Received: 20 July 2019 | Revised: 20 October 2019 | Accepted: 6 November 2019

DOI: 10.1002/dmrr.3283

SUPPLEMENT ARTICLE

WILEY

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

International Working Group on the Diabetic Foot (IWGDF); www.iwgdfguidelines.org

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 al[1] 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 al[1] 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 found[10] 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 nonadherent 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 unclear[26] 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 depth[27] 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 P1G10[33] 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 dropout 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 bias[35] 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 $TcPO_2$ 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 studies[42] 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 RCT[53] 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 grafting[54] 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-β3 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 sno 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 DFUs[85] 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 care[88]; but a second three-arm RCT[89] 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 RCT[90] 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 ultrasound[96] 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 compression[106] . All were of high risk of bias or showed no evidence of benefit. One RCT study of therapeutic magnetic resonance therapy[107] 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 micronutrient usage.[109] We found one study on zinc supplementation,[110] one study on magnesium replacement,[111] one on omega-3 supplementation[112] 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 al[1] 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 have 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 PICOs 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, Reapplix, 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/

REFERENCES

1. Jeffcoate WJ, Bus SA, Game FL, et al. The European wound management a. reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. *Lancet Diabetes Endocrinol*. 2016;4(9):781-788.
2. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE evidence to decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ*. 2016;353:i2089.
3. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
4. Vas P, Rayman G, Dhatariya K, et al. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(S1):e3284.
5. Bus SA, van Netten JJ, Hinchliffe RJ, Apelqvist J, Lipsky BA, Schaper NC, IWGDF Editorial Board. Standards for the development and methodology of the 2019 International Working Group on the Diabetic Foot guidelines. *Diabetes Metab Res Rev*. 2020;36(S1):e3267.
6. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. *Cochrane Database Syst Rev*. 2013;7:CD009101.
7. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. *Cochrane Database Syst Rev*. 2011;9:CD009101.
8. Motley TA, Caporusso JM, Lange DL, Eichelkraut RA, Cargill DI, Dickerson JE Jr. Clinical outcomes for diabetic foot ulcers treated with Clostridial collagenase ointment or with a product containing silver. *Adv Wound Care (New Rochelle)*. 2018;7(10):339-348.
9. Motley TA, Lange DL, Dickerson JE Jr, Slade HB. Clinical outcomes associated with serial sharp debridement of diabetic foot ulcers with and without clostridial collagenase ointment. *Wounds*. 2014;26(3):57-64.
10. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Repair Regen*. 2002;10(6):354-359.
11. Caputo WJ, Beggs DJ, DeFede JL, Simm L, Dharma H. A prospective randomised controlled clinical trial comparing hydrosurgery debridement with conventional surgical debridement in lower extremity ulcers. *Int Wound J*. 2008;5(2):288-294.
12. Sherman RA. Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy. *Diabetes Care*. 2003;26(2):446-451.
13. Armstrong DG, Salas P, Short B, et al. Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J Am Podiatr Med Assoc*. 2005;95(3):254-257.
14. Paul AG, Ahmad NW, Lee HL, et al. Maggot debridement therapy with Lucilia cuprina: a comparison with conventional debridement in diabetic foot ulcers. *Int Wound J*. 2009;6(1):39-46.
15. Wang SY, Wang JN, Lv DC, Diao YP, Zhang Z. Clinical research on the bio-debridement effect of maggot therapy for treatment of chronically infected lesions. *Orthop Surg*. 2010;2(3):201-206.
16. Wilasrusmee C, Marjareonrungrung M, Eamkong S, et al. Maggot therapy for chronic ulcer: a retrospective cohort and a meta-analysis. *Asian J Surg*. 2014;37(3):138-147.
17. Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, Amery CM, Edmonds ME, Gibby OM, Johnson AB, **et al.** Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. *Health Technol Assess* 2009. 13(54):1–86, iii-iv.
18. Delgado-Enciso I, Madrigal-Perez VM, Lara-Esqueda A, et al. Topical 5% potassium permanganate solution accelerates the healing process in chronic diabetic foot ulcers. *Biomed Rep*. 2018;8(2):156-159.
19. Dumville JC, Lipsky BA, Hoey C, Cruciani M, Fiscon M, Xia J. Topical antimicrobial agents for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2017;6:CD011038.
20. Tsang K-K, Kwong EW-Y, Woo KY, To TS-S, Chung JW-Y, Wong TK-S. The anti-inflammatory and antibacterial action of Nano-crystalline silver and Manuka honey on the molecular alternation of diabetic foot ulcer: a comprehensive literature review. *Evid Based Complement Alternat Med*. 2015;2015:19.

21. Shukrimi A, Sulaiman AR, Halim AY, Azril A. A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. *Med J Malaysia*. 2008;63(1):44-46.
22. Rehman E, Afzal M, Ali A, Qureshi A, Rashid M. Comparison between honey and povidone-iodine/normal saline dressing for management of Wagner'grade s I & II diabetic foot ulcers. *Pak J Med Health Sci*. 2013;7(4):1082-1108.
23. Jan WA, Shah H, Khan M, Fayaz M, Ullah N. Comparison of conventional pyodine dressing with honey dressing for the treatment of diabetic foot ulcers. *Journal of Postgraduate Medical Institute (Peshawar-Pakistan)*. 2012;26(4): 402–407.
24. Kamaratos AV, Tzirogiannis KN, Iraklianou SA, Panoutsopoulos GI, Kanellos IE, Melidonis AI. Manuka honey-impregnated dressings in the treatment of neuropathic diabetic foot ulcers. *Int Wound J*. 2014;11(3):259-263.
25. Imran M, Hussain MB, Baig M. A randomized, controlled clinical trial of honey-impregnated dressing for treating diabetic foot ulcer. *J Coll Physicians Surg Pak*. 2015;25(10):721-725.
26. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev*. 2015;3:CD005083.
27. Piaggesi A, Baccetti F, Rizzo L, Romanelli M, Navalesi R, Benzi L. Sodium carboxyl-methyl-cellulose dressings in the management of deep ulcerations of diabetic foot. *Diabet Med*. 2001;18(4):320-324.
28. Janka-Zires M, Almeda-Valdes P, Uribe-Wiechers AC, et al. Topical administration of pirfenidone increases healing of chronic diabetic foot ulcers: a randomized crossover study. *Journal of Diabetes Research*. 2016;2016:1-7.
29. Gasca-Lozano LE, Lucano-Landeros S, Ruiz-Mercado H, et al. Pirfenidone accelerates wound healing in chronic diabetic foot ulcers: a randomized, double-blind controlled trial. *Journal of Diabetes Research*. 2017;2017:1-12.
30. Totsuka Sutto SE, Rodríguez Roldan YI, Cardona Muñoz EG, et al. Efficacy and safety of the combination of isosorbide dinitrate spray and chitosan gel for the treatment of diabetic foot ulcers: a double-blind, randomized, clinical trial. *Diabetes and Vascular Disease Research*. 2018;1479164118769528: 348–351.
31. Lee M, Han SH, Choi WJ, Chung KH, Lee JW. Hyaluronic acid dressing (Healoderm) in the treatment of diabetic foot ulcer: a prospective, randomized, placebo-controlled, single-center study. *Wound Repair Regen*. 2016;24(3):581-588.
32. Campitiello F, Mancone M, Della Corte A, Guerniero R, Canonico S. To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. *Updates Surg*. 2017;69(4): 523-529.
33. Tonaco LAB, Gomes FL, Velasquez-Melendez G, Lopes MTP, Salas CE. The proteolytic fraction from latex of Vasconcellea cundinamarcensis (P1G10) enhances wound healing of diabetic foot ulcers: a double-blind randomized pilot study. *Adv Ther*. 2018;35(4): 494-502.
34. Grek CL, Prasad GM, Viswanathan V, Armstrong DG, Gourdie RG, Ghatnekar GS. Topical administration of a connexin43-based peptide augments healing of chronic neuropathic diabetic foot ulcers: a multicenter, randomized trial. *Wound Repair Regen*. 2015;23(2): 203-212.
35. Edmonds M, Lazaro-Martinez JL, Alfayate-Garcia JM, et al. Sucrose octasulfate dressing versus control dressing in patients with neuro-ischaemic diabetic foot ulcers (explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(3):186-196.
36. Kessler L, Bilbault P, Ortega F, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care*. 2003;26(8): 2378-2382.
37. Aydin F, Kaya A, Karapinar L, et al. IGF-1 increases with hyperbaric oxygen therapy and promotes wound healing in diabetic foot ulcers. *J Diabetes Res*. 2013;2013:567834.
38. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg*. 2003;25(6): 513-518.
39. Londahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care*. 2010;33(5):998-1003.
40. Margolis DJ, Gupta J, Hoffstad O, et al. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. *Diabetes Care*. 2013;36(7):1961-1966.
41. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. *Diabetes Care*. 2016;39(3): 392-399.
42. Santema KTB, Stoekenbroek RM, Koelemay MJW, et al. Hyperbaric oxygen therapy in the treatment of ischemic lower extremity ulcers in patients with diabetes: results of the DAMO2CLES Multicenter randomized clinical trial. *Diabetes Care*. 2018;41(1):112–119.
43. Londahl M, Katzman P, Hammarlund C, Nilsson A, Landin-Olsson M. Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and ankle-brachial index in patients with diabetes and chronic foot ulcers. *Diabetologia*. 2011;54(1):65-68.
44. Blackman E, Moore C, Hyatt J, Railton R, Frye C. Topical wound oxygen therapy in the treatment of severe diabetic foot ulcers: a prospective controlled study. *Ostomy Wound Manage*. 2010;56(6): 24-31.
45. Heng M, Harker J, Bardakjian V, Ayvazian H. Enhanced healing and cost-effectiveness of low-pressure oxygen therapy in healing necrotic wounds: a feasibility study of technology transfer. *Ostomy Wound Manage* 2000. 46(3):52–60, 62.
46. Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. *Journal of Wound Care*. 2018;27(Sup9):S30-S45.
47. Driver VR, Reyzelman A, Kawalec J, French M. A prospective, randomized, blinded, controlled trial comparing transdermal continuous oxygen delivery to moist wound therapy for the treatment of diabetic foot ulcers. *Ostomy Wound Manage*. 2017;63(4):12-28.
48. Liu Z, Dumville JC, Hinchliffe RJ, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2018;10:CD010318.
49. Li Z, Yu A. Complications of negative pressure wound therapy: a mini review. *Wound Repair Regen*. 2014;22(4):457-461.
50. Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet*. 2005;366(9498):1704-1710.
51. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care*. 2008;31(4):631-636.
52. Sepúlveda G, Espíndola M, Maureira M, et al. Negative-pressure wound therapy versus standard wound dressing in the treatment of diabetic foot amputation. A randomised controlled trial. *Cirugía Española (English Edition)*. 2009;86(3):171-177.
53. Chiang N, Rodda OA, Sleigh J, Vasudevan T. Effects of topical negative pressure therapy on tissue oxygenation and wound healing in vascular foot wounds. *J Vasc Surg*. 2017;66(2):564-571.

54. Dalla Paola L, Carone A, Ricci S, Russo A, Ceccacci T, Ninkovic S. Use of vacuum assisted closure therapy in the treatment of diabetic foot wounds. *J Diabetic Foot Complications*. 2010;2(2):33-44.
55. Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg*. 2003;17(6):645-649.
56. McCallon SK, Knight CA, Valiulus JP, Cunningham MW, McCulloch JM, Farinas LP. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. *Ostomy Wound Manage* 2000. 46(8):28–32, 34.
57. Frykberg RG, Williams DV. Negative-pressure wound therapy and diabetic foot amputations: a retrospective study of payer claims data. *J Am Podiatr Med Assoc*. 2007;97(5):351-359.
58. Peinemann F, McGauran N, Sauerland S, Lange S. Negative pressure wound therapy: potential publication bias caused by lack of access to unpublished study results data. *BMC Med Res Methodol*. 2008;8:4.
59. Sajid MT, Mustafa Q, Shaheen N, Hussain SM, Shukr I, Ahmed M. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers. *J Coll Physicians Surg Pak*. 2015;25(11):789-793.
60. Vassallo IM, Formosa C. Comparing calcium alginate dressings to vacuum-assisted closure: a clinical trial. *Wounds*. 2015;27(7): 180-190.
61. Lone AM, Zaroo MI, Laway BA, Pala NA, Bashir SA, Rasool A. Vacuum-assisted closure versus conventional dressings in the management of diabetic foot ulcers: a prospective case-control study. *Diabet Foot Ankle*. 2014;5:1, https://doi.org/10.3402/dfa.v5.23345
62. Niknejad H, Peirovi H, Jorjani M, Ahmadiani A, Ghanavi J, Seifalian AM. Properties of the amniotic membrane for potential use in tissue engineering. *Eur Cells Mater*. 2008;15:88-99.
63. Raspovic KM, Wukich DK, Naiman DQ, et al. Effectiveness of viable cryopreserved placental membranes for management of diabetic foot ulcers in a real world setting. *Wound Repair Regen*. 2018;26(2):213-220.
64. Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J*. 2013;10(5):502-507.
65. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix([R]) for the treatment of chronic diabetic foot ulcers: results of a multi-Centre, controlled, randomised, blinded, clinical trial. *Int Wound J*. 2014;11(5):554-560.
66. Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-Centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J*. 2015;12(6):724-732.
67. DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. *Plast Reconstr Surg Glob Open*. 2016;4(10):e1095.
68. Mohajeri-Tehrani MR, Variji Z, Mohseni S, et al. Comparison of a bioimplant dressing with a wet dressing for the treatment of diabetic foot ulcers: a randomized. *Controlled Clinical Trial Wounds*. 2016;28 (7):248-254.
69. Snyder RJ, Shimozaki K, Tallis A, et al. A prospective, randomized, multicenter, controlled evaluation of the use of dehydrated amniotic membrane allograft compared to standard of care for the closure of chronic diabetic foot ulcer. *Wounds: A Compendium of Clinical Research and Practice*. 2016;28(3):70-77.
70. Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. *Wound Repair Regen*. 2018;26(3):274-283.
71. Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: a prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. *Int Wound J*. 2019;16(1):19-29.
72. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. *Int Wound J*. 2019;16(1):122-130.
73. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multicentre comparative study examining clinical efficacy and cost. *Int Wound J*. 2016;13(2):272-282.
74. Kirsner RS, Sabolinski ML, Parsons NB, Skornicki M, Marston WA. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. *Wound Repair Regen*. 2015;23(5):737-744.
75. Krupski WC, Reilly LM, Perez S, Moss KM, Crombleholme PA, Rapp JH. A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic nonhealing wounds: a preliminary report. *J Vasc Surg*. 1991;14(4):526-536.
76. Driver VR, Hanft J, Fylling CP, Beriou JM, Autologel Diabetic Foot Ulcer Study G. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Manage*. 2006. 52(6):68–87, 72, 74 passim.
77. Jeong S-H, Han S-K, Kim W-K. Treatment of diabetic foot ulcers using a blood bank platelet concentrate. *Plast Reconstr Surg*. 2010; 125(3):944-952.
78. Li L, Chen D, Wang C, et al. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: a prospective, randomized clinical trial. *Wound Repair Regen*. 2015;23(4):495-505.
79. Ahmed M, Reffat SA, Hassan A, Eskander F. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann Vasc Surg*. 2017;38: 206-211.
80. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic ulcer study group. *J Vasc Surg* 1995. 21(1):71–78; discussion 79-81.
81. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care*. 1998;21(5):822-827.
82. Feng J, Du W, Wang J. Clinical study of various growth factors on the improvement of impaired healing ulcers in patients with diabetic disease. *Zhongguo xiu fu chong jian wai ke za zhi= Zhongguo xiufu chongjian waike zazhi= Chinese journal of reparative and reconstructive surgery*. 1999;13(5):273-277.
83. Khandelwal S, Chaudhary P, Poddar DD, Saxena N, Singh RA, Biswal UC. Comparative study of different treatment options of grade III and IV diabetic foot ulcers to reduce the incidence of amputations. *Clin Pract*. 2013;3(1):e9.
84. Landsman A, Agnew P, Parish L, Joseph R, Galiano RD. Diabetic foot ulcers treated with becaplermin and TheraGauze, a moisture-controlling smart dressing: a randomized, multicenter, prospective analysis. *J Am Podiatr Med Assoc*. 2010;100(3):155-160.
85. Ma C, Hernandez MA, Kirkpatrick VE, Liang LJ, Nouvong AL, Gordon II. Topical platelet-derived growth factor vs placebo therapy of diabetic foot ulcers offloaded with windowed casts: a randomized, controlled trial. *Wounds*. 2015;27(4):83-91.
86. Samuel A, Mahajan A, Mam MK, Prakash JS. Platelet derived growth factor in diabetic lower extremity ulcer: a randomized, double blind, placebo controlled study in Indian condition.

International Journal of Pharmaceutical Sciences and Research. 2016;7(9):3887-3892.

87. Game F, Jeffcoate W, Tarnow L, et al. LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(11):870-878.
88. Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of Integra template for diabetic foot ulcer treatment. *Wound Repair Regen*. 2015;23(6):891-900.
89. Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing rates in a Multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. *Eplasty*. 2016;16:e10.
90. Hu Z, Zhu J, Cao X, et al. Composite skin grafting with human acellular dermal matrix scaffold for treatment of diabetic foot ulcers: a randomized controlled trial. *J Am Coll Surg*. 2016;222(6):1171-1179.
91. Loots MA, Lamme EN, Mekkes JR, Bos JD, Middelkoop E. Cultured fibroblasts from chronic diabetic wounds on the lower extremity (non-insulin-dependent diabetes mellitus) show disturbed proliferation. *Arch Dermatol Res*. 1999;291(2–3):93-99.
92. Game FL, Apelqvist J, Attinger C, Hartemann A, Hinchliffe RJ, Londahl M, Price PE, Jeffcoate WJ, International Working Group on the Diabetic F. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016. 32 Suppl 1:154–168.
93. Game FL, Hinchliffe RJ, Apelqvist J, et al. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev*. 2012;28(Suppl 1):119-141.
94. Gomez-Villa R, Aguilar-Rebolledo F, Lozano-Platonoff A, et al. Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: a randomized double-blinded controlled trial. *Wound Repair Regen*. 2014;22(4):497-503.
95. Singla S, Garg R, Kumar A, Gill C. Efficacy of topical application of beta urogastrone (recombinant human epidermal growth factor) in Wagner's grade 1 and 2 diabetic foot ulcers: comparative analysis of 50 patients. *J Nat Sci Biol Med*. 2014;5(2):273-277.
96. Yao M, Hasturk H, Kantarci A, et al. A pilot study evaluating non-contact low-frequency ultrasound and underlying molecular mechanism on diabetic foot ulcers. *Int Wound J*. 2014;11(6):586-593.
97. Jeppesen SM, Yderstraede KB, Rasmussen BS, Hanna M, Lund L. Extracorporeal shockwave therapy in the treatment of chronic diabetic foot ulcers: a prospective randomised trial. *J Wound Care*. 2016;25(11):641-649.
98. Omar MT, Alghadir A, Al-Wahhabi KK, Al-Askar AB. Efficacy of shock wave therapy on chronic diabetic foot ulcer: a single-blinded randomized controlled clinical trial. *Diabetes Res Clin Pract*. 2014;106(3):548-554.
99. Mathur RK, Sahu K, Saraf S, Patheja P, Khan F, Gupta PK. Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers. *Lasers Med Sci*. 2017;32(2):275-282.
100. Feitosa MC, Carvalho AF, Feitosa VC, Coelho IM, Oliveira RA, Arisawa EA. Effects of the low-level laser therapy (LLLT) in the process of healing diabetic foot ulcers. *Acta Cir Bras*. 2015;30(12):852-857.
101. Sandoval Ortíz MC, Herrera Villabona E, Camargo Lemos DM, Castellanos R. Effects of low level laser therapy and high voltage stimulation on diabetic wound healing. *Revista de la Universidad Industrial de Santander. Salud*. 2014;46:107-117.
102. Maltese G, Karalliedde J, Rapley H, Amor T, Lakhani A, Gnudi L. A pilot study to evaluate the efficacy of class IV lasers on nonhealing neuroischemic diabetic foot ulcers in patients with type 2 diabetes. *Diabetes Care*. 2015;38(10):e152-e153.
103. Nteleki B, Abrahamse H, Houreld NN. Conventional podiatric intervention and phototherapy in the treatment of diabetic ulcers. *Semin Vasc Surg*. 2015;28(3):172-183.
104. Tardivo JP, Adami F, Correa JA, Pinhal MAS, Baptista MS. A clinical trial testing the efficacy of PDT in preventing amputation in diabetic patients. *Photodiagnosis Photodyn Ther*. 2014;11(3):342-350.
105. Hakim A, Sadeghi Moghadam A, Shariati A, Karimi H, Haghighizadeh MH. Effect of infrared radiation on the healing of diabetic foot ulcer. *Int J Endocrinol Metab*. 2016;14(3):e32444.
106. Alvarez OM, Wendelken ME, Markowitz L, Comfort C. Effect of high-pressure, intermittent pneumatic compression for the treatment of peripheral arterial disease and critical limb ischemia in patients without a surgical option. *Wounds*. 2015;27(11):293-301.
107. Piaggesi A, Sambataro M, Nicoletti C, Goretti C, Lacopi E, Coppelli A. Safety and effectiveness of therapeutic magnetic resonance in diabetic foot ulcers: a prospective randomised controlled trial. *J Wound Care*. 2016;25(12):704-711.
108. Abbruzzese L, Iacopi E, Coppelli A, Bonino G, Goretti C, Piaggesi A. Safety and effectiveness of therapeutic magnetic resonance in the management of postsurgical lesion of the diabetic foot. *Int J Low Extrem Wounds*. 2015;14(1):4-10.
109. Vas PRJ, Edmonds ME, Papanas N. Nutritional supplementation for diabetic foot ulcers: the big challenge. *Int J Low Extrem Wounds*. 2017;16(4):226-229.
110. Momen-Heravi M, Barahimi E, Razzaghi R, Bahmani F, Gilasi HR, Asemi Z. The effects of zinc supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *Wound Repair Regen*. 2017;25(3):512-520.
111. Razzaghi R, Pidar F, Momen-Heravi M, Bahmani F, Akbari H, Asemi Z. Magnesium supplementation and the effects on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind. *Placebo-Controlled Trial Biol Trace Elem Res*. 2018;181(2):207-215.
112. Soleimani Z, Hashemdokht F, Bahmani F, Taghizadeh M, Memarzadeh MR, Asemi Z. Clinical and metabolic response to flaxseed oil omega-3 fatty acids supplementation in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *J Diabetes Complications*. 2017;31(9):1394-1400.
113. Razzaghi R, Pourbagheri H, Momen-Heravi M, et al. The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *J Diabetes Complications*. 2017;31(4):766-772.
114. Mohseni S, Bayani M, Bahmani F, et al. The beneficial effects of probiotic administration on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *Diabetes Metab Res Rev*. 2018;34(3):e2970.
115. M. Eneroth MD P, J. Larsson MD P, RN CO, J. Apelqvist MD P. Nutritional supplementation for diabetic foot ulcers: the first RCT. *J Wound Care* 2004. 13(6):230–234.
116. Rullan M, Cerda L, Frontera G, Masmiquel L, Llobera J. Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple-blind, placebo-controlled, clinical trial. *Diabet Med*. 2008;25(9):1090-1095.
117. Sert M, Aikimbaev K, Tetiker T. Effects of iloprost (a prostacyclin analogue) on the endothelial dysfunction and foot ulcers in diabetic patients with peripheral arterial disease. *International Journal of Diabetes and Metabolism*. 2008;16:7-11.
118. Rewale V, Prabhakar KR, Chitale AM. Pentoxifylline: a new armamentarium in diabetic foot ulcers. *J Clin Diagn Res*. 2014;8(1):84-86.
119. Larijani B, Heshmat R, Bahrami A, et al. Effects of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: a multicenter clinical trial. *DARU Journal of Pharmaceutical Sciences*. 2008;16(Suppl. 1):35-40.
120. Bahrami A, Kamali K, Ali-Asgharzadeh A, Hosseini P, Heshmat R, Khorram Khorshid HR, Gharibdoust F, Madani S, Larijani B. Clinical

application of oral form of ANGIPARSTM and in combination with topical form as a new treatment for diabetic foot ulcers: a randomized clinical trial. *DARU Journal of Pharmaceutical Sciences*. 2008;16 (Suppl. 1):41-48.

121. Marfella R, Sasso FC, Rizzo MR, et al. Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Exp Diabetes Res*. 2012;2012:892706.

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