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## Update on management of diabetic foot ulcers

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### Abstract

Diabetic foot ulcers (DFUs) are a serious complication of diabetes that results in significant morbidity and mortality. Mortality rates associated with development of a DFU are estimated to be 5% in the first 12 months, and 5-year mortality rates have been estimated at 42%. The standard practices in DFU management include surgical debridement, dressings to facilitate a moist wound environment and exudate control, wound off-loading, vascular assessment, and infection and glycemic control. These practices are best coordinated by a multidisciplinary diabetic foot wound clinic. Even with this comprehensive approach, there is still room for improvement in DFU outcomes. Several adjuvant therapies have been studied to reduce DFU healing times and amputation rates. We reviewed the rationale and guidelines for current standard of care practices and reviewed the evidence for the efficacy of adjuvant agents. The adjuvant therapies reviewed include the following categories: non-surgical debridement agents, dressings and topical agents, oxygen therapies, negative pressure wound therapy, acellular bioproducts, human growth factors, energy based therapies, and systemic therapies. Many of these agents have been found to be beneficial in improving wound healing rates, although a large proportion of the data are small randomized controlled trials with high risks of bias.

### Keywords

diabetes; diabetic foot ulcers; wound healing; diabetic foot management

### Introduction

Diabetic foot ulcers (DFUs) are a prevalent complication of diabetes mellitus and account for significant morbidity, mortality, and healthcare expenditures. It is estimated that 19–34% of patients with diabetes are likely to be affected with a diabetic foot ulcer in their lifetimes, and the International Diabetes Federation reports that 9.1–26.1 million people will develop DFUs annually.<sup>1</sup> These numbers are alarming, as the clinical implications for the development of a DFU are not negligible. A population-based cohort study in the United Kingdom demonstrated that the development of a DFU is associated with a 5% mortality in the first 12 months and a 42% mortality within 5 years. Patients with DFUs were also found

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#### Competing interests

The authors declare no competing interests.

to have a 2.5-fold increased risk of death compared with their diabetic counterparts without foot wounds.<sup>2</sup> Furthermore, patients living with DFUs suffer great morbidity, lower health-related quality of life, and poorer psychosocial adjustment<sup>3</sup> and have a high burden of healthcare interactions.<sup>4</sup>

Treatment of DFUs accounts for approximately one-third the total cost of diabetic care, which was estimated to be U.S \$176 billion in direct healthcare expenditures in 2012.<sup>45</sup> Despite these high healthcare costs, about 20% of patients have unhealed DFUs at 1 year.<sup>6</sup> Even after wound resolution, subsequent DFUs are common, with a recurrence rate of roughly 40% of patients within 1 year.<sup>1</sup> Although there are well-established principles to managing DFUs, treatment of DFUs is often challenging. A broad spectrum of novel interventions is being studied to improve wound healing. In this review, we discuss the current standard of care and review current guidelines in DFU management. We also explore the rationale and evidence for several adjuvant agents currently in use or being studied to improve DFU outcomes.

## Standard of care

Shortly after DFUs were described in the 19th century, the most prevalent treatment approach was prolonged bedrest. Dr. Frederick Treves (1853–1923) revolutionized the management of DFUs when he established three important principles in DFU treatment, which continue to be the basis of modern day care: sharp debridement, off-loading, and diabetic foot education.<sup>7</sup> Building on these principles, the pillars of treatment today include the following: local wound care with surgical debridement, dressings promoting a moist wound environment, wound off-loading, vascular assessment, treatment of active infection, and glycemic control (Table 1).<sup>8–10</sup> In addition to these principles, multidisciplinary diabetic foot care is now becoming a mainstay of therapy.

## Surgical debridement

Wound debridement involves removal of all necrotic and devitalized tissue that is incompatible with healing, as well as surrounding callus. This process aids in granulation tissue formation and re-epithelialization and reduces plantar pressures at callused areas.<sup>9</sup> Debridement also plays an important role in infection control, as devitalized tissues provide a nidus for bacterial proliferation, act as a physical barrier for antibiotics, and limit immune response to fighting infection.<sup>11</sup> The Infectious Disease Society of America (IDSA) and the Wound Healing Society (WHS) recommend sharp debridement over topical debridement agents (i.e., autolytic dressing or biological debridement).<sup>8,9</sup> Sharp debridement has been found to be efficacious in several clinical trials, although overall data are limited.<sup>12–14</sup>

## Choice of dressing

DFUs are heterogeneous, so no single dressing is ideal for all wound types. It is generally agreed that the goal of a dressing should be to create a moist environment that promotes granulation, autolytic processes, angiogenesis, and more rapid migration of epidermal cells across the wound base.<sup>9,11,15</sup> The selected dressing should also be appropriate to manage excess wound exudates. A wide range of dressing types are available, and several are

currently being studied. Currently, there are insufficient data to recommend any particular dressing type.<sup>9,12</sup>

### **Wound off-loading**

Plantar shear stress, which is the horizontal component of ground reaction forces, and, to a lesser degree vertical plantar pressure are major causative factors in the development and poor healing of DFUs.<sup>16</sup> Relieving plantar pressure and shear stress from a DFU is a vital part of wound care, as it promotes healing and prevents recurrence.<sup>11</sup> Off-loading can be achieved by many mechanisms, including shoe modifications, boots, and orthotic walkers.<sup>11</sup> The modality choice should be based on the location of the wound and history of peripheral arterial disease (PAD). Total contact casting (TCC) is often considered the gold standard device, although TCC, as well as other non-removable devices, should not be used in those with significant PAD or infection.<sup>9,17</sup> Studies have shown that both TCC and knee-high removable walkers reduce peak pressure in the forefoot up to 87%, as they redistribute plantar pressure to the entire weight-bearing surface of the foot, as well as lower the leg, through the device wall.<sup>18</sup> Devices that extend to the ankle are generally less effective for this reason.<sup>18</sup> Although there was a randomized controlled trial (RCT) that showed similar healing rates between TCC and removable walkers, there are numerous studies demonstrating that non-removable off-loading is more effective than removable off-loading in terms of time to healing and percentage of wounds healed. While TCC has historically been considered the gold standard, it is becoming evident that any non-removable knee-high device can achieve similar results. This is congruent with the International Working Group on the Diabetic Foot (IWGDF) consensus guidelines. Generally considering a non-removable knee-high device as the gold standard also allows for effective off-loading options at facilities where skills in casting are unavailable.

Offloading shoes, cast shoes, and custom-made temporary shoes appear to be effective in healing DFUs, although the evidence comes only from retrospective studies. The IWGDF recommends that these options be used for plantar ulcers in patients for whom knee-high devices are contraindicated or not tolerated or in those with non-plantar ulcers.<sup>17</sup> Felted foam with appropriate footwear can be used if no other biomechanical off-loading is available. Surgical off-loading should only be used if conservative management has failed in a high-risk patient.<sup>17</sup>

### **Vascular assessment**

PAD is estimated to occur in 40% of patients with DFUs.<sup>6</sup> Patients who have co-morbid DFUs and PAD have slower healing, higher major amputation rates, and higher mortality rates.<sup>6</sup> It is recommended that those with DFUs be evaluated for PAD by palpating pedal pulses or ankle brachial index (ABI).<sup>11</sup> An ABI below 0.7 correlates with some degree of arterial insufficiency, and those with ABI less than 0.4 have severe PAD. Patients with ABI greater than 1.4 likely have non-compressible vessels at the ankle due to vascular calcifications. This is not uncommon in patients with diabetes and is also observed in renal insufficiency.<sup>19</sup> Those with non-compressible vessels should undergo alternative testing, including toe systolic pressures, pulse volume recordings, transcutaneous oxygen

measurement, or duplex ultrasound. Abnormalities in any of these secondary tests reliably confirms the diagnosis of PAD.<sup>19,11</sup>

### **Treatment of active infection**

Wound infection is a known predictor of poor wound healing and amputation.<sup>20</sup> The appropriate recognition of infection and treatment with antibiotics in diabetic foot infection is imperative to improve outcomes. Conversely, inappropriately treating with antibiotics, often in the setting of fear of missing an infection, to reduce bacterial burden or prophylaxis is associated with several adverse effects, including antibacterial resistance.<sup>21</sup> The IDSA has outlined specific guidelines for the treatment of diabetic foot infections.<sup>9</sup> The IDSA recommends treatment of wounds with at least two signs or symptoms of inflammation (erythema, warmth, tenderness, pain, induration) or purulent secretion. It is recommended that, before antibiotic therapy, a deep tissue culture via biopsy or curettage after debridement be obtained. Swab specimens should be avoided, especially in inadequately debrided wounds.<sup>9</sup> Antibiotic therapy should be targeted to aerobic Gram-positive cocci in mild to moderate infections. Severe infections should be treated with broad-spectrum empiric antibiotics pending cultures. IDSA recommends 1- to 2-week antibiotic course for mild infections and 2–3 weeks for moderate to severe infections, but antibiotics can usually be discontinued once clinical signs and symptoms of infections have resolved.<sup>9</sup> To avoid antibacterial resistance and other adverse outcome of therapy, it is best practice that treatment of clinical diabetic foot infections be completed with narrow=spectrum antibiotics for the shortest duration possible.<sup>9,22</sup>

### **Glycemic control**

It is widely recommended that blood glucose be optimized to improve wound healing and limit adverse effects on cellular immunity and infection.<sup>11</sup> Although a recent Cochrane review was unable to conclude whether intensive glycemic control had a positive or detrimental effect on treatment of DFUs, due to lack of RCTs, several observational studies have found positive correlations with glycemic control and wound healing.<sup>23–25</sup> Furthermore, another Cochrane review assessing effects of glycemic targets in type 2 diabetes found that those with intensive glycemic control had a 35% reduction in risk of lower-extremity amputation.<sup>26</sup>

### **Multidisciplinary care**

Specialty diabetes foot care is becoming the new standard of care in areas where the resources are available. Most expert guidelines now recommend referral to a multidisciplinary care center for management of DFUs.<sup>9,15,27</sup> Numerous studies and systematic reviews have showed positive effects on multidisciplinary care in reducing wound healing times, amputation rates, and severity of amputation.<sup>28–31</sup> The definition of multidisciplinary diabetic foot care varies broadly in the literature but often includes a surgeon (general, vascular, orthopedic), podiatrist, diabetes specialist, physical therapist, and wound care nurse.

## Adjuvant therapies

In addition to standard practices in DFU care, there are a wide range of agents available or currently being studied as adjuvant therapies. In this review, we will characterize these agents in the following categories: non-surgical debridement agents, dressings and topical products, oxygen therapies, negative pressure wound therapy, acellular bioproducts, human growth factors, skin grafts and bioengineered skin, energy-based therapies, and systemic therapies (Table 2). We will review the rationale for use and the data evaluating the efficacy of these interventions.

### Non-surgical debridement agents

Although sharp debridement is the preferred method of debridement, there are other non-surgical options available, including autolytic debridement with hydrogels, enzymatic debridement, biosurgery, and mechanical debridement with hydrotherapy.

**Autolytic debridement with hydrogels**—Hydrogels are specialized dressings that are made of insoluble polymers that bind a relatively large volume of water.<sup>32</sup> This water can be donated to wounds, but, given that the polymer matrix is not fully saturated, it can absorb wound exudate, resulting in an optimal moisture level in the wound. A moist environment provides optimal conditions for cells and facilitates autolytic debridement, which enhances the breakdown of necrotic tissue through endogenous proteolytic enzymes.<sup>32</sup> A 2013 Cochrane review and meta-analysis of three RCTs found that hydrogel dressings had significantly greater healing when compared with basic wound dressings.<sup>32</sup>

**Enzymatic debridement**—Clostridial collagenase ointment (CCO) is the most common agent used for enzymatic debridement. Although one study found that CCO is used as management for 17% of DFUs, the evidence for its use is lacking.<sup>33</sup> There are only three RCTs specifically exploring the efficacy of CCO in DFU. The first was a 12-week parallel multicenter, open-label RCT of 48 patients in 2012, which showed improved healing in the group treated with CCO compared with saline-moistened gauze with selective sharp debridement.<sup>34</sup> It has been questioned whether the control group received usual best care, as the average wound size increased during the study in this group.<sup>12</sup> Mline *et al.* compared CCO with hydrogel in a small randomized RCT and found no difference between the groups in days to complete healing. Most recently, in 2017, Jimenez *et al.* compared CCO to standard care plus hydrogel and also found no difference in the wound size at 6 and 12 weeks.<sup>35</sup>

**Biosurgery**—Maggot and larval debridement has been thought to confer several benefits to wounds, including reducing bacterial burden, regulating proteases, degrading the extracellular matrix, promoting fibroblast migration, and potentially improving skin perfusion.<sup>36</sup> Data on the efficacy on this treatment are limited. A case-controlled trial in non-ambulatory patients with DFUs showed that there was no difference in the proportion who healed at 6 months. In those who healed, time to healing was shorter in patients who received maggot debridement. Amputation rates were also lower in the intervention group.<sup>37</sup> Several other studies have shown no difference in healing or amputation rates.<sup>12</sup> There are

current ongoing studies exploring a new generation of maggot debridement therapy with transgenic *Lucilia sericata* larvae that produce and secrete human growth factors.<sup>38</sup>

**Hydrotherapy**—The Verajet™ hydrosurgery system is a form of mechanical debridement that uses a high-pressure stream of sterile normal saline that is pumped to a hand-held cutting and aspirating tool. There has only been one RCT evaluating the efficacy of Verajet™, comparing it to surgical debridement in lower-extremity ulcers. Although debridement times were shorter, there was no difference in time to wound closure.<sup>12</sup>

There are several options available for non-surgical wound debridement that may be beneficial, but there is presently insufficient evidence to recommend one approach over other methods.

### Dressings and topical products

**Alginate and other dressings**—Alginate dressings are derived from seaweed and come in the form of calcium alginate or calcium sodium alginate or alginic acid. These alginate products form a highly absorbent gel that can absorb large volume of wound exudates to avoid skin maceration yet still maintain a moist environment. A Cochrane review and meta-analysis in 2013 showed no significant difference in ulcer healing with alginate products when compared with basic contact dressings or silver hydrocolloid dressings. Another systematic review in 2016 also found no difference in healing time between other synthetic active dressings and traditional dressings, including wet to dry saline moistened gauze, Vaseline gauze, and hydrofiber. As an exception, moderate-quality evidence suggested that hydrogel was more effective in healing DFUs.<sup>39</sup>

**Topical antiseptics and antimicrobials**—Several agents are currently being studied as topical antiseptic and antimicrobial agents for DFUs. A natural substance of popular interest is the use of honey. Honey is thought to have antibacterial activity and other benefits due to its ability to draw fluid from surrounding vessels and provide a moist environment and topical nutrition. Several animal models have shown that honey may accelerate healing.<sup>40</sup> A systematic review in 2016, including five RCTs and 10 observational studies, was conducted to evaluate the efficacy of honey in wound healing. A meta-analysis of three of the five non-blinded RCTs concluded that honey dressings were better than conventional dressings. Given the heterogeneity of studies and lack of high-quality evidence, honey dressings were concluded to be safe, but there was insufficient data to conclude true efficacy.<sup>41</sup> One new RCT published since that time compared honey dressing to dressing with normal saline and found that honey dressing were more effective in terms of time to healing and number of wound healed at 120 days.<sup>42</sup>

Other topical antimicrobials that have been studied but have not been found to have clear benefits include cadexomer-iodine, carboxymethylcellulose hydrofiber, superoxidized solutions, tobramycin beads, and chloramine treatment.<sup>12,43</sup> Nanocrystalline silver was found to cause greater ulcer size reduction rate than both Manuka honey and conventional dressing in one study.<sup>44</sup> Bacteriophage therapy, which uses viruses that target specific bacteria, is being studied in DFUs. There was one compassionate-use study of six patients

with culture-proven *Staphylococcus aureus* infections of soft tissue and bone. All infections reportedly responded to therapy, with an average healing time of 7 weeks.

**Other topical products**—The 2016 systematic review by the IWGDF showed that topical products, such as phenytoin, angiotensin, and topical insulin, have positive effects on wound healing compared with controls, but these studies had high risk for bias. Since that time, a study exploring phenytoin compared with honey and saline treatment found that phenytoin was comparable to honey, but both show significantly higher reduction in wound area and eradication of infection at 3 weeks of treatment. There has been no additional studies on NorLeu-angiotensin therapy or topical insulin. Studies have also found no difference in wound healing with the use of QRB7 oak extract, polyherbal cream, or bismuth subgallare/borneol.<sup>12</sup>

### Oxygen therapies

Oxygen is vital to the wound healing process, as it is involved in cell proliferation, collagen synthesis, re-epithelization, and defense against bacteria.<sup>45</sup> Many patients with DFUs have impaired oxygenation to wounded areas, especially in the setting of vascular disease. Therapeutic strategies to correct this include local delivery of oxygen to the wound and systemic oxygen administration.

**Topical oxygen**—The IWGDF 2016 systematic review did not find that there was enough evidence to support the use of topical oxygen therapy to enhance healing in DFUs on the basis of three available studies with mixed results. These studies included a RCT that showed no difference in healing at 14 days, a prospective cohort study showing benefit at 4 weeks, and a small cohort study that showed apparent improvement in healing at 90 days.<sup>12,46</sup> Since that time, Yu *et al.* performed a small RCT that showed increased wound closure rates in stage 2 and stage 3 DFUs at 8 weeks in those treated with topical oxygen therapy.<sup>47</sup> A larger blinded RCT showed no added benefit when comparing continuous transdermal oxygen with standard of care. A subgroup analysis showed a shorter median healing time to closure in patients greater than 65 years of age.<sup>48</sup> A newer topical agent currently being studied is hemoglobin spray. Topical hemoglobin can transport oxygen from the atmosphere to hypoxic wounds through facilitated diffusion.<sup>49</sup> Hunt *et al.* showed significant benefit in wound closure at 28 weeks.<sup>50</sup> Larger RCTs are needed to evaluate its true efficacy.

**Systemic oxygen**—Supplemental inspired oxygen has been explored in wound healing but is limited by the need for intact blood supply to the wound tissue. This mode of treatment has been studied primarily in surgical wounds and is not well studied in DFUs.<sup>45</sup> Hyperbaric oxygen (HBOT) is administered in a compression chamber, which provides 100% oxygen and delivers a greatly increased partial pressure of oxygen to tissues. A 2015 Cochrane review that pooled data from 10 RCTs showed that there was a significant increase rate in healing with HBOT at 6 weeks, although this benefit was not evident at follow-up at 1 year.<sup>51</sup> It was recommended that the results be interpreted with caution owing to various flaws in design in available studies. In 2016, Fedorko *et al.* published a double-blinded RCT concluding that hyperbaric oxygen therapy does not reduce indication for amputations in patients with Wagner grade 2–4 DFUs as assessed by a vascular surgeon after 12 weeks of

HBOT.<sup>52</sup> This study has been criticized because the end points were not amputation events.<sup>53–55</sup> Rather, the primary outcome was whether the patient met criteria for amputation, which was a decision made by a vascular surgeon based on a photograph of the wound.

### Negative-pressure wound therapy

Negative-pressure wound therapy (NPWT) is often used in wound management, as this vacuum device collects high volumes of wound exudate, the reduces frequency of dressing changes, keeps wounds that are anatomically challenging clean, and reduces odor. It is also theorized that the vacuum forces aid in wound healing by increasing perfusion, extracting infectious material, and approximating wound edges.<sup>56</sup> A recent systematic review analyzing 11 RCTs comparing NPWT with standard dressing changes showed that NPWT had a higher rate of complete healing, shorter healing time, and few amputations. There was no difference in incidence of treatment-related adverse effects.<sup>57</sup>

### Acellular bioproducts

Acellular dermal matrix (ADM) has been used for several years for wound healing, tissue repair, and reconstruction. Extracellular matrix plays an important role in wound healing in that it provides structural support and facilitates signals to modulate cellular responses.<sup>58</sup> Donor dermis that is decellularized retains bioactive agents and acts as a scaffold for host cell repopulation. It is thought that it aids in wound healing by promoting vascularization and providing a barrier to bacteria and a moist wound environment, which increases cell regeneration.<sup>58</sup> In 2016, a systematic review of 12 RCTs, six of which were subject to meta-analysis, found that, when compared with standard of care, patients treated with ADM had higher healing rates at 6 and 12 weeks.<sup>58</sup> Since that publication, Zelen *et al.* published similar findings.<sup>59,60</sup> Campitiello *et al.* published data on an acellular flowable matrix that has a liquid composition that can fill deep cavities and tunneled wounds. They found that healing rates were higher at 6 weeks when compared with usual care with wet dressing. They also noted lower amputation and re-hospitalization rates.<sup>61</sup> Hu *et al.* compared split grafting with ADM with split grafting alone and found that, in the ADM group, recurrence rates were lower, and wound and scar appearance was better, but wound closure rates were similar in both groups.<sup>62</sup> DermACELL, an ADM that has undergone a unique decellularization process resulting in thorough DNA removal, was evaluated in two studies compared with conventional care and Graftjacket ADM. Both studies showed a higher proportion of ulcers healed with DermACell compared with conventional treatment.<sup>63,64</sup> Graftjacket ADM performed variably in these two studies.

Acellular dermal matrix may have benefits in accelerating wound healing when compared with conventional treatment. There is insufficient evidence to recommend a particular type of ADM product.

### Human growth factors

Several human growth factors have been studied for adjunct use in the management of DFUs, including fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, granulocyte colony-stimulating factor, and platelet-derived growth factors.



**Fibroblast growth factor**—There have been limited studies on adjuvant fibroblast growth factors in DFUs. The first RCTs were performed in the mid-1990s and showed no difference in wound closure rates or percent healed at 12 weeks.<sup>65</sup> Another RCT was conducted in 2009 and found a greater proportion of patients with reduction in wound size by at least 75% at 8 weeks.<sup>66</sup> This was on the per protocol analysis. There have been no other published RCTs, but a completed study in 2014 (documented on ClinicalTrials.gov) showed no differences in wound closure at 12 weeks between those randomized to fibroblast growth factor versus placebo.<sup>67</sup>

**Epidermal growth factors**—Data evaluating the efficacy of epidermal growth factor (EGF) are also limited. There have been a few RCTs with mixed results. Tsang *et al.* showed no significant improvement in healing in a double-blinded RCT of topical EGF cream at 12 weeks, but two additional RCTs showed no overall benefit.<sup>12</sup> More recent studies have found some benefit in healing, although they are very small studies with high risk of bias.<sup>68–70</sup>

**Vascular endothelial growth factor**—There has only been one RCT evaluating the efficacy of vascular endothelial growth factor in DFUs. Kusmanto *et al.* completed a double-blinded RCT assessing intramuscular vascular endothelial growth factor (VEGF) versus placebo. In this study, a statistically significant number of patients achieved > 60% reduction in ulcer size when compared with controls.<sup>12</sup> There was also a study comparing VEGF to epidermal growth factor, which found that there was a statistically higher proportion of complete wound healing in the EGF group.<sup>71</sup>

**Granulocyte colony-stimulating factor**—The majority of RCTs studying granulocyte colony-stimulating factor (G-CSF) in DFUs were designed to evaluate its impact on infection. Nearly all of these studies show no apparent benefit in wound healing or reduction in amputation rates.<sup>12</sup>

**Platelet-derived products**—Interest in autologous platelet-rich plasma (PRP) to propagate wound healing has increased over the years. PRP is typically derived from a sample of blood from the patient that is centrifuged, and subsequently the platelets are separated into a highly concentrated suspension rich in platelet growth factors. Growth factors can be liberated from platelets by several techniques, including adding thrombin or calcium, freezing, or sonication. A 2016 Cochrane review examined 11 RCTs evaluating the use of PRP in patients with chronic wounds, DFUs, and venous leg ulcers. Although there was an unclear benefit in those with chronic wounds and venous ulcers, there was an apparent benefit in those with DFUs, although the quality of the evidence was poor. Since this review, there have been other RCTs that have found favorable results when PRP was compared with standard of care in patients with clean-base DFUs and chronic refractory DFUs.<sup>72,73</sup> There was also a retrospective study that found a positive response even in those with severe peripheral arterial disease.<sup>74</sup> Other platelet products that are currently being studied include combined leukocyte- and platelet-rich fibrin membranes and patches, which are theorized to prolong the release of growth factors and matrix proteins.<sup>75,76</sup>

There are limited data to conclude the efficacy of growth factors on wound healing in DFUs, but studies evaluating platelet-derived growth factors may show some benefits.

### **Skin grafts and bioengineered skin**

Skin grafting and tissue replacement can be used to reconstruct skin defects in DFUs. There are various types of skin grafts, including autographs, allografts, xenografts, and bioengineered skin. Although the mechanism is unclear, it is thought to promote wound healing by adding extracellular matrices that induce helpful growth factors and cytokines.<sup>77</sup> A 2016 Cochrane review and meta-analysis evaluated RCTs of a variety of skin grafts and tissue replacement products and found that there was increased healing rates of DFUs with these products compared with standard care.<sup>77</sup> This paper notes that the quality of evidence was low and the impact of the intervention varied greatly depending on the product type. It was also noted that nearly all studies had connections to commercial organizations.<sup>77</sup>

There is a growing interest in allografts originating from dehydrated human amniotic and chorionic membranes (dHACM). There have been several recent studies comparing dHACM to standard of care that have found improved rates of wound healing and wound closure.<sup>78,79</sup> Studies comparing dHACM to bioengineered skin substitutes have had various outcomes.<sup>80,81</sup> Another area of interest is the use of cryopreserved umbilical cord as adjunctive therapy. Small retrospective studies show that it may be helpful in wound healing, but RCTs are warranted to evaluate its true efficacy.<sup>82,83</sup>

### **Energy-based therapies**

Energy-based therapies employ technology to externally stimulate growth in wounds. Modalities currently being studied include electrical stimulation, shockwave therapy, electromagnetic therapy, laser therapy, and phototherapy.

**Electrical stimulation**—Electrical stimulation has been shown in several basic science studies to aid in wound healing, as it promotes angiogenesis, synthesis of collagen, and migration of keratinocytes, through the release of several factors, including vascular growth factors, hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), and VEGF in ischemic DFUs.<sup>84,85</sup> Unfortunately, the majority of RCTs (limited in number) show no benefit in improving wound healing outcomes.<sup>12</sup>

**Shockwave therapy**—Extracorporeal shockwave therapy (ESWT) is thought to stimulate wound healing by promoting angiogenesis through VEGF and endothelial nitric oxide synthases. It also has been suggested that ESWT propagates immune response and fibroblast proliferation.<sup>86</sup> The few RCTs comparing ESWT with standard care are small and show variable efficacy.<sup>12,87</sup> Moretti *et al.* showed no benefit in healing at 20 weeks. Both Omar *et al.* and Jeppsen *et al.* demonstrated a beneficial difference in reduction in wound size and median time for healing when evaluated at 20 weeks and 7 weeks, respectively.<sup>87,86</sup> One study show apparent superiority of ESWT when compared with HBOT.<sup>12</sup>

**Electromagnetic therapy**—Therapeutic electromagnetic resonance is thought to locally stimulate and activate physiological healing through factors that reduce oxidative stress and

inflammation, as well as increasing proliferation of cells responsible in wound repair.<sup>88</sup> RCTs in patients with DFUs have not demonstrated benefits.<sup>12,89,88</sup>

**Laser therapy**—Laser therapy promotes reduction of inflammation, angiogenesis, and production of extracellular matrix components.<sup>90</sup> Specifically, CO<sub>2</sub> laser therapy is found to significantly reduce wound bacterial load.<sup>91</sup> The RCTs exploring the efficacy of laser therapy on wound healing are few, have small sample sizes, and show variable results.<sup>92–94</sup>

**Phototherapy**—Phototherapy causes photochemical reactions that lead to a rapid increase in cellular metabolic activity and cell growth, vasodilation, and angiogenesis, which can result in faster wound healing.<sup>95</sup> A 2017 Cochrane review and meta-analysis concluded that phototherapy may result in greater reduction in ulcer size when compared with placebo after 2–4 weeks, but the quality of the evidence was low.<sup>95</sup>

Although many of these energy-based modalities have been found to be beneficial in some studies, there is currently inadequate quality evidence to recommend any these therapies.

### Systemic therapies

Several systemic agents have been studied in wound healing, including low-molecular-weight heparin, iloprost infusion, vildagliptin, oral pentoxifylline, and many herbs, but there is insufficient evidence to show efficacy in any of these agents. Systemic insulin use has been associated with a higher chance of complete wound healing when adjusted for multiple co-founders.<sup>96,97</sup>

There has been growing interest in various vitamins and supplements and their impact on wound healing. In 2017, there several RCTs have evaluated the use of magnesium, omega-3 fatty acids, zinc sulfate, and vitamin D.<sup>98–101</sup> All of the aforementioned studies showed significant benefits in reduction in wound size when compared with placebo. More studies will need to be performed to validate these findings.

### Conclusions

DFUs are a concern for the growing population of diabetic patients around the world. Although the principles that guide the standard of care are sound, there is still a significant gap between our current and desired wound healing outcomes. The breadth of DFU treatment currently being studied is promising, but there is a need for well-designed blinded randomized controlled trials to determine the true efficacy of these interventions and to develop evidence-based practice guidelines. Until then, good clinical judgment—considering the patient’s clinical context and wound characteristics—is essential to assess the risk and benefits of these adjuvant interventions for current clinical use. One of the challenges of achieving the aforementioned research goals is the staggering disparity in funding for DFU research. Armstrong et al described that between 2002–2011, the National Institute of Health granted over 7 million dollars for diabetes research but only 0.17% of that funding was allocated to DFU studies.<sup>102</sup> This funding gap is alarming considering that DFU care accounts for a third of overall diabetic health care expenditures. Given the large public

health burden of DFU, assuring adequate allocation of research dollars must be addressed soon.<sup>102</sup>

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**Table 1**

## Standard of care practices

Practice	Recommendations	Strength of recommendation	Level of evidence
Debridement	Sharp debridement preferred	Strong <sup>8,9,10</sup>	Moderate Low (preference of sharp debridement)
Dressing choice	Dressing should allow moist environment and provide exudate control	Strong <sup>8,9,10</sup>	Low Strong (exudate control)
Wound off-loading	Pressures should be redistributed off the wound	Strong <sup>8,9,10</sup>	High
Vascular assessment	Patients should be evaluated for arterial insufficiency with ABI	Strong <sup>8,9,10</sup>	Moderate
Infection control	Infection should be diagnosed by two signs of inflammation or purulence	Strong <sup>8,9,10</sup>	low
	Cultures should be obtained before antibiotic treatment	Strong <sup>9,10</sup>	Moderate
	Antibiotics course should be 1–2 weeks for mild infections and 2–3 weeks for moderate to severe infections	Weak <sup>9</sup>	Low
Glycemic control	Optimize blood glucose control for wound healing	Strong <sup>8,9,10</sup>	Low
Multidisciplinary care	Patients with DFUs should be evaluated by a multidisciplinary DFU team	Strong <sup>9,10</sup>	Moderate

**Table 2**

Efficacy of adjuvant therapies.

Therapy	Wound healing benefit compared to standard of care	Level of evidence (SIGN)
<i>Non-surgical debridement</i>		
Hydrogels	Apparent benefit, but RCTs have high risk of bias	1–
Clostridial collagenase ointment	Unclear benefit; few, small RCTs with variable results	1–
Maggot/larval therapy	Unclear benefit; few, small RCTs with variable results	1–
Hydrosurgery	No apparent benefit, but data limited to one RCT	1–
<i>Dressings and topical agents</i>		
Various dressing types	No apparent benefit for a particular dressing type except for hydrogel	1–
Honey	Apparent benefit, but RCTs have high risk of bias	1–
Other topical antimicrobials	Unclear benefit; few, small RCTs with variable results	1–
<i>Oxygen therapies</i>		
Topical oxygen	Unclear benefit; few, small RCTs with variable results	1–
Hyperbaric oxygen therapy	No apparent benefit in long-term healing, but RCTs have high risk of bias	1–
<i>Negative-pressure wound therapy</i>		
Negative-pressure wound therapy	Apparent benefit, but RCTs have high risk of bias	1–
<i>Acellular bioproducts</i>		
Acellular bioproducts	Apparent benefit, but RCTs have high risk of bias	1–
<i>Human growth factors</i>		
Fibroblast growth factor	Unclear benefit; few, small RCTs with variable results	1–
Epidermal growth factor	Unclear benefit; few, small RCTs with variable results	1– to 1+
Vascular endothelial growth factor	Apparent benefit, but data limited to one RCT	1++
Granulocyte colony-stimulating factor	No apparent benefit, but studies were not designed to evaluate wound healing	1– to 1++
Platelet-derived growth factor	Apparent benefit, but RCTs have high risk of bias	1–
<i>Skin graft and bioengineered skin</i>		
Skin graft and bioengineered skin	Apparent benefit, but RCTs have high risk of bias	1–
<i>Energy-based therapies</i>		
Electrical stimulation	Unclear benefit; few, small RCTs with variable results	1–
Shockwave therapy	Unclear benefit; few, small RCTs with variable results	1–
Electromagnetic therapy	No apparent benefit, but data limited to few small RCTs	1–
Laser therapy	Unclear benefit; few, small RCTs with variable results	1–
Phototherapy	Apparent benefit, but RCTs have high risk of bias	1–
<i>Systemic therapies</i>		
Insulin therapy	Apparent benefit, but RCTs are lacking	2+
Other systemic therapies	Unclear benefit; few, small RCTs with high bias, some with variable results	1–