Guidelines on interventions to enhance healing of foot ulcers in people with diabetes

IWGDF 2023 update

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

Principles of wound management, including debridement, wound bed preparation and newer technologies involving alternation of wound physiology to facilitate healing, are of utmost importance when attempting to heal a chronic diabetes-related foot ulcer. However, the rising incidence and costs of diabetes-related foot ulcer management necessitates that interventions to enhance wound healing of chronic diabetes-related foot ulcers are supported by high quality evidence of efficacy and cost effectiveness, when used in conjunction with established aspects of gold-standard multidisciplinary care. This is the 2023 International Working Group on the Diabetic Foot (IWGDF) evidence-based guideline on wound healing interventions to promote healing of foot ulcers in persons with diabetes. It serves as an update of the 2019 IWGDF guideline.

We followed the GRADE approach by devising clinical questions and important outcomes in the PICO (Patient-Intervention-Control-Outcome) format, undertaking a systematic review, developing summary of judgements tables and writing recommendations and rationale for each question. Each recommendation is based on the evidence found in the systematic review and, using the GRADE summary of judgement items including desirable and undesirable effects, certainty of evidence, patient values, resources required, cost effectiveness, equity, feasibility and acceptability, we formulated recommendations which were agreed by the authors and reviewed by independent experts and stakeholders.

From the results of the systematic review and evidence-to-decision making process we were able to make 29 separate recommendations. We made a number of conditional supportive recommendations for the use of interventions to improve healing of foot ulcers in people with diabetes. These include the use of sucrose octasulfate dressings, the use of negative pressure wound therapies for post-operative wounds, the use of placental derived products, the use of the autologous leucocyte/platelet/fibrin patch, the use of topical oxygen therapy, and the use of hyperbaric oxygen, although in all cases it was stressed that these should be used where best standard of care was not able to heal the wound alone and where resources were available for the interventions.

These wound healing recommendations should support improved outcomes for people with diabetes and ulcers of the foot, and we hope that widescale implementation will follow. However, although the certainty of much of the evidence on which to base the recommendations is improving, it remains poor overall and we encourage, not more, but better quality trials including those with a health economic analysis, into this area.

LIST OF RECOMMENDATIONS

All recommendations should be considered to be adjunctive to best standard of care when best standard of care alone has failed to heal the ulcers. This should include sharp debridement and basic wound dressings, which according to the IWGDF Practical Guidelines, should be dressings to absorb exudate and maintain a moist wound healing environment (1).

1. Do not use autolytic, biosurgical, hydrosurgical, chemical or laser debridement over standard of care. (GRADE Strength of recommendation: Strong; Certainty of evidence: Low)
2. Do not routinely use enzymatic debridement as opposed to standard of care (i.e. sharp debridement) to improve wound healing outcomes in people with diabetes and a foot ulcer. (Strong; Low)

2a. In specific situations where the availability of sharp debridement may be limited by access to resources and/ or availability of skilled personnel, consider using enzymatic debridement. (Conditional; Low)

3. Do not use any form of ultrasonic debridement over standard of care (i.e. sharp debridement). (Strong; Low)
4. Do not use surgical debridement in those for whom sharp debridement can be performed outside a sterile environment. (Strong; Low)
5. We recommend the frequency of sharp debridement should be determined by the clinician based on clinical need. (Strong; Low)
6. Do not use topical antiseptic or antimicrobial dressings for wound healing of diabetes-related foot ulcers. (Strong; Moderate)
7. Do not use honey (or bee related products) for the purpose of wound healing in diabetes-related foot ulcers. (Strong; Low)
8. Do not use collagen or alginate dressings for the purpose of wound healing of diabetes-related foot ulcers. (Strong; Low)
9. Consider the use of the sucrose-octasulfate impregnated dressing as an adjunctive treatment, in addition to the best standard of care, in non-infected, neuro-ischaemic diabetes-related foot ulcers which have had insufficient change in ulcer area with best standard of care including appropriate offloading for at least 2 weeks. (Conditional; Moderate)
10. Do not use topical phenytoin for the purpose of wound healing in diabetes-related foot ulcers. (Strong; Low)
11. Do not use any dressing based or topical applications impregnated with herbal remedies for the sole purpose of wound healing in diabetes-related foot ulcers. (Strong; Low)
12. Consider the use of hyperbaric oxygen as an adjunct therapy in neuro-ischemic or ischemic diabetes-related foot ulcers where standard of care alone has failed and where resources already exist to support this intervention. (Conditional; Low)
13. Consider the use of topical oxygen as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention. (Conditional; Low)

14. Do not use other gases (e.g. cold atmospheric plasma, ozone, nitric oxide, CO2) in comparison to standard of care for wound healing in people with diabetes-related foot ulcers. (Strong; Low)
15. Do not use any interventions reported in the field of physical therapies for wound healing in the management of diabetes-related foot ulcers. (Strong; Low)
16. We suggest not using cellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)
17. We suggest not using acellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)
18. Do not use autologous skin graft skin substitute products as an adjunct therapy for wound healing in patients with diabetes-related foot ulcers. (Strong; Low)
19. With the exception of the autologous leucocyte, platelet and fibrin patch we suggest not using autologous platelets therapy (including blood bank derived platelets) as an adjunct therapy to standard of care. (Conditional; Low)
20. Consider the use of autologous leucocyte, platelet and fibrin patch for diabetes-related foot ulcers as an adjunctive therapy to standard of care, where best standard of care alone has been ineffective, and where the resources and expertise exist for the regular venepuncture required. (Conditional; Moderate)
21. We suggest not using other cell therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)
22. We suggest not using growth factor therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)
23. Consider the use of placental derived products as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed. (Conditional; Low)
24. Do not use pharmacological agents promoting perfusion and angiogenesis to improve wound healing outcomes over standard of care. (Strong; Low)
25. Do not use pharmacological agents that supplement vitamins and trace elements to improve wound healing outcomes over standard of care. (Strong; Low)
26. Do not use pharmacological agents that stimulate red cell production or protein supplementation to improve wound healing outcomes over standard of care. (Strong; Low)
27. Do not use other pharmacological agents to improve wound healing outcomes over standard of care. (Strong; Low)
28. Consider the use of Negative Pressure Wound Therapy as an adjunct therapy to standard of care for the healing of postsurgical diabetes-related foot wounds. (Conditional; Low)

28a. Do not use Negative Pressure Wound Therapy as an adjunct therapy to standard of care for the healing of non-surgically related diabetes foot ulcers. (Strong; Low)

29. We do not recommend any specific educational and lifestyle support programmes over standard of care to improve healing of diabetes-related foot ulcers. (Strong; Low)

INTRODUCTION

Diabetes-related foot ulcer management remains challenging and costly, posing high financial burdens on healthcare economies and having impacts on morbidity, mortality and quality of life. Principles of wound management, including debridement, wound bed preparation and newer technologies involving alternation of wound physiology to facilitate healing, are thus of utmost importance when attempting to heal a chronic diabetes-related foot ulcer. However, the rising incidence and costs of diabetes-related foot ulcer management necessitates that interventions promoted to enhance wound healing of chronic diabetes-related foot ulcers are adequately supported by high quality evidence promoting efficacy and cost-effectiveness, when used in conjunction with established aspects of gold-standard multidisciplinary care (2-4).

Since 2008, the International Working Group of the Diabetic Foot (IWGDF) have commissioned evidence-based guidelines, updated every four years, with a chapter focusing on interventions to enhance wound healing. Up until 2019, each systematic review and guideline represented an update of previous search results. However, updated standards (5) for assessment of diabetes-related foot ulcer healing therapies have resulted in better quality studies in recent years. To enable consistent benchmarking across newer and older studies alike, the aim of developing this edition of the guidelines and systematic review was thus to undertake a complete search and re-evaluation of the literature, describing trials of interventions intended to improve wound healing of foot ulcers in people with diabetes (6, 7).

WHAT'S NEW

We have made several changes to the recommendations included in this updated 2023 wound healing interventions guideline compared to the previous 2019 wound healing interventions guideline. The main changes are as follows:

- Instead of a 4-yearly update we performed a new systematic review of wound healing interventions and re-evaluated previous interventions in line with newest benchmarking and risk of bias assessments according to GRADE methodology (7)
- We only evaluated RCTs to ensure only evidence at the highest level was included
- We increased the number of outcomes critical to decision making in wound healing, including sustained healing, resource utilisation, quality of life, maintenance of function and ability to perform activities of daily living, new infection and mortality
- We added new clinical questions on behavioural, educational and pharmacological interventions
- We changed categorisation of dressings, autologous products and skin substitutes
- We have 29 new recommendations with six interventions receiving conditional positive recommendations

METHODS

In this guideline we have followed the key steps of the GRADE evidence-to-decision framework, including: i) establishing a diverse expert panel to develop the guideline, ii) defining key clinical questions and important outcomes in the PICO-format (Patient-Intervention-Comparison-Outcome), iii) performing systematic reviews and rigorous appraisals of all available evidence that address the questions, iv) assessing key summary of judgements items for each question, v) developing recommendations and their rationale based on these summary of judgements, and vi) consulting external stakeholders on each step (8, 9). The methodology for this guideline is summarised below; we refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document (10).

First, a multidisciplinary working group of independent international experts in wound healing for diabetes-related foot ulcers (the authors of this guideline) was invited by the IWGDF Editorial Board to develop and author this guideline. International experts were defined as those having significant experience in practising or studying the healing of diabetes-related foot ulcers. The working group comprised members from, podiatric surgery, podiatry, and endocrinology disciplines from the USA, Caribbean, Europe, Asia and Australia.

Second, the working group devised important clinical questions and associated outcomes, building on the last version of the guideline, to be answered using the GRADE approach. The questions and outcomes were reviewed and prioritised with the help of fifteen external clinical experts and two persons with lived diabetes-related foot ulcer experience from various geographical regions, and the IWGDF Editorial Board. The aim was to ensure the questions and outcomes were of relevance to a wide range of healthcare professionals and people with the disease so as to provide the most useful clinical information on wound healing interventions to treat foot ulcers in people with diabetes. The working group classified the outcomes as critically important or important, aligning with international diabetes-related foot ulcer standards (5, 11) or the expert opinion of the working group if standards did not exist.

Interventions (topical and systemic therapeutic agents) included were those previously addressed in the previous guidelines (6) where it was known that trials had been performed to address our clinical questions. In addition the working group agreed interventions not previously looked at, including educational and behavioural interventions designed to aid wound healing were important additions. We did not include offloading interventions, or systemic interventions designed to treat infection or interventions that were designed to improve limb perfusion unless they were pharmacological in nature and reported wound healing, as these interventions were included in other working group guidelines (12-14).

Third, we systematically reviewed the literature and appraised all studies addressing the above agreed upon clinical questions. Unlike previous versions of the guidelines, in view of the huge increase in the volume of literature and the need to assess only the evidence of the highest quality in formulating guidelines, we included only randomised controlled trials (RCTs) in our systematic review. We

considered as a comparator best standard of care, defined as those described in the practical guidelines (1), that is, local debridement, offloading, revascularisation, treatment of infection where appropriate.

For each assessable outcome we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and any evidence of publication bias (where appropriate) (15). We then rated the quality of evidence as 'high', 'moderate' or 'low' according to GRADE methodology (8). Finally, we developed summary of findings tables, including evidence statements, for each assessable outcome for each question which we presented in full in the systematic review. The systematic review supporting this guideline is published separately (7)

Fourth, based on the systematic review, summary of findings tables and expert opinion, teams of two members of the working group developed summary of judgements tables for each question following GRADE (see Supporting Information S1). The summary of judgement items assessed included desirable and undesirable effects, balance of effects, certainty of evidence, values, resource use, cost-effectiveness, equity, acceptability and feasibility. Definitions for these items can be found in the Summary of Judgements table in the Supporting Information S1. For the resources required, the group considered potential financial and/or human resources directly linked to the implementation of the intervention in clinical practice and any specific expertise required. Where such information was missing, the group made a pragmatic decision based on their clinical expertise. The group defined equity in this context as the ability of all people with a diabetes-related foot ulcer (i.e. on a societal level) to have equitable access to the procedures required for the intervention application.

Acceptability to stakeholders was based on expert opinion and consideration of the balance of effects and any resources required by the users themselves. Feasibility was determined based on the groups' experience and the ease of use of the interventions

After careful weighing of the summary of judgements, the team proposed to the working group a direction, strength, certainty of evidence and wording of recommendation(s) and rationale to address the question concerned. Certainty of evidence was rated as 'high', 'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Rationale for each recommendation was also provided and based on the summary of judgements tables (see Supporting Information S1) (8, 9).

Fifth, summary of judgements tables and recommendations for each question were extensively discussed in online meetings with the working group. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention, and the strength of each recommendation as 'strong' or 'conditional'. A quorum of 60% of members were needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the supplementary material.

Finally, all recommendations, with the rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same clinical experts and persons with lived experience who reviewed the clinical questions, as well as by members of the IWGDF Editorial Board. The working

group then collated, reviewed and discussed all feedback on the consultation manuscript and revised accordingly to produce the final guideline manuscript.

To aid consideration of the literature the interventions were grouped into nine broad categories of i) debridement ii) dressings and topical applications iii) oxygen and other gases iv) therapies involving physical alteration of wound bed properties v) skin substitutes vi) autologous and other cellular products including growth factors and placental-derived products vii) pharmacological interventions viii) negative pressure and ix) educational and psychological interventions. Ten outcomes were identified as critical to decision making in wound healing, which were a) Complete wound healing; b) Time to healing; c) Sustained healing; d) Reduction in ulcer area; e) Amputation (major or minor); f) Quality of life; g) Maintenance of function and ability to perform activities of daily living; h) New infection; i) Resource utilisation; and j) death/mortality.

RECOMMENDATIONS

Overall, nine clinical questions, each with up to 10 outcomes critical to decision making were addressed by this guideline. This has led to the formulation of 29 separate recommendations. The accompanying systematic review (7) has been published and we developed 27 summary of judgement tables (available as online-only Supporting Information S1).

We considered the interventions to be adjunctive to best standard of care when best standard of care alone has failed to heal the ulcers. This should include basic wound dressings, which according to the IWGDF Practical Guidelines should be dressings to absorb exudate and maintain a moist wound healing environment (1). Additionally, these should be of the lowest acquisition cost for the local health care economy.

INTERVENTION: DEBRIDEMENT

Clinical question 1: In people with diabetes-related foot ulcers, is enzymatic debridement, autolytic debridement, biosurgical debridement, ultrasonic debridement, hydrosurgical abrasion or chemical debridement more effective for achieving wound healing compared to best standard of care (including sharp debridement)?

Debridement involves the removal of dead and devitalised tissue (necrosis and slough) from wounds in order to create a clean wound bed and is designed to promote wound healing. There are several different types of debridement including physical (e.g. surgical, sharp, hydro-debridement, or gaseous debridement), biological (larvae), autolytic (hydrogels) or biochemical (enzymes). Although there is unequivocal consensus amongst experts in support of the need for regular wound debridement to facilitate healing, high quality evidence to justify debridement in general, and to identify the best form of debridement is limited. For types of debridement, we found ten RCTs that met our prespecified inclusion criteria as described in our systematic review (16-25). There were five RCTs (16-20) of enzymatic debridement, 3 RCTs (21-23) of low frequency ultrasonic debridement, 1 RCT (24) of surgical debridement and 1 RCT (26) on frequency of sharp debridement. However we found no RCTs of other types of debridement.

Recommendation 1: Do not use autolytic, biosurgical, hydrosurgical, chemical or laser debridement over standard of care. (GRADE Strength of recommendation: Strong; Certainty of evidence: Low)

Rationale: No publications of RCTs were found on the use of autolytic, biosurgical, hydrosurgical, chemical or laser debridement that met our prespecified inclusion criteria, or had sufficient cost effectiveness data to warrant their use. Thus we were unable to make a recommendation supporting their use.

ENZYMATIC DEBRIDEMENT

Recommendation 2: Do not routinely use enzymatic debridement as opposed to standard of care (i.e. sharp debridement) to improve wound healing outcomes in people with diabetes and a foot ulcer. (Strong; Low)

Recommendation 2a: In specific situations where the availability of sharp debridement may be limited by access to resources and/ or availability of skilled personnel, consider using enzymatic debridement. (Conditional; Low).

Rationale: We found five RCTs on clostridial collagenase ointment (16-20) all of which were 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. Outcomes were assessed at different time points, between 4 to 6 weeks, with limited long-term follow up and different definitions of healing making comparisons between studies difficult.

Overall, the evidence behind the use of enzymatic debridement is limited and the certainty of evidence is low. This reflects the methodological limitations of the studies and the resultant high risk of bias. Overall, the balance of effects did not favour either enzymatic debridement or sharp debridement in terms of complete wound healing, or wound area reduction. One specific type of enzymatic debridement, topical clostridium collagenase, would probably have higher resource implications but there was low certainty of evidence of the required resources, and no formal cost effectiveness data were found. Due to the additional resources required to provide topical clostridium collagenase, we considered that equity may be reduced, particularly in low and middle income regions. However we also recognise that in some lower income regions access to standard of care (i.e. sharp debridement) may be limited as this requires skilled personnel, training programmes and sterile instruments. Hence, in health care systems where such skills are not available, alternative methods with enzymatic debriding agents could be considered.

ULTRASONIC DEBRIDEMENT

Recommendation 3: Do not use any form of ultrasonic debridement over standard of care (i.e. sharp debridement). (Strong; Low)

Rationale: We found three RCTs (21-23) 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 being blinded. Only one (21) 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 (22, 23) presented either no difference between the two groups or did not present any between group analyses.

One of the three identified RCTs showed small desirable effects in regards to wound healing outcomes. Thus, ultrasonic debridement may be associated with decreased time to wound healing versus standard

of care, albeit with low certainty evidence, thus these findings should be interpreted with caution. No differences in complete wound healing or sustained healing were reported between groups. Thus, overall, the balance of effects does not favour either the intervention or control. The intervention, ultrasonic debridement, has a higher resource implication although with low certainty of evidence of the required resources and no formal cost effectiveness data found. From the limited data available it is uncertain as to whether the higher costs incurred could be offset by the small desirable effects in terms of decreased time to healing in the intervention group; although it seems unlikely, given the low certainty of the evidence of the beneficial effect. Due to the additional resources required to provide ultrasonic debridement, equity is probably reduced, particularly in lower income regions; however, the intervention is probably acceptable to patients and its use in a health care system was thought to be feasible. Due to all the above reasons, but mostly the low certainty of evidence of benefit and an absence of cost effectiveness data, we do not recommend the use of ultrasonic debridement over standard of care, that is, sharp debridement.

SURGICAL DEBRIDEMENT

Recommendation 4: Do not use surgical debridement in those for whom sharp debridement can be performed outside a sterile environment. (Strong; Low)

Rationale: We found one RCT (24) of surgical debridement compared to standard of care (i.e. sharp debridement), which reported two of our critical outcomes, time to healing and sustained healing but was assessed as being at high risk of bias; and any positive benefits reported should be treated with caution.

Overall, we considered that the balance of effects did not favour either the intervention or control. The intervention, surgical debridement, has a higher resource implication with large costs albeit with low certainty of the evidence of the required resources, and no formal cost effectiveness data were found. From the limited data available it is uncertain as to whether the higher costs incurred could be offset by the small desirable effects in terms of greater sustained healing in the intervention group although this seems unlikely. Due to the additional resources required to provide surgical debridement equity was felt to be reduced, particularly in low income regions, however the intervention is probably acceptable to patients and feasible. For all the above reasons but particularly the low certainty of evidence of benefit, we do not recommend the routine use of surgical debridement in those for whom sharp debridement can be performed outside of a sterile environment. However, in the absence of high-quality evidence the opinion of the expert group was that a) people with diabetes-related foot ulcers that can be managed appropriately with sharp debridement in an outpatient setting should not be taken to theatre for unnecessary surgical debridement as this approach is more expensive, resource intensive and might actually delay debridement if it could be undertaken at the chairside. b) People with diabetes-related foot ulcers with limb or life threatening features (e.g extensive necrosis, collections, or gas forming infections) must always be referred urgently for a surgical opinion to assess the need for surgical intervention to avoid the risk of further deterioration and worse outcomes (see Recommendation 18 of the 2023 Infection Guidelines) (14). The type of debridement modality, that is, sharp versus surgical

should be made by an experienced clinician based upon clinical severity and the presence or absence of any limb-threatening features.

FREQUENCY OF SHARP DEBRIDEMENT

Recommendation 5: We recommend the frequency of sharp debridement should be determined by the clinician based on clinical need. (Strong; Low)

Rationale: We found one RCT (25) at high risk of bias that investigated 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 or healing times at 12 weeks between groups. The certainty of the evidence is low, as this is based on one unblinded study at high risk of bias Overall, we felt that the balance of effects does not favour either the weekly or fortnightly sharp debridement. No formal cost effectiveness data were found. From the limited data, it is uncertain as to whether there would be a difference in costs based on frequency of sharp debridement given all participants were attending clinics weekly. Sharp debridement, regardless of frequency is acceptable to patients and feasible. Due to limited evidence we do not recommend a specific frequency of debridement. The frequency should thus be determined by the clinician based on clinical need.

INTERVENTION: DRESSINGS

Clinical question 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

We identified 50 published RCTs related to our interventions and reporting our outcomes of choice which informed these guidelines. All but four studies reviewed were considered at high or moderate risk of bias. The duration of treatment and follow-up period varied widely between the studies reviewed (24 hours to 34 weeks) and many studies provided limited description of the ulcer and patient characteristics, but typically recruited superficial ulcers or non-infected ulcers. Additionally, most studies recruited individuals without peripheral artery disease (PAD) or with mild PAD (in most studies, but not all, defined as Ankle Brachial Index (ABI) 0.7 to 0.9, Transcutaneous Oxygen pressure ($TcPO_2$) 30 - 50mmHg). Therefore, the certainty of evidence and assessment of balance of effect in favour of the intervention in addition to generalizability to the typical diabetes-related foot ulcers seen in clinical practice was hard to determine. Furthermore, we also noted a significant lack of clear descriptions of standard of care provision including the type and quality of offloading provided, type and impact of any additional supportive interventions undertaken, such as revascularization.

Given this is a large group of interventions, we have broken down the key recommendations into smaller sections, based on the groups of types of products and applications currently available.

TOPICAL ANTIMICROBIAL OR ANTISEPTIC DRESSINGS

Recommendation 6: Do not use topical antiseptic or antimicrobial dressings for wound healing of diabetes-related foot ulcers (Strong; Moderate)

Rationale: We found 12 studies (27-38) evaluating anti-septic or antimicrobial dressings or topical antiseptic applications. Five evaluated the use of silver impregnated dressings in comparison with usual care (27-30, 37) but all were considered at high or moderate risk of bias. Four of these showed no significant improvement in terms of complete healing (27-30), or percentage area wound reduction.

We found three studies investigating the use of iodine impregnated dressings (31-33). Apart from one (32), all were at high risk of bias. This, the only study with blinding regarding the evaluation of outcomes, showed no difference in the incidence of outcomes of importance when compared with usual care. Thus, any positive benefits reported by the other studies should be treated with caution.

One study on Diperoxochloric Acid (34) was found which evaluated the impact of this intervention in hospitalised patients. Although with double blinding, usual care was not well defined and the clinical significance of the apparent positive results are not clear.

We identified two studies of topical gentamicin (35, 36) which fulfilled our inclusion criteria, although both were considered at high risk of bias, and only one reported apparent superiority of the intervention on wound healing after minor amputations. Thus, any apparent benefit on wound healing is of low certainty.

We identified only one non-blind study on a superoxidised solution (38). Although no differences were reported in complete wound healing a shorter time to heal and lower rates of reinfection were reported at 6 months in the intervention arm. The study was however at high risk of bias and thus we have low confidence in this result.

The evidence to support positive impact on wound healing of surface antiseptics or antimicrobials is thus inconsistent, and where present, the effect size was small with low certainty of evidence. There was significant heterogeneity in the type and size of diabetes-related foot ulcers recruited and the standard of care provided, making comparison between studies using the same type of dressing/application difficult. Thus the balance of effects was felt not to be in favour of the intervention. Although costs were thought to be moderate/low and equity, feasibility and acceptability were not thought to be affected, given the low certainty of evidence of benefit, we do not recommend the use of any of these products for the sole purpose of promoting wound healing of diabetes foot ulcers.

HONEY OR BEE PRODUCTS

Recommendation 7: Do not use honey (or bee related products) for the purpose of wound healing in diabetes-related foot ulcers (Strong; Low)

Rationale: We found six RCTs (28, 39-43) of interventions containing topical bee or honey products which reported some of our outcomes of importance. All were deemed at high risk of bias and any positive results on wound healing should be treated with caution. The only blinded study of a royal jelly found no difference in healing over 12 weeks (40). No studies reporting data on amputation, cost effectiveness or quality of life were found.

Overall, therefore, the certainty of any positive benefit of the topical use of honey or bee related products is very low. Although adverse effects were rarely reported, the groups' experience was that any undesirable effects are likely to be trivial. However, the balance of effects could not be ascertained as either favouring the intervention or the comparison. Resource use was thought to be similar to standard of care but no formal cost-effectiveness data was found. Although thought to be feasible, and acceptable to patients and with equity unaffected it was felt that in the absence of certainty of benefit we cannot recommend the use of any of these products for promoting wound healing in diabetes-related foot ulcers.

COLLAGEN OR ALGINATE

Recommendation 8: Do not use collagen or alginate dressings for the purpose of wound healing of diabetes-related foot ulcers (Strong; Low)

Rationale: We found twelve RCTs (29, 44-54) of collagen or alginate (or both) as an intervention to enhance wound healing and which fulfilled our inclusion criteria. All were at moderate or high risk of bias and most were non-blinded. Four studies compared collagen only with moist wound therapy (45, 47, 48, 52), one study (46) used collagen-alginate, one used a calcium alginate. (51), one compared a collagen/oxidised regenerated cellulose/silver treatment with foam (29), one the same collagen/oxidised regenerated cellulose but without silver (54), one compared collagen with negative pressure wound therapy(50), one compared collagen with gauze or hydrocolloid dressings (49) and another two (51, 53) alginate alone as the intervention. Of the twelve studies, nine of them (29, 45-47, 49, 51-54) did not report a difference in wound healing or reduction in ulcer area at the end of study duration. Thus any reported positive outcomes should be treated with caution.

The group agreed that in view of the known low incidence of undesirable effects, it is possible that the balance of effects favours the intervention, although the certainty of this was very low. The cost of these interventions was thought to be moderate, although no formal cost effectiveness studies were found and so the certainty of this was low. Equity, acceptability and feasibility were agreed to be unlikely to be affected. Nevertheless given the uncertainty of benefit and possible cost implications, we do not recommend the use of any of these products for promoting wound healing in diabetes-related foot ulcers.

SUCROSE OCTASULFATE

Recommendation 9: Consider the use of the sucrose-octasulfate impregnated dressing as an adjunctive treatment, in addition to the best standard of care, in non-infected, neuro-ischaemic diabetes-related foot ulcers which have had insufficient change in ulcer area with best standard of care including appropriate offloading for at least 2 weeks (Conditional; Moderate).

Rationale: We found one large double blind multinational RCT (55) assessed to be at low risk of bias investigating the use of sucrose-octasulfate impregnated dressings in non-infected neuro-ischaemic foot ulcers which were deemed hard to heal at the end of a 2 weeks run-in period. There was a significant improvement in complete wound healing at week 20, a significantly faster estimated time to heal and increased percentage area reduction compared to the placebo dressing; and we considered this evidence to be of high certainty. We therefore concluded that, in neuro-ischaemic foot ulcers where there has been insufficient change in ulcer area with best standard of care including appropriate offloading, there is sufficient evidence to consider the use the sucrose-octasulfate impregnated dressing. We found few data on harms and concluded that the balance of risks and benefits were in favour of the intervention. Resource use was considered to be low/moderate and we are aware that there is cost-effectiveness data from modelling studies now available for various Western health-care systems which are supportive (56-59). Equity was not thought to be reduced with this intervention and it was felt to be feasible and acceptable to patients in all health care settings. However, the optimal timing of initiating treatment remains to be established. Furthermore, it is recognised that this is the only study of this intervention, and so despite the quality of the data in this one study, the evidence was considered to be moderate and the strength of the recommendation limited to conditional.

TOPICAL PHENYTOIN

Recommendation 10: Do not use topical phenytoin for the purpose of wound healing in diabetes-related foot ulcers (Strong; Low)

Rationale: Despite there being 12 RCTs (60-71) investigating the use of topical phenytoin for wound healing of diabetes-related foot ulcers, with some benefit of its use on time to healing and reduction in ulcer area, the evidence to support any benefit was of low certainty, as all were at moderate to high risk of bias and most were unblinded. Although the intervention is not likely to be expensive, and equity and feasibility is unlikely to be unaffected, the certainty of the evidence is such that we cannot recommend this intervention.

TOPICAL HERBAL OR TRADITIONAL MEDICINAL PREPARATIONS

Recommendation 11: Do not use any dressing based or topical applications impregnated with herbal remedies for the sole purpose of wound healing in diabetes-related foot ulcers (Strong; Low)

Rationale: We found nine RCTs which reported on the use of topical herbal or traditional medicinal preparations which fulfilled our inclusion criteria (72-80). Of seven studies reporting on complete wound healing (72-77, 79), all were at moderate or high risk of bias, and any positive effects on wound healing should be interpreted cautiously. Further, reduction in ulcer area was reported in six studies (72, 74, 75, 77, 79, 80) of which only two (72, 77) found an apparent improvement in comparison to the control. Again, these were at high risk of bias. No differences in amputation rates (74) or mortality (78) were reported. No studies reported on quality of life, new infection, resource utilisation or maintenance of function.

Overall, we found nine studies assessing the impact of traditional or herbal based remedies, although all were rated at high risk of bias. Despite some of the studies reporting positive effects on wound healing including reduction in ulcer area, the low confidence in the results and the fact that no two studies evaluated the same product, meant the balance of effects could not be ascertained as either favouring the intervention or the comparison. Furthermore, there was significant heterogeneity in the ulcer type and patients recruited, adherence to standard of care was unclear in many studies, and no cost-effectiveness data was found. Therefore, on balance, given the poor quality of evidence, presently we do not recommend the use of any of these products for the sole purpose of promoting wound healing in difficult to heal diabetes-related foot ulcers.

INTERVENTION: OXYGEN AND OTHER GASES

Clinical question 3: In people with diabetes-related foot ulcers, is hyperbaric oxygen, topical oxygen or the use of other gases compared to standard of care more effective for achieving wound healing?

Oxygen is a critical element in key processes of wound healing including angiogenesis, collagen deposition, and epithelialisation. Hyperbaric oxygen therapy involves breathing 100% oxygen at a pressurised atmosphere of 2ATA or above (i.e twice the atmospheric pressure exerted at sea level), which increases the partial pressure of oxygen in hypoxic or ischemic tissues. This has been proposed as a key mechanism for improving wound healing in diabetes-related foot ulcers with ischaemia or hypoxia. Previous guidelines (6) have conditionally recommended the use of hyperbaric oxygen therapy as an adjunctive treatment on the basis of several RCTs. For this guideline, we included 18 RCTs on hyperbaric oxygen (81-98) with no new studies published in the last four years.

Topical oxygen is a relatively new(er) therapy, and this involves the administration of oxygen topically over tissue by continuous diffusion or pressurised systems using mechanical devices (99). Whilst there was insufficient evidence to recommend its use for healing diabetes-related foot ulcers in 2019 (6), the evidence on topical oxygen has substantially expanded in the last four years with several new RCTs (100-103) with a total of ten included in the systematic review for these guidelines (100-109).

We found additionally one study on nitric oxide (110), three on ozone therapy (111-113), two on cold atmospheric plasma (114, 115) and one on carbon dioxide (116). With all of these studies being either at high risk of bias and/or with lack of demonstrable effect, these were grouped together as "other gases".

Recommendation 12: Consider the use of hyperbaric oxygen as an adjunct therapy in neuro-ischemic or ischemic diabetes-related foot ulcers where standard of care alone has failed and where resources already exist to support this intervention. (Conditional; Low)

Rationale: Of the 18 studies on the evaluation of the use of hyperbaric oxygen as an adjunct therapy to improve diabetes-related foot ulcer healing, only three were double-blinded RCTs (87, 89, 91). One of these showed no difference in the critical outcome of wound healing (87) with both the others showing improved wound healing (89, 91). Overall, the evidence is conflicting, 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. Good evidence of benefit in preventing amputation is, however, lacking. Different time points (ranging between 30 days and 12 months), degree of ischaemia and definitions of healing make comparisons between studies difficult.

Overall, the evidence at low risk of bias behind the use of hyperbaric oxygen therapy was limited. The majority of studies were at high risk of bias although there was one good quality study showing evidence of benefit on the critical outcomes of healing and time to healing. Overall the certainty of evidence was low and although there were moderate desirable effects with benefit in improving absolute wound healing and reduction in ulcer area, evidence of amputation reduction was not found. People with diabetes require assessment for suitability for hyperbaric oxygen therapy; and those with general frailty and comorbid conditions may have to be excluded from this treatment modality due to increased risks of adverse events. Amongst those assessed as suitable, however, reported undesirable effects were small. Overall, the group felt the balance of effects will likely favour the use of hyperbaric oxygen over standard of care alone. However, hyperbaric oxygen therapy requires large costs and although several poor quality in-trial studies have demonstrated cost savings with its use, these fail to account for costs of construction of hyperbaric oxygen units. Nonetheless, where there are already established hyperbaric oxygen units used for treating other medical conditions, there may be cost effectiveness justifying the use of this intervention if desirable effects of improved wound healing are achieved. Although time consuming, hyperbaric oxygen was thought to be acceptable to most patients and clinicians. Overall, because hyperbaric oxygen is only limited to individuals assessed as being suitable, who live in close proximity to established hyperbaric units, and are able to commit to weeks of intense treatment, we acknowledge that this conditional recommendation is likely to reduce equity.

Our ratings are consistent with findings from previous guidelines; and with no new good quality evidence published in the last four years, we continue to conditionally recommend the use of hyperbaric oxygen as an adjunct therapy where standard of care alone has failed although we recognise that the groups most likely to benefit still requires evaluation.

TOPICAL OXYGEN

Recommendation 13: Consider the use of topical oxygen as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention. (Conditional; Low)

Rationale: We found three double-blinded RCTs (100, 104, 105) and seven non-blinded studies(101-103, 106-109) for the use of topical oxygen. Of the double-blinded studies, one was terminated early and had uneven baseline characteristics between control and intervention group (100). Two double-blinded trials were at low risk of bias, but only one had statistically significant results for complete wound healing in favour of topical oxygen at 12 weeks (104) with the other showing no difference between topical oxygen and standard of care (105). 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.

The evidence behind the use of topical oxygen in diabetes-related foot ulcers was of low certainty, with overall desirable effects rated as moderate with benefit on achieving absolute wound healing and reduction in ulcer area, but no evidence for reduction in amputation up to 12 weeks. Undesirable effects were poorly reported in the studies available to us, but assumed to be trivial based on expert opinion. Overall, the group felt that the balance of effects would favour the use of topical oxygen, but the certainty of evidence is rated as low across the different devices delivering topical oxygen, and at present it is difficult to say which devices, if any, are superior. There was also a lack of cost effectiveness or published data on resource use, but expert opinion agreed upon moderate costs, with therapy requiring multiple units of single-use topical oxygen delivery devices. Unlike hyperbaric oxygen, topical oxygen therapy can be administered in patients' homes, and is likely to be feasible and acceptable to patients and clinicians alike but due to the moderate costs for mainly single-use devices, it was felt that equity may be reduced. Overall, despite the balance of effects being in favour of the intervention, a conditional recommendation only for topical oxygen was made because of the costs involved and their effect on equity.

OTHER GASES

Recommendation 14: Do not use other gases (e.g. cold atmospheric plasma, ozone, nitric oxide, CO2) in comparison to standard of care for wound healing in people with diabetes-related foot ulcers. (Strong; Low)

Rationale: 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 (110-116) . Overall, the desirable and undesirable effects were both rated to be trivial, although the latter was an assumption with lack of data on adverse events reported in trials. Due to high risk of bias, the certainty of evidence is rated as very low, and the balance of effects was felt unlikely to favour the use of other gases over standard of care. Expert opinion rated the costs of therapy as moderate, again with lack of cost effectiveness data from trials. Thus, the use of other gases is probably not as cost-effective when compared to standard of care. Due to limited availability and information about use, storage and administration of these gases, these therapies are unlikely to be acceptable or feasible for wide use. Thus, we cannot recommend the use of these interventions to support wound healing of diabetes-related foot ulcers.

INTERVENTION: PHYSICAL ALTERATION OF WOUND BED

Clinical question 4: In people with diabetes-related foot ulceration, is the use of interventions which physically alter the wound bed compared to standard of care more effective for wound healing?

We found a number of studies relating to the use of "physical wound bed alteration therapies" including; heat application, therapeutic ultrasound, compression, electrical or electromagnetic stimulation (ES/EM), light and laser treatment, Extracorporeal Shock Wave Therapy (ESWT), ischaemic preconditioning, therapeutic magnetic resonance and connective tissue manipulation.

As there were few studies on each of these interventions individually, and those that we did identify were either at high risk or moderate risk of bias and/or showed no benefit, we have taken this group all together in making a recommendation.

Recommendation 15: Do not use any interventions reported in the field of physical therapies for wound healing in the management of diabetes-related foot ulcers. (Strong; Low)

Rationale: The evidence to support the use of heat application for diabetes-related foot ulcer management is weak, depending on only three small, non-blinded RCTs (117-119) all at high risk of bias and in one of which (117) the incidence of healing in the comparator group seemed to be much lower than expected for the type of ulcers included. We found just two studies of therapeutic ultrasound (120, 121), only one of which was methodologically sound(120), although healing rates were again lower than expected in the control arm.

Three studies (122-124) evaluated compression on some of our outcomes of importance. All three were at moderate or high risk of bias.

We identified six studies investigating the use electrical or electromagnetic stimulation on some of our outcomes of importance (125-130).

Eight studies were found on the use of light and laser therapy (131-138). Only three of these (131-133) reported complete healing or time to healing, the remainder reporting only area reduction. Results were conflicting, possibly contributed by the heterogeneity of treatment protocols

We identified four studies of extra corporeal shock wave therapy (139-142). Of our outcomes of importance only complete healing (139-141), time to healing (139, 141) and percentage area reduction of the ulcer (142) were reported.

The evidence available from the single study (143) of ischaemic preconditioning identified does not support its use of due to its high risk of bias.

We identified only one study identified of therapeutic magnetic resonance (144), which was at moderate risk of bias, and did not show any differences in outcome between the two groups.

We found only one study of connective tissue manipulation (145), reporting only percentage area reduction, and no benefit was shown in the use of the intervention.

The analysis of the studies dealing with different physical therapies proposed for diabetes-related foot ulcer management provided limited evidence to suggest that these therapies might be beneficial in improving outcomes in diabetes-related foot ulcers. While a small number of studies were at low risk of bias, none of these indicated any effect. Overall, the desirable effects of physical therapies on wound healing were considered small, and in most cases no significant differences emerged when compared to standard of care. As the studies focussed on a number of interventions and as the results were not strong, it was decided to consider them as part of the whole group of "physical therapies", rather than analysing them separately. It was also noted that undesirable effects were rarely reported, and no severe adverse events were described. It was considered, therefore, that the balance of effects would not favour either the intervention or usual care, but that this was based on low certainty evidence. In addition, it was considered that most, if not all, of the treatments might be associated with appreciable extra costs and resources. Although formal cost-effectiveness studies were not found, it was felt that cost-effectiveness would be unlikely given the small size of effects noted. It was also noted that some treatments might have reduced acceptability and equity for patients, and hence feasibility. For these reasons, we do not currently recommend the use of any of the physical therapies described either as first-line or as adjuvant therapies for diabetes-related foot ulcer management.

INTERVENTION: SKIN SUBSTITUTES

Clinical question 5: In people with diabetes-related foot ulcers, are skin substitutes more effective for wound healing compared to best standard of care?

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 suture, 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 28 RCTs across the wider 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 intention to treat. A helpful way to categorize 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. For the systematic review (7), we found 10 RCTs (146-155) on celular products, 13 RCTs (150, 156-167) on acellular products, and 5 RCTs (168-172) on autologous skin graft products.

CELLULAR SKIN SUBSTITUTES

Recommendation 16: We suggest not using cellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)

Rationale: Although evidence from 10 RCTs (146-155) suggest that Cellular Skin Substitutes may improve the healing and reduce the time to healing in patients with diabetes-related foot ulcers when provided in addition to standard of care, all studies were at high risk of bias due to non-blinding, had high dropout rates and per-protocol analyses. Moreover, there is insufficient evidence to establish which particular cellular skin substitutes may be more effective. There is, additionally, limited evidence to indicate that cellular skin substitutes are associated with a reduction in amputation rates. Minimal undesirable effects were reported with its use, and whilst the overall balance of effects are likely to favour the intervention, cellular skin substitutes are likely to require moderate costs/resources. Despite the certainty of evidence of resources being low with lack of formal cost effectiveness data, the moderate resources required meant that the group decided that cost effectiveness would not favours cellular skin substitutes over standard of care. This raises concerns for equity, and whilst likely acceptable for general use, feasibility is low due to the expertise and costs required in using these products.

ACELLULAR SKIN SUBSTITUTES

Recommendation 17: We suggest not using acellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)

Rationale: Based on the review of the 13 RCTs (150, 156-167) found on acellular skin substitutes we concluded that these interventions may improve the incidence of healing and reduce the time to healing in patients with diabetes-related foot ulcers, when provided in addition to standard of care. However, all of the studies were considered at high risk of bias with the majority having no blinding as part of the protocol and only three (158, 160, 166) being blinded for outcome assessment. Thus any positive effects should be considered with caution. In addition, evidence to establish which, if any, particular acellular skin substitutes are superior is lacking, and there was insufficient evidence on cost effectiveness of this modality. There is limited evidence to indicate that acellular skin substitutes are associated with a reduction in amputation rates, with only two studies, and conflicting results reporting on this outcome (156, 159). Moreover, the lack of negative studies may suggest a degree of publication bias, and most studies were industry-sponsored. Thus, while there is some evidence that the balance of effects probably favours the intervention, the certainty of the evidence is low. Limited resource utilisation data were found, indicating moderate costs in a single heath care setting, but it was agreed that these products do come with a significant cost and that this raises concern for equity and availability, although limited data is available on cost effectiveness. The groups agreed that the products would be acceptable for general use, but feasibility is probably low due to expertise and costs required.

AUTOLOGOUS SKIN GRAFT SKIN SUBSTITUTES

Recommendation 18: Do not use autologous skin graft skin substitute products as an adjunct therapy for wound healing in patients with diabetes-related foot ulcers. (Strong; Low)

Rationale: We identified just five RCTs (168-172) with publication dates ranging from 2003 to 2021. All were at high risk of bias and thus the positive outcomes of two of them should be treated with caution. There is insufficient evidence to establish their effectiveness or cost utility. Overall, we considered the balance of effects is not likely to favour autologous skin substitutes over standard of care. Although backed by limited evidence, the resources required come at moderate costs and thus cost effectiveness does not favour autologous skin substitutes over standard of care. Concerns are raised for equity and availability along with the additional challenge of autologous harvest from the patient. Whilst acceptable for general use, feasibility is probably low due to expertise and costs required.

INTERVENTION: AUTOLOGOUS PRODUCTS

Clinical question 6: In people with diabetes-related foot ulcers, is the use of autologous and other cellular products including growth factors and placental-derived products more effective for wound healing compared to standard of care?

One possible treatment option for nonhealing ulcers is the use of interventions which either promote the release of cytokines and growth factors involved in tissue repair, angiogenesis, and inflammation or directly donate these factors to the ulcer bed.

Thus the use of autologous cells including autologous platelets, cells which are fundamental to the co-ordination of normal wound healing has been investigated in a few trials. Most cells including adipocytes derived stem cells, and fibroblasts require relatively invasive methods to extract the relevant cells from donor sites. Although only requiring venepuncture, the difficulty of the volume of blood required to produce sufficient platelets has hampered their wider use, although the use of the leucocyte fibrin and platelet patch has largely overcome this.

Individual growth factors applied directly to the wound including platelet derived growth factors (although this is only one of the many types of cytokines released by platelets) have also been trialled, although researchers have noted that individual growth factors alone may not be sufficient to ensure the whole wound healing cascade of cytokines is enhanced.

Human placental membranes contain a combination of growth factors, collagen-rich extracellular matrix, and cells, including mesenchymal stem cells, neonatal fibroblasts, and epithelial cells, that provide mechanisms for coordinated wound healing. Several products derived from different components of the placenta and umbilical cord have been developed. Cryopreserved preparations contain living cells and growth factors, whereas dehydrated products, which are easier to store and handle, contain growth factors but no living cells.

We divided this group of interventions into autologous cells, human/recombinant growth factors, and human placental-derived products.

Of the autologous cells, there were a number of studies utilising platelets in various formulations, but with the exception of the autologous leucocyte, fibrin and platelet patch, the evidence to support the use of any other formulation of platelets or other autologous cells as detailed in our systematic review (7) was limited. For this reason we have considered this intervention separately but grouped platelets together as the evidence to support any particular formulation of this intervention was less certain.

Similarly we have considered other autologous cells, growth factors and placental derived products as separate groups of interventions.

AUTOLOGOUS PLATELETS – WITH EXCEPTION OF THE AUTOLOGOUS LEUCOCYTE AND PLATELET PATCH

Recommendation 19: With the exception of the autologous leucocyte, platelet and fibrin patch we suggest not using autologous platelets therapy (including blood bank derived platelets) as an adjunct therapy to standard of care. (Conditional; Low)

Rationale: We included 15 RCTs (173-187) on the use of platelet products for the management of diabetes-related foot ulcers. The majority of studies investigated the use of platelet gel, with the inherent problem of requiring moderate amounts of autologous venous blood to generate the product.

Of the studies looking at complete wound healing all were at risk of bias with only one of a platelet gel being outcome blinded (174), however the positive outcome in this study was of low certainty with per protocol analysis only. The problem of autologous blood volumes was overcome in one study using a blood bank of platelets (179) but the apparent superior outcome of healing was marred by non-blinded outcomes' assessment and was considered at high risk of bias. A number of these studies also assessed percentage wound area reduction as well as absolute wound healing, but all were at high risk of bias or did not report a difference between groups. Only one study reported an apparent benefit in terms of amputation but the evidence was of low certainty (176). The only study reporting resource use (182) was limited by including hospitalised patients only.

The different timescales to the outcomes chosen made comparison of different interventions difficult to establish.

Although there were 15 included RCTs, the studies were at high risk of bias overall, with only one being

outcome blinded and one with patient- but not outcome-blind. Those at the lowest risk of bias demonstrated the lowest improvement in healing outcomes casting doubt on the size of the effect seen in the majority of the studies. On this basis we evaluated the size of the potential positive effect as small although the certainty of this was very low. Few studies published adverse effects but expert opinion suggested that undesirable effects would be small. Overall it was felt that it would be difficult to be certain that in clinical practice a positive effect on healing would be seen consistently above what would

be expected with good standard of care. The costs of these interventions was thought to be moderately high, although no formal cost effectiveness analyses were found. Thus, it was felt that the use of these interventions would decrease equity given the costs involved, and the need for venous samples to be taken for the autologous platelet gel products, and hence feasibility would be reduced in some lower income countries. Where resources existed in health care systems their use might, however be feasible and acceptable to patients.

Overall weighing up the lack of certainty around the effectiveness of these interventions, the resource use and possible lack of feasibility in most health care systems we felt we could not recommend these interventions as an adjunctive therapy to good standard of care.

LEUCOCYTE, FIBRIN AND PLATELET PATCH

Recommendation 20: Consider the use of autologous leucocyte, platelet and fibrin patch for diabetes-related foot ulcers as an adjunctive therapy to standard of care, where best standard of care alone has been ineffective, and where the resources and expertise exist for the regular venepuncture required. (Conditional; Moderate)

Rationale: One high quality multicentre outcome blinded RCT (188) at low risk of bias was identified which showed significant improvements in healing, time to healing and wound area reduction at 20 and 26 weeks after weekly treatment with the intervention in patients with hard to heal ulcers, when used in addition to best standard of care. Participants in the intervention arm had weekly visits for venesection to produce the patch. No differences were seen in the outcomes of new infection, major or minor amputations or mortality. Although 18-36 mL of venous blood was required weekly to create the patch at the bedside, no increase in the incidence of new anaemia was found and there were no other additional reported undesirable effects. For these reasons it was felt that there was a favourable balance of effects in favour of the intervention but the findings of a single study suggested that the certainty of this was moderate at best. We found no formal published cost effectiveness data even though it was recognised that the weekly venepuncture would incur costs and that in some health care systems the expertise for this may not be readily available. If confirmed, these could have a negative impact on equity and feasibility in some health care systems. However, where such a resource exists, it was felt that the use of this intervention would be acceptable to patients. Hence we concluded that the use of autologous leucocytes, platelets, and fibrin patches could be conditionally recommended for hard to heal ulcers in addition to best standard of care where the best standard of care including offloading (where appropriate) had not healed the ulcer. Nevertheless, we recognise that this may not be feasible where expertise and resources for regular venepuncture are not available.

OTHER CELL THERAPIES

This group of interventions included other cell therapies for the promotion of healing of diabetes-related foot ulcers including adipocytes (189-193), fibroblasts (194), keratinocytes(195, 196), bone marrow derived stem cells (197), allogeneic bone marrow mesenchymal stromal cells (allohBM MSC)

and cultured allogeneic bone marrow mesenchymal stromal cells derivatives (cultured allohBM MSCs) (198).

Recommendation 21: We suggest not using other cell therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)

Rationale: In total, 10 studies were identified. These included studies investigating autologous adipocytes (189-193), fibroblasts (194), keratinocytes (195, 196), bone marrow derived stem cells (197), allogeneic bone marrow mesenchymal stromal cells (allohBM MSC) and allogeneic bone marrow mesenchymal stromal cells derivatives (cultured allohBM MSCs) (198)

Of the adipocyte or adipocyte stem cell studies which reported complete healing only two were outcome-blinded. There was heterogeneity of outcomes with some studies showing no improvement in healing, and those reporting positive benefit being at high risk of bias. Similarly the single studies of autologous fibroblast or keratinocytes were assessed at being high risk of bias, neither being blinded. The single study of the use of periwound autologous bone marrow stem cells in patients with critical limb ischaemia was outcome blind but there was a high loss to follow-up with a per-protocol analysis only presented. A second study of allogeneic bone marrow mesenchymal stromal cells (allohBM MSC) and allogeneic bone marrow mesenchymal stromal cells derivatives (cultured allohBM MSCs) was at high risk of bias and consequently no clear conclusions could be drawn.

Only one study at moderate risk of bias (197) reported major amputation at 12 weeks noting no difference between the groups. Only one described resource utilisation (192) but this was, however, not a full health economic analysis and the trial was considered at high risk of bias.

Overall, 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 and bone marrow derived cells is currently poor, with most studies being at moderate to high risk of bias.

The available evidence as described suggested moderate beneficial effects on healing although the confidence in this was low. Few studies published adverse effects or serious adverse effects but expert opinion suggested that undesirable effects could be present. The one study which published quality of life suggested that there was little improvement. Overall it was felt that the balance of effects may favour the intervention but this was based on limited studies with high risk of bias. The resource use involved in these interventions was thought to be high as they required access to cell culture and the ability to harvest the cells from patients. Thus, this would decrease equity and feasibility, particularly in health care systems in low income countries.

Overall, weighing up the lack of certainty around the effectiveness of these interventions and the costs and possible lack of feasibility in some health care systems we felt we could not recommend these interventions as an adjunctive therapy to good standard of care.

GROWTH FACTORS

Within this category we included: Platelet derived growth factor (PDGF), granulocyte stimulating factor (GCSF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and studies of combined growth factors.

Recommendation 22: We suggest not using growth factor therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)

Rationale: We identified seven studies (199-205) investigating the use of PDGF. Only two of the studies were double blind (200) only one of which was considered to be at low risk of bias and this, like one of the other large studies (202), showed no difference in healing between the two groups. An earlier large trial did show a difference in healing and time to healing (204) but was at moderate risk of bias thus reducing confidence in the result. The other studies reporting a positive outcome for those treated with the intervention, were considered at high risk of bias, thus any positive results should be treated with caution.

None of the studies reported on the outcomes of sustained healing, amputation, resource utilisation, maintenance of function or mortality and, therefore, the evidence to support the use of PDGF was poor with the majority of studies being assessed as being at high risk of bias.

Three studies were identified investigating the use of GCSF (206-208). None of the studies showed benefit in terms of wound healing, amputation or any other of our outcomes of importance, however the studies identified were mainly aimed at the treatment of infection.

We identified four studies investigating the use of EGF (209-212) which reported wound healing of diabetes-related foot ulcers at 6 and 12 weeks. With the exception of one study (210), which investigated topical EGFR spray, all were at high risk of bias. The single low risk of bias study reported improved healing at 12 weeks, although the effect size was only moderate.

Two studies investigating FGF (213, 214) also reported healing in double blinded RCTs. The small size of one study and the high risk of bias in the other mean that the positive results reported should be treated with caution

A single study (215) investigated a combination of growth factors (EGF, & FGF) but was judged to be at high risk of bias. It also showed no difference in time to healing between the four groups.

No studies of any GFs reporting on the outcomes of sustained healing, amputation, quality of life, new infection, resource utilisation or mortality.

Few studies of any of the growth factors published adverse effects but expert opinion suggested that these would be small. Overall it was felt that the balance of effects was therefore not in favour of the intervention for PDGF or GCSF and possibly in favour for EGF although this was based on very low certainty evidence. Resource use was thought to be moderate for all growth factors although formal cost effectiveness data was not found. Thus, although feasible, equity would likely to be reduced especially in lower income countries where resource use may be limited.

On balance, it was felt that the lack of certainty of effectiveness of these interventions and the costs and possible lack of feasibility in some health care systems we felt we could not recommend these interventions as an adjunctive therapy to good standard of care.

PLACENTAL DERIVED PRODUCTS

Recommendation 23: Consider the use of placental derived products as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed. (Conditional; Low)

Rationale: We identified ten studies of placental derived products (153, 203, 216-223). Of these, one described the use of dehydrated amnion/chorion graft (221), seven used dehydrated human amniotic membrane (dHAM) (153, 203, 216, 218, 219, 222, 223), one the use of cryopreserved placental membrane (217), one the use of dehydrated human umbilical cord (220)

All of the studies described absolute wound healing at times points between 4 and 20 weeks, however only three studies were assessed at being at low risk of bias (219, 220, 223), and only one (223), a small pilot/feasibility study was double blinded. All suggested improved healing and time to healing. Reports of percentage area reduction in five studies (203, 216, 217, 221, 223) suggested improvements in favour of the intervention, although two of these studies were at high risk of bias and so the positive results should be treated with caution. New infection was reported to be similar in one study (219), although no studies reported any effect on amputation.

Two papers reported the cost of the intervention per healed ulcer (219, 220). 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. Cost effectiveness data was only published in one post hoc analysis of a study otherwise judged at high risk of bias (224).

There were no studies reporting quality of life or maintenance of function.

Although most of the studies were considered at high risk of bias, and none of the definitive studies were patient or care giver blind, those at low risk of bias suggest that the use of placental derived products (and particularly of amniotic membrane) are associated with improved absolute healing at times up to 20 week, 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 incidence of amputation. No formal cost effectiveness data were found but the resource use data suggest the interventions may be less expensive for some providers compared to other skin substitutes.

Overall the group felt that the balance of effects was in favour of the intervention although the certainty of the evidence was low. Although formal cost effectiveness data was not available and resource use was noted to be lower than skin substitutes in one study, it was recognised that there would be moderate costs involved in their use. Thus it was felt that equity may be reduced in some health care

systems particularly those of lower countries. However, where resources existed it was felt that, apart from cryopreserved products which would need storage and defrosting time, acceptability and feasibility would not be reduced in most settings.

INTERVENTION: PHARMACOLOGICAL INTERVENTIONS

Clinical question 7: In people with diabetes-related foot ulcers, is the use of pharmacological interventions more effective for wound healing compared to best standard of care?

This intervention is the systemic administration of naturally occurring or pharmacological agents prescribed to the person with diabetes-related foot ulcers in an attempt to improve wound healing outcomes. These agents may consist of 'over-the-counter' (e.g., vitamins and minerals), or physician only prescribed agents, including traditional Chinese herbal medicines. We included 18 full papers describing randomised trials of pharmacological interventions promoting wound healing.

AGENTS PROMOTING PERFUSION AND ANGIOGENESIS

Recommendation 24: Do not use pharmacological agents promoting perfusion and angiogenesis to improve wound healing outcomes over standard of care. (Strong; Low).

Rationale: We found nine studies (225-233) of agents promoting perfusion and angiogenesis. The studies comparing the use of pentoxyfilline (225), resveratrol (226), low-dose erythropoietin (EPO) (227), subcutaneous injection dalteparin (228), insulin plus sulodexide to insulin plus placebo (229), a two-herb traditional chinese medicine formula (232) and an intravenous native herbal extract, angipars (230) contained too few patients to be certain of the results, and only the latter performed an intention-to-treat analysis. As such, any apparent improvement in healing should be treated with caution. One study (231) investigating injections of a DNA derivative, polydeoxyribonucleotide, although double blinded was considered to be at moderate risk of bias. A second study of polydeoxyribonucleotide was too small to show any difference between the two groups (233). Overall, the evidence suggests that certain pharmacological interventions that promote perfusion and angiogenesis may improve wound healing but the quality of evidence is low and findings should be interpreted with caution.

Of the studies identified, none provided cost effectiveness data.

Overall, the studies showed only small beneficial effects on wound healing, with trivial undesirable effects even though the level of certainty was very low. Overall, therefore, it was felt that the balance of effects suggested little difference between intervention or control. It is also likely that the intervention has a resource implication of moderate costs but with a lack of published data there was low certainty of the required resources. Due to the additional resources required to provide agents promoting perfusion and angiogenesis, equity is probably reduced, particularly in lower income regions, even though the intervention is probably acceptable to patients and would be feasible. Due to limited evidence, we cannot recommend agents promoting perfusion and angiogenesis over standard of care.

AGENTS THAT SUPPLEMENT VITAMINS AND TRACE ELEMENTS

Recommendation 25: Do not use pharmacological agents that supplement vitamins and trace elements to improve wound healing outcomes over standard of care. (Strong; Low)

Rationale: We identified four studies using systemic supplementation of vitamins and trace elements (234-237), all at moderate or high risk of bias. The interventions investigated were daily doses of Vitamins E and C (with platelet-rich plasma-fibrin glue) (237), oral weekly doses Vitamin D (234), a daily probiotic (235), and oral omega-3 fatty acids (236). Although the latter two studies were double blinded 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 reported should be treated with caution. We found no studies of these interventions reporting on outcomes of complete wound healing, time to healing, sustained healing, amputation, quality of life, maintenance of function and ability to perform activities of daily living, new infection, resource utilization and mortality. The available evidence suggests that certain pharmacological interventions, that is, probiotic or omega-3 fatty acids supplementation, may promote reduction in ulcer area with no overall difference in complete healing; however, the quality of evidence is low and findings should be interpreted with caution.

The studies were at moderate or high risk of bias with no cost effectiveness data. The studies showed small desirable effects in regards to wound healing outcomes with trivial undesirable effects, but this was considered to be of low certainty of evidence. Overall, therefore the balance of effects was thought to favour neither the intervention nor control. It is likely that the intervention has a resource implication of moderate costs however the certainty of this was as no formal evaluation was found. From the limited data it is uncertain as to whether the costs incurred would be offset by the small desirable effects. Due to the additional resources required to provide the vitamin and trace element supplementation equity is probably reduced, particularly in lower income regions, however the intervention is probably acceptable to patients and feasible. Due to limited evidence, we cannot recommend agents that supplement vitamins and trace elements over standard of care.

AGENTS THAT STIMULATE RED CELL PRODUCTION OR PROTEIN SUPPLEMENTATION

Recommendation 26: Do not use pharmacological agents that stimulate red cell production or protein supplementation to improve wound healing outcomes over standard of care. (Strong; Low)

Rationale: We identified one study of an agent that stimulates red cell production or protein supplementation that matched our prespecified inclusion criteria (238). This study was considered at moderate risk of bias. There were no differences in wound healing outcomes when the whole group was considered, although there were small desirable effects on wound healing limited to those with a low albumin, with trivial undesirable effects. Overall, the balance of effects was felt to favour neither the intervention nor the control. It is likely that the intervention has a resource implication of moderate costs with low certainty of evidence of the required resources. From the limited data it is uncertain as to whether the costs incurred would be offset by the small desirable effects in those with low albumin.

Due to the additional resources required to provide the protein supplementation equity is probably reduced, however the intervention is probably acceptable to patients and feasible. Due to limited evidence, we cannot recommend agents that stimulate red cell production or protein supplementation over standard of care.

OTHER PHARMACOLOGICAL AGENTS

Recommendation 27: Do not use other pharmacological agents to improve wound healing outcomes over standard of care. (Strong; Low)

Rationale: We identified four studies of other pharmacological agents (239-242), all at moderate or high risk of bias. One study (240), suggested that time to healing was lower with the use of fluconazole in wounds with invasive fungal infections. However, the certainty of these results was considered to be very low. The other study of a Chinese Herb preparation (239) showed no difference in wound healing outcomes when compared to standard of care. One study designed to stimulate the release of bone marrow stem cells, which although at low risk of bias, was not powered to show a difference in healing (242). The final study showed no difference in ulcer area reduction with use of nanocurcumin supplements compared to placebo (241).

Overall, the balance of effects was not thought to favour either the interventions or control. It is likely that the interventions have a resource implication of moderate costs with low certainty of evidence of the required resources. From the limited data it is uncertain as to whether the costs incurred are offset by the small desirable effects. Due to the additional resources required to provide other pharmacological agents equity is probably reduced; however, the interventions are probably acceptable to patients and feasible. Due to limited evidence, we cannot recommend other pharmacological agents over standard of care.

INTERVENTION: NEGATIVE PRESSURE WOUND THERAPY (NPWT)

Clinical question 8: In people with diabetes-related foot ulcers, is the use of negative pressure wound therapy more effective for wound healing when compared to standard of care?

Negative Pressure Wound Therapy (NPWT) involves the controlled application of sub-atmospheric pressure to a wound using a sealed wound dressing connected to a vacuum pump. The sub-atmospheric pressure may be applied continuously or intermittently. The mechanism of action for NPWT has been described to include macro- and micro- deformation of wound tissue, drainage of extracellular inflammatory fluids, and stabilization of the wound environment (243).

Recommendation 28: Consider the use of NPWT as an adjunct therapy to standard of care for the healing of postsurgical diabetes-related foot wounds. (Conditional; Low)

Recommendation 28a: Do not use NPWT as an adjunct therapy to standard of care for the healing of non-surgically related diabetes foot ulcers. (Strong; Low)

Rationale: We identified 19 studies which fulfilled our inclusion criteria (50, 152, 244-260). All studies were thought to be at moderate to high risk of bias.

Of all the studies only three (244, 250, 256) were undertaken in non-surgical wounds, two of which were in a mixed population comprising post-surgical and non-surgical wounds (244, 256). The one study in entirely non-surgical wounds was at high risk of bias, and reported per protocol analyses only, hence the positive benefits reported should be treated with caution (250). The first study in a mixed population (256) although at risk of bias, had blinded outcomes, but reported no difference in healing or time to healing between the two groups. The latter was a nonblinded study at high risk of bias (244). Hence, any evidence to support the use of NPWT in non-surgical wounds is of low certainty.

The remaining studies investigated the use of NPWT in post operative wounds alone. Two studies thought to be of moderate risk of bias reported positive benefit after partial foot amputation (257) and beneficial effects in terms of healing (255), although these outcomes were not assessed blind. Another study at moderate risk of bias reported no difference in healing after soft tissue incision and drainage (258).

Amputation was reported as an outcome in nine studies (244, 246, 247, 249, 254-258). Those at the lowest risk of bias noted no difference in amputation; however the studies were of relatively short duration. Only one study at high risk of bias (244) noted any improvement in quality of life, although this should be treated with caution. New infection was reported in 5 studies with no difference between the groups, although all were at moderate or high risk of bias (244, 245, 255, 257, 258).

Three studies documented resource utilization as an outcome (259, 261, 262). The first two were post hoc analyses of previously reported studies (255, 257) and one only reported resource use (259). All three reported either lower resource use or better cost effectiveness than the comparator although the certainty was thought to be low because of the use of post hoc analyses. We identified no studies which documented death/ mortality as an outcome. NPWT may thus reduce the time to healing in postsurgical wounds when provided in addition to standard of care. For chronic ulcers, there is insufficient evidence to establish whether NPWT reduces time to healing when provided in addition to standard of care.

Thus, overall, the evidence behind the use of NPWT was of low certainty. There were moderate desirable effects that NPWT may reduce the time to healing in postsurgical wounds, but not in chronic wounds, when provided in addition to standard of care. Our conclusions are consistent with the findings from previous guidelines, as no new good quality evidence has been published in the last four years. In regions where NPWT is a widely available and affordable modality, undesirable effects are considered small and it is therefore likely that the use of NPWT will be favoured as an addition to high standard of care. NPWT may require moderate to high costs, and in areas where NPWT is widely available there may be cost effectiveness justifying its use. This is of low certainty though. NPWT was generally considered acceptable to most patients and clinicians. We acknowledge that this recommendation may

reduce equity when considering the limited access to and financial burden of starting NPWT in regions where this modality is not already widely available.

EDUCATION AND LIFESTYLE PROGRAMMES

Clinical question 9: In people with diabetes-related foot ulcers, are education and lifestyle programmes compared to standard of care more effective for wound healing?

Recommendation 29: We do not recommend any specific educational and lifestyle support programmes over standard of care to improve healing of diabetes-related foot ulcers. (Strong; Low)

Rationale: We found one RCT of educational and lifestyle support programmes that met our predefined inclusion criteria but was judged to be at high risk of bias (263). The evidence from this one study showed small desirable effects in regards to reduction in wound area. The certainty of the evidence is therefore low. The educational and lifestyle support programme would have incurred moderate costs but there was very low evidence of the resources required. From the limited data it is uncertain as to whether the costs incurred are offset by the small desirable effects. Due to the additional resources required to deliver the educational and lifestyle programme equity is probably reduced even though the programme is likely acceptable to patients and feasible to deliver. Due to an absence of evidence we cannot recommend any specific educational and lifestyle support programmes over current standards of care, which should include ongoing advice on foot health. Further high quality evidence for the impact of educational and lifestyle programmes are needed.

FURTHER CONSIDERATIONS

This document represents the update of our 2019 recommendations on interventions designed to support healing of foot ulcers in people with diabetes (6). However, we have not simply updated the systematic review done in 2019 but completely re-reviewed the published literature, as our clinical questions and outcomes have changed after consultation with external experts and patients. We have, additionally, considered only randomised controlled trials for inclusion in our current systematic review (7). Thus some interventions previously supported have not been recommended in these guidelines, particularly where more recent studies have not shown the positive results seen in earlier controlled but non-randomised studies. Furthermore we have used the full GRADE approach (8) for the evidence analysis and development of the recommendations, and this has led to a change in the certainty of evidence for several interventions.

The group decided to not undertake any meta-analyses, because for most groups of interventions it was considered that heterogeneity of patients characteristics, follow-up and clinical settings would be high. However where high quality meta-analyses were found we took them into consideration in our discussions.

With this process we have developed 29 recommendations based on our systematic review (7). The systematic review described a number of different interventions which the expert clinical group divided into nine different overarching groups of interventions as described above. Given the change in the number of articles retrieved for some interventions and the lack of any new data from others we have regrouped some of the intervention categories compared to our last guideline. In particular, surgical debridement of the wound has been regrouped with other debridement interventions, skin substitutes and placental derived products were grouped together, albeit with separate recommendations, and we looked for the first time at educational and behavioural interventions which reported any of our outcomes of importance.

It is of note that since the last review, there has been a significant increase in research activity in this field with over 400 articles retrieved describing RCTs of our chosen interventions compared with just 284 controlled (but not necessarily randomised) studies from our previous systematic review (264). However, despite the number of RCTs being published, many are at high risk of bias and for many commonly used wound healing interventions there is a complete lack of RCTs at low risk of bias to guide health care practitioners as to the relevance of their use. In addition, it is still the case that many of the studies included types of ulcers that should heal with good standard of care alone (1) and that good standard of care was either not well described or not well implemented in many cases. It is also the case that in many health care systems people with diabetes and ulcers of the feet are increasingly frail and may have multiple co-morbidities (265), a patient cohort which is frequently excluded from clinical trials, and hence, for whom, even more uncertainty about treatment choices remains.

Due to the limitations in the available evidence we were only able to conditionally recommend the use of six interventions or types of intervention. In some cases we were unable to make a decision on a particular intervention within a groups of interventions, either because comparative data were not available, or because the patient cohorts differed, or because we had little information on resource use for the majority of the interventions. Indeed we were disappointed to see so few studies which looked within trial at the resource use of interventions, and so much of the information was based on post hoc modelling. It was also disappointing that it is still the case that the majority of trials are done outside countries or regions where health care resource is lacking, and as such it was difficult for the group to draw conclusions as to the feasibility and equity for many interventions. Thus, their applicability outside these settings, in particular, where there are limitations of human and financial resource, and where climate, humidity and other environmental issues may impact on ulcer healing remains unknown.

FUTURE RESEARCH AGENDA

Whilst writing this guideline based on our systematic review we were encouraged to see that the numbers of randomised controlled trials had increased since we last reviewed this group of interventions. Nevertheless the quality of the trials remains poor, the majority being at moderate or high risk of bias, with outcomes poorly described, lack of blinding or even any attempt to blind outcome assessors and frequently with sample sizes which were either not pre-defined or which were too small to any lead to confidence in any positive results. We have repeatedly called for researchers and journal editors to be aware of the IWGDF/EWMA standards of reporting of trials of this type (5) and make no apology for repeating this advice here.

Equally many of the studies reported included ulcers which, according to international and national audits should have healed anyway should best standard of care have been instituted early as described in the IWGDF practical guidelines (1). That few studies adequately described best standard of care, including relevant offloading means that we can have little confidence of the ability of some interventions to provide not just effective, but cost effective improvements in outcome.

Information on undesirable effects (such as adverse events, quality of life and costs), equity, acceptability, and feasibility is critical in clinical decision for any intervention. Using the GRADE methodology in these 2023 guidelines (8) we have paid more attention to the these outcomes than previous versions of these guidelines. Few studies however reported these outcomes. As above, we urge future researchers to ensure all outcomes whether positive or negative are reported.

Costs and particularly cost-effectiveness have also received little attention in many studies. Whilst accepting that cost effectiveness in particular varies between health care systems and providers, the fact that costs are rarely reported is disappointing given the cost pressures on health care systems, throughout the world.

Inconsistency in timeframes for measuring critical outcomes also limited ability to perform meaningful comparisons between studies. A significant number of studies reported very short follow-up periods whereas yet others reported outcomes over timeframes as long as 12 months. Consensus on a minimum or recommended timeframe for outcome collection across wound healing or indeed other diabetes-related foot ulcer intervention studies will reduce heterogeneity between studies and may lead to better quality meta-analyses in the future.

Finally we are aware that wound healing is a cascade of physiological processes and that wound healing interventions may not be appropriate in all phases of the wound healing cycle. Thus more innovative approaches to trial design may be needed to ensure that a wound healing protocol is relevant to all stages of the process and that outcomes relevant to this are developed, agreed and objectively measured.

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GUIDELINE WORKING GROUP CONFLICT OF INTEREST POLICY

The IWGDF is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major conflict of interest (COI) members of the guideline 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 guideline. 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.

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

AUTHOR CONTRIBUTIONS

The working group was chaired by FG (on behalf of the IWGDF). PC acted as scientific secretary. All members of the guideline were involved in summarising available evidence in the supporting systematic reviews which are published separately (7) and in writing this guideline. All members were assigned to individual sections of the guideline, and all authors reviewed and discussed during group meetings the evidence obtained, the evidence to decision making items according to GRADE and each recommendation (further details are available in the Methods section). All authors reviewed and agreed with the final document before external review and subsequent submission for endorsement. The list of authors and their contributions to the guideline is listed at the end of this document. 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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