

“Strategies in the Management of Diabetic Foot Ulcer: A Comprehensive Review”

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ABSTRACT:

DFUs (Diabetic Foot Ulcers) are defined as foot lesions (ulcers) that may affect the skin, soft tissue, and bone in lower limbs causing an aggravating infection in diabetic patients that can lead to serious consequences such as lower limb amputations and equally severe social, physiological and economic outcomes. One out of four patients with diabetes develop DFU in their lifetime and more than half of them become infected. Hence, it is important to manage infection and ulcer to prevent negative outcomes. According to National Institute for health and clinical excellence strategies, early effective management of diabetic foot ulcer can reduce the severity of complications and can improve overall quality of life.

Management of diabetic foot ulcer should be optimized by using a multidisciplinary team due to comprehensive approach to wound management. The available information plays a significant role in keeping both physicians and patients aware of the emerging therapies against DFUs.

The purpose of this review is to put together the currently available approaches in the management and treatment of diabetic foot ulcer to offer an overview of the assessment of this condition and for rapid healing of DFU. So, it is suggested that with appropriate patient education, encourages them to regular foot care in order to prevent DFU and its complications.

KEYWORDS: Diabetic foot ulcer, wound management, healing, foot care.

I. INTRODUCTION:

Diabetes mellitus (DM) is a global public health threat that has increased in the recent two decades. Diabetes is the primary cause of non-traumatic lower extremity amputations, adult-onset blindness, and end-stage renal failure. Complications from diabetes can be fatal or severely paralyzing. Diabetic foot ulcers (DFUs) are a common consequence among patients with diabetes mellitus (DM), although patients with

other conditions may also acquire them. According to the International Working Group on the Diabetic Foot (IWGDF), a diabetic foot ulcer is a full-thickness wound penetrating through the dermis (the deep vascular and collagenous inner layer of the skin) located below the ankle in a diabetic patient¹. Numerous conditions, including peripheral artery disease and neuropathy (damage or malfunctioning of the nerves) can result in diabetic foot ulcers (which may lead to ischemia, a limitation in blood flow).

One of the most serious and expensive consequences of diabetes is diabetic foot ulcers. Lower limb amputation is frequently necessary for patients with diabetic foot ulcers². It describes the presence of a break in the skin of the foot in a person with diabetes, which does not promptly heal, but indicates nothing of its type³. It has previously been demonstrated that the five-year survival rate for individuals with diabetic foot ulceration is as low as 50%, and that it is even lower for those with vascular disease. A person's chance of developing diabetic foot ulceration is increased if they have peripheral vascular disease, loss of protective foot sensation, foot deformity, or both. Those who have already experienced an ulceration are much more vulnerable. Regular foot care, managing blood sugar and seeking medical attention for any signs of infection are crucial⁴. There is limited mortality related data for patients who developed DFU, although some recent studies prove that mortality rate is more than two folds higher among diabetic foot ulcer patients when compared to non-diabetic group and patients with history of diabetic foot ulcer have almost 40% higher mortality than diabetic patients without history of DFU⁵.

The organizing committee of the International Working Group on the Diabetic Foot (IWGDF) published the 'IWGDF guidelines on the prevention and treatment of diabetic foot disease' in 2019 after many years of thorough discussion involving experts from multiple countries and disciplines. Diabetic foot is frequently a

challenging condition in clinical practice, with issues including infection, neuropathy and vascular lesions. Therefore, the assessment should be comprehensive and thorough, with special focus on infections, lower extremity peripheral vascular disease, preoperative risk stratification and treatment risk assessment⁶

GRADES OF DIABETIC'S FOOT ULCER :

In order to classify diabetic foot ulcers for the sake of this study, we used the Wagner system, which employs six wound grades (rated 0 to 5) to gauge ulcer depth.

Grade 0 diabetic foot ulcer: There isn't an ulcer, but the foot could develop one gradually.

Grade 1 diabetic foot ulcer: Superficial ulceration

Grade 2 diabetic foot ulcer: profound infection, but no bone involvement

Grade 3 diabetic foot ulcer: Ulcer with osteomyelitis.

Grade 4 diabetic foot ulcer: Localized gangrene present on the foot.

Grade 5 diabetic foot ulcer: Gangrene across the entire foot is present⁹

RISK FACTORS:

Diabetic foot ulcers are a consequence of many factors including loss of protective sensation due to peripheral neuropathy where the feet become numb and the injury goes unnoticed. Also, arterial insufficiency complicates the neuropathic ulcer which leads to poor wound healing.

- Higher BMI (overweight and obesity)
- Inappropriate antibiotics given
- Neuropathy
- Advanced grade of diabetic foot ulcer⁹
- Poor glycaemic control
- Diastolic hypertension
- Dyslipidaemia
- Older age
- Infections
- Poor self-care⁸

were factors that predicted the amputation among DFU patients. The rate of amputation of the DFU was found to be high in which most of the patients were amputated below the ankle. Recently, vitamin D deficiency was proposed as a risk factor for diabetic foot infection.

MANAGEMENT :

DFU have a lifetime prevalence of 15-25%. DFU is a risk factor for both mortality and

morbidity when it comes to lower limb amputation complications. The diagnosis of DFU is often difficult, leading to inappropriate use of antibiotics¹⁰.

The management of patients with a DFU is a multidisciplinary approach that includes all relevant specialties (i.e., nursing, orthopedics, plastic surgery, vascular surgery, nutrition, infectious diseases, microbiology, and endocrinology departments). To aid the clinician during the management of DFUs, classification of stage and severity of the wound must be established. In the past, there hasn't been any evidence-based topical treatment available to speed up the healing of diabetic foot ulcers. However, multicentre, randomised, controlled trials have lately produced novel evidence-based treatments⁷.

Traditionally, the management of diabetic foot ulcers (DFUs) has focused on perfusion, pressure reduction, infection control, glycaemic balance regulation, foot discharge, and debridement¹⁰.

EDUCATION:

Effective education has been demonstrated to be able to prevent up to 50% of DFU cases. In fact, it's believed that teaching people how to take care of their feet is the greatest method to prevent DFU⁹. The ultimate goal of diabetic foot care education is to prevent foot ulcers and amputations. Many patient education techniques, such as practical instruction and demonstration, are currently being investigated to prevent DFU. The length of these interventions ranges from in-depth to superficial education. Patients with diabetic foot ulcers should be educated about risk factors and the importance of foot care, including self-checking, controlling blood sugar, wearing appropriate footwear, keeping feet clean on a daily basis, and keeping an eye on foot temperature. However, education works best when combined with other treatment techniques in a holistic manner. Together, these techniques can reduce the incidence and morbidity of limb-threatening complications brought on by DFU.

GLYCEMIC CONTROL:

Considering the known negative effect of hyperglycemia on wound healing and immune defense, hyperglycemia may be associated with negative consequences in patients with DFUs¹². High fasting plasma glucose and HbA1c levels were linked to a higher incidence of amputations, according to a meta-analysis¹¹. Apart

from its impact on the process of wound healing, hyperglycemia also results in compromised immune systems and a reduced ability to respond to infections¹³

For the majority of inpatients, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) advise aiming for glucose levels between 140 and 180 mg/dL without resulting in hypoglycemia¹⁴. These levels should be maintained by patients with DFU.

A number of oral antidiabetics possess attributes beyond their ability to lower blood glucose levels. For example, in patients with type-2 diabetes, canagliflozin, an inhibitor of sodium-glucose cotransporter-2 (SGLT-2), is linked to a roughly two-fold increased risk of LEA (mostly at the toe or metatarsal level)¹⁵. A pharmacovigilance research found that dapagliflozin, empagliflozin, and canagliflozin (for toe amputations) increased the risk of LEAs. This research made use of multiple LEA cases¹⁶. There aren't many high-quality systematic studies on the side effects of SGLT-2 inhibitors, according to a study analyzing systematic reviews¹⁷.

May be a group effect whereby SGLT-2 inhibitors increase the likelihood of LEA in patients with DFU. Caution is advised due to the contradicting information that is currently available regarding this traffic.

DEBRIMENT:

Debridement is the process of removing foreign and infected materials from a wound, along with necrotic and senescent tissues. It is regarded as the first and most crucial treatment step toward wound healing and a reduction in the risk of limb amputation in DFU⁹ patients. Debridement may help with wound drainage and gives the physician a clearer idea of the size of the wound¹⁸.

Depending on the wound tissue type, different debridement techniques are recommended,

- Surgical or sharp debridement is advised in cases of infected and necrotic wounds. While some doctors refer to surgical debridement as being performed in an operating room, sharp debridement is performed in a clinic. The phrases surgical debridement and sharp debridement are frequently used identically. The fastest and most efficient technique of debridement is sharp surgical debridement.
- Autolytic debridement is liquefying the necrotic tissue through a selected procedure. When an occlusive dressing is applied to a

wound, tissue fluids comprising neutrophils, macrophages, and enzymes can accumulate. These substances help to break down necrotic tissues and eliminate pathogens. An atmosphere that promotes moist wound healing does this. For the treatment of infected pressure ulcers, autolytic debridement is not recommended¹⁹

- Mechanical debridement-involves removal of unhealthy tissue using a dressing, which is changed regularly by wound irrigation (pressure: 4-15 psi), without damaging healthy/new tissues. Scrubbing the wound aids in removal of exudates and devitalized tissues, however this leads to bleeding as well as pain resulting from wound trauma. Venous leg ulcers and surgical wounds are treated with this method. The method's limitations include its high cost and time requirements²⁰
- Enzymatic debridement: topical enzymes such as collagenase, fibrinolysin, or papain are used to debriding devitalized tissue. advised for necrotic, sloughy wounds that are infected and for which surgical debridement is not advised.
- Maggot debridement: this method uses fly larvae or maggots reared in a sterile environment. *Lucilia sericata* is the most widely utilized fly, used to cure human wounds when other methods are ineffective. After applying maggots to the wound, a secondary dressing is applied. The larvae release antibacterial enzymes that aid in the healing of wounds while feeding on germs and necrotic (dead) tissue at the wound site.²¹

PLATELET RICH PLASMA THERAPY:

In the current decade, many reports suggested the administration of platelets or the supernatant (obtained from the platelet suspension) to improve wound healing. This suspension of blood plasma enriched with a high concentration of platelets and abundant platelet growth factors also has a fraction of autologous blood platelets, which contain various growth factors and cytokines. PRP induces cell division, which attracts undifferentiated cells to the lesion site to promote wound healing. The PRP's platelet protein signaling draws macrophages and is crucial to the host's defense response at the location of the wound.³¹

OFFLOADING:

Relieving pressure from the foot's weight-bearing area, either fully or partially, with the goal of resting the injured area with mechanical support

promotes recovery. Once ulcers have formed, they tend to persist for two main reasons: high plantar pressure on the ulcer bed and repetitive trauma. Offloading plays a critical role in the healing of diabetic wounds. There are numerous unloading methods, such as wheelchair mobilization, wedge footwear, half shoes, removable cast footwear, and entire contact casts. The gold standard for treating and relieving diabetic individuals with neuropathic ulcers is thought to be total contact casts.²¹ TCC is contraindicated in neuro-ischemic diabetic foot²².

TOPICAL ANTIMICROBIALS:

Topical antimicrobials are selected based on their low toxicity to the host tissue. some topical antiseptics/antimicrobials available for DFIs are ,

- Povidone iodine 10% solution
- Chlorhexidine
- Acetic acid 5%
- Silver compounds
- Sodium hypochloride
- Hydrogen peroxide
- Benzalkonium chloride

ANTIBIOTIC THERAPY:

When there are indications of localized, progressive, or systemic infections, systemic antibiotic therapy should be started. The results of a microbiological culture, the intensity of the clinical manifestations, the body structures involved, and the patient's immune competence all influence the type of antimicrobial agent to be employed and the appropriate delivery route³⁷. Broad-spectrum antibiotics are usually given first during regular treatment, then, after the findings of the bacterial culture are known, a more focused drug is used. Intravenous (IV) antibiotic therapy and hospitalization may be necessary in cases of severe, non-responsive, or spreading infections, or in cases when serious osteomyelitis is suspected. Activities against streptococci and Gram-positive staphylococci can be treated by oral antibiotic treatment.

A second antibiotic is added if the infection is not resolved by the first treatment. Antibiotics should be used for one to two weeks for mild infections and for two to three weeks for moderate-to-severe infections, according to IDSA recommendations³¹. However, once the clinical signs and symptoms go away, antibiotics can normally be stopped. Broad-spectrum drugs that are most frequently employed are carbapenems, β -lactams, or β -lactamase inhibitor combinations like

ampicillin/sulbactam, ticarcillin/clavulanic acid, or piperacillin/tazobactam.

When treating Gram-negative bacteria that are resistant to many drugs, carbapenems are a standard. Metronidazole is the preferred treatment for anaerobic bacteria and is also used to treat persistent DFU infection. The recommended empirical antibiotics for DFIs, according to current guidelines, are cefoperazone/sulbactam or piperacillin/tazobactam with clindamycin. Depending on the culture's sensitivity report, an escalation to carbapenem (meropenem) with teicoplanin may be necessary³¹.

Patients with DFUs frequently contract MRSA (methicillin-resistant *Staphylococcus aureus*), which is a major issue in hospital settings. Vancomycin is the most commonly used agent in the treatment of MRSA; however, due to a 50% rise in reports of resistance to this medication, linezolid has been chosen as an alternative. An oxazolidinone, linezolid exhibits antibacterial properties against Gram-positive bacteria, including vancomycin-resistant isolates of staphylococci, streptococci, and MSSA and MRSA isolates. Skin and skin structure infections (SSSIs) are a complication that can arise from DFIs . For this condition, linezolid and a combination of piperacillin and tazobactam are the recommended treatment³⁸.

SURGERY:

Diabetic foot surgery plays an essential role in the prevention and management of diabetic foot ulcer. The infection component with or without bone involvement is the first goal of salvage surgery, by performing aggressive surgical debridement, and only subsequently should the correction of the deformities be considered through procedures of increasing difficulty such as decompressive exostectomies, osteotomies and arthrodesis²³. In general, surgery for DFU healing includes nonvascular foot surgery, vascular foot surgery, and in some cases amputation.

Nonvascular foot surgery is divided into elective, prophylactic, curative, and emergent surgeries that aim to correct deformities that increase plantar pressure.

Class 1: Elective: Reconstructive operations on non-neuropathic patients. Examples include osteotomy, bunion, hammertoe, Achilles lengthening (TAL), and so on.

Class 2: Prophylactic: Reconstructive techniques used on neuropathic patients without an open

wound to lower the danger of ulcers or re-ulceration. Examples include Charcot reconstruction, exostectomy, TAL, Keller arthroplasty, and so on.

Class 3: Curative: Actions taken to aid in the healing of open wounds. Examples include toe amputation, Keller arthroplasty, and metatarsal head resection.

Class 4: Emergent: actions taken to stop or slow the spread of an infection. Examples include fasciotomy, guillotine/open amputation, incision and drainage, etc.

-Vascular foot surgery such as bypass grafts from femoral to pedal arteries and peripheral angioplasty to improve blood flow for an ischemic foot have been recently developed³³.

-Amputation is considered as an urgent or curative surgery and should be the last resort after all other salvage techniques have been explored, and the patient must be in agreement. LEA is defined as surgical removal of bones and soft tissue by transecting at any level of the lower extremity and can be classified into minor and major amputation. The globally accepted definition of minor amputation is below ankle joint encompassing forefoot and toe while major amputations are at or proximal to the ankle joint such as below or above knee amputation³⁴.

Diabetic complications account for 40% to 60% of non-traumatic lower limb amputations globally, with diabetic foot ulcers being the cause of 80% of these amputations. Only 59% of patients survive five years, even after minor amputations. An amputation may be necessary to remove gangrenous or contaminated tissues, treat an infection, or create a functional foot or stump that can support a prosthesis or shoes³⁵.

ADVANCED THERAPY:

HYPERBARIC OXYGEN THERAPY:

Hyperbaric oxygen therapy (HBOT) has shown promise in the treatments of serious cases of non-healing DFU, which are resistant to other therapeutic methods. HBOT involves intermittent administration of 100% oxygen, usually in daily sessions. Patients underwent three 30-minute sessions (totaling ninety minutes) of pure oxygen breathing at 1.4–3.0 absolute atmospheres, separated by 5-minute intervals, in a hyperbaric chamber during each session²⁴.

The exact mechanism of HBOT remains poorly understood. Some studies have reported that HBOT improved wound tissues hypoxia, enhanced perfusion, reduced edema, down regulated

inflammatory cytokines, and promoted fibroblasts proliferation, collagen productions, and angiogenesis. In addition, it was demonstrated that HBOT stimulated vasculogenic stem cells mobilizations from bone marrow and recruited them to the skin wound. HBOT does not substitute for antibiotic therapy, local humid therapy, or surgical wound debridement. Moreover, because HBOT is costly and time-consuming (requiring an average of 60 hours in the chamber), it is only available in a small number of areas.²⁴.

NEGATIVE PRESSURE WOUND THERAPY:

Negative pressures wound therapy action results in two types of tissue deformations macrodeformation, such as wounds contraction, and micro-deformation occurring at microscopic level. Both of them stimulate a wound healing cascade including tissue granulation promotion, vessel proliferation, neoangiogenesis, epithelialization and excess extracellular fluids removal. On the molecular level, NPWT results in an alteration towards more pro-angiogenic and anti-inflammatory conditions. It increases expression of several key growth factors, including vascular endothelial growth factors and fibroblasts growth factor 2, while expression of inflammatory cytokines reduced. The NPWT applications also alters the presence and functions of matrix metalloproteinases. Clinical trials in DFU patients demonstrated that NPWT was superior to standard therapy in terms of efficacious results, including the rate of amputation and wound healing, without increasing the incidence of side effects. According to international recommendations, NPWT is a crucial adjuvant therapy for DFU, and its use is anticipated to rise.²⁵.

ELECTRICAL STIMULATION:

One low-cost, simple-to-use, non-invasive physical therapy is electrical stimulation (ES). To enhance the existing standard of care for chronic ulcerations in terms of HR, HT, and the percentage of wounds healed (PWH), ES has been proposed as an adjuvant therapy. By imitating the COI, ES seeks to restore the physiological cell movement. Furthermore, ES seeks to enhance physiological cell activity. Particularly, direct current (DC) and pulsed current (PC) have demonstrated the previously described advantages among ES modalities. DC is distinguished by a unidirectional flow of charged particles and a constant current intensity. Throughout the entire ES process, one electrode is constantly maintained positive (anode)

and the other negative (cathode) to ensure a unidirectional flow²⁶.

In other words, the exposure is conducted with an identical polarity throughout. On the other hand, PC is distinguished by a brief current pulse that is followed by a period of no current flow. There are two types of PC: bidirectional (biphasic PC) and unidirectional (monophasic PC), which occur when the polarity alternates during the process²⁶. Direct DC and PC exposure between 50 and 300 mV/mm has been shown in vitro to dramatically enhance macrophage, fibroblast, keratinocyte, and endothelial cell motility²⁷⁻²⁹.

In fact, it has been demonstrated that ulcers treated with ES and standard of care significantly improve their HR compared to ulcers treated with standard of care alone, despite the vast array of diverse modalities and intervention protocols that have been used²⁸.

CELL AND GENE THERAPY:

Cell and gene therapy are in-development techniques used to improve DFU treatments. Treatments for persistent wounds have included the investigation of stem cells, fibroblasts, and keratinocytes. Stem-cell treatment is used to improve blood flow in ischemia-affected limbs. Although research on this treatment is still primarily theoretical, it is believed that this process can aid in the healing of chronic wounds. Several trials using autologous stem cells, mesenchymal bone marrow cells, and bone marrow-derived mononuclear cells for DFU healing showed encouraging outcomes.³²

DRESSINGS:

The purpose of the wound dressing is to maintain a moist region to encourage the creation of new tissue and autolytic debridement, as well as to shield it from infection and environmental exposure³⁰. Some of the existing dressing types include,

- **Hydrogels:** Hydrogel dressings are composed of insoluble copolymers that have the ability to bind water molecules. Wounds can get water from the matrix, and the matrix can also absorb exudates from the wound to keep the wound at the ideal moisture content. According to certain data, hydrogel dressings work better than conventional dressings to heal DFUs³⁰.
- **Acrylics:** The dressing (usually a thin clear film) is permeable to water vapor. However, it might be difficult to remove and has a limited absorption capability.

- **Hydrocolloids:** This kind of dressing is made of hydrophobic methylcellulose bonded to a polyurethane film and hydrophilic carboxy components. These components are long-wearing, self-adherent, and support autolytic debridement. Nevertheless, during removal, this procedure may cause discomfort to the incision region and trigger allergic reactions.³⁰
- **Alginate dressings:** Alginate products (calcium alginate, calcium sodium alginate, or alginic acid) are derived from seaweed. Through the absorption of wound exudates and preservation of a moist wound environment, these compounds function similarly to hydrogels. There was little difference between standard contact dressings and silver hydrocolloid dressings, according to earlier evaluations and meta-analyses.³¹
- **Hydrofibers :** Hydrofibers are composed of carboxymethylcellulose sheets. Their strong absorptive capacity and simplicity of removal are a couple of their benefits. But a secondary dressing is required.
- **Foam Adhesives:** This kind of adhesive can be used to apply ibuprofen and silver to wounds. It is made of absorbent polyurethane with varying pore sizes. Foam adhesives do, however, have the drawback of causing macerations in the surrounding skin.
- **Honey dressing:** Honey has been processed to meet physiochemical testing norms for medical use and it is also packed on regular surgical gauze, which is applied to facilitate wound healing. According to research, honey has broad-spectrum antibacterial qualities, promotes the growth of epithelium around the wound, helps control wound infection, and absorbs edema³⁶.

Wounds with high secretion levels require absorbent dressings, while dry wounds require moisture-balancing dressings to replenish moisture. The rates at which dressings promote healing are comparable across all types³¹.

II. CONCLUSION:

Diabetic Foot Ulcer is a life threatening condition frequently leading to lower limb amputation unless a prompt, rational, multidisciplinary approach to therapy is taken. The management of DFU remains a challenge therapeutically which suggests a haste need to review the strategies and treatments in order to achieve the goals and decrease the burden of care in an efficient and cost effective way .It is crucial to

determine which foot is at risk by closely and physically examining it, followed by neuropathy and vascular testing. The key elements of DFU management that can guarantee a successful and speedy recovery are blood sugar regulation, wound debridement, advanced dressing, unloading, surgery, and clinically applied advanced therapies. In order to lower the high morbidity and risk of major complications from foot ulcers, these strategies must be applied whenever possible. To avoid amputation, diabetic foot ulcers should be closely assessed and treated with the highest standards of care. In order to strengthen the current evidence about the clinical efficacy of novel strategies for the treatment of diabetic ulcers, more clinical research is required.

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