuous pressure and NPWT with simultaneous 0.1% polyhexanide-betaine irrigation in people with diabetic foot infections needing incision and drainage. It reported no difference in complete wound healing between the two groups. The study lacked a true control group, however, comprising standard wound care, and the determination of wound closure by the treating physician may be interpreted as subjective.

The fourth study[267] compared NPWT with standard moist wound care in the treatment of both chronic and post-surgical diabetes-related foot wounds in 345 participants, and reported no difference in complete wound healing between the two groups. Although the study was outcome blind, it had a high (55%) dropout rate.

The remaining 6 studies were smaller, lacked baseline definitions of the wounds, were unblinded, or presented per protocol analysis only. All were considered at high risk of bias, and any positive results reported should be treated with caution.[256,260–263,265]

3.8.2 | Outcome: Time to healing

Eight studies of NPWT reported on time to healing, five of which were at high risk of bias[256,259,260,262,263] and a further three at unclear risk of bias.[266,268,269]

The two studies in post-operative wounds described above.[266,268] Which reported complete wound additionally reported on time to healing. The use of NPWT was associated with a faster time to healing in both studies when compared to standard of care.[266,268] However, both studies had no blinding of participants, caregivers, or outcome measures and were at an unclear risk of bias. In the study comparing NPWT with and without irrigation of 0.1% polyhexadine-betadine solution,[269] similar time to healing was described in both groups.

The other 5 studies which reported time to healing[256,259,260,262,263] were all at high risk of bias, and any positive results should be treated with caution.

3.8.3 | Outcome: Sustained healing

Two studies reported on sustained healing with the use of NPWT.[258,267] One[267] compared NPWT with standard moist wound care in a mixed population of chronic and post-surgical diabetes-related foot wounds. The recurrence of DFU after complete, sustained and confirmed closure within 6 months and after 6 months was similar in both groups. The other study investigating the use of NPWT with installation of an ozone solution versus NPWT alone[258] showed no difference in recurrence of ulceration at 1 year. The study was non-blind, however, and at high risk of bias.

3.8.4 | Outcome: Reduction in ulcer area

Nine studies on NPWT reported on the outcome of reduction in ulcer area.[255,257,258,260–264,271] Of the two largest reports on complete healing in post-operative wounds, only one[266] reported on wound area reduction, reporting a greater reduction in ulcer area on day 28 favouring the NPWT group. The study had no blinding of patients, caregivers, or outcome measures and had a high (30%) dropout rate. Two studies looking at instillation with NPWT versus NPWT alone also reported on wound are area reduction, the first with instillation of 0.1% polyhexanide-betaine irrigation[269] and the other with an ozone solution. Neither reported any differences in this outcome between the 2 groups at 16 weeks [269] or 4 weeks.[258] However, both studies were unblinded and at high risk of bias. The remaining studies were either small, non-blinded or marred by per protocol analysis only. All were at high risk of bias and any positive results reported should be treated with caution.

3.8.5 | Outcome: Amputation

Nine studies reported on major or minor amputation. Five were at high risk of bias[255,257,258,260,265] and four were at acceptable risk of bias.[266–269]

Of the four at acceptable risk of bias,[266–269] three reported no difference in amputation rate between NPWT and standard of care arms.[267–269] Only one[266] reported significantly fewer amputations in the NPWT arm; however, as previously described, due to a high drop-out rate and risk of bias, positive results should be interpreted with caution.

3.8.6 | Outcome: Quality of life

Two studies reported on quality of life,[259,267] one at high risk of bias and not described further.[259] The other[267] compared NPWT with standard moist wound care and noted low QoL in all patients at baseline with increased QoL in both groups reaching end of therapy and at 6 months follow up but with no difference between the two groups.

3.8.7 | Outcome: Maintenance of function and ability to perform activities of daily living

Only one study, which was at high risk of bias, reported on this outcome.[255] The use of NPWT significantly reduced the post-treatment disability period in patients. However, this was a small nonblind study at high risk of bias and thus this positive finding should be interpreted with caution.

3.8.8 | Outcome: New infection

Five studies reported new infections; two were at high risk of bias[255,256] and three at acceptable risk of bias.[266,268,269] The latter three reported no difference in new infection between the NPWT and standard of care arms.

3.8.9 | Outcome: Resource utilisation

Three studies reported resource utilisation as an outcome.[270,272,273]

The first study,[270] undertaken in India, compared the number of dressings required with both NPWT and conventional treatment to the end-point of success, defined as when the wound had healthy granulation tissue and was ready for skin grafting. Although the cost of NPWT was half that of conventional care, it was unclear as to how

these calculations were obtained and the investigators reported that they failed to take into account daily treatment, hospitalisation and morbidity. Thus, any positive results should be cautiously interpreted.

The second study[272] was a post hoc analysis of an earlier trial.[268] Lower resource utilisation was reported in the NPWT arm compared to standard of care; the original study was at acceptable risk of bias. The final study[273] was another post-hoc analysis of an earlier study,[266] and reported greater cost effectiveness with NPWT; however, it was at high risk of bias.

3.8.10 | Outcome: Mortality

One study reported on mortality, with no difference reported between the NPWT and control arms.[266]

Evidence Statement: *The evidence suggests an apparent benefit of NPWT in achieving complete wound closure and faster time to healing versus standard of care in post-operative diabetic foot wounds but not in non-surgical wounds. Two studies noted no difference in complete wound healing and healing time between traditional NPWT and NPWT with irrigation. The evidence suggests no difference in sustained healing, rate of amputation, or rates of infection between NPWT and standard wound care. Data from post hoc secondary analyses suggest greater cost effectiveness and lower resource utilisation with NPWT when compared to moist wound therapy, but this is of low certainty. For chronic (non-surgical) ulcers, there is insufficient evidence to establish whether NPWT reduces time to healing when provided in addition to standard of care.*

3.9 | Intervention 9: Educational interventions

We found one RCT of educational and lifestyle support programmes that met our predefined inclusion criteria[274], which was of high risk of bias.

3.9.1 | Outcome: Reduction in ulcer area

This study[274] undertook a 3-month self- and family management support programme (intensive health education, skill training, and motivational interviewing vs. usual care (diabetes health education). It reported a significant reduction in wound size in the intervention group versus the control group; however, the intervention and standard of care were poorly defined.

Evidence statement: *The evidence from one study at high risk of bias does not support the use of this educational intervention to improve wound healing of diabetes-related foot ulcers in addition to usual best care.*

3.9.2 | Other interventions

There were no studies on psychological intervention or metabolic interventions which met the pre-specified inclusion criteria.

4 | DISCUSSION

Diabetes-related foot ulceration remains a costly challenge to manage. This systematic review is the supporting evidence behind our 2023 recommendations on interventions designed to support wound healing of foot ulcers in diabetes.[275] However, unlike in previous years where a 4-yearly search update was performed, this systematic review was a complete re-evaluation of the literature in response to new clinical questions formulated after consultation with experts and people with lived experience of diabetes-related foot ulceration. As a result, nine overarching categories of interventions were described, which represents a slight regrouping since the previous systematic review,[4] and data were extracted on 10 different clinical outcomes deemed critical to decision making. Furthermore, we evaluated only randomized controlled trials to ensure that the resulting guidelines[275] included studies of the highest levels of evidence.

We systematically reviewed the full text papers of 532 studies, and included 262 in this review. One of the strengths of this systematic review is that we included papers from any country and any language where the study otherwise fulfilled our inclusion criteria. We are aware that specific literature searches may miss papers; however, our validation check[276] found all of the papers identified. We also checked other systematic reviews, but we did not search the grey literature. As the purpose of this systematic review was to inform international guidelines, we feel it unlikely that any definitive RCT at low risk of bias that would have altered the decision making process in the summary of judgements of the guidelines has been missed. We did not exclude any study specifically on the basis of being written in a language other than English, but some were unavailable to us or we were unable to get it translated within the timeframe for the review. It is unlikely that any of these would have made a material difference to our conclusions from the information available to us in the abstracts. However, this is a limitation of our work, which would affect non-English speaking scientific communities, and interventions arising from those communities more than others.

Another strength of our approach was that all the authors are health care professionals working in the field of the diabetes-related foot disease, and as such are aware of expected standards of care and the generalisability of any results reported in the studies.

Despite introduction of new reporting standards and markers of quality for trials in the management of diabetes-related foot ulcers in 2016[5], only a handful of studies were assessed as being at low risk of bias. Equally, although a much larger number of new RCTs have been published in the last 4 years, the majority were still independently assessed to be at either unclear or high risk of bias with key trial design problems such as nonblinding, analysis per-protocol only, lack of description of the randomisation method (and hence uncertainty about selection bias), lack of description of key baseline characteristics, or any description of the usual care in the study protocol. Where usual care was described it frequently fell short of the standards suggested by the IWGDF practical guidelines,[277] which makes it unclear as to the magnitude of any additional benefit of an intervention (and hence its cost effectiveness) that might have been

obtained if the best standard of usual care had also been applied. We reiterate that future trials designed or published on wound healing in diabetes-related foot ulcers should aspire to most or all of the required standards by Jeffcoate et al[5] to maximise the impact of trial results on future clinical care.

There was also significant heterogeneity amongst the studies evaluated, which limited our ability to perform meaningful meta-analyses. In many circumstances direct comparison amongst trials were difficult where conflicting results were reported due to differences in participant characteristics, outcomes (and definitions of outcomes) as well as timeframe for evaluation of studies. An overwhelming majority of the trials included only reported complete wound healing, time to healing, or reduction in ulcer area. Data on new infection, amputation, quality of life, resource utilisation and mortality, which were identified as critical to decision making through our consultation process, were often omitted or studies were under-powered to detect these outcomes. Although several cost-effectiveness studies were reported, these were based on post-hoc modelling and in-trial data was lacking. Reporting on these outcomes is critical to the evidence-to-decision making process for guideline development according to GRADE[7] and we strongly encourage future trials to ensure these are reported.

We are aware of many other systematic reviews of many of the interventions we have assessed in this review. Many have associated meta-analyses despite the clinical heterogeneity of patients included, poor outcome definition, lack of standardised follow-up and many of the included studies being at risk of bias. None use the same suite of outcomes critical to decision making agreed by our working group members, and on which we subsequently based the evidence to decision making required for the associated guidelines. We do not feel therefore that we required any formal direct comparison between our own systematic review and those of others, as the aims and methodology of the work were different.

Finally, the majority of trials were limited to participants with foot ulcers of lower severity (e.g. Wagner 1 or 2) and the presence of underlying osteomyelitis, or other significant comorbidities were a key exclusion criteria for study recruitment. It is thus uncertain if evidence from this review can be generalised beyond the characteristics of in-trial populations and if there are benefits in adjunctive treatment options for patients with significant frailty or comorbidity beyond the best standard of care as described in the IWGDF practical guidelines.[278]

AUTHOR CONTRIBUTIONS

The working group was chaired by FG (on behalf of the IWGDF). PC acted as the scientific secretary. All members of the guideline were involved in summarising available evidence and writing this systematic review. All members were assigned to individual sections of the review, and all authors reviewed and discussed the evidence obtained during group meetings. All authors reviewed and agreed with the final document before external review and subsequent submission for endorsement. All members of the working group undertook Level 1 GRADE training and both FG and PC additionally undertook Level 2 Guideline Methodology training (McMaster University).

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CONFLICT OF INTEREST STATEMENT

The IWGDF is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of systematic review and guideline development. In order to prevent a major conflict of interest (COI), the authors of the systematic review were not allowed to serve as an officer, board member, trustee, owner or employee of a company directly or indirectly involved in the topic of this review. At each

working group meeting, members were asked to report on any new conflicts of interest in writing, and any conflicts were declared on a written COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownership of stocks/options or bonds of a company, any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents etc. These incomes could either be personal or obtained by an institution with which the member had a relationship. Working group members were additionally requested to declare COI and refrain from the risk of bias scoring process or voting process for particular interventions if they had a professional working relationship with any of the co-authors on a particular paper. Full conflict of interest statements of all authors can be found online at www.iwgdfguidelines.org.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

Not applicable.

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PEER REVIEW

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SUPPORTING INFORMATION

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

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