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REVIEW

Update on management of diabetic foot ulcers

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Diabetic foot ulcers (DFUs) are a serious complication of diabetes that results in significant morbidity and mortality. Mortality rates associated with the development of a DFU are estimated to be 5% in the first 12 months, and 5-year morality 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: nonsurgical 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 DFU in their lifetimes, and the International Diabetes Federation reports that 9.1–26.1 million people will develop DFUs annually.[1] 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 to have a 2.5-fold increased risk of death compared with their diabetic counterparts without foot wounds.[2] Furthermore, patients living with DFUs suffer great morbidity, lower health-related quality of life, and poorer psychosocial adjustment[3] and have a high burden of healthcare interactions.[4]

Treatment of DFUs accounts for approximately one-third of the total cost of diabetic care, which was estimated to be U.S. $176 billion in direct healthcare expenditures in 2012.[5] Despite these high healthcare costs, about 20% of patients have unhealed DFUs at 1 year.[6] Even after wound resolution, subsequent DFUs are common, with a recurrence rate of roughly 40% of patients within 1 year.[1] Although there are well-established principles for 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.

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Table 1. Standard of care practices

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

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.[7] 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).[8–10] 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.[9] 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.[11] The Infectious Disease Society of America (IDSA) and the Wound Healing Society recommend sharp debridement over topical debridement agents (i.e., autolytic dressing or biological debridement).[8,9] Sharp debridement has been found to be efficacious in several clinical trials, although overall data are limited.[12–14]

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.[9,11,15] The selected dressing should also be appropriate to manage excess wound exudates. A wide range of dressing types is available, and several are currently being studied. Currently, there are insufficient data to recommend any particular dressing type.[9,12]

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.[16] Relieving plantar pressure and shear stress from a DFU is a vital part of wound care, as it promotes healing and prevents recurrence.[11] Off-loading can be achieved by many mechanisms, including shoe modifications, boots, and orthotic walkers.[11] 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 nonremovable devices, should not be used in those with significant PAD or infection.[17] 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 the lower leg, through the device wall.[18] Devices that extend to the ankle are generally less effective for this reason.[18] Although there was a randomized controlled trial (RCT) that showed similar healing rates between TCC and removable walkers, there are numerous studies demonstrating that nonremovable 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 nonremovable 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 nonremovable 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 nonplantar ulcers.[17] 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.[17]

Vascular assessment

PAD is estimated to occur in 40% of patients with DFUs.[6] Patients who have comorbid DFUs and PAD have slower healing, higher major amputation rates, and higher mortality rates.[6] It is recommended that those with DFUs be evaluated for PAD by palpating pedal pulses or ankle brachial index (ABI).[11] 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 noncompressible vessels at the ankle due to vascular calcifications. This is not uncommon in patients with diabetes and is also observed in renal insufficiency.[19] Those with noncompressible 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 confirm the diagnosis of PAD.[11,19]

Treatment of active infection

Wound infection is a known predictor of poor wound healing and amputation.[20] 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.[21] The IDSA has outlined specific guidelines for the treatment of diabetic foot infections.[9] The IDSA recommends treatment of wounds with at least two signs or symptoms of inflammation (erythema, warmth, tenderness, pain, and 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.[9] 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.[9] 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.[22]

Glycemic control

It is widely recommended that blood glucose be optimized to improve wound healing and limit adverse effects on cellular immunity and infection.[11] 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 a lack of RCTs, several observational studies have found positive correlations with glycemic control and wound healing.[23–25] 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.[26]

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 the management of DFUs.[9,15,27] Numerous studies and systematic reviews have showed positive effects on multidisciplinary care in reducing wound healing times, amputation rates, and severity of amputation.[28–31] The definition of multidisciplinary diabetic foot care varies broadly in the literature but often includes a surgeon (general, vascular, and 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. Here, we characterize these agents in the following categories: nonsurgical 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 review the rationale for use and the data evaluating the efficacy of these interventions.

Nonsurgical debridement agents

Although sharp debridement is the preferred method of debridement, there are other nonsurgical 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.[32] 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.[32] A 2013 Cochrane review and meta-analysis of three RCTs found that hydrogel dressings had significantly greater healing when compared with basic wound dressings.[32]

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.[33] There are only three RCTs specifically exploring the efficacy of CCO in DFUs. 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.[34] It has been questioned whether the control group received usual best care, as the average wound size increased during the study in this group.[12] 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.[35]

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.[36] Data on the efficacy on this treatment are limited. A case–control trial in nonambulatory 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.[37] Several other studies have shown no difference in healing or amputation rates.[12] There are current ongoing studies exploring

Table 2. Efficacy of adjuvant therapies

Therapy	Wound healing benefit compared with standard of care	Level of evidence (SIGN)
Nonsurgical debridement		
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–
Dressings and topical agents		
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–
Oxygen therapies		
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–
Negative-pressure wound therapy		
Negative-pressure wound therapy	Apparent benefit, but RCTs have high risk of bias	1–
Acellular bioproducts		
Acellular bioproducts	Apparent benefit, but RCTs have high risk of bias	1–
Human growth factors		
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–
Skin graft and bioengineered skin		
Skin graft and bioengineered skin	Apparent benefit, but RCTs have high risk of bias	1–
Energy-based therapies		
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 a 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–
Systemic therapies		
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–

a new generation of maggot debridement therapy with transgenic *Lucilia sericata* larvae that produce and secrete human growth factors.[38]

Hydrotherapy. The Versajet™ (Smith & Nephew, Inc., Andover, MA) 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 Versajet™, comparing it to surgical debridement in lower extremity ulcers. Although debridement times were shorter, there was no difference in time to wound closure.[12]

There are several options available for nonsurgical 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, calcium sodium alginate, or alginic acid. These alginate products form a highly absorbent gel that can absorb a 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.[39]

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 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.[40] 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 nonblinded 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 were insufficient data to determine true efficacy.[41] One new RCT published since that time compared honey dressing to dressing with normal saline and found that honey dressings were more effective in terms of time to healing and number of wounds healed at 120 days.[42]

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.[12,43] Nanocrystalline silver was found to cause a greater ulcer size reduction rate than both Manuka honey and conventional dressing in one study.[44] 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 have 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.[12]

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.[45] 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 2016 IWGDF 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 an 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.[12,46] 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.[47] 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 older than 65 years of age.[48] A newer topical agent currently being studied is hemoglobin spray. Topical hemoglobin can transport oxygen from the atmosphere to hypoxic wounds through facilitated

diffusion.[49] Hunt *et al.* showed significant benefit in wound closure at 28 weeks.[50] 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 has not been well studied in DFUs.[45] 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 in rate in healing with HBOT at 6 weeks, although this benefit was not evident at follow-up at 1 year.[51] It was recommended that the results be interpreted with caution owing to various flaws in design in the available studies. In 2016, Fedorko *et al.* published a double-blinded RCT concluding that HBOT 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.[52] This study has been criticized because the end points were not amputation events.[53–55] 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, reduces the 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.[56] 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 fewer amputations. There was no difference in incidence of treatment-related adverse effects.[57]

Acellular bioproducts

Acelluar 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.[58] 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.[58] 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.[58] Since that publication, Zelen *et al.* published similar findings.[59,60] 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 rehospitalization rates.[61] 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.[62] 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.[63,64] 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 (EGF), vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), 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.[65] 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.[66] 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.[67]

Epidermal growth factors. Data evaluating the efficacy of 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.[12] More recent studies have found some benefit in healing, although they are very small studies with high risk of bias.[68–70]

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

Granulocyte colony-stimulating factor. The majority of RCTs studying 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.[12]

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 to standard of care in patients with clean-base DFUs and chronic refractory DFUs.[72,73] There was also a retrospective study that found a positive response even in those with severe PAD.[74] 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.[75,76]

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.[77] 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.[77] 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.[77]

There is a growing interest in allografts originating from dehydrated human amniotic and chorionic membranes (dHACMs). There have been several recent studies comparing dHACMs to standard of care that have found improved rates of wound healing and wound closure.[78,79] Studies comparing dHACMs to bioengineered skin substitutes have had various outcomes.[80,81] 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.[82,83]

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 1α, and VEGF in ischemic DFUs.[84,85] Unfortunately, the majority of RCTs (limited in number) show no benefit in improving wound healing outcomes.[12]

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

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 for wound repair.[88] RCTs in patients with DFUs have not demonstrated benefits.[12,88,89]

Laser therapy. Laser therapy promotes reduction of inflammation, angiogenesis, and production of extracellular matrix components.[90] Specifically, CO_2 laser therapy was found to significantly reduce wound bacterial load.[91] The RCTs exploring the efficacy of laser therapy on wound healing are few, have small sample sizes, and show variable results.[92–94]

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.[95] 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.[95]

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 of these therapies.

Systemic therapies

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

There has been growing interest in various vitamins and supplements and their impact on wound healing. In 2017, several RCTs evaluated the use of magnesium, omega-3 fatty acids, zinc sulfate, and vitamin D.[98–101] 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 RCTs 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 and 2011, the National Institutes of Health granted over seven million dollars for diabetes research, but only 0.17% of that funding was allocated to DFU studies.[102] This funding gap is alarming, considering that DFU care accounts for a third of overall diabetic healthcare expenditures. Given the large public health burden of DFUs, assuring adequate allocation of research dollars must be addressed soon.[102]

Competing interests

The authors declare no competing interests.

References

1. Armstrong, D.G., A.J.M. Boulton, S.A. Bus, *et al.* 2017. Diabetic foot ulcers and their recurrence. *N. Engl. J. Med.* **376:** 2367–2375.
2. Walsh, J.W., O.J. Hoffstad, M.O. Sullivan, *et al.* 2016. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. *Diabet. Med.* **33:** 1493–1498.
3. Goodridge, D., E. Trepman & J.M. Embil. 2005. Health-related quality of life in diabetic patients with foot ulcers: literature review. *J. Wound Ostomy Continence Nurs.* **32:** 368–377.
4. Skrepnek, G.H., J.L. Mills, Sr., L.A. Lavery & D.G. Armstrong. 2017. Health care service and outcomes among an estimated 6.7 million ambulatory care diabetic foot cases in the U.S. *Diabetes Care* **40:** 936–942.
5. Driver, V.R., M. Fabbi, L.A. Lavery, *et al.* 2010. The costs of diabetic foot: the economic case for the limb salvage team. *J. Vasc. Surg.* **52**(3 Suppl.): 17S–22S.
6. Prompers, L., N. Schaper, J. Apelqvist, *et al.* 2008. Prediction of outcome in individuals with diabetic footulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia* **51:** 747–755.
7. Naves, C.C.L.M. 2016. The diabetic foot: a historical overview and gaps in current treatment. *Adv. Wound Care* **5:** 191–197.
8. Lavery, L.A., K.E. Davis, S.J. Berriman, *et al.* 2016. WHS guidelines update: diabetic foot ulcer treatment guidelines. *Wound Repair Regen.* **24:** 112–126.
9. Lipsky, B.A., A.R. Berendt, P.B. Cornia, *et al.* 2012. 2012 Infectious Diseases Society of America Clinical Practice Guideline for the diagnosis and treatment of diabetic foot infections. *Clin. Infect. Dis.* **54:** e132–e173.
10. Bakker, K., J. Apelqvist, B.A. Lipsky, *et al.* 2016. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. *Diabetes Metab. Res. Rev.* **32**(Suppl. 1): 2–6.
11. Braun, L., P.J. Kim, D. Margolis, *et al.* 2014. What's new in the literature: an update of new research since the original WHS diabetic foot ulcer guidelines in 2006. *Wound Repair Regen.* **22:** 594–604.
12. Game, F.L., J. Apelqvist, C. Attinger, *et al.* 2016. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab. Res. Rev.* **32**(Suppl. 1): 154–168.
13. Elraiyah, T., J. Pablo Domecq, G. Prutsky, *et al.* 2016. A systematic review and meta-analysis of débridement methods for chronic diabetic foot ulcers. *J. Vasc. Surg.* **63**(2 Suppl.): 37S–47S.e1–2.
14. Hinchliffe, R.J., G.D. Valk, J. Apelqvist, *et al.* 2008. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab. Res. Rev.* **24**(Suppl. 1): S119–S144.
15. Bakker, K., J. Apelqvist & N.C. Schaper. 2012. Practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes Metab. Res. Rev.* **28**(Suppl. 1): 225–231.
16. Yavuz, M., A. Ersen, J. Hartos, *et al.* 2017. Plantar shear stress in individuals with a history of diabetic foot ulcer: an emerging predictive marker for foot ulceration. *Diabetes Care* **40:** e14–e15.
17. Bus, S.A., D.G. Armstrong, R.W. Deursen, *et al.* 2016. IWGDF guidance on footwear and offloading interventions to prevent and heal foot ulcers in patients with diabetes. *Diabetes Metab. Res. Rev.* **32**(Suppl. 1): 25–36.
18. Bus, S.A. 2016. The role of pressure offloading on diabetic foot ulcer healing and prevention of recurrence. *Plast. Reconstr. Surg.* **138**(3 Suppl.): 179S–187S.
19. Norgren, L., W.R. Hiatt, J.A. Dormandy, *et al.* 2007. Inter-Society Consensus for the management of peripheral arterial disease (TASC II). *Eur. J. Vasc. Endovasc. Surg.* **33:** S1–S75.
20. Acar, E. & B.K. Kacıra 2017. Predictors of lower extremity amputation and reamputation associated with the diabetic foot. *J. Foot Ankle Surg.* **56:** 1218–1222.
21. Abbas, M., I. Uçkay & B.A. Lipsky. 2015. In diabetic foot infections antibiotics are to treat infection, not to heal wounds. *Expert Opin. Pharmacother.* **16:** 821–832.
22. Barwell, N.D., M.C. Devers, B. Kennon, *et al.* 2017. Diabetic foot infection: antibiotic therapy and good practice recommendations. *Int. J. Clin. Pract.* **71:** e13006.
23. Fernando, M.E., R.M. Seneviratne, Y.M. Tan, *et al.* 2016. Intensive versus conventional glycaemic control for treating diabetic foot ulcers. *Cochrane Database Syst. Rev.* **13:** CD010764.
24. Markuson, M., D. Hanson, J. Anderson, *et al.* 2009. The relationship between hemoglobin A(1c) values and healing time for lower extremity ulcers in individuals with diabetes. *Adv. Skin Wound Care* **22:** 365–372.
25. Christman, A.L., E. Selvin, D.J. Margolis, *et al.* 2011. Hemoglobin A1c predicts healing rate in diabetic wounds. *J. Invest. Dermatol.* **131:** 2121–2127.
26. Hemmingsen, B., S.S. Lund, C. Gluud, *et al.* 2013. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* **11:** CD008143.
27. Internal Clinical Guidelines Team. 2015. Diabetic foot problems: prevention and management. National Institute for Health and Care Excellence Clinical Guidelines. Accessed August 9, 2017. https://www.nice.org.uk/guidance/ng19/resources/diabetic-foot-problems-prevention-and-management-1837279828933.
28. Buggy, A. & Z. Moore. 2017. The impact of the multidisciplinary team in the management of individuals with diabetic foot ulcers: a systematic review. *J. Wound Care* **26:** 324–339.
29. Wang, C., L. Mai, C. Yang, *et al.* 2016. Reducing major lower extremity amputations after the introduction of a multidisciplinary team in patient with diabetes foot ulcer. *BMC Endocr. Disord.* **16:** 38.
30. Rubio, J.A., J. Aragón-Sánchez, S. Jiménez, *et al.* 2014. Reducing major lower extremity amputations after the introduction of a multidisciplinary team for the diabetic foot. *Int. J. Low Extrem. Wounds* **13:** 22–26.
31. Krishnan, S., F. Nash, N. Baker, *et al.* 2008. Reduction in diabetic amputations over 11 years in a defined U.K.

population: benefits of multidisciplinary team work and continuous prospective audit. *Diabetes Care* **31:** 99–101.
32. Dumville, J.C., S. O'Meara, S. Deshpande, *et al.* 2013. Hydrogel dressings for healing diabetic foot ulcers. *Cochrane Database Syst. Rev.* **12:** CD009101.
33. Motley, T.A., A.M. Gilligan, D.L. Lange, *et al.* 2015. Cost-effectiveness of clostridial collagenase ointment on wound closure in patients with diabetic foot ulcers: economic analysis of results from a multicenter, randomized, open-label trial. *J. Foot Ankle Res.* **8:** 7.
34. Tallis, A., T.A. Motley, R.P. Wunderlich, *et al.* 2013. Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study. *Clin. Ther.* **35:** 1805–1820.
35. Jimenez, J.C., P.S. Agnew, P. Mayer, *et al.* 2017. Enzymatic debridement of chronic nonischemic diabetic foot ulcers: results of a randomized, controlled trial. *Wounds* **29:** 133–139.
36. Abela, G. 2017. Benefits of maggot debridement therapy on leg ulcers: a literature review. *Br. J. Community Nurs.* **22**(Suppl. 6): S14–S19.
37. Armstrong, D.G., P. Salas, B. Short, *et al.* 2005. Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J. Am. Podiatr. Med. Assoc.* **95:** 254–257.
38. Linger, R.J., E.J. Belikoff, Y. Yan, *et al.* 2016. Towards next generation maggot debridement therapy: transgenic *Lucilia sericata* larvae that produce and secrete a human growth factor. *BMC Biotechnol.* **16:** 1–12.
39. Saco, M., N. Howe, R. Nathoo, *et al.* 2016. Comparing the efficacies of alginate, foam, hydrocolloid, hydrofiber, and hydrogel dressings in the management of diabetic foot ulcers and venous leg ulcers: a systematic review and meta-analysis examining how to dress for success. *Dermatol. Online J.* **22**. http://escholarship.org/uc/item/7ph5v17z.
40. Jull, A.B., N. Cullum, J.C. Dumville, *et al.* 2015. Honey as a topical treatment for wounds. *Cochrane Database Syst. Rev.* **6:** CD005083.
41. Kateel, R., P. Adhikari, A.J. Augustine, *et al.* 2016. Topical honey for the treatment of diabetic foot ulcer: a systematic review. *Complement Ther. Clin. Pract.* **24:** 130–133.
42. Imran, M., M.B. Hussain & M. Baig. 2015. A randomized, controlled clinical trial of honey-impregnated dressing for treating diabetic foot ulcer. *J. Coll. Physicians Surg. Pak.* **25:** 721–725.
43. Bergqvist, K., U. Almhöjd, I. Herrmann, *et al.* 2016. The role of chloramines in treatment of diabetic foot ulcers: an exploratory multicentre randomised controlled trial. *Clin. Diabetes Endocrinol.* **2:** 1–7.
44. Tsang, K.-K., E. Wai-Yung Kwong, T. Shing-Shun To, *et al.* 2017. A pilot randomized, controlled study of nanocrystalline silver, manuka honey, and conventional dressing in healing diabetic foot ulcer. *Evid. Based Complement. Altern. Med.* **2017:** 1–15.
45. de Smet, G.H.J., L.F. Kroese, A.G. Menon, *et al.* 2017. Oxygen therapies and their effects on wound healing. *Wound Repair Regen.* **25:** 591–608.
46. Heng, M.C., J. Harker, V.B. Bardakjian, *et al.* 2000. Enhanced healing and cost-effectiveness of low-pressure oxygen therapy in healing necrotic wounds: a feasibility study of technology transfer. *Ostomy Wound Manage.* **46:** 52–60, 62.
47. Yu, J., S. Lu, A.-M. McLaren, *et al.* 2016. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. *Wound Repair Regen.* **24:** 1066–1072.
48. Driver, V.R., A. Reyzelman, J. Kawalec, *et al.* 2017. 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.* **63:** 12–28.
49. Dawn, S.H. 2016. Evaluating the effect of a haemoglobin spray on size redution in chronic DFUs—clinical outcomes at 12 weeks. *Br. J. Nurs.* **25:** S59–S64.
50. Hunt, S.D. & F. Elg. 2016. Clinical effectiveness of hemoglobin spray (Granulox(®)) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. *Diabet. Foot Ankle* **7:** 33101.
51. Kranke, P., M.H. Bennett, M. Martyn-St James, *et al.* 2015. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst. Rev.* **24:** CD004123.
52. Fedorko, L., J.M. Bowen, W. Jones, *et al.* 2016. 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* **39:** 392–399.
53. Murad, M.H. 2016. Comment on Fedorko *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:** 392–399. *Diabetes Care* **39:** e135.
54. Huang, E.T. 2016. Comment on Fedorko *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:** 392–399. *Diabetes Care* **39:** e133–e134.
55. Mutluoglu, M., G. Uzun, M. Bennett, *et al.* 2016. Poorly designed research does not help clarify the role of hyperbaric oxygen in the treatment of chronic diabetic foot ulcers. *Diving Hyperb. Med.* **46:** 133–134.
56. Dumville, J.C., R.J. Hinchliffe, N. Cullum, *et al.* 2013. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst. Rev.* **10:** CD010318.
57. Liu, S., C.-Z. He, Y.-T. Cai, *et al.* 2017. Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis. *Ther. Clin. Risk Manag.* **13:** 533–544.
58. Guo, X., D. Mu & F. Gao. 2017. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: a systematic review and meta-analysis. *Int. J. Surg.* **40:** 1–7.
59. Zelen, C.M., D.P. Orgill, T. Serena, *et al.* 2017. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care

in the treatment of chronic diabetic foot ulcers. *Int. Wound J.* **14:** 307–315.
60. Zelen, C.M., D.P. Orgill, T.E. Serena, *et al.* 2017. Human reticular acellular dermal matrix in the healing of chronic diabetic foot ulcerations that failed standard conservative treatment: a retrospective crossover study. *Wounds* **29:** 39–45.
61. Campitiello, F., M. Mancone, A. Della Corte, *et al.* 2017. 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.* **69:** 523–529.
62. Hu, Z., J. Zhu, X. Cao, *et al.* 2016. Composite skin grafting with human acellular dermal matrix scaffold for treatment of diabetic foot ulcers: a randomized controlled trial. *J. Am. Coll. Surg.* **222:** 1171–1179.
63. Walters, J., S. Cazzell, H. Pham, *et al.* 2016. 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* **16:** e10.
64. Cazzell, S., D. Vayser, H. Pham, *et al.* 2017. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. *Wound Repair Regen.* **25:** 483–497.
65. Richard, J.-L., C. Parer-Richard, J.-P. Daures, *et al.* 1995. Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot: a pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care* **18:** 64–69.
66. Uchi, H., A. Igarshi, K. Urabe, *et al.* Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *Eur. J. Dermatol.* **19:** 461–468.
67. Olympus Biotech Corporation. The TRAfermin in neuropathic diabetic foot ulcer study—Northern Europe The TRANS-North Study—study results—ClinicalTrials.gov. Accessed August 16, 2017. https://clinicaltrials.gov/ct2/show/results/NCT01217476?term=bFGF+diabetes&sect=X01256.
68. Singla, S., R. Garg, A. Kumar, *et al.* 2014. 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.* **5:** 273–277.
69. Gomez-Villa, R., F. Aguilar-Rebolledo, A. Lozano-Platonoff, *et al.* 2014. Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: a randomized double-blinded controlled trial. *Wound Repair Regen.* **22:** 497–503.
70. Aktaş, Ş., S. Baktıroğlu, L. Demir, *et al.* 2016. Intralesional application of epidermal growth factor in limb-threatening ischemic diabetic foot ulcers. *Acta Orthop. Traumatol. Turc.* **50:** 277–283.
71. Martí-Carvajal, A.J., C. Gluud, S. Nicola, *et al.* 2015. Growth factors for treating diabetic foot ulcers. *Cochrane Database Syst. Rev.* CD008548. https://doi.org/10.1002/14651858.CD008548.pub2.
72. Ahmed, M., S.A. Reffat, A. Hassan, *et al.* 2017. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann. Vasc. Surg.* **38:** 206–211.
73. Li, L., D. Chen, C. Wang, *et al.* 2015. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: a prospective, randomized clinical trial. *Wound Repair Regen.* **23:** 495–505.
74. Kontopodis, N., E. Tavlas, G. Papadopoulos, *et al.* 2016. Effectiveness of platelet-rich plasma to enhance healing of diabetic foot ulcers in patients with concomitant peripheral arterial disease and critical limb ischemia. *Int. J. Low Extrem. Wounds* **15:** 45–51.
75. Pinto, N.R., M. Ubilla, Y. Zamora, *et al.* 2017. Leucocyte- and platelet-rich fibrin (L-PRF) as a regenerative medicine strategy for the treatment of refractory leg ulcers: a prospective cohort study. *Platelets* https://doi.org/10.1080/09537104.2017.1327654.
76. Löndahl, M., L. Tarnow, T. Karlsmark, *et al.* 2015. Use of an autologous leucocyte and platelet-rich fibrin patch on hard-to-heal DFUs: a pilot study. *J. Wound Care* **24:** 172–174, 176–178.
77. Santema, T.B., P.P.C. Poyck & D.T. Ubbink. 2016. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. *Cochrane Database Syst. Rev.* **2:** CD011255.
78. DiDomenico, L.A., D.P. Orgill, R.D. Galiano, *et al.* 2016. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. *Plast. Reconstr. Surg. Glob. Open* **4:** 1095.
79. Snyder, R.J., K. Shimozaki, A. Tallis, *et al.* 2016. 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* **28:** 70–77.
80. Zelen, C.M., T.E. Serena, L. Gould, *et al.* 2016. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. *Int. Wound J.* **13:** 272–282.
81. Kirsner, R.S., M.L. Sabolinski, N.B. Parsons, *et al.* 2015. 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.* **23:** 737–744.
82. Caputo, W.J., C. Vaquero, A. Monterosa, *et al.* 2016. A retrospective study of cryopreserved umbilical cord as an adjunctive therapy to promote the healing of chronic, complex foot ulcers with underlying osteomyelitis. *Wound Repair Regen.* **24:** 885–893.
83. Couture, M. 2016. A single-center, retrospective study of cryopreserved umbilical cord for wound healing in patients suffering from chronic wounds of the foot and ankle. *Wounds* **28:** 217–225.
84. Wirsing, P.G., A.D. Habrom, T.M. Zehnder, *et al.* 2015. Wireless micro current stimulation—an innovative electrical stimulation method for the treatment of patients with leg and diabetic foot ulcers. *Int. Wound J.* **12:** 693–698.
85. Asadi, M.R., G. Torkaman, M. Hedayati, *et al.* 2017. Angiogenic effects of low-intensity cathodal direct current on

ischemic diabetic foot ulcers: a randomized controlled trial. *Diabetes Res. Clin. Pract.* **127:** 147–155.
86. Jeppesen, S.M., K.B. Yderstraede, B.S.B. Rasmussen, *et al.* 2016. Extracorporeal shockwave therapy in the treatment of chronic diabetic foot ulcers: a prospective randomised trial. *J. Wound Care* **25:** 641–649.
87. Omar, M.T.A., A. Alghadir, K.K. Al-Wahhabi, *et al.* 2014. Efficacy of shock wave therapy on chronic diabetic foot ulcer: a single-blinded randomized controlled clinical trial. *Diabetes Res. Clin. Pract.* **106:** 548–554.
88. Piaggesi, A., M. Sambataro, C. Nicoletti, *et al.* 2016. Safety and effectiveness of therapeutic magnetic resonance in diabetic foot ulcers: a prospective randomised controlled trial. *J. Wound Care* **25:** 704–711.
89. Lai-Chu Kwan, R., W.-C. Wong, S.-L. Yip, *et al.* 2015. Pulsed electromagnetic field therapy promotes healing and microcirculation of chronic diabetic foot ulcers: a pilot study. *Adv. Skin Wound Care* **28:** 212–219.
90. de Sousa, R.G. & K. de Nazaré Madureira Batista. 2016. Laser therapy in wound healing associated with diabetes mellitus—review. *An. Bras. Dermatol.* **91:** 489–493.
91. Monami, M., A. Scatena, S. Zannoni, *et al.* 2017. A randomized, open-label, controlled trial to evaluate the antimicrobial and surgical effect of CO_2 laser treatment in diabetic infected foot ulcers: DULCIS (diabetic ulcer, CO_2 laser, and infections) study. *J. Endocrinol. Invest.* **40:** 985–989.
92. Maltese, G., J. Karalliedde, H. Rapley, *et al.* 2015. 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* **38:** e152–e153.
93. Feitosa, M.C.P., A.F.M. de Carvalho, V.C. Feitosa, *et al.* 2015. Effects of the low-level laser therapy (LLLT) in the process of healing diabetic foot ulcers. *Acta Cir. Bras.* **30:** 852–857.
94. Mathur, R.K., K. Sahu, S. Saraf, *et al.* 2017. Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers. *Lasers Med. Sci.* **32:** 275–282.
95. Wang, H.-T., J.-Q. Yuan, B. Zhang, *et al.* 2017. Phototherapy for treating foot ulcers in people with diabetes. *Cochrane Database Syst. Rev.* **6:** CD011979.
96. Vatankhah, N., Y. Jahangiri, G.J. Landry, *et al.* 2017. Effect of systemic insulin treatment on diabetic wound healing. *Wound Repair Regen.* **25:** 288–291.
97. Oryan, A. & E. Alemzadeh. 2017. Effects of insulin on wound healing: a review of animal and human evidences. *Life Sci.* **174:** 59–67.
98. Razzaghi, R., F. Pidar, M. Momen-Heravi, *et al.* 2017. 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.* https://doi.org/10.1007/s12011-017-1056-5.
99. Soleimani, Z., F. Hashemdokht, F. Bahmani, *et al.* 2017. 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* **31:** 1394–1400.
100. Momen-Heravi, M., E. Barahimi, R. Razzaghi, *et al.* 2017. 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.* **25:** 512–520.
101. Razzaghi, R., H. Pourbagheri, M. Momen-Heravi, *et al.* 2017. 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* **31:** 766–772.
102. Armstrong, D.G., V.A. Kanda, L.A. Lavery, *et al.* 2013. Mind the gap: disparity between research funding and costs of care for diabetic foot ulcers. *Diabetes Care* **36:** 1815–1817.