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REVIEW ARTICLE

Diabetic Foot Ulcers: Appraising Standard of Care and Reviewing New Trends in Management

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Abstract
Diabetic foot ulcers (DFU) are one of the most common diabetes complications and are associated with significant morbidity and mortality. Current DFU standard of care (SOC) involves four principles: (1) pressure relief, (2) debridement, (3) infection management, and (4) revascularization when indicated. Despite the current SOC, many DFU persist, warranting a new approach for the management of these complex wounds. This review aims to summarize the current SOC as well as the latest trends in adjunctive therapies that may become the new SOC in DFU management. These include negative pressure wound therapy and hyperbaric oxygen therapy, bioengineered skin substitutes, growth factors, shockwave therapy, and several others. These novel therapies have shown significant DFU clinical improvement among subsets of DFU patients. However, much of the literature comes from smaller trials with inconsistent patient selection and outcomes measured, making it difficult to assess the true clinical benefit of these treatments. While novel therapies are promising for the interdisciplinary approach to DFU management, many still lack sufficient evidence, and their efficacy remains to be determined.

Key Points

The current gold standard of care (SOC) for diabetic foot ulcers (DFU) involves (1) pressure relief, (2) debridement, (3) infection management, and (4) revascularization.

Current SOC alone may not be sufficient to prevent and treat DFU.

New trends in DFU management involve the use of adjunctive therapies to prevent DFU formation and promote DFU wound healing.

Novel adjunctive therapies are promising to become part of the new SOC for DFU; however, more robust data on their efficacy and cost–benefit ratio are needed to support their use.

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1 Introduction: Reappraisal of Diabetic Foot Ulcer (DFU) Care

With an estimated 34% lifetime risk, diabetic foot ulcers (DFU) are one of the most common complications among patients with diabetes [1]. These wounds are associated with significant morbidity and mortality as they can result in life-threatening and quality-of-life–reducing complications, such as infection and major lower extremity amputations [2]. DFU represent a complex entity resulting from several contributing pathways including neuropathy, vascular disease, and metabolic derangement, which may occur alone or in concert with each other.

Since DFU are due to various pathological mechanisms, their management requires a multimodal and interdisciplinary approach that should include (1) prevention, (2) targeting the various mechanisms that contribute to their formation, and (3) promotion of wound healing. The current mainstay of DFU management includes prevention with standard principles of wound care. However, 30% of DFU fail to heal despite 20 weeks of standard of care (SOC), as SOC may not properly address all of the factors that allow these complex wounds to persist [3]. Thus, there is a need for new therapies that target *all* aspects of DFU wound care, including prevention of ulceration *and* promotion of wound healing.

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New trends in DFU management involve the use of adjunctive therapies that promote wound healing as well as target the factors that contribute to their formation. Adjunct therapies are often indicated when DFU have failed SOC and may become the new principle in the standard of DFU care. However, many of these treatments are costly, and there is still little known about their true clinical efficacy. In this review, we aim to reappraise that standard of DFU care requires a comprehensive approach, including therapies that target the various DFU etiologies *and* promote wound healing. We also review the latest trends in DFU management.

2 Prevention of DFU

Since it is estimated that 20–35% of patients will develop DFU in their lifetime and these wounds are associated with significant diabetes morbidity and mortality [1], prevention is crucial to DFU management.

Prevention begins with appropriate screening in patients with diabetes. The American Diabetes Association (ADA) recommends annual screening for neuropathy, beginning at the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes [4]. Screening for neuropathy should include a careful history, making sure to ask about symptoms of paresthesias, burning, and diminished or absent sensation. Each patient should also undergo a neurological assessment using 10-g monofilament testing to determine loss of protective sensation and identify individual risk for ulceration and amputation. Additional testing may include temperature and pinprick sensation and vibration testing using a 128-Hz tuning fork [4].

Since inappropriate footwear and foot deformity commonly contribute to the development of foot ulcers [5], shoes should always be inspected to determine if they are appropriate for the patient. Appropriate footwear includes shoes that are made of forgiving materials (e.g., leather) and are able to accommodate foot deformities and edema [5]. Appropriate footwear can relieve areas of pressure, reduce shock, shear stress, and the formation of calluses. More importantly, it has actually been shown to prevent DFU [6]. Inappropriately fitting shoes, those that are worn excessively, or those that cause rubbing, erythema, blisters, or calluses should be avoided.

Since there are many underlying factors that contribute to DFU, altering one's risk factors is also a major component in prevention. Strict glycemic control has been shown to effectively delay or prevent diabetic neuropathy [7]. However, tight glucose control in patients with DFU may have less of a contribution to ischemia [8]; therefore patients should attempt to alter other risk factors for ischemia, such as atherosclerosis. This may include revascularization for critical ischemia, weight loss, smoking cessation, and limiting alcohol intake. Patients may also consider leg elevation and compression stocking to reduce edema if venous insufficiency is present. Finally, calluses are major risk factors for ulceration, since they increase plantar pressure, leading to tissue breakdown [5]. Therefore, regular removal of calluses is recommended.

Although it is well known that adequate nutrition is important for wound healing and that metabolic imbalance contributes to DFU development, the role of nutrition and supplementation in preventing DFU is unclear. Malnourishment is common in DFU patients, but there is little sound evidence to show that better nutrition or supplementation will improve wound healing or prevent DFU in the first place. Most studies on nutrition and DFU are not randomized controlled trials (RCTs), often have a wide range of outcome variables, and do not provide clear longitudinal and clinically relevant data [9]. For example, recent RCTs studying the effect of vitamin D, vitamin E, and magnesium supplementation on DFU found reduced ulcer sizes, but did not actually report complete ulcer healing [10, 11]. These may be some of the reasons why the ADA does not specifically advocate for nutritional supplementation in the management of diabetes foot care [4].

3 Current Standard of Care (SOC) in DFU Management

The current gold standard of DFU care consists of four principals: (1) pressure relief, (2) debridement, (3) infection management, and (4) revascularization when indicated. This SOC is provided for approximately 4 weeks, since studies have shown that DFU that do not reduce in size by 50% within that time are less likely to heal by 12 weeks [12]. Below we outline each principal.

3.1 Pressure Relief

Using devices or surgical procedures to reduce abnormal pressure and shear stress at the site of the ulcer is probably one of the most important interventions to facilitate healing. Inadequate relief of pressure at the ulcer site can delay ulcer healing even in adequately perfused limbs and increase the risk of recurrence after the ulcer has healed [13, 14]. The current gold standard method to offload pressure and protect the ulcer is the use of the total contact cast. This technique uses a minimal amount of padding, but conforms closely to the patient's anatomy to limit the amount of foot and ankle movement within the cast [15]. However, it has several challenges and is not widely used

since casting requires trained personnel and the cast may be inconvenient for activities of daily living [15]. Other acceptable offloading techniques include therapeutic/modified shoes, custom inserts, and orthotics [13].

3.2 Debridement

Debridement involves the excision of necrotic, damaged, or infected tissue in order to optimize healing of the viable tissue that remains [15]. It improves healing by promoting the production of granulation tissue and can be achieved by different means.

Surgical debridement is the preferred method recommended by the Infectious Disease Society of America and the Wound Healing Society [16]. It uses a scalpel blade to remove all nonviable tissue until a healthy bleeding ulcer bed is produced [17]. It is the fastest form of debridement and is most effective for progressively large or recalcitrant wounds that are in abnormal locations, are grossly infected, or require biopsy [15].

Mechanical debridement is the most traditional form and involves the application of moist and wet flushes or dressings. This method is effective because ulcers heal more quickly and are less likely to become infected when they are allowed a moist environment to heal [17].

Enzymatic debridement uses chemical agents derived from microorganisms or plants such as collagenase and streptokinase. It selectively targets necrotic tissue without damaging healthy tissue and is indicated for ischemic wounds. However, this method can be expensive [17]; thus it may not always be accessible.

Autolytic debridement is a painless and highly selective method that uses the body's own enzymatic processes and defense mechanisms to selectively debride slough and necrotic tissue. It is indicated when dead tissue is not extensive or infected, and the process is slow and must be monitored for infection [15]. Thus, it is often reserved for those with poor access to resources or patients who have exhausted other debridement methods [15].

Biologic debridement utilizes sterile maggots to digest bacteria, surface debris, and necrotic tissues only [17]. This method has been shown to be effective in eliminating drug-resistant pathogens from wound surfaces, such as *Staphylococcus aureus* [18], and works faster than autolytic and enzymatic debridement [15]. However, many patients may have an aversion to it.

3.3 Infection Management

Since more than half of DFU show evidence of infection (i.e., warmth, erythema, purulence, foul odor) at the time of presentation, management of infection is crucial to DFU care [19]. The recommendation is that only wounds showing evidence of infection should be cultured and treated with antibiotics. Mild to moderate infections can be treated with agents that target Gram-positive cocci, while more severe infections should be treated with broad-spectrum empiric therapy. Antibiotic therapy should then be narrowed once the pathogen and sensitivities are known [16]. Mild soft-tissue infections should be treated for 1–2 weeks and more severe ones for 2–3 weeks. Bone infections should be debrided and should receive prolonged antibiotic therapy ($\geq$4 weeks) with broad-spectrum agents, such as piperacillin/tazobactam [16]. While antibiotics treat infection complicating the ulcer, they do not actually heal the wound itself. Therefore, antibiotic therapy should always be combined with other DFU SOC.

3.4 Revascularization

Revascularization is generally indicated in most DFU patients and those with grade 3 ischemia, according to the Society of Vascular Surgery Wound Ischemia and Foot Infection (WIfI) clinical staging [15]. The WIfI clinical staging system is a classification system based on limb ischemia and infection, and is recommended by the ADA to determine the risk of limb amputation in DFU [15]. However, the decision to proceed with revascularization depends on several factors, including wound stage, presence of infection, and patient factors such as older age and comorbidities [15]. Revascularization can be performed using the endovascular approach or open bypass. Currently, there are no RCTs that compare the two methods based on WIfI staging, but studies have suggested that bypass may be more effective and have fewer complications than the endovascular approach [20]. Although studies have shown that aggressive, timely revascularization can reduce amputation rates among DFU patients, those with higher grade ischemia tend to have higher rates of amputation even when aggressive revascularization is performed [21].

3.5 Effectiveness of Current SOC

Even though these management strategies are considered the gold standard for DFU care, less than 30% of DFU will heal after 20 weeks of SOC [3]. Furthermore, studies have reported that 40% of DFU will recur within 1 year and 65% within 5 years of healing [1]. Therefore, current SOC may not be adequate to prevent and heal all ulcers, especially those that are more complex due to multiple etiologies. Therefore, new therapies are needed to target the various molecular pathways involved in DFU pathogenesis to prevent their formation and promote healing once they occur.

Table 1 Novel therapies for the management of DFU

Therapy	Mechanism	Indication	Administration	Associated outcomes
Negative pressure wound therapy [24]	Creates sub-atmospheric pressure around wound to remove exudate, contract wound edges, and promote angiogenesis	Recalcitrant DFU Following surgical debridement	Mechanical unit attached to a dressing via plastic tube Connected to suction device around wound	Reduced amputation rates Greater granulation tissue formation Reduced ulcer size
Hyperbaric oxygen therapy	Has bactericidal action, promotes neovascularization, enhances ECM formation, mobilizes stem cell progenitor cells, and reduces tissue edema [27]	Wagner grade 3 and 4 DFU [26]	100% oxygen given in hyperbaric chamber Pressures > 1 ATA [25] Daily 90- to 120-min sessions 30–40 treatments [27]	Reduced amputation rates [28] Improved ulcer healing [27] Increased oxidative stress on wound [31]
Bioengineered skin substitutes	Contain cytokines, signaling molecules, and growth factors that promote tissue regeneration [37] Replace ECM and provide physical barrier, antimicrobial activity, and moist environment for wound healing [32]	Full thickness DFU DFU not responsive to other therapies for at least 4 weeks [32]	Directly applied to DFU Duration of about 12 weeks	Increased rates of complete wound healing [33] Accelerated wound closure Increased cosmetic and functional benefits [36] May be costly [36]
PDGFs [41]	Interact with fibroblasts, smooth muscle cells, and endothelial cells to promote wound healing Induce production of fibronectin and hyaluronic acid	DFU patients with evidence of ischemia	Applied as a topical gel Treatment duration varies 1–3 months	Increased rates of complete wound healing Accelerated wound closure Cost-effective compared to SOC alone Increased cancer incidence when used at high doses
Platelet-rich plasma [43]	Plasma contains hemodynamically active growth factors and molecules including PDGF, TGF-β, VEGF, EGF, serotonin, histamine, dopamine, and calcium	DFU associated with peripheral vascular disease	Applied topically as gel after irrigation and debridement with standard wound dressing Usually applied twice weekly	Accelerated wound closure Less complication rates (i.e., wound infection, skin maceration) compared to SOC alone [43]
Stem cell therapy	Stem cells synthesize and secrete cytokines that promote cell recruitment, ECM remodeling, and angiogenesis Differentiate into various cell types that aid in wound healing (i.e., myofibroblasts, keratinocytes) [44]	DFU contributed to by ischemia	Autologous or allogenic stem cells injected locally, applied topically or endovascularly [44] Recommended optimal dose 5 μg/kg/day BID [45]	Reduced amputation rates Increased rates of ulcer healing Improved limb ABI Increased wound angiogenesis [44] Improved patient quality of life, pain, and cold sensation [45]
Extracorporeal shockwave therapy [47]	Upregulates the expression of angiogenesis-related growth factors, shortens the inflammatory phase, and lowers wound infection risk	Chronic DFU that have failed conventional therapy	0.5–2 sessions per week for a duration of 1.5–8 weeks Impulse: 100–500 pulses/cm^2 Energy density: 0.03–0.23 mJ/mm^2	Reduction in DFU surface area Increased DFU epithelialization Increased rates of complete ulcer healing [47, 48] Shortened healing time by 19 days

Table 1 (continued)

Therapy	Mechanism	Indication	Administration	Associated outcomes
Wireless micro current electrical stimulation	Transfers electrons to wound, increasing blood and oxygen flow and promoting angiogenesis, collagen synthesis, and keratinocyte migration [50] Additional bactericidal effect [49]	Recalcitrant DFU DFU unresponsive to SOC	Patient connected to device at the wrist with a strap wire Current intensity 1.5 µA Device held 12–15 cm from ulcer [50]	Increased rates of complete ulcer healing [49] Reduction in DFU surface area [50]
Pressure and temperature feedback devices	Sensors in insoles and socks detect foot pressure and temperature changes Provide real-time alerts to users so that users may alter position/activity	Patients with diabetic peripheral neuropathy and history of DFU [51, 52]	Worn daily as socks or shoe insoles	Accuracy of sensors Readings correlate with clinical findings Feasible and wearable technology [55] Reduction of DFU incidence [52]

ABI ankle brachial index, *ATA* atmosphere absolute, *BID* twice daily, *DFU* diabetic foot ulcer(s), *ECM* extracellular matrix, *EGF* epidermal growth factor, *PDGF* platelet-derived growth factor, *SOC* standard of care, *TGF-β* transforming growth factor beta, *VEGF* vascular endothelial growth factor

4 New Trends in DFU Management

The new trend in managing DFU involves the use of adjunctive therapy for ulcers that persist beyond treatment with the recommended 4 weeks of SOC. We begin our discussion of adjunctive treatments with negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy (HBOT) (Table 1), since they are the most extensively studied adjunctive therapies in DFU and have been used to treat other diabetes skin manifestations such as necrobiosis lipoidica [22, 23]. We follow this discussion with other novel therapeutic trends (Table 1).

4.1 Negative Pressure Wound Therapy and Hyperbaric Oxygen Therapy

NPWT applies intermittent or continuous negative pressure to a wound through a specialized pump and is thought to promote wound healing by removing exudate, contracting wound edges, and promoting angiogenesis [24]. It has been recommended for recalcitrant DFU requiring debridement. Studies have reported improved clinical outcomes with its use, including reductions in amputation and increased rates of ulcer healing compared to SOC alone [24]. However, a recent systematic review found that most of these reports were based on a few studies that were either short duration, used non-validated wound assessment tools, or had inadequate power calculations; therefore they provided little information on the clinical use of NPWT for DFU [24]. Due to the limitations in the current literature, the promise of NPWT to heal DFU and prevent amputation remains unclear and the use of NPWT for DFU may not be clinically indicated.

HBOT has been used to treat several dermatological conditions, but its efficacy in DFU is also controversial. This therapy involves administering 100% oxygen to patients in hyperbaric chambers with pressures > 1 atmosphere absolute (ATA) and is currently recommended for Wagner grade 3 and 4 DFU [25, 26]. Previous high-quality RCTs have shown significantly improved ulcer healing and decreased rates of amputations among DFU patients treated with adjunctive HBOT compared to SOC alone [27, 28]. However, two recent RCTs on HBOT therapy have failed to show a significant difference in ulcer healing or amputation risk between HBOT with SOC and SOC alone [29, 30]. This discrepancy may be due to inconsistent patient selection and matching, vague measures of wound healing and amputation risk, and loss to follow-up due to treatment cost and availability in these studies. Furthermore, studies have raised concern over the oxidative stress caused by HBOT and whether long-term use may be counterproductive to the healing of DFU [31]. While HBOT therapy may show efficacy in select DFU

patients, the overall evidence supporting the use of HBOT for DFU is inconclusive. Future studies must aim to identify the DFU patients for whom it would be the most beneficial and cost-effective.

4.2 Bioengineered Skin Substitutes

Bioengineered skin substitutes are increasingly being used as adjuncts to treat acute and chronic wounds, including DFU. They accelerate wound healing by replacing the extracellular matrix (ECM) and providing a physical barrier to bacteria and trauma, antimicrobial activity, and a moist environment for proper wound healing [32]. In fact, studies have shown that the use of skin substitutes can increase the likelihood (1.55, 95% confidence interval [CI] 1.30–1.85) of achieving complete DFU wound closure in conjunction with SOC compared to SOC alone [33]. Currently, there are numerous skin substitutes that have been used for DFU and are discussed below.

Skin substitutes for DFU include dermal substitutes composed of cellular or acellular ECM and composite substitutes composed of both dermal and epidermal components. Dermagraft (Organogenesis Inc., Canton, MA, USA) is a *dermal* allograph made from human newborn foreskin and is the current Food and Drug Administration (FDA) licensed dermal substitute indicated for treatment of full-thickness DFU [32, 34]. OASIS Wound Matrix (Cook Biotech, West Lafayette, IN, USA) and Matristem (ACell, Columbia, MD, USA) are acellular *dermal* substitutes derived from porcine jejunum submucosa and have also shown success in DFU [32, 35]. Alternatively, Apligraf (Organogenesis Inc., Canton, MA, USA) is a *composite* substitute made of bovine collagen, neonatal fibroblasts, and neonatal keratinocytes and is licensed by the FDA for treatment of DFU that have been unresponsive to other treatments for at least 1 month [32, 34]. It has shown accelerated wound closure, with increased cosmetic and functional benefits [36]. In a comparative analysis, OASIS and Matristem were associated with shorter duration of DFU and lower payer reimbursements compared to Dermagraft and Apligraf [35]. These findings suggest that OASIS and Matristem may have better clinical outcomes and be more preferable for DFU patients who lack access to resources.

Skin substitutes made of human amniotic membrane are also emerging treatments for DFU. Amniotic membrane contains various cytokines, signaling molecules, and growth factors that are critical for tissue regeneration and wound healing [37]. Epifix (MiMedxGroup Inc., Marietta, GA, USA) is a cellular bioactive multi-layered tissue matrix allograft made from dehydrated human amnion and chorion membrane [32]. A recently published RCT comparing adjunctive Epifix with SOC alone showed significantly improved time to heal in DFU patients receiving Epifix. Additionally, subjects treated with Epifix were more than twice as likely to completely heal within 12 weeks of treatment [38]. Since the use of human amniotic membrane is relatively new, studies have aimed to compare these treatments to other dermal skin substitutes. In a 2015 study, Epifix was reported to be superior to Apligraf as it worked faster and was less costly in achieving complete DFU closure [39].

Interestingly, recent interim results from a non-industry RCT showed that Dermagraft and OASIS were comparable to SOC alone in treating DFU [40]. This study, by Tchanque-Fossuo et al., found that there were no differences in complete wound closure and reduction in wound size after 12 and 28 weeks of either regimen [40]. These findings suggest that there may be inherent bias in industry-sponsored studies that favors lower efficacy of SOC compared to treatment groups. Additionally, most studies reporting improved DFU healing with skin substitutes are small with short follow-up periods [33]; therefore, the long-term outcomes and cost-effectiveness of these products remains unclear. For this reason, we recommend that skin substitutes be used for select DFU, once cost-benefit ratios are carefully considered.

4.3 Topical Growth Factors and Platelet-Rich Plasma

Topical growth factors are also increasingly being used in the treatment of DFU. Regranex (OMJ Pharmaceuticals, Inc., San German, PR) is the only topical recombinant human platelet-derived growth factor (PDGR) FDA-approved therapy for the treatment of DFU [41]. It is applied as a gel and is indicated for ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply [41]. As adjunctive therapy, it has been shown to be more cost-effective compared to SOC alone, having significant effects on ulcer healing and possibly reducing risk of amputation [42]. However, it has been associated with an increased incidence of cancer, especially when used at high doses [41]. Therefore, topical growth factors may be useful in DFU patients with evidence of ischemia and those that do not have an increased risk of malignancy.

There is also growing evidence for the use of topical platelet-rich plasma (PRP) gel. Platelets contain several hemodynamically active molecules that aid in wound healing such as growth factors, neurotransmitters, and calcium [43]. In a large systematic review, PRP application was found to have significantly faster healing rates compared to SOC and fewer complications, such as incidence of wound infection and skin maceration [43]. However, the preparations of autologous PRP varied between studies, there was large heterogeneity in the outcome measures, and follow-up was short. Although promising, this therapy is still very novel and lacks high-quality, long-term evidence to determine its true efficacy.

4.4 Stem Cell Therapy

Stem cell therapy (SCT) is also emerging in DFU management. Stem cells heal wounds by secreting cytokines and growth factors that promote cell growth and angiogenesis. They also have the potential to differentiate into various cell types that aid in wound healing [44]. The most clinically studied SCTs are autologous bone-marrow and peripheral-blood derived. To date, there are only eight RCTs that have reported on SCT for DFU. Overall, these studies have shown improved outcomes with SCT, including increased endothelial progenitor cells and angiogenesis at the ulcer and improved pain, quality of life, and amputation rates for DFU patients [45, 46]. However, most of these studies where done on DFU patients with ischemia; therefore they may not be generalizable to the large proportion of DFU patients for which ischemia is not a contributing DFU cause. Additionally, too much heterogeneity exists among the studies in terms of SCT type used, treatments being compared, and outcomes being measured. Therefore, there needs to be a more consistent evidence base to draw significant conclusions and recommendations for the clinical use of SCT for DFU.

4.5 Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy (ESWT) is emerging as an effective and safe adjuvant therapy for DFU. Histological examination suggests that ESWT can facilitate wound healing through growth factor generation, neovascularization of tissue, and improved blood profusion [47]. A recent meta-analysis of eight RCTs studying ESWT in DFU patients found that DFU treated with ESWT experienced a greater reduction in wound surface area and increased wound epithelialization compared to those treated with SOC alone. Additionally, ESWT significantly increased the incidence of complete DFU cure by 2.22-fold compared to SOC alone and shortened the average healing time by 19 days [47]. In a pooled analysis of two RCTs comparing ESWT and sham for DFU, Snyder et al. found that a significantly greater proportion of patients receiving ESWT and SOC achieved complete closure after 20 (35.5 vs 24.2%, $p = 0.027$) and 24 weeks (37.8 vs 26.2%, $p = 0.023$) of treatment, compared to those receiving sham and SOC [48]. Adverse reactions of ESWT are reported to be minimal and include transitory skin reddening, slight pain, and small hematomas [47]. Despite its promise in promotion of DFU healing, a major limitation of the ESWT literature is that this treatment's cost-effectiveness has not yet been explored.

4.6 Electrical Stimulation: Wireless Micro Current Stimulation

The use of electrical stimulation, specifically wireless micro current stimulation (WMCS) technology, is emerging as a method to treat hard-to-heal wounds. This technology uses oxygen to transfer negatively charged electrons to the wound area to reinitiate or accelerate the healing process [49]. Most of the evidence on WMCS is based on individual case reports and small studies, which have shown success in treating hard-to-heal wounds, including DFU. In a study of 47 wound patients treated with adjunctive WMCS for 3 months, progress was seen in all after only 2 weeks, with a 95% reduction in wound surface after 8 weeks [50]. Specifically, in two DFU patients with chronic and infected wounds that had failed SOC, WMCS completely healed the ulcers after four and 45 sessions [49]. Neither of these patients reported discomfort. Additionally, infection risk was minimized since there is no direct contact with the device. Despite the promising data for WMCS, there is a need for large RCTs (specifically in DFU patients) in order to determine its efficacy in DFU.

4.7 Pressure and Temperature Feedback Devices

One of the newest trends in DFU adjuvant therapy involves the use of pressure and temperature sensing devices to prevent DFU in patients with diabetic peripheral neuropathy. SurroSense Rx (Orpyx Medical Technologies Inc., Calgary, CA) is a pressure-sensing shoe insole that provides real-time alerts via smartwatch when elevated plantar pressures are detected at eight individual sensors, so that users can alter their activities and relieve unsafe pressures [51]. The device has FDA clearance and is available in the USA for $3399 per set [51]. While there is no published data supporting the use of SurroSense Rx to prevent DFU, a recent interim analysis of 58 patients showed a 71% lower incidence in DFU after 18 months in those using the device compared to controls [52]. With two clinical trials [53, 54] studying the efficacy of and adherence rate for SurroSense Rx underway [51], we may soon have more concrete evidence on the ability of this system to prevent ulceration in patients with diabetes.

Similarly, continuous temperature monitoring informs patients about temperature increases in the feet and may facilitate the early detection of DFU. Handheld, infrared, dermal thermometers have shown that temperature differences ≥ 4 °F (2.22 °C) between comparable spots on both feet serve as an early sign of DFU [55]. In a pilot observational study that aimed to assess the accuracy of temperature sensor socks in diabetic patients with peripheral neuropathy, Reyzelman et al. found high agreement with a reference

standard high precision water bath ($R^2 = 1$). Furthermore, patients reported them easy to use and comfortable, and investigators were able to correlate observed temperatures with clinical findings [55]. While temperature sensing systems have shown accuracy and feasibility, there are currently no published RCTs evaluating their efficacy in ulcer prevention and thus supporting their use in the overall management of DFU.

5 Conclusion

Despite current SOC, DFU continue to be a major source of morbidity and mortality among diabetes patients. DFU are complex wounds due to numerous pathological mechanisms and should thus be managed through various approaches instead of a single one. The new DFU SOC should integrate a multimodal approach that addresses the many factors that contribute to ulcer development as well as those that promote wound healing. This includes prevention, standard wound care measures, and new adjunctive therapies that target various pathological pathways, especially for more complex, non-healing ulcers. Although new trends in DFU care are promising, clinicians should be aware that many are still very novel and lack sufficient evidence to determine their clinical efficacy and cost-effectiveness. As a higher level of evidence on these therapies emerges, current principles of DFU care combined with novel adjunctive treatments may become the new SOC in DFU management.

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