

Developments in the management of diabetic foot ulcers (Review)

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Abstract. Diabetic foot ulcers (DFUs) represent a severe complication of diabetes mellitus (DM), contributing to increased morbidity and mortality rates, and to a reduced quality of life. The impaired wound healing observed in DFUs is attributed to the dysregulation of multiple biological mechanisms essential for tissue repair. Several advanced treatment modalities have been explored as potential adjunct therapies for difficult-to-heal DFUs, targeting specific pathophysiological processes involved in wound healing. These modalities include treatments recommended by the International Working Group on the Diabetic Foot (IWGDF), such as sucrose octasulfate, which modulates matrix metalloproteinase activity, and LeucoPatch, an autologous preparation of leukocytes, platelets and fibrin applied to the wound surface. Additionally, several emerging therapies that have not yet been endorsed by the IWGDF have shown promise in the management of DFUs. These include regenerating agents that modify the extracellular matrix, the EDX110 nitric oxide-generating dressing with vasodilatory and antimicrobial properties and ON101 cream, which regulates the pro-inflammatory M1 to anti-inflammatory M2 macrophage transition to improve the wound microenvironment. Furthermore, desferrioxamine that stimulates angiogenesis and maggot therapy, a bio-debridement method, are being examined for their potential benefits. Despite these advancements, further high-quality clinical studies are required to establish the efficacy, safety and cost-effectiveness of these therapies in routine DFU management. The present review provides an updated overview of recent advancements in the treatment of DFUs, discussing their mechanisms of action, clinical evidence and implementation challenges.

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1. Introduction

Diabetic foot ulcers (DFUs) are a severe complication of diabetes mellitus (DM), with a lifetime risk of occurrence estimated between 19 and 34% (1). Beyond their impact on morbidity, DFUs are a strong predictor of mortality, with a 5-year patient survival rate ranging from 50 to 60% following onset (2). Between 5 and 24% of DFU cases progress to amputation within 6 to 18 months of initial evaluation, contributing to a 10- to 20-fold increase in the incidence of non-traumatic lower-limb amputations in individuals with DM compared to those without DM (1,2). DFUs also impose a significant burden on patients with DM, adversely affecting their quality of life by limiting mobility, increasing healthcare needs and contributing to psychological distress (3).

Neuropathy, peripheral arterial disease and trauma are the primary risk factors for the development of DFUs (4,5). Additional risk factors include elevated plantar pressure, Charcot neuro-osteoarthropathy, a history of prior DFU or amputations, as well as foot deformities (1,6). Nevertheless, impaired wound healing is considered the main factor contributing to the formation of chronic ulcers in individuals with DM (6).

The current approach to the management of DFUs involves several key components: Pressure off-loading, wound care, the restoration of tissue perfusion, the treatment of infection, glycemic control, the management of comorbidities, as well as patient and family education (7,8). Additionally, various innovative and advanced therapies have been introduced as supplementary treatments for managing DFUs aiming to enhance the healing process of difficult-to-heal ulcers (8-10).

The 2023 International Working Group on the Diabetic Foot (IWGDF) issued recommendations for the management

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of foot ulcers in individuals with DM (11). The present review aimed to provide a comprehensive overview of recent advancements in the management of DFUs, focusing on emerging treatment options, their underlying mechanisms and clinical efficacy, while also discussing the strengths and limitations of the studies evaluating these therapies.

2. Diabetic wound healing

Wound healing is a complex dynamic process initiated by tissue damage and consists of four interconnected stages: Hemostasis, inflammation, proliferation and remodeling (6). Numerous growth factors, proteases, cytokines as well as cellular and extracellular elements play a role in the wound healing process. The healing process in DFUs is disrupted and prolonged at multiple stages, often resulting in chronic, non-healing ulcers that require specialized management. It is estimated that 60% of DFUs require an average healing time of ~6 months (6).

The main mechanisms that disrupt the healing process in DFUs include hyperglycemia, increased oxidative stress, topical and systemic low-grade chronic inflammation, impaired angiogenesis, tissue hypoxia, microvascular and endothelial dysfunction, peripheral arterial disease, as well as impaired neuropeptide signaling (6,12,13). Therapeutic interventions for DFUs should be designed to directly address the underlying pathophysiological factors, thereby promoting faster and more effective wound healing.

Additionally, DFUs face several unique challenges. Currently, there are no etiological treatments for diabetic neuropathy (autonomic or peripheral), microangiopathy, or endothelial dysfunction. Moreover, DFUs are commonly complicated by infection. In a previous study on 1,229 patients newly diagnosed with DFUs, 58% of the patients were found to have an infection (14). Moreover, neuropathic DFUs are commonly located in the plantar surface of the foot, and pressure off-loading is crucial; however, adherence to pressure reduction is poor (15).

3. Adjunctive treatments for diabetic foot ulcers recommended by the IWGDF

Dressings are widely used in wound care to protect wounds and facilitate healing (16). They serve as a protective barrier for the wound, shield it from bacterial contamination and help maintain an optimal level of moisture, which is critical for facilitating wound healing. The classification of dressing typically depends on the primary material used in its composition (16). Edmonds *et al* (17) performed a randomized controlled trial (RCT) to examine the efficacy of treatment with either sucrose octasulfate wound dressing or control dressing (the same dressing without sucrose octasulfate) in non-infected neuro-ischemic DFUs. Overall, 240 participants were recruited in the study. The duration of their study was 20 weeks, and the primary endpoint was the proportion of patients with wound closure at week 20. Their study demonstrated that by week 20, there was a significant improvement in complete wound healing [adjusted odds ratio (OR), 2.60; 95% confidence interval, 1.43-4.73; $P=0.002$], a significantly more rapid estimated time to healing, and a greater decrease

in the percentage area reduction compared to wounds treated with placebo dressing (17). Modelling studies conducted in various Western healthcare systems have provided favorable evidence for the cost-effectiveness of sucrose octasulfate in the treatment of DFUs (18-20).

DFUs remain in the inflammatory stage of the healing process and are characterized by dysfunctional fibroblasts, impaired neovascularization and elevated levels of matrix metalloproteinases (MMP) (6). MMPs impede wound healing by degrading growth factors and proteins of the extracellular matrix (6). The potassium salt of sucrose octasulfate functions at the tissue level and inhibits excess MMP production (17). Additionally, the distinctive structure of the potassium salt of sucrose octasulfate enables interactions with growth factors, restoring their biological functions and facilitating tissue formation (17,21,22). Hence, it is recommended that when inadequate improvement of the ulcer area has been observed in spite of the standard of care, which includes appropriate offloading for a minimum of 2 weeks, sucrose octasulfate dressing as a supplementary treatment may be used for non-infected, neuro-ischemic DFUs (7).

Treatment options that either stimulate the secretion of cytokines and growth factors essential for the process of repairing tissue, forming new blood vessels and initiating inflammatory responses, or the direct delivery of these factors to the ulcer bed may be used in subjects with DFUs (7). The LeucoPatch device uses bedside centrifugation without additional reagents to generate a disc comprising of autologous leukocytes, platelets and fibrin that is applied to the wound surface (23). Game *et al* (23) conducted a RCT to examine the effect of the LeucoPatch device for the management of chronic, difficult-to-heal DFUs. The primary endpoint of their study was the percentage of DFUs that healed in a period of 20 weeks. In their study, 18-36 ml venous blood was collected to produce the patch directly at the bedside every week. A total of 134 individuals were allocated to standard care and 132 were allocated to LeucoPatch plus standard care. In the LeucoPatch treatment arm, 45 (34%) of 132 ulcers healed within 20 weeks vs. 29 (22%) of 134 ulcers in the standard care group (OR, 1.58; 95% CI, 1.04-2.40; $P=0.0235$) (23). The time to healing was shorter in the LeucoPatch group ($P=0.0246$) when compared with the standard care group. No differences in adverse events were observed between the groups (23). No data on the cost-effectiveness of LeucoPatch have been published to date, at least to the best of our knowledge. Autologous leukocytes, platelets and fibrin patches are recommended for the treatment of hard-to-heal ulcers alongside the optimal standard of care (7).

4. Emerging adjunctive treatment options for diabetic foot ulcers

The extracellular matrix (ECM) is a complex system of large molecules, such as structural proteins (collagens, glycoproteins, and proteoglycans), enzymes and soluble factors that interact dynamically with surrounding cells to maintain tissue integrity (24,25). Heparan sulfates are sulfated glycosaminoglycans that are important elements of the ECM serve two functions in maintaining its balance. Firstly, they protect proteins from degradation, and secondly, they bind growth

factors to control their levels and influence signaling activities (24,25). Throughout the inflammatory phase of wound healing, heparanases and proteases are secreted from inflammatory cells and degrade heparan sulfates, resulting in the degradation of the ECM scaffold and the release of heparan sulfate-bound growth factors (24,25).

Regenerating Agents (RGTA) are large polymers that are structurally and functionally similar to natural heparan sulfate, but resistant to enzymatic degradation. They bind 'heparin binding sites' and therefore protect proteins from degradation, promote reconstruction of the ECM scaffold, and reinforce the action of signaling molecules (24,25). Preclinical evidence indicates that RGTA improve the efficacy of cutaneous wound healing by boosting neovascularization, reducing inflammation, and stimulating granulation tissue formation and collagen maturation (26,27).

In clinical practice, RGTA technology has been applied in the treatment of various types of chronic wounds, such as DFUs, wounds resulting from radiation therapy, burns, as well as ischemic and venous ulcers (24,25). In a previous study, a novel heparan sulfate glycosaminoglycan mimetic product [CACIPLIQ20 (CACIPLIQ, OTR3 Company, Paris, France)] was administered to 12 patients with type 2 DM and chronic lower-extremity ulcers (28). All participants achieved complete ulcer healing within an average treatment period of 4.92 months, with a duration ranging from 2 to 12 months. No adverse events were observed. That study had several limitations that should be acknowledged. The small sample size (12 patients) limits statistical power and generalizability to broader DFU populations. Additionally, the absence of a control group renders it difficult to determine whether the observed healing outcomes were due to heparan sulfate glycosaminoglycan mimetic product or standard wound care.

To overcome some of these drawbacks, the authors previously performed an open-label study to examine the effectiveness of RGTA matrix technology in the management of DFUs (29). Individuals with chronic, neuroischemic DFUs were randomized 1:1 to the control group, which received the standard of care, and to the treatment group, which additionally received RGTA matrix twice per week. The duration of the study was 12 weeks (29). The primary outcome of the trial was the number of ulcers that healed completely after 12 weeks of treatment. A total of 16 participants were randomized to the intervention group and 15 to the control group. The trial demonstrated that 5 (31.2%) subjects in the intervention group achieved complete healing vs. 0 in the control group after 12 weeks of treatment ($P=0.043$). With regard to the other endpoints, the intervention group showed significant superiority in terms of the number of ulcers with at least 80% healing of their surface [10 (66.7%) vs. 2 (13.3%), $P=0.008$], the absolute surface reduction [1.5 (0.7, 5.2) cm^2 vs. 0.6 (0.3, 1.0) cm^2 , $P=0.026$] and the percentage of surface reduction at the end of the intervention period. There was no significant difference in adverse effects observed between the two groups (29). However, it is important to acknowledge that the relatively small sample size of that study may limit the generalizability of its findings. Furthermore, the absence of double-blinding, where neither patients nor investigators were blinded to treatment allocation, introduces a potential source of bias. Additionally, the lack of a placebo treatment

in the control group may have contributed to performance and assessment bias, further influencing the outcomes of the study. To address these limitations, future studies are required performing larger, double-blinded, placebo-controlled trials with longer follow-up periods and standardized offloading protocols in order to examine the efficacy of RGTA technology in DFUs.

In addition, DFUs are characterized by a dysregulation of pro-inflammatory M1 and anti-inflammatory M2 macrophages. The M1 to M2 macrophage ratio, a marker of chronic inflammation, has been found increased in the skin of diabetic rabbits both pre- and post-injury compared with control animals (6,30). ON101 cream (Oneness Biotech Co, Ltd. induces its therapeutic effect by regulating the balance between M1 and M2 macrophages (31). ON101 is composed of two active pharmaceutical ingredients: PA-F4 from an extract of *Plectranthus amboinicus* and S1 from an extract of *Centella asiatica* (31). These two ingredients produce a synergistic effect in regulating the M1:M2 macrophage ratio. PA-F4 notably reduces M1 macrophages by inhibiting the NLRP3-mediated inflammasome pathway and the secretion of downstream inflammatory cytokines, including interleukin 1β and interleukin 6 (31). The S1 extract has been shown to activate M2 macrophages by promoting collagen synthesis, stimulating fibroblast proliferation, and enhancing keratinocyte migration (31).

Huang *et al* (31) performed an evaluator-blinded RCT to assess the efficacy of ON101 in the management of DFUs. Twice-daily applications of ON101 or an absorbent dressing changed were applied once a day or two to three times per week for 16 weeks. The primary endpoint of that study was the incidence of complete healing, defined as complete re-epithelialization at two consecutive visits during the treatment period (31). Overall, 122 and 114 participants were randomized to the intervention and control groups, respectively. Complete healing was achieved in 74 participants (60.7%) in the ON101 group and in 40 patients (35.1%) in the control group during the 16-week treatment period (OR, 2.84; 95% CI, 1.66-4.84; $P<0.001$). No significant difference in adverse events was noted between the two groups (31). Despite the use of blinded evaluators for wound assessment, that study was not fully double-blinded, as both patients and treating clinicians were aware of treatment allocation (31). This open-label design introduces a risk of performance and assessment bias, as patient expectations and clinician interactions may have influenced the outcomes. A placebo-controlled, double-blinded trial would enhance the reliability of the findings by minimizing potential bias. Additionally, the aforementioned study compared ON101 with an absorbent dressing (Hydrofiber) rather than a placebo or sham treatment. While the control group received standard wound care, the absence of a placebo arm makes it difficult to differentiate the specific effects of ON101 from the general benefits of standard wound management (31).

Nitric oxide (NO) is essential for preserving microvascular supply and its deficiency in DM impairs wound healing (32). The involvement of NO in ulcer healing encompasses three established aspects: i) Vascular, as it induces vasodilation and promotes the formation of new blood vessels; ii) inflammation, as it influences the immune response of the body; and

Table I. Comparison of emerging adjunctive treatment options for diabetic foot ulcers.

Treatment modality	Mechanism of action	Evidence strength (Refs.)	Limitations
Regenerating agents (RGTA's)	Mimics heparan sulfate, protects extracellular matrix proteins from degradation	Small case series (n=12) and small RCT (n=31); significant wound healing improvement (28,29)	Small sample size, open label study, lack of placebo comparator
ON101 cream	Regulates M1/M2 macrophage ratio, inhibits inflammatory pathways	RCT (n=236) significantly higher complete healing rates vs. control (31)	Not fully double-blinded, lack of placebo comparator
EDX110 (nitric oxide-generating dressing)	Generates nitric oxide, which induces vasodilation and has antimicrobial properties	RCT (n=147); significant ulcer area reduction, but complete healing not statistically significant (32)	Primary endpoint was ulcer area reduction rather than complete healing
Desferrioxamine	Upregulates HIF-1 α , increasing VEGF and SDF-1 α expression, promoting angiogenesis	Preclinical <i>in vitro</i> and <i>in vivo</i> studies (37-39)	No human RCTs, requires further clinical trials for validation
Maggot therapy	Biological debridement using maggots to remove necrotic tissue	Retrospective study (n=18); faster debridement and healing compared to conventional care (45)	Retrospective study, small sample size

RCT, randomized controlled trial; HIF-1 α , hypoxia-inducible factor-1 α ; VEGF, vascular endothelial growth factor; SDF-1 α , stromal cell-derived factor-1 α .

iii) antimicrobial, as it exhibits strong and wide-ranging antimicrobial properties (32-34).

EDX110 (Edixomed) is a two-layer system designed to generate NO *in situ* (32). EDX110 creates a moist wound environment, absorbs exudates, and initiates autolytic debridement (32). Additionally, when the two layers come into contact and are applied to the wound, NO is produced (32). Furthermore, EDX110 has microbicidal activity against strains of both Gram-positive and -negative bacteria, as well as mold, yeast and biofilms (32). Edmonds *et al* (32) examined the effectiveness and safety of EDX110 compared to standard of care dressings for the management of DFUs. The treatment duration in their study was 12 weeks. The primary endpoint of their study was the percentage of ulcer area reduction from baseline compared to the control group at 12 weeks (32). Of note, patients with DFU infection were included in the study. Overall, 72 participants were allocated to the intervention arm, and 75 to the control arm. That study demonstrated a significant improvement in the median percentage of ulcer area reduction at 12 weeks in the EDX110 group compared with the control group in both the intention-to-treat ($P=0.016$) and per-protocol ($P=0.012$) populations (32). The primary efficacy endpoint was percentage ulcer area reduction at 12 weeks, rather than complete ulcer healing. While percentage ulcer area reduction provides a quantitative measure of wound improvement, complete wound closure is the clinically relevant endpoint. Although the complete healing rate was higher in the EDX110 group (40 vs. 26%), this difference was not statistically significant in the intention-to-treat (ITT) analysis ($P=0.07$), but became significant ($P=0.049$) when strict ITT criteria were applied (32). A major strength of that study is the inclusion of patients with clinically infected DFUs, which is often an

exclusion criterion in many trials. By allowing participants with infected DFUs, the study better reflects real-world clinical practice, where infection is a common and significant barrier to wound healing. EDX110 was well-tolerated and no significant difference was found in the total number of adverse effects between the two groups (32).

Furthermore, DFUs are characterized by impaired angiogenesis (6). Various techniques, including the implementation of drug delivery systems (35) and stem cell therapies (36) have been developed to promote the formation of new blood vessels in diabetic wounds. However, their effectiveness is limited by their short half-life, high cost, and potential cancer risk (37). Desferrioxamine is a small-molecule drug approved by the FDA, known for its capability to stimulate bone angiogenesis and skin regeneration (37-39). Ding *et al* (37) used desferrioxamine-laden silk nanofiber hydrogels that ensured a continuous release of desferrioxamine for >40 days to manage DFUs. Their study demonstrated that, *in vitro*, desferrioxamine upregulated hypoxia-inducible factor-1 α expression, leading to increased expression of vascular endothelial growth factor and stromal cell-derived factor-1 α , both of which are critical for angiogenesis (37). This pro-angiogenic effect was further validated in *in vivo* diabetic wound models, where DFO-laden hydrogels accelerated wound closure by enhancing endothelial cell migration, vascular tube formation, and neovascularization (37). Future studies are required however, to focus on clinical trials to assess the efficacy and safety of desferrioxamine in DFUs, evaluating wound closure rates, recurrence, and long-term outcomes. Research is also required to explore optimized delivery systems, to enhance controlled drug release and bioavailability. Additionally, investigations into combination therapies with growth factors or stem cells could

provide insight into the synergistic effects for the enhanced management of DFUs.

Debridement is a process that involves removing dead and devitalized tissues, including necrosis and slough from wounds (11). The primary aim is to establish a clean wound bed to facilitate optimal conditions for wound healing (11). Debridement basically accelerates the wound healing process by transforming a chronic wound into an acute wound and it reduces the bacterial load within the wound (40,41). Debridement is regarded as the crucial initial step preceding the application of any local wound therapy or dressing (42). Debridement methods include physical approaches (e.g., surgical, sharp, hydro-debridement, or gaseous debridement), biological methods (e.g., larvae), autolytic techniques (e.g., hydrogels), and biochemical methods (e.g., enzymes) (11). Sharp debridement is the standard of care (11). However, its efficacy can vary largely depending on the experience and expertise of the practitioner, making it a subjective measure.

Maggot therapy (also called larval therapy) involves the application of live fly larvae to wounds to aid wound debridement (cleaning), disinfection and healing (43). The most used species is *Lucilia (Phaenicia) sericata*. The primary effect of maggot therapy is the removal of sloughy and infected tissue, resulting in a cleaner, healthier wound bed that promotes healing (43). A recent study demonstrated that maggot therapy promoted wound healing by modulating macrophage activation (44). Maggot debridement is indicated in heavily exudative ulcers and/or ulcers with infection, in which surgical debridement is difficult to perform. Another previous study retrospectively examined the effectiveness of maggot therapy in treating DFUs that were unresponsive to conventional therapy (45). Overall, 18 participants with 20 non-healing DFUs were recruited; six DFUs were treated with conventional therapy, six with maggot therapy, and eight with conventional therapy first, followed by maggot therapy. That study demonstrated that maggot therapy was associated with a more rapid debridement and more rapid wound healing compared to conventional therapy (45). However, that study had several limitations that should be acknowledged: The small sample size (18 patients, 20 wounds) limits generalizability to broader DFU populations. The lack of randomization and blinding further increases the risk of bias, as treatment allocation was not controlled, and both patients and clinicians were aware of the therapy used. Further well-designed, randomized controlled trials with larger sample sizes and standardized methodologies are required to overcome these limitations and establish the role of maggot therapy in DFU management. The comparison of emerging adjunctive treatment options for DFUs is presented in Table I.

5. Accessibility and barriers to implementation

A significant challenge in the management of DFUs is the shortage of experienced diabetic foot clinics (46). Specialized care is crucial for wound assessment, infection control, offloading strategies and advanced therapies, yet such expertise is often unavailable, particularly in low-resource settings (47). A number of advanced DFU treatments require specialized equipment or trained personnel, which are frequently lacking

in primary care or rural healthcare facilities. As a result, patients in these areas may not receive optimal treatment, leading to delayed wound healing and an increased risk of amputations.

In addition to the lack of specialized clinics, other factors limit access to advanced DFU treatments. High costs associated with bioengineered dressings, growth factor therapies, and innovative wound care solutions make them difficult to implement in healthcare systems with limited resources. Moreover, offloading devices, which are critical for the management of DFUs, are often underutilized due to financial barriers and poor patient adherence. Inconsistent supply chains further restrict the availability of essential wound care products, particularly in resource-limited settings. Addressing these challenges requires establishing and expanding diabetic foot clinics staffed with trained professionals, especially in underserved areas. Furthermore, research efforts are required to focus on cost-effectiveness analyses, while healthcare systems must prioritize scalable, sustainable strategies that ensure both feasibility and clinical benefit in real-world settings.

6. Conclusion and future perspectives

Advancements in the management of DFUs are increasingly focusing on innovative wound dressings, bioengineered skin substitutes, and nanotechnology-based therapies. These emerging treatments aim to reduce inflammation, stimulate new blood vessel formation, and support tissue regeneration, addressing key challenges in wound healing. Nanotechnology-based dressings offer the potential for controlled delivery of growth factors, antimicrobial agents and regenerative compounds, fostering a more favorable healing environment.

Alongside these advancements, digital health technologies are reshaping DFU care. AI-powered wound assessment tools have the potential to enhance wound measurement, classification, and predictive analysis, allowing for earlier detection and personalized treatment adjustments. Additionally, telemedicine platforms are becoming increasingly valuable for tracking healing progress and refining treatment strategies, particularly in areas where access to specialized diabetic foot care is limited.

In conclusion, the management of DFUs is particularly challenging due to impaired wound healing, patient non-adherence to treatment, and suboptimal implementation of existing guidelines. According to the latest IWGDF guidelines, certain treatment modalities are considered adjunctive options for select patients whose ulcers fail to heal despite receiving standard care. However, additional research is necessary to evaluate the efficacy of emerging adjunctive therapies that are not yet recommended by the IWGDF, ensuring their potential role in DFU management is well-defined.

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AT drafted the manuscript. AT and GS conducted the literature search. IE and NT contributed to the editing of the manuscript. All authors have read and approved the final version of the manuscript for publication. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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