

**SUPPLEMENT ARTICLE**

Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update)

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Abstract

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. In conjunction with advice from internal and external reviewers and expert consultants in the field, this update is based on a systematic review of the literature centred on the following: the Population (P), Intervention (I), Comparator (C) and Outcomes (O) framework; the use of the SIGN guideline/Cochrane review system; and the 21 point scoring system advocated by IWGDF/EWMA. This has resulted in 13 recommendations. The recommendation on sharp debridement and the selection of dressings remain unchanged from the last recommendations published in 2016. The recommendation to consider negative pressure wound therapy in post-surgical wounds and the judicious use of hyperbaric oxygen therapy in certain non-healing ischaemic ulcers also remains unchanged. Recommendations against the use of growth factors, autologous platelet gels, bioengineered skin products, ozone, topical carbon dioxide, nitric oxide or interventions reporting improvement of ulcer healing through an alteration of the physical environment or through other systemic medical or nutritional means also remain. New recommendations include consideration of the use of sucrose-octasulfate impregnated dressings in difficult to heal neuro-ischaemic ulcers and consideration of the use of autologous combined leucocyte, platelet and fibrin patch in ulcers that are difficult to heal, in both cases when used in addition to best standard of care. A further new recommendation is the consideration of topical placental derived products when used in addition to best standard of care.

KEYWORDS

diabetic foot, dressing, foot ulcer, guidelines, wound healing

List of recommendations

1. Remove slough, necrotic tissue, and surrounding callus of a diabetic foot ulcer with sharp debridement in preference to other methods, taking relative contraindications such as pain or severe ischemia into account (GRADE strength of recommendation: strong; quality of evidence: low).
2. Dressings should be selected principally on the basis of exudate control, comfort, and cost (strong; low).
3. Do not use dressings/applications containing surface antimicrobial agents with the sole aim of accelerating the healing of an ulcer (strong; low).
4. Consider the use of the sucrose-octasulfate impregnated dressing as an adjunctive treatment, in addition to best standard of care, in noninfected, neuro-ischaemic diabetic foot ulcers that are difficult to heal (weak; moderate).
5. Consider the use of systemic hyperbaric oxygen therapy as an adjunctive treatment in non-healing ischaemic diabetic foot ulcers despite best standard of care (weak; moderate).
6. We suggest not using topical oxygen therapy as a primary or adjunctive intervention in diabetic foot ulcers including those that are difficult to heal (weak; low).
7. Consider the use of negative pressure wound therapy to reduce wound size, in addition to best standard of care, in patients with diabetes and a post-operative (surgical) wound on the foot (weak; low).
8. We suggest not using negative pressure wound therapy in preference to best standard of care in nonsurgical diabetic foot ulcers (weak; low).
9. Consider the use of placental-derived products as an adjunctive treatment, in addition to best standard of care, when the latter alone has failed to reduce the size of the wound (weak; low).
10. We suggest not using growth factors, autologous platelet gels, bioengineered skin products, ozone, topical carbon dioxide, and nitric oxide in preference to best standard of care (weak; low).
11. Consider the use of autologous combined leucocyte, platelet and fibrin as an adjunctive treatment, in addition to best standard of care, in noninfected diabetic foot ulcers that are difficult to heal (weak, moderate).
12. Do not use agents reported to have an effect on wound healing through alteration of the physical environment including through the use of electricity, magnetism, ultrasound, and shockwaves in preference to best standard of care (strong; low).
13. Do not use interventions aimed at correcting the nutritional status (including supplementation of protein, vitamins and trace elements, pharmacotherapy with agents promoting angiogenesis) of patients with a diabetic foot ulcer, with the aim of improving healing, in preference to best standard of care (strong; low).

1 | INTRODUCTION

The management of diabetic foot ulcers (DFUs) remains a challenge. They are often associated with adverse outcomes including protracted

healing, failure to heal, infection, sepsis, amputation, a high risk of recurrence in those which do heal, and death. There are a number of key biological elements that have been suggested to adversely affect ulcer healing including persistent inflammation, loss of protective sensation that may be exacerbated by abnormal biomechanics, peripheral arterial disease, and infection. The rising cost of the management of DFUs in many health care settings means that there is a need to ensure that the use of interventions, which are promoted to enhance healing of chronic ulcers of the foot in diabetes, are supported by appropriate good quality evidence of effectiveness and cost-effectiveness. Previous systematic reviews, including the four undertaken for the International Working Group on the Diabetic Foot (IWGDF) in the last 14 years, have repeatedly drawn attention to poor study design as a key factor preventing critical assessment of the majority of DFU healing therapies and have recommended an urgent need for higher quality studies. Perhaps as a result of these publications and the publication in 2016 by Jeffcoate et al¹ outlining key features expected in the design and reporting of clinical studies in people with diabetes and ulcers of the foot, a number of well-designed and executed studies have since been reported. Thus, this latest guidance on interventions designed to achieve improved healing in DFU comes at an opportune time.

2 | METHODS

In this guideline, we have followed the GRADE methodology, which is structured around clinical questions in the patient-intervention-comparison-outcome (PICO) format, systematic searches and assessment of the available evidence, followed by developing recommendations and their rationale.^{2,3}

First, a multidisciplinary working group of independent experts (the authors of this guideline) was installed by the IWGDF editorial board. The members of the working group devised the clinical questions, which were revised after consultation with external experts from a number of geographical regions and the IWGDF Editorial Board. The aim was to ensure the relevance of the questions for clinicians and other health care professionals in providing useful information on the use of interventions to enhance healing of chronic DFUs. We also formulated what we considered critically important outcomes relevant for daily care, using the set of outcomes defined by Jeffcoate et al¹ as a reference guide.

Second, we systematically reviewed the literature to address the agreed upon clinical questions. 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 evidence of publication bias (the latter where appropriate). We then rated the quality of evidence as "high," "moderate," or "low." The systematic review supporting this guideline is published separately.⁴

Third, we formulated recommendations to address each clinical question. We aimed to be clear, specific, and unambiguous on what we recommend, for which persons, and under what circumstances. Using the GRADE system, we provided the rationale for how we

arrived at each recommendation based on the evidence from our systematic review (4), expert opinion where evidence was not available, and a careful weighing of the benefits and harms, patient preferences, and financial costs (resource utilization) related to the intervention or diagnostic method.^{2,3} On the basis of these factors, we graded the strength of each recommendation as “strong” or “weak,” and for or against a particular intervention or diagnostic method. All our recommendations (with their rationales) were reviewed by the same international experts who reviewed the clinical questions, as well as by the members of the IWGDF Editorial Board.

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.⁵

3 | RECOMMENDATIONS

3.1 | In individuals with active diabetic foot ulcers, which method of debridement should be used to promote healing?

1. Remove slough, necrotic tissue, and surrounding callus of a diabetic foot ulcer with sharp debridement in preference to other methods, taking relative contraindications such as pain or severe ischemia into account. (GRADE strength of recommendation: strong; quality of evidence: low).

Rationale:

Debridement involves the removal of surface debris, slough, and necrotic tissue with the purpose of leaving clean and viable tissue to support healing. The different techniques to undertake debridement include physical (eg, surgical, sharp, hydro-debridement, or gaseous debridement), biological (larvae), autolytic (hydrogels), or biochemical (enzymes) methods. Although there is unequivocal consensus in support of the use of debridement to clean the surface of the wound, high quality evidence to justify debridement in general and identify the best form of debridement is limited.

Six randomized controlled trials (RCTs) and five controlled cohort studies were found as described in our systematic review (ref our paper). All of these were assessed as being at moderate to high risk of bias. Three studies on hydrogel-based autolytic debridement suggested these agents may have a beneficial effect on ulcer healing when compared with saline moistened gauze, but the risk of bias was high—a conclusion supported by two previous Cochrane reviews.^{6,7} Two studies on clostridial collagenase ointment compared with best practice or a comparator form of debridement showed benefit (refs needed), but three other studies^{8,9} failed to observe any benefit; all had significant methodological limitations and a high risk of bias.

One study on sharp debridement was found¹⁰ which showed benefit, was a post hoc subgroup analysis of cases from an RCT (ref) of another intervention. One RCT was found on hydrosurgical debridement but was of poor methodological quality and did not show benefit in terms of wound healing compared with standard sharp debridement.¹¹

The use of larval therapy to enhance wound healing remains unsupported with only five studies identified, each of which had a high risk of bias.¹²⁻¹⁶

Overall, there are data of low quality to suggest that debridement of some sort is beneficial and effective, but insufficient good quality evidence to support one form of debridement over another. Current expert opinion recommends that sharp debridement should be adopted in preference to other techniques, particularly as this is the least expensive of the methods and available in all geographic areas. This recommendation should take into account relative contraindications such as severity of ischaemia and pain and is made in the understanding that it is undertaken by those skilled in debridement avoiding the potential of damage to healthy skin. Furthermore, there is general agreement that urgent surgical debridement, undertaken in an operating theatre, is indicated in the presence of gas forming infection, abscess, or necrotising fasciitis.

3.2 | In individuals with active diabetic foot ulcers, what is the best dressing/application to choose in addition to usual best care with the aim of enhancing wound healing?

2. Dressings should be selected principally on the basis of exudate control, comfort, and cost (strong; low).
3. Do not use dressings/applications containing surface antimicrobial agents with the sole aim of accelerating healing of an ulcer (strong; low).
4. Consider the use of the sucrose-octasulfate-impregnated dressing as an adjunctive treatment, in addition to best standard of care, in noninfected, neuro-ischaemic diabetic foot ulcers that are difficult to heal (weak; moderate).

Rationale:

Dressings are commonly used in DFU care, and the rationale for their use includes the provision of comfort, protection of the ulcer, and exudate control. These include basic contact dressings (low adherence dressings such as paraffin gauze or simple absorbent dressings) and advanced dressings (alginate, hydrogel, films, hydrocolloid, foam). Some dressings contain agents with antimicrobial properties (honey, iodine, silver, polyhexamethylene) and some contain agents designed to alter the biology of the chronic wound, for example influencing surface protease activity.

3.2.1 | Basic contact and advanced dressings

The evidence to support the adoption of any of these dressings or application above any other is poor because the available studies are small, usually of short duration of follow-up and are at a high risk of bias.

3.2.2 | Dressings/applications with surface antimicrobial properties

There remains widespread use of dressings and/or applications containing antimicrobial agents, such as silver or iodine or those delivering antibiotics directly to the wound surface. A single study reporting the use of antibiotic impregnated beads after transmetatarsal amputation found no impact on wound healing.¹⁰

A large multicentre RCT with low risk of bias comparing a non-adherent dressing with an iodine-impregnated dressing and a carboxymethylcellulose hydrofibre dressing showed no difference between the three products in terms of either wound healing or the incidence of new infection.¹⁷ An underpowered RCT with potassium permanganate in 2018 did not permit any conclusion.¹⁸ The findings of this review echo those of a Cochrane review from 2017 concluding that evidence for the effectiveness and safety of topical antimicrobial treatments for diabetic foot ulcers (dressings as well as other topical formulations) was limited by the availability of relatively few, frequently small, and poorly designed studies.¹⁹

3.2.3 | Dressings/applications with honey

Topical applications of honey products have been used for many years with the goal of improving healing. They are thought to possess anti-inflammatory and antimicrobial properties, although this requires confirmation.²⁰ There is, however, little good quality-controlled trial evidence to support their use for either the promotion of healing or the prevention of secondary infection. Five controlled studies (four small and one large) on the use of topical honey have been identified.²¹⁻²⁵ The larger study identified did report apparent improvement in healing of ulcers compared with saline-soaked gauze, but was unblinded and results were analysed per protocol.²⁵ A Cochrane review of honey-based dressings in all wound types in 2015 concluded that the effects of honey relative to its comparators on healing was unclear²⁶ and suggested that health services may wish to consider avoiding routine use of honey dressings until sufficient evidence of effect is available. The current review did not find new studies which would change these conclusions.

3.2.4 | Dressings/applications influencing chronic wound biology

The results of an early study with carboxymethylcellulose dressing suggesting that the intervention improved ulcer depth²⁷ were not born out by a large outcome blind RCT.¹⁷ Two recent RCTs with topical Pirferidone (with potential anti-inflammatory/antifibrotic properties) had methodological limitations; neither were blinded, results were analysed per protocol, and there was a high dropout rate in one,²⁸ and an unexpectedly low healing rate in the control group in the other.²⁹ Four RCTs of products designed to promote healing; Chitosan and Isosorbide dinitrate,³⁰ hyaluronic acid,³¹ an acellular flowable matrix,³² and the

proteolytic fraction from latex P1G10³³ provided little support for the use of these agents in clinical practice because of a small number of recruited patients, nonblinding, per protocol analysis, and/or high drop-out rates. One RCT of a gap-junctional protein (ACT1, a connexin43-based gel) in patients with noninfected neuropathic ulcers showed a significantly greater reduction in mean percent ulcer area from baseline to 12 weeks but with a high rate of withdrawal of consent and protocol noncompliance.³⁴

One recent large double blind multicentre RCT with a low risk of bias³⁵ investigated the efficacy of sucrose-octasulfate impregnated dressings in noninfected ulcers in patients with an index limb ABI < 0.9 or TBI < 0.7 but toe pressure > 50 mmHg. Patients were excluded if they had a reduction in the wound area of more than 30% during a 2-week period of good standard of care including appropriate prespecified offloading. There was a significant relative benefit with an adjusted odds ratio of 2.60 (95% CI, 1.43-4.73) for healing with the use of sucrose-octasulfate dressing at week 20, and faster estimated time to heal compared with the placebo dressing. Considering these data, we conclude that in moderately ischaemic neuropathic and noninfected DFUs, where there has been insufficient change in diabetic foot ulcer area with best standard of care including appropriate offloading, there is sufficient evidence to consider the use the sucrose-octasulfate-impregnated dressing. However, the timing of initiating treatment and the cost-effectiveness remain to be established. It is also recognized that this is the only study of this intervention, and so despite the quality of the data, the evidence was considered to be moderate and the strength of the recommendation weak. Further studies may alter this recommendation.

3.3 | In individuals with active diabetic foot ulcers, does systemic hyperbaric oxygen or topical oxygen therapy in comparison to standard care help promote healing?

5. Consider the use of systemic hyperbaric oxygen therapy as an adjunctive treatment in nonhealing ischaemic diabetic foot ulcers despite best standard of care (weak; moderate).
6. Do not use topical oxygen therapy as a primary or adjunctive intervention in diabetic foot ulcers including those that are difficult to heal (weak; low).

Rationale:

3.3.1 | Systemic hyperbaric oxygen therapy

The use of *systemic* HBOT is based on the principle that overcoming wound hypoxia could expedite the healing process and promote epithelialisation.^{36,37}

Of two early RCTs^{38,39} with low risk of bias, the larger demonstrated a significantly improved outcome in the intervention group, whose ulcers were more likely to heal within 12 months.³⁹ Of note, the intervention group included patients who either had no evidence of PAD or who

were deemed unsuitable for vascular reconstruction, unlike the previous RCT,³⁸ where only patients with nonreconstructable critical limb ischaemia were included. Subsequently, however, a large retrospective cohort study of patients treated in 83 centres in the United States concluded that HBOT did not appear to be useful for the prevention of amputation and did not improve the likelihood that an ulcer would heal.⁴⁰

More recent studies include two further large outcome blinded RCTs^{41,42} neither of which demonstrated any additional benefit above usual care of the intervention. Both had significant methodological limitations including being underpowered, the use of subjective outcome measures and were therefore considered at high risk of bias.^{41,42}

Marked heterogeneity was noted in the patient and ulcer inclusion criteria in these studies and it is unclear if individuals who are able to augment their TcPO₂ above a certain threshold have a higher probability of benefit or whether those with a particular degree of arterial insufficiency would demonstrate no effect.⁴³ One important secondary result from one of the most recent studies⁴² was the finding that many patients are unable to complete the full HBOT regimen, frequently because of their overall poor health.

It is recognized that in some countries, there is limited or even no access to HBOT and thus not a treatment option. In others, this will be an expensive treatment with significant patient burden in terms of visits and potential for side effects. Further, blinded and randomized trials are required to confirm the cost-effectiveness of systemic HBO, as well as to identify the population most likely to benefit from its use.

3.3.2 | Topical oxygen therapy

Topical oxygen therapy can be defined as a therapy that supplies continuous or cyclical diffusion of pure oxygen over the surface wound. Four randomized controlled studies of topical oxygen therapy were identified. The results of two earlier nonrandomized studies^{44,45} showing apparent benefit should be viewed with caution because of methodological flaws. Two more larger blinded RCTs have subsequently been published, both considered at low risk of bias.^{46,47} The former demonstrated that continuous diffusion of oxygen led to higher proportion of healed DFUs in 12 weeks and a significant faster time to closure compared with standard care,⁴⁶ however, these results were not confirmed in the other equally large blinded RCT conducted over a similar time frame.⁴⁷ Given these conflicting results, we could not recommend this type of therapy until further blinded independent RCTs are performed which would need to take into consideration costs, adverse outcomes, and patient views.

3.4 | In individuals with active diabetic foot ulcers, does negative pressure wound therapy in comparison to standard care help promote healing? If so, when? And in which setting?

7. Consider the use of negative pressure wound therapy to reduce wound size, in addition to best standard of care, in patients with

diabetes and a post-operative (surgical) wound on the foot (weak; low).

8. We suggest not using negative pressure wound therapy in preference to best standard of care in nonsurgical diabetic foot ulcers (weak; low).

Rationale:

Negative pressure wound therapy (NPWT) involves the application of a wound dressing through which continuous or intermittent negative pressure (or vacuum) is applied, allowing tissue fluid to drain away from the area and collected in a canister. NPWT appears to stimulate granulation tissue formation and contraction of the wound.⁴⁸ Potential adverse effects of NPWT have been described, including wound maceration, retention of dressings and potentially, wound infection.⁴⁹

There are two distinct types of wounds in which NPWT has been studied in the management of DFUs, the post-surgical and the chronic nonsurgical wound.

3.4.1 | Post-surgical wounds

In total, four RCTs (two large and two small), all with a high risk of bias, suggested that time to healing of postsurgical diabetic foot wounds were shortened in comparison with usual standard of care (SOC).⁵⁰⁻⁵³ In one relatively large study of post-amputation wounds, there was small but significant benefit, but in this study, there was a high dropout rate and the outcome was unusual as it included those healed as well as those unhealed but rendered suitable for surgical wound closure.⁵⁰ In the other relatively large study of postoperative wounds, a greater proportion of foot ulcers achieved complete ulcer closure with NPWT than with advanced wound therapy within 112-day active treatment phase but the study was unblinded and there was a relatively high dropout rate.⁵¹ The most recent RCT⁵³ was a small study primarily in postoperative vascular wounds with only 80% of participants having diabetes. There was no significant change in the primary outcome of wound volume reported. Of note, the significant reduction in wound depth was a secondary outcome. The study was found to high risk of bias and does not change the previous recommendation. A further study suggested that split skin grafting⁵⁴ was more successful with the addition of NPWT, however this was a small study with a high risk of bias.

The cost, burden to the patient and applicability in daily practice need to be considered when embarking on negative pressure therapy.

From the available evidence, we recommend considering the use of negative pressure wound therapy to reduce wound size, in addition to best standard of care, in patients with diabetes and a post-operative (surgical) wound on the foot (weak; low).

3.4.2 | Non-surgical wounds

In total, four RCTs, two cohort studies, and one case-control were found, comparing the use of NPWT with SOC all of which were at high risk of bias.⁵⁵⁻⁶¹

Of the three additional studies following the last recommendations, the first was a nonrandomized case control (allocation by hospital number) study which reported a significant benefit from using NPWT but did not provide the results of statistical analysis.⁶¹ The second, a larger RCT also suggested benefit of NPWT over “advanced moist wound therapy” in terms of reduced ulcer area after 2 weeks but did not provide a clear description of the statistical basis of the conclusion.⁵⁹ The final was a smaller, nonrandomized cohort study in which the use of NPWT was associated with a reduction in ulcer area when compared with a calcium alginate dressing. This study was at high risk of bias, with a high dropout rate, and the statistical basis of the conclusion was not clear.⁶⁰

In view of the available evidence, we do not recommend NPWT to enhance the healing of nonsurgical diabetic wounds.

3.5 | In individuals with active diabetic foot ulcers that are hard-to-heal, does the use of placental derived products in addition to standard care in comparison to standard care alone help promote healing?

9. Consider the use of placental derived products as an adjunctive treatment, in addition to best standard of care, when the latter alone has failed to reduce the size of the ulcer (weak; low).

Rationale:

Human placental membranes contain a combination of growth factors, collagen-rich extracellular matrix, and cells including mesenchymal stem cells, neonatal fibroblasts, and epithelial cells that provide the necessary mechanisms for coordinated wound healing. Multiple growth factors and proteins including TGF- β 3 and human growth factor, antimicrobial proteins and angiogenic factors (VEGF, PDGF, and basic fibroblast growth factor) are present in the matrix.^{62,63} A number of products derived from different components of the placental and umbilical cord have been developed to enhance healing in a variety of tissues including diabetic foot skin wounds. Cryopreserved preparations contain living cells as well as growth factors whereas dehydrated products which are easier to store and handle contain growth factors but no living cells.

The previous review reported a single study of an amniotic membrane wound graft but commented that the study was of high risk of bias and the conclusions marred by the low rate of healing in the comparator group.⁶⁴ In the relatively short period of time since that study, interest in this type of therapy has developed rapidly as shown by the number of new placental-derived products available and the publication of eight RCTs and a cohort registry study.⁶⁴⁻⁷⁴

The effect of an amniotic membrane allograft was compared with standard care in a well-designed RCT.⁶⁵ The incidence of ulcer closure was greater, as was median time to ulcer closure in those receiving the amniotic membrane allograft.⁶⁵ It was unclear however whether the outcome was truly blinded as the local investigators were the first to note healing, only subsequently confirmed by blinded independent image analysis. A 3-arm RCT compared weekly treatment with bioengineered skin substitute, with an amniotic membrane product and a collagen-alginate dressing.⁷³ The incidence of healing within 12 weeks was reported as being highest in those receiving the amniotic membrane product. Outcomes were unblinded however, and a planned interim analysis had been previously reported, leading to a moderate risk of bias.

Two other RCTs, one comparing the use of a bioimplant of amniotic membrane tissue with a wet dressing,⁶⁸ the other amniotic membrane allograft with SOC.⁶⁹ Both reported improvements in healing with those treated with amniotic membrane products, although both studies were considered high risk of bias and the significance of the findings is uncertain.

A single blind study of an umbilical cord product was recently reported to show a significant improvement in healing compared with good SOC.⁷² Neither patient nor investigator were blind to treatment allocation, and digital images assessed by a blinded outcome committee were used to assess the primary outcome of healing. These interesting early data need confirming in a further independent RCT. A further study designed to show non-inferiority of a placental product compared with a human fibroblast-derived dermal substitute was also found, however, the significance of this finding is unclear given the comparator.⁷⁰

A cohort registry study compared the use of a dehydrated human amniotic membrane allograft with a commercially available bilayered “living cellular construct.”⁷⁴ The median time to closure was significantly less in those receiving the amniotic membrane allograft. The significance of the finding is weakened by the high risk of bias of the study.⁷⁴

Thus, the available evidence from a number of studies (including those of moderate bias) suggests that placenta-derived products may have a beneficial effect on ulcer healing. This overall finding needs to be confirmed in further large randomized trials, evaluating potential side effects such as increased risk of infection, applicability in daily practice, and associated health economic outcomes. Currently, the available evidence is insufficient to support the superiority of one product above another.

3.6 | In individuals with active diabetic foot ulcers that are difficult to heal, do products designed to improve ulcer healing by altering the biology: growth factors, platelet related products, bioengineered skin products and gases or a combination of leucocyte platelet and fibrin, in comparison to standard care alone help promote healing?

10. We suggest not using growth factors, autologous platelet gels, bioengineered skin products, ozone, topical carbon dioxide, and nitric oxide in preference to best standard of care (weak; low).

11. Consider the use of autologous combined leucocyte, platelet and fibrin as an adjunctive treatment, in addition to best standard of care, in non-infected diabetic foot ulcers that are difficult to heal (weak, moderate).

Rationale

We identified seven studies on platelet-based applications and seven on the use of platelet-derived growth factors (PDGF).

3.6.1 | Platelet-based applications

The earliest of these studies reported a benefit of autologous platelet factor on ulcer healing but included leg and foot ulcers and was conducted in both people with and without diabetes.⁷⁵ A later study using platelet concentrate reported an apparent improvement in ulcer healing but was marred by there being high number of dropouts and the use of per protocol analysis.⁶¹ Another RCT using platelet autogel, reported a positive result for complete ulcer healing at 12 weeks, however, there was a very high exclusion rate which necessitated the use of per protocol analysis.⁷⁶ To overcome the problem of the volume of blood required from an individual for the preparation of autologous platelet gel or fluid, one study used blood bank-derived platelets.⁷⁷ Although benefit on ulcer healing was reported few details of the inclusion criteria were provided. One recent large RCT of autologous platelet gel reported benefit in time to complete ulcer closure at 12 weeks in comparison to standard care, however, this study was confined to inpatients and there was a moderate risk of bias.⁷⁸ Using povidone iodine 10% ointment as comparator, another RCT also suggested a higher probability of ulcer healing with autologous platelet gel but did not report of DFU characteristics, additional medical and vascular interventions provided, and was therefore regarded to be at a high risk of bias.⁷⁹ One large retrospective cohort study found platelet releasate was more effective than standard therapy with more pronounced effect in wounds of higher severity but there were limitations of the study design and analysis including the use of propensity scoring.

Overall, although the trial results of autologous platelets may suggest a potential benefit in ulcer healing, the evidence is inclusive, there is the problem of the volume of blood required and it is unclear as to the optimal frequency of applying the various products. Given their expense and the inclusive evidence routine use of these products is not recommended.

3.6.2 | Recombinant platelet derived growth factor

Eight RCTs evaluating the effect of recombinant platelet-derived growth factor (r-PDGF) on ulcer healing in DFUs were identified;

these showed either no improvement when compared with the control groups or were marred by significant methodological problems.⁸⁰⁻⁸⁶ Of the two recent studies, one with 16 weeks follow-up did not report any benefit over standard care and good quality offloading in neuropathic DFUs⁸⁵ and the other thought reporting a higher odds of complete healing at 24 weeks had significant methodological limitations including small sample size and a lack of intention-to-treat analysis.⁸⁶ Given the cost of the product, additional information is required for both its effectiveness and particularly cost-effectiveness before it is considered for use in routine care.

3.6.3 | Autologous combined leucocytes, platelets, and fibrin

The use of a multilayered patch of autologous leucocytes, platelets, and fibrin was recently assessed in patients with hard to heal ulcers defined as those with less than 50% reduction in ulcer size after a 4-week run-in period.⁸⁷ This well-designed multicentre study reported significantly more ulcers achieving complete ulcer healing in the intervention group compared with the group receiving standard of care only (34% vs 22%). A limitation of this study was that it was not possible to blind the patients or those delivering the therapy; however, healing was assessed by an independent assessor blinded to treatment allocation. The intervention involved weekly visits for venesection, preparation, and application of the patch, which may have significant cost implications. Further, RCTs are also required to assess if the effect is consistent. Therefore, while the quality of the one available study is strong, the lack of cost effectiveness, applicability in daily practice and the importantly, the absence of additional supportive studies means that the strength of our recommendation is weak.

3.6.4 | Dermal-derived substitutes

In total, we identified three RCTs on dermal substitutes, as described in our systematic review.² A single well-designed multicentre RCT of low risk of bias reported the benefit of an acellular, bi-layered matrix on the healing of neuropathic DFUs when compared with standard care⁸⁸; but a second three-arm RCT⁸⁹ reported no difference in healing by 16 weeks when the management of DFUs with one acellular dermal matrix was compared with another and with usual care. It is difficult to assess the importance of the reported weakly significant difference between one product and usual care because of limitations in trial design and reporting.

A moderate sized nonblinded RCT⁹⁰ has reported that the addition of an acellular dermal matrix during the course of skin grafting conferred no significant benefit in terms of time to healing.

These agents are expensive and cost-effective studies have not been performed. Thus, given the lack of consistent trial data and since the indications for their use are not yet completely defined, the strength of the recommendation not to employ the use of dermal substitutes in addition to best standard care in hard-to-heal wounds is

strong, although the quality of the evidence against their use is moderate.

3.6.5 | Dermal derived growth factors

The demonstrated reduction in growth factors released by the cells involved in ulcer healing in people with diabetes has been suggested as one possible reason for the impaired healing of DFUs. The topical supplementation of growth factors has therefore been suggested as an adjunct to standard of care to enhance healing of these lesions.⁹¹

Previous systematic reviews^{92,93} found no quality trials to support the use of dermal cell derived growth factors to enhance healing of DFUs. Two further controlled studies have been identified more recently.^{94,95} The first was a small study, which compared the application of 75 µg of recombinant human epidermal growth factor thrice a week against placebo demonstrated a weakly significant difference in the proportion of ulcers healed and in reduction in ulcer size.⁹⁴ That none of the ulcers in the control arm healed is surprising, but usual care especially offloading was not described. The second study, which had a high risk of bias, reported an unorthodox mixed endpoint and the chosen statistical analysis was inappropriate. The reported benefit of the intervention should therefore be treated with caution.⁹⁵

Thus, the evidence for the effectiveness or cost effectiveness of the use of dermal-derived growth factors to enhance healing of DFUs remains poor and we strongly recommend to not use topical growth factors in hard-to-heal DFUs.

3.7 | In individuals with active diabetic foot ulcers that are difficult to heal, does the use of other products that alter wound biology through mechanical and physical means (lasers, shockwaves, ultrasound, magnetism, and electric current) in addition to standard care in comparison with standard care alone help promote healing?

12. Do not use agents reported to have an effect on ulcer healing through alteration of the physical environment including through the use of electricity, magnetism, ultrasound, and shockwaves, in preference to best standard of care (strong; low).

Rationale

The previous reviews found nine studies of physical therapies, including shockwaves, ultrasound, laser therapy, magnetism, and electrical current. The current review found a number of new controlled studies; one study of ultrasound⁹⁶ two of extracorporeal shockwaves^{97,98}, three of low level Laser therapy,⁹⁹⁻¹⁰¹ one of advanced class IV laser emitting four wavelengths,¹⁰² two using photodynamic therapy (PDT),^{103,104} one using infrared radiation,¹⁰⁵ and one on pneumatic

compression¹⁰⁶. All were of high risk of bias or showed no evidence of benefit. One RCT study of therapeutic magnetic resonance therapy¹⁰⁷ was at low risk of bias but showed no benefit on the healing of DFUs despite the promise of an earlier pilot.¹⁰⁸

Overall, because of poor study design, it was concluded that there was little evidence to recommend the use of mechanical and physical therapies in the management of hard-to-heal diabetic foot ulcers.

3.8 | In individuals with active diabetic foot ulcers that are difficult to heal, do interventions aimed at correcting the nutritional status (including supplementation of vitamins and trace elements, pharmacotherapy with agents promoting angiogenesis) in comparison to standard care help promote healing?

13. Do not use interventions aimed at correcting the nutritional status (including supplementation of protein, vitamins and trace elements, pharmacotherapy with agents promoting angiogenesis) of patients with a diabetic foot ulcer, with the aim of improving healing, in preference to best standard of care (strong; Low)

Rationale.

It is recognized that in individuals with DFUs, infection, antimicrobial agent use, and reduced mobility coupled with possible suboptimal glycaemic control may drive a catabolic state leading to protein energy malnutrition as well as inherent inability to optimize macro and micro-nutrient usage.¹⁰⁹ We found one study on zinc supplementation,¹¹⁰ one study on magnesium replacement,¹¹¹ one on omega-3 supplementation¹¹² another on the effect of vitamin D replacement on diabetic foot ulceration,¹¹³ and one on the use of probiotics.¹¹⁴ All observed an apparent benefit from supplementation, on ulcer length, width, and depth as secondary outcome measures. However, no patient characteristics, or demographics were provided, and usual standard of care was not defined. One RCT of moderate risk of bias did not find benefit on ulcer healing at 4 weeks with an oral nutritional supplement.¹¹⁵ The authors reported several challenges while undertaking studies with systemic supplementation in individuals with diabetic foot ulcers, including the lack of clear definitions and the uncertainty of ensuring patient compliance with the intervention. Another RCT, undertook supplementation with a protein energy drink (arginine, glutamine, and b-hydroxy-b-methylbutyrate or a control drink) and found no group differences in ulcer closure or time to ulcer healing at 16 weeks.¹¹⁵

Trials of low molecular weight heparin,¹¹⁶ iloprost infusion,¹¹⁷ pentoxifylline,¹¹⁸ and of herbal preparations (administered orally in two studies and intravenously in one) were of poor quality, and none showed any major improvement in outcome.^{119,120} One study of the use of oral vildagliptin reported apparent improvement in healing at 12 weeks, but the very low incidence of healing in the control group casts doubt on the likely clinical benefit of this product if used in addition to good clinical care.¹²¹ Despite a number of randomized controlled studies, these interventions, given the significant methodological

limitations and moderate to high risk of bias, the quality of evidence was graded as low. Thus, there is no evidence to justify the recommendation for the adoption of any other systemic therapy to enhance the healing of DFUs in routine practice.

4 | CONSIDERATIONS

The recommendations in this guidance have been derived from critical systematic review of all relevant publications utilizing the Cochrane scoring system. For the first time, the 21-point system recommended by Jeffcoate et al¹ was also used to score all relevant publications found since the last review by the IWGDF. We believe the latter has improved the review process and the strength of the recommendations. However, as previously stated, in several areas where evidence was not available, the recommendations were based on expert opinion and established practice, taking into consideration financial implications; for example, where sharp debridement was recommended in preference to other forms of debridement.

It is of note that since the last review, there has been a significant increase in research activity in DFU healing with 97 published clinical trials identified for review between 2015 and 2019, whereas there were only 33 between 2011 and 2015. Furthermore, for the first time, we able to recommend two specific therapies, each of which have been demonstrated to hasten ulcer healing in well-conducted single large RCTs.^{35,87} However, it should be noted that these studies apply to well-defined patient groups, each with predefined vascular and neuropathic criteria for recruitment into the study. Thus, it is not possible to generalize the findings to all DFU where the vascular and neuropathic status may differ. Further, studies looking at other patient groups as well as an economic analysis of their individual cost benefit are therefore required, the results of which may change the weak recommendation they have been assigned. Since the last review, there have also been promising developments in other areas of DFU healing therapies. The studies on placental derived wound products show promising results although the majority were unblinded and/or subject to other biases. We expectantly await high quality RCTs in this area. At present the availability and use of these products outside the United States is limited. If further RCTs confirm benefit, the widespread availability of placental tissue and the possibility of less expensive processing methods could make this a cost-effective treatment with applicability in lower economy countries.

Although it is encouraging to see an increase in high-quality clinical diabetes ulcer care trials, it is disappointing that there have been few new studies of NWPT and systemic hyperbaric oxygen therapies. There thus remains a paucity of well-designed studies for these therapies which is surprising and lamentable given their expense and widespread use in a number of countries.

Finally, it is also important to recognize that these recommendations have been based on studies conducted in specialist multidisciplinary foot clinics, mostly in first world countries. 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.

5 | RECOMMENDATIONS FOR FUTURE RESEARCH

5.1 | Study design

The 21 recommendations suggested by Jeffcoate et al is an excellent tool on which to plan and report intervention studies.¹ It is of interest that the only two studies to convincingly demonstrate benefit were large studies also fulfilling nearly all 21 recommendations. It is possible that had such rigour been applied to the design and conduct of previous studies, the results of these recommendations may have been different. Going forward, we would recommend investigators conducting studies use trial designs and reporting that meet these recommendations, otherwise, even if they demonstrated positive outcomes, it is likely that they would be rated as low-quality evidence. We would therefore recommend that all future trials should be RCTs with sufficient numbers of patients and conform to the 21 recommendations.

5.2 | Recurrence

Over 40% of DFUs will recur within 1 year and 65% within 5 years. Although there are many reasons for recurrence including patient behaviours and biomechanics, ulcer healing therapies may, in addition to enhancing closure, alter the quality of the tissue in the healed ulcer and thus influence recurrence. Thus, long-term follow-up should be included in future trial design to assess the benefit or otherwise of therapies on recurrence.

5.3 | Standard of care and patient characteristics

We would encourage researchers to more fully describe what they mean by the standard of care as this was not often well-described. Thus, for example, it was not always clear whether the ulcer care was provided by podiatrists, surgeons, diabetologists, or wound care specialists particularly as it is known this can vary both within and across countries. Patient characteristics are also not well-described, in particular, their neurological and/or vascular status. Furthermore, details of offloading and the type of dressings applied as standard were unclear in many of the studies reviewed.

5.4 | Independent well-designed studies to evaluate the efficacy and cost effectiveness of frequently used interventions where the evidence for their use is weak

A number of therapies including NWPT and hyperbaric oxygen therapy have, in this and previous reviews, been found to have weak evidence of benefit. Given that they have widespread use and utilize considerable financial resources, it is important that there are

independent well-designed and conducted studies to confirm their benefit in diabetic foot ulceration.

5.5 | Comparative cost effectiveness

Given that for the first time, research evidence for a number of effective therapies are available, head-to-head comparisons should include evaluation of their comparative cost effectiveness.

5.6 | Combinations of therapies and timing of their use

The process of healing is highly complex involving interaction of many different cell types and signalling pathways. Furthermore, the ulcer healing process lasts for weeks or months. Most of the new therapies are effective at specific phases in the ulcer healing process. Future research should explore whether a combination of therapies used at the same time but targeting different pathways in the same healing phase would further enhance healing. Additionally, research should determine whether therapies which target different phases of the ulcer healing process used sequentially enhance healing.

ACKNOWLEDGEMENTS

We would like to thank the following external experts for their review of our PICO and guideline for clinical relevance: Paul Wraight (Australia); Didac Mauricio (Spain); Glynis Beaton (Guyana); Abdul Basit (Pakistan); Grace Spencer (Caribbean/St Maarten); Mohamed ElMakki Ahmed (Sudan); Teresa Que (Philippines); Tomislav Novinscak (Croatia); Klaus Kirketerp Moller (Denmark); Ioan Veresiu (Romania); and Yamile Jubiz (Colombia).

CONFLICT OF INTEREST

Production of the 2019 IWGDF Guidelines was supported by unrestricted grants from: Molnlycke Healthcare, Acelity, ConvaTec, Urgo Medical, Edixomed, Klaveness, Reaplix, Podartis, Aurealis, SoftOx, Woundcare Circle, and Essity. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines, and have not seen any guideline or guideline-related document before publication.

All individual conflict of interest statement of authors of this guideline can be found at: <https://iwgdfguidelines.org/about-iwgdf-guidelines/biographies/>

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How to cite this article: Rayman G, Vas P, Dhatariya K, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(S1):e3283. <https://doi.org/10.1002/dmrr.3283>