Diabetic Foot Ulcers (DFUs); Management Updates

Magdy Helmy Megallaa
Professor of Diabetes Medicine, Head of the Unit of Diabetes & Metabolism,
Alexandria University, Egypt

ABSTRACT
Diabetic foot ulcer (DFU) represents a serious and debilitating outcome of poorly managed diabetes, typically appearing as ulcers on the bottom of the foot. It's estimated that around 15% of people with diabetes will experience DFU at some point. The development of DFU is driven by three key factors: nerve damage, poor blood circulation, and infections that occur as a result. Conventional treatment combined with innovative strategies such as stem cell therapy can help lessen complications, lower the risk of amputation, and improve survival rates.

INTRODUCTION
Diabetes mellitus impacts around 422 million individuals globally and contributes to approximately 2 million fatalities each year. (1) One of the most severe and incapacitating outcomes of unmanaged and chronic diabetes is the diabetic foot ulcer (DFU), which typically manifests as an ulceration on the bottom of the foot. It is estimated that about 15% of those with diabetes will experience these ulcers, and within this group, 10-18% may face amputation of the affected foot due to bone infections or other complications associated with the ulcer. (2) Given the significant morbidity linked to serious conditions like osteomyelitis and the risk of amputation in DFU patients, it is crucial to effectively identify and treat the root causes of these ulcers.

PATHOGENESIS OF DIABETIC FOOT ULCERS
Diabetic foot ulcers (DFU) are characterized by full-thickness wounds that penetrate the dermis, typically found in weight-bearing or exposed regions beneath the ankle. The Wagner classification system is employed to evaluate the severity of these ulcers, rating them from 1 to 5. The underlying mechanisms of DFU can be understood through a triadic framework that includes neuropathy, vascular insufficiency, and secondary infections stemming from foot injuries. (3) Firstly, diabetes can lead to a loss of protective sensation in the feet, making patients more vulnerable to trauma and ulceration. This sensory loss is primarily caused by hyperglycaemia, which stimulates the upregulation of aldose reductase and sorbitol dehydrogenase, resulting in increased synthesis of fructose and sorbitol. The accumulation of these glucose-derived compounds creates osmotic stress, ultimately diminishing the synthesis of myoinositol in nerve cells and impairing nerve conduction. (4) Moreover, it's important to consider advanced glycation end-products (AGEs), which are non-enzymatic adducts formed from proteins, amino acids, and DNA due to interactions with dicarbonyl compounds and glucose. In diabetic conditions, the rate of AGE formation increases, contributing significantly to the onset of various complications. (5) Along with sensory neuropathy, diabetes can also provoke autonomic dysfunction in neurons, leading to decreased sweat production. This results in dry feet, which may crack or fissure due to lack of moisture. (6) Additionally, motor neuron damage can lead to muscle atrophy and structural irregularities in the foot, creating localized pressure points on the plantar surface and heightening the likelihood of ulcer development. (7)

Besides the triad, inadequate wound healing is recognized as a significant factor in the progression of diabetic foot ulcers (DFUs). (8) Notably, molecular alterations at the DFU site occur before any visible tissue damage arises. The transition from hyperglycaemia to DFU is characterized by intricate molecular dysfunctions impacting the wound-healing process. (9) Typically, wound healing unfolds through distinct stages: haemostasis, inflammation, proliferation, and remodeling. While acute wounds typically progress smoothly through these phases, chronic nonhealing DFUs often become halted in one or more stages. In the initial phases of healing, neutrophils normally release granular substances to eliminate foreign pathogens via a mechanism called neutrophil extracellular traps (NETosis). (10) However, in a diabetic environment, NETosis is disrupted, leading to a cascade of inflammation and excessive cytokine and superoxide production, thereby delaying the healing process. (11)

Additionally, hyperglycaemia promotes the formation of advanced glycation end-products (AGEs), which instigate both structural and functional changes in crucial proteins. (12) Specifically, AGEs can interact with the receptor for advanced glycation end-products (RAGE), which typically has low expression under normal glycemic conditions. (13) This interaction activates nuclear factor kappa-B (NF-κB), resulting in increased cytokine release through a self-perpetuating process that prolongs inflammation and encourages apoptosis. (14) In summary, hyperglycaemia creates an inflammatory environment primarily due to the dysregulation of cytokine release, NETosis, and AGE formation.

Inflammation, combined with significant changes in the extracellular matrix (ECM), is crucial in the ongoing challenge of non-healing diabetic foot ulcers (DFU). In healthy wound healing processes, there is a fine balance between the synthesis and breakdown of ECM proteins like collagen and fibrin. Collagen, which constitutes the majority of the soft tissue ECM, is vital for effective wound healing, and any abnormalities in its metabolism can have serious repercussions. Specifically, the activity of collagen-degrading enzymes known as matrix metalloproteinases (MMPs) increases, creating a highly proteolytic environment that diminishes collagen levels. Consequently, the ECM becomes disorganized and unable to facilitate proper wound healing. In addition to the heightened activity of MMPs, the build-up of advanced glycation end products (AGEs) leads to a decrease in fibroblast growth factor (FGF) and transforming growth factor-beta, further lowering collagen content by promoting fibroblast apoptosis. Moreover, poor angiogenesis is a significant factor hindering diabetic wound healing. (15)

Angiogenesis is typically a key process during the proliferative phase of wound healing, aiding in the formation of granulation tissue and ensuring a proper supply of nutrients and oxygen to the affected area. However, in DFU, there is a notable decline in angiogenic factors such as vascular endothelial growth factor (VEGF) and FGF-2. VEGF is essential for starting the angiogenesis process and promoting endothelial cell growth, while FGF-2 assists in the migration of new blood vessels through the ECM. A decrease in the expression of both VEGF and FGF-2 results in impaired wound healing. Furthermore, endothelial progenitor cells (EPCs) are known for expressing proangiogenic factors and their receptors, including VEGF and FGF. Research shows that patients with type 2 diabetes mellitus experience a reduction in both the function and quantity of EPCs, largely due to the accumulation of

AGEs. The overall dysfunction of EPCs, along with the decrease in circulating growth factors, plays a significant role in the onset and worsening of DFU by disrupting the angiogenesis process. (16)

MANAGEMENT OF DIABETIC FOOT ULCERS

The management of DFU encompasses both preventive strategies and a range of treatment options, which include non-invasive and invasive techniques.

PREVENTIVE CARE

Diabetes significantly increases the risk of developing underlying peripheral vascular disease, which means that most diabetic foot ulcers (DFUs) often go unnoticed until they become severe enough to show more serious symptoms. In fact, during the diagnosis of a DFU, nerve damage may conceal reduced blood flow and vice versa. As a result, the key strategy for prevention is conducting regular screenings for diabetic foot conditions, enabling early detection of DFUs and prompt treatment when necessary. This proactive approach is crucial in preventing complications like gangrene and potential amputations. Screening involves patients regularly examining their own feet for any signs of injury or ulceration and undergoing routine checks during medical appointments. (17)

OFFLOADING OF DIABETIC FOOT ULCERS

Pressure offloading is a key treatment for diabetic foot ulcers (DFUs), especially in cases where neuropathy is present, with various techniques being employed. In contrast, for ischemic DFUs, revascularization is typically preferred. Common offloading strategies include bed rest, wheelchair usage, crutch-assisted ambulation, total contact casting (TCC), felted foam, therapeutic footwear, and removable cast walkers. (18)

Among these methods, TCC stands out as the most effective, wherein a skilled physiotherapist applies full casts that are changed weekly over a period of 2-3 weeks or until sufficient healing is achieved. A randomized controlled trial demonstrated that TCC significantly enhances ulcer healing rates and reduces infection risks compared to standard dressing changes and other offloading approaches, showing a remarkable 91% healing rate in the TCC group versus just 32% in the control group after two months. Additional studies have corroborated these findings, highlighting TCC's superiority over traditional methods for treating DFUs. However, an adverse effect associated with TCC is the risk of fungal infections, which can be managed with topical treatments without hindering the casting process.

Despite TCC's evident success, a survey conducted across 48 states in the U.S. revealed that only 1.7% of foot clinics utilized this method, likely due to the complex and labour-intensive nature of the treatment. (19) TCC requires the expertise of a qualified physiotherapist and involves ongoing maintenance and replacement of the cast, which can be uncomfortable for patients. The survey further indicated that shoe modifications were the most employed treatment in these clinics.

MAGGOT THERAPY

Maggot therapy is a thoroughly studied approach for managing chronic wounds, involving the application of maggots directly on the affected area. Research indicates that this method notably improves the debridement process. One particular study revealed that maggot therapy led to a quicker formation of granulation tissue and a more considerable reduction in wound size when compared to alternative topical treatments like hydrogel dressings. However, it was found that maggot therapy did not impact the

disinfection process or the overall healing rate of the wound. (20)

HUMAN SKIN EQUIVALENTS (HSEs)

HSE has shown superior effectiveness over traditional methods involving saline-moistened gauze in lowering amputation and infection rates, as well as enhancing the healing of ulcers. A randomized controlled trial (RCT) investigated the efficacy of Graftskin, a living skin equivalent specifically designed for noninfected, nonischemic diabetic foot ulcers (DFU). In this study, Graftskin was administered weekly for up to four weeks or until the ulcer healed completely. Results from this trial demonstrated that HSE significantly outperformed the control group, which received only saline-moistened gauze for ulcer treatment. Specifically, HSE achieved an 18% increase in complete wound healing compared to the control group. (21) However, a noted drawback of this treatment option is the potential limitation in the availability or accessibility of HSE.

TOPICAL GROWTH FACTORS

Topical growth factors, especially those derived from platelets, have shown significant effectiveness in enhancing healing rates of ulcers when contrasted with placebo treatments. These growth factors act as key immediate agents in the wound healing process, and their application in diabetic foot ulcers (DFUs) can expedite healing. A comprehensive meta-analysis reviewed 26 randomized controlled trials involving 2,088 participants, focusing on three specific treatments: recombinant epidermal growth factor, autologous platelet-rich plasma, and recombinant human platelet-derived growth factor. The findings reveal that all three therapies notably accelerated healing rates when used in conjunction with standard care, with recombinant human epidermal growth factor showing a slight advantage over the other growth factors. (22)

SHOCKWAVE THERAPY (ESWT)

Extracorporeal shockwave therapy (ESWT) has been documented to enhance the healing process of soft tissue wounds in patients with diabetic foot ulcers (DFU). This therapy works by stimulating osteoblast activity, promoting the healing of soft tissues. Clinical trials have shown promising outcomes, suggesting that ESWT is more effective than conventional treatments for DFU. Two multinational randomized controlled trials (RCTs) were carried out to evaluate the effectiveness of combining ESWT with standard care and other DFU therapies. Both studies, lasting 12 weeks, demonstrated a significant reduction in wound volume, over 50%, when ESWT was used alongside traditional treatment methods. (23)

NEGATIVE PRESSURE WOUND THERAPY (NPWT)

A recent advancement in the treatment of diabetic foot ulcers (DFUs) is the introduction of negative pressure wound therapy (NPWT). This method employs vacuum pressure to extract fluid from the wound and enhance blood circulation to the affected area, thereby facilitating the healing process. Initially focused on burn victims, NPWT has recently been applied to DFU patients with encouraging outcomes. The use of NPWT leads to two main types of tissue deformation: macro deformation, which is observed in wound contraction, and micro deformation, which happens at a cellular level. Both of these processes boost blood flow and trigger a wound healing response that includes granulation of tissue, growth of blood vessels, formation of new blood vessels (neoangiogenesis), skin cell regeneration (epithelialization), and removal of excess extracellular fluid. Additionally, NPWT

fosters a more anti-inflammatory state in patients. Research involving DFU patients has demonstrated that NPWT is more effective than traditional therapies, particularly in terms of wound healing and reducing amputation rates, without an increase in side effects. (24)

DEBRIDEMENT OF DIABETIC FOOT ULCERS

Debridement plays a crucial role in managing diabetic foot ulcers (DFU) by enhancing the wound environment. It achieves this by removing dead or nonviable tissue and any foreign matter that hinders the healing process. Although debridement may not always result in the complete healing of a DFU, it is a vital initial step in the overall treatment approach. After debridement, the wound undergoes further assessment, and if needed, additional treatment options are explored. This procedure is often combined with other therapeutic methods to optimize healing. (25)

SKIN GRAFTING

Skin grafting can be an effective option for more severe diabetic foot ulcers (DFUs), providing the opportunity to replace infected skin and enhance the healing process. Various skin grafting methods are available, such as bioengineered or synthetic skin, autografts (harvested from the patient's own body), allografts (obtained from another individual), and xenografts (derived from animal sources). A review that examined 17 randomized controlled trials found that combining skin grafting and tissue replacement with standard treatment resulted in improved healing rates for DFUs and a slight reduction in the likelihood of amputation. However, the evidence regarding the long-term efficacy of these procedures remains inconclusive. (26)

ROLE OF REVACULARIZATION

Patients with diabetic foot ulcers (DFU) who have a history of peripheral arterial disease (PAD) often experience slower healing, increased complication rates, and a heightened risk of potential amputation. Therefore, when DFU is accompanied by chronic limb ischemia, revascularization emerges as a valuable therapeutic option. Research indicates that the healing rate for ulcers post-revascularization is between 46% and 91%, which is significantly higher than that of PAD patients who do not receive this intervention. (27)

Revascularization may involve procedures such as stenting or surgical bypass when alternative methods are not applicable. Additionally, techniques like atherectomy, shockwave therapy for calcified lesions, and various forms of balloon revascularization (including cutting, drug-coated, and cryoplasty) can be utilized individually or alongside stenting. (28)

A clinical trial involving 80 patients subjected to foot revascularization showed favorable outcomes. All participants underwent an endovascular procedure, specifically balloon angioplasty, and were monitored for 12 months afterward. Results demonstrated that 56.2% of the patients achieved full recovery, 58.7% underwent minor amputations, and just 16.2% required major amputations. Thus, revascularization proves to be an effective approach for managing DFU, especially for those at risk of amputation. However, patient responses to vascular procedures can vary, and these interventions do not mitigate the mortality risk linked to PAD. (29)

It is crucial to integrate comprehensive therapy, which includes medical management, alongside revascularization for optimal DFU treatment. This involves diligent monitoring of glucose levels, lipids, and blood pressure, as well as

administering antiplatelet therapy post-surgery. Studies have shown that combining endovascular therapy with initial supervised exercise training (SET) leads to remarkable enhancements in total walking distance, ankle-brachial index (ABI), and a reduced likelihood of future revascularization or amputation, unlike endovascular therapy alone, which does not improve functional capacity. Additionally, patients who undergo endovascular procedures should initiate dual antiplatelet therapy with aspirin and clopidogrel or ticagrelor for several months. Statin therapy is also beneficial in stabilizing any existing plaques before and after the revascularization process.

HYPERBARIC OXYGEN THERAPY (HBOT)

One approach for treating diabetic foot ulcers (DFU) is systemic hyperbaric oxygen therapy (HBOT), which is primarily utilized for more severe cases to help mitigate the risk of amputation. This treatment is particularly common for managing infected DFUs, with one systematic review highlighting six randomized controlled trials (RCTs) focused on chronic DFUs. Typically, systemic HBOT is administered in sessions lasting between 45 to 120 minutes, occurring once or twice a day at pressures ranging from 1.5 to 3.0 ATA. This therapy has been shown to significantly lower the rates of major amputations compared to standard care for DFU. While HBOT is generally considered a supplementary treatment alongside conventional wound care practices, it is important to note that it is relatively costly, not fully researched, and may require additional studies. (30)

ROLE OF STEM CELL THERAPY

Current treatment options for diabetic foot ulcers (DFUs) primarily involve managing infections, performing surgical debridement, and implementing revascularization techniques. (31) A deeper understanding of the tissue remodeling process, which includes inflammation, cell migration, neovascularization, and tissue proliferation, has made stem cell-based therapies a promising avenue for DFU treatment. (32)

Stem cells contribute to wound healing through the secretion of cytokines essential for cell migration, angiogenesis, extracellular matrix remodeling, and nerve regeneration. Their ability to differentiate into various cell types, such as myofibroblasts and endothelial cells, enhances the wound-healing process. (33) Among the stem cells explored for diabetic foot treatment, adult stem cells (ASCs) are predominantly studied. Bone marrow-derived mesenchymal stem cells (BM-MSCs) are the most thoroughly researched ASCs, while other types include adipose-derived stem cells, umbilical cord-derived mesenchymal stem cells (UC-MSCs), and peripheral blood-derived mesenchymal stem cells. (34)

The application of BM-MSCs in DFU treatment has shown significant improvements in ulcer healing, as indicated by enhancements in the Ankle-Brachial Index (ABI), angiogenesis, and blood flow compared to conventional treatments. Functional improvements have also been noted, including reduced rest pain and increased claudication distance, alongside a reduced need for amputations. Moreover, combining UC-MSC therapy with traditional angioplasty has led to further advancements in ABI, claudication distance, and skin temperature. (35)

Embryonic stem cells (ESCs), derived from the inner cell mass of blastocysts through in vitro fertilization, have drawn ethical concerns due to their sourcing and the potential risks of tumor formation and immune rejection. These issues have hindered extensive research on ESCs. Nonetheless, one animal study indicated that ESCs did not increase tumor formation in rats; however, additional clinical trials are necessary to evaluate the effectiveness of ESC treatment in diabetic foot conditions. Overall, stem cell therapy presents a promising therapeutic option for DFUs, particularly when used in conjunction with traditional therapies like angioplasty to achieve enhanced results. (36)

CONCLUSION

Diabetic foot ulcers (DFUs) contribute significantly to both illness and death among individuals with diabetes. They often result in extended hospital stays and increased healthcare expenses. Therefore, timely diagnosis and tailored treatment are crucial for addressing this common complication of diabetes. Conventional local and invasive treatments, along with innovative methods such as stem cell therapy, offer promising solutions to lower morbidity rates, minimize the necessity for amputations, and reduce mortality linked to DFUs. Ongoing research into new techniques that facilitate swift and effective management is vital for lessening the healthcare burden associated with DFUs.

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