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## Diabetic foot ulcer: A comprehensive review of pathophysiology and management modalities

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### Abstract

Diabetic foot ulcer (DFU) is a debilitating and severe manifestation of uncontrolled and prolonged diabetes that presents as ulceration, usually located on the plantar aspect of the foot. Approximately 15% of individuals with diabetes will eventually develop DFU, and 14%-24% of them will require amputation of the ulcerated foot due to bone infection or other ulcer-related complications. The pathologic mechanisms underlying DFU are comprise a triad: Neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot. Standard local and invasive care along with novel approaches like stem cell therapy pave the way to reduce morbidity, decrease amputations, and prevent mortality from DFU. In this manuscript, we review the current literature with focus on the pathophysiology, preventive options, and definitive management of DFU.

**Key Words:** Diabetes; Ulcer; Foot; Antibiotics; Revascularization; Cell therapy

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**Core Tip:** Diabetic foot ulcer: Pathophysiology: - Neuropathy including sensory and motor - Vascular insufficiency leading to ischemia - Secondary infection with inflammation. Overview of management: (1) Preventive care including self-screening, health care screening, insoles, podiatric care; (2) Noninvasive modalities including wound dressing, human skin equivalent, topical growth factors, shock wave therapy, stem cell therapy, hyperbaric oxygen, negative pressure, shock wave therapy, maggot therapy, antibiotics; and (3) Invasive modalities including debridement, revascularization, skin grafting, amputation.

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## INTRODUCTION

Diabetes mellitus affects approximately 422 million people worldwide and is responsible for an estimated 2 million deaths per year[1]. It affects 11.3% of the United States population[2]. Diabetic foot ulcer (DFU) is a debilitating and severe manifestation of uncontrolled and prolonged diabetes that presents as an ulceration, usually located at the plantar aspect of the foot. Approximately 15% of individuals with diabetes will eventually develop one of these ulcers, and out of these individuals, 14%-24% of them will require amputation of the ulcerated foot due to bone infection or other ulcer-related complications[3]. With such a high level of morbidity stemming from debilitating osteomyelitis and amputation in patients with DFU, it is of the utmost importance to properly address and treat the underlying causes of DFU. In this paper, we review the current literature with focus on the pathophysiology, preventive options, and definitive management of DFU.

## PATHOPHYSIOLOGY

DFU comprises a full-thickness wound involving the dermis, located in the weight-bearing or exposed area below the ankle. The Wagner system aids in categorizing the severity of the ulcer, ranking it on a scale of 1 to 5 (Table 1). The pathologic mechanisms of DFU are described in terms of a triad. This triad includes neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot[4] (Figure 1).

First, the lack of protective sensation in the feet predisposes patients with diabetes to developing trauma and ulcers. This sensory impairment occurs due to hyperglycemia-induced upregulation of aldose reductase and sorbitol dehydrogenase, which in turn increase the production of fructose and sorbitol. These glucose products accumulate and induce osmotic stress, thereby reducing nerve cell myoinositol synthesis and nerve conduction[5]. Also, from a pathological stance, advanced glycation end-products (AGEs) must be considered. AGEs are non-enzymatic protein, amino acid, and DNA adducts which form from dicarbonyls and glucose. AGE formation is enhanced in diabetes and is associated with the development of diabetic complications[6]. In addition to sensory neuropathy, diabetes can induce neuronal autonomic dysfunction that results in impaired sweat production, leaving the foot susceptible to dryness, skin cracking, and fissuring[7]. Furthermore, motor neuron dysfunction can give rise to muscle wasting and structural abnormalities of the foot[8]. This causes focally elevated pressures at various zones of the plantar foot and increases the risk of ulceration[9].

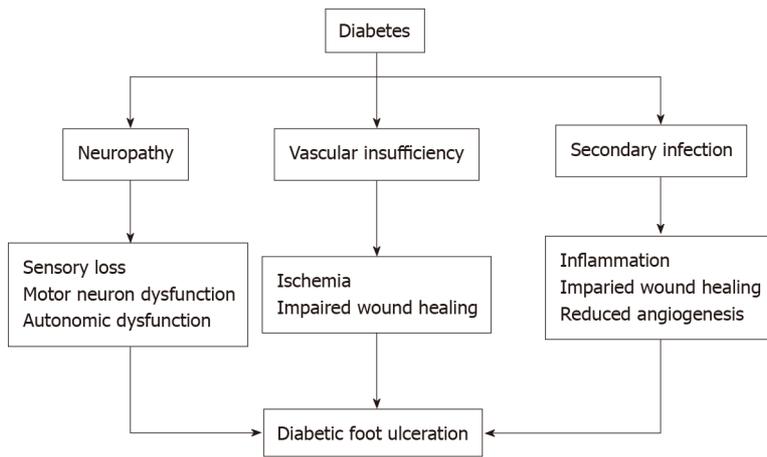
In addition to the triad, impaired wound healing has been established as a key means of DFU progression[10]. Importantly, molecular changes at the site of DFU precede the grossly visualized tissue abnormalities[11]. In fact, the route from hyperglycemia to DFU involves complex molecular dysfunctions in wound healing. Ordinarily, wounds undergo several healing stages involving hemostasis, inflammation, proliferation, and remodeling. Acute wounds advance linearly through these stages; however, chronic nonhealing DFUs stall in 1 or more phases. In the early phases of wound healing, neutrophils normally release granular molecules to kill foreign pathogens in a process known as neutrophil extracellular traps (NETosis)[12]. However, in a diabetic microenvironment, NETosis becomes dysregulated, causing a proinflammatory cascade and overproduction of cytokines and superoxide, which delay wound healing[13,14]. Moreover, hyperglycemia induces formation of AGEs that cause structural and functional changes in key proteins[15]. Specifically, AGEs can bind to the receptor of advanced glycation end-products (RAGE), which is normally minimally expressed in normoglycemic conditions[16]. This in turn activates nuclear factor kappa-B (NF- $\kappa$ B). Ultimately, cytokine release is enhanced with a self-sustaining cascade that prolongs inflammation and favors apoptosis[17]. Overall, hyperglycemia induces a proinflammatory environment largely due to the dysregulation of cytokine release, NETosis, and AGE production.

Along with inflammation, substantial alterations of the extracellular matrix (ECM) also play a significant role in perpetuating the non-healing DFU. In cases of normal wound healing, the production and degradation of ECM proteins such as collagen and fibrin are tightly regulated[18]. Collagen comprises most of the soft tissue ECM, and thus, abnormalities of collagen metabolism have significant consequences on wound healing. Specifically, collagen-degrading enzymes known as matrix metalloproteinases (MMPs) become hyperactive, resulting in a highly-proteolytic environment with reduced collagen content[19,20]. Overall, the ECM becomes disorganized and insufficient to support wound healing. Alongside elevated MMP activity, the accumulation of AGEs results in a reduction of fibroblast

**Table 1 Wagner's classification of diabetic foot ulcers**

Grade	Characteristic
Wagner grade 1	Partial- or full-thickness ulcer (superficial)
Wagner grade 2	Deep ulcer extending to ligament, tendon, joint capsule, bone, or deep fascia without abscess or OM
Wagner grade 3	Deep abscess, OM, or joint sepsis
Wagner grade 4	Partial-foot gangrene

OM: Osteomyelitis.



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**Figure 1 Pathophysiology of diabetic foot ulceration.**

growth factor (FGF) and transforming growth factor-beta[21,22]. This has a similar effect of reducing the collagen content *via* the induction of fibroblast apoptosis[23].

Lastly, impaired angiogenesis plays a key role in the disruption of diabetic wound healing. Angiogenesis ordinarily occurs during the proliferative phase of wound healing, and is responsible for both the formation of granulation tissue and delivery of nutrition and oxygen to the wound[24]. In the case of DFU, there is a reduction of angiogenic growth factors such as vascular endothelial growth factor (VEGF) 20 and FGF-2[25]. Essentially, VEGF initiates angiogenesis and mediates endothelial cell proliferation while FGF-2 facilitates migration of new blood vessels through the ECM[26,27]. When VEGF and FGF-2 expression is compromised, wound healing declines. Furthermore, endothelial progenitor cells (EPCs) have been implicated as expressors of proangiogenic factors and receptors including VEGF and FGF[28]. A deficiency of function and number of EPCs has been demonstrated in patients with type 2 diabetes mellitus, which is attributed to AGE accumulation[29-31]. Overall, the dysfunction of EPCs and circulating growth factors contributes significantly to the development and progression of DFU by way of disrupting angiogenesis.

## MANAGEMENT

The management of DFU involves preventative care as well as various treatment modalities, including both noninvasive and invasive measures (Figure 2).

### Preventative care

Due to diabetes being a risk factor for the development of underlying peripheral vascular disease, the majority of DFUs are asymptomatic until advanced enough to recognize more severe signs and symptoms. During the diagnosis of DFU, neuropathy may mask ischemia and vice versa. Therefore, the primary preventative strategy is regular diabetic foot screening to allow early identification of DFU, followed by initiation of treatment if appropriate. Ultimately, early detection and management work to avoid further complications such as gangrene and amputation[32]. Screening comprises the patient checking his or her own feet for trauma or ulceration every day and routine screening during health care visits.

Preventive care	Non-invasive modalities	Invasive modalities
Self screening Health care screening Insoles Podiatric care	Wound dressing Human skin equivalent Total-contact casting Hyperbaric oxygen Topical growth factors Shock wave therapy Stem cell therapy Antibiotics Negative pressure wound care Maggot therapy	Debridement Revascularization Skin grafting Amputation

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Figure 2 Overview of management of diabetic foot ulceration.

### **Noninvasive care**

The most prevalent management modality for DFU is local care, in which many potential avenues of treatment can be utilized. These include wound dressings, human skin equivalents (HSEs), pressure offloading, total-contact casting (TCC), systemic hyperbaric oxygen, larvae therapy (maggot therapy), and topical growth factors.

### **Wound dressings**

Wound dressings are the most basic and common treatment measure, and although they serve a vital purpose in the management of DFU, other methods have proven vastly more effective in comparison to or in adjunct with wound dressings.

### **Human skin equivalent**

HSE is more effective compared to the standard treatment of saline-moistened gauze in reducing the rates of amputation and infection and in improving the rate of ulcer healing. One randomized controlled trial (RCT) assessed the effectiveness of Graftskin, a living skin equivalent indicated for use in noninfected, nonischemic DFU. In this study, Graftskin was applied weekly for a maximum of 4 wk or until complete healing occurred. The results of the trial highlighted the increased effectiveness of HSE in comparison to the control group, in which ulcers were treated only with saline-moistened gauze. The use of HSE resulted in an 18% increase in complete wound healing when compared to the control group [33]. Despite these impressive results, one limitation to this treatment is that HSE may have limited availability or accessibility.

### **Offloading, TCC**

Pressure offloading serves as one of the primary treatments of DFU, primarily in ulcers accompanied by neuropathy, with many variants being utilized. For ischemic DFUs, however, revascularization is more commonly used. Common methods of offloading include bed rest, wheelchair use, implementation of a crutch-assisted gait, total contact casting, use of felted foam, use of therapeutic shoes, and use of removable cast walkers[34]. The most effective offloading treatment is TCC, in which full casts are applied by an experienced physiotherapist and are changed weekly for 2-3 wk or until healing has occurred. One RCT found that TCC was extremely effective in increasing ulcer healing and reducing infection when compared to traditional dressing changes and other offloading methods. The study reported a 91% rate of healing within the TCC population, compared to a 32% rate of healing in the control group. This rate was reported following a 65 d period. Furthermore, the TCC group reported a 0% incidence of infection, with the same in the control group reported as 26%[35]. Multiple other studies have reported similar results, with TCC being an extremely effective treatment to DFU, particularly when compared to traditional dressing changes. One adverse effect of this treatment, however, is fungal infection, but this was addressed with topical treatment and did not prevent continued casting. Despite the evident success of TCC, one national survey in the United States evaluating 901 foot clinics in 48 states and the District of Columbia indicated that TCCs were used only by 1.7% of centers; this is potentially due to the tedious nature of this treatment option. TCC requires an experienced physiotherapist, and constant replacement and care. The application of the cast is a timely and intricate endeavor, and tends to cause patients discomfort according to the survey. The survey also indicated that the primary treatment across the foot clinics was shoe modifications.

### **Hyperbaric oxygen therapy**

Another treatment for DFU is systemic hyperbaric oxygen therapy (HBOT), which is reserved for advanced cases and aimed at reducing the risk of amputation. This treatment is prevalent particularly in

the treatment of infected DFU, where 1 systematic review identified 6 RCTs that evaluated chronic DFU. Systemic HBOT sessions are usually conducted in 45 to 120 min sessions once or twice daily at pressures between 1.5-3.0 ATA. This method resulted in significantly reduced rates of major amputation compared with usual care of DFU. HBOT is typically used as an adjunctive therapy to normal wound care measures[36]. However, this treatment modality is quite expensive, is still not fully researched, and may warrant further trials.

### **Larvae therapy (maggot therapy)**

Maggot therapy is another well-researched technique with respect to the treatment of chronic wounds in which maggots are placed on the wound area. This treatment method has been shown to significantly facilitate debridement. In one study, maggot therapy also enabled faster development of granulation tissue and more significantly decreased wound surface area compared to other topical treatments such as hydrogel dressings. Maggot therapy also had no effect on disinfection or complete healing rate for the wound[37].

### **Topical growth factors**

Topical growth factors, particularly platelet-derived growth factors, have also proven effective in increasing ulcer healing rates when compared with placebo. Growth factors serve as principal immediate mediators of wound healing, and when applied in the setting of DFU, accelerate ulcer healing. One meta-analysis evaluated 26 RCTs with 2088 participants, and focused on recombinant epidermal growth factor, autologous platelet rich plasma, and recombinant human platelet-derived growth factor. Overall, each of the 3 treatments significantly improved rate of healing when used alongside standard treatment, with recombinant human epidermal growth factor slightly favored when compared to other growth factors[38].

### **Shock wave therapy**

Extracorporeal shockwave therapy (ESWT) has been reported to accelerate the healing of soft tissue wounds when treating DFU. ESWT is utilized to stimulate osteoblasts and in turn facilitate soft tissue healing. There have been promising clinical trial results, indicating that ESWT is more effective in the treatment of DFU when compared to traditional methods. Two multi-national RCTs were conducted to compare the efficacy of ESWT when used adjunctively with standard care and other DFU treatments. The trials both lasted 12 wk and showed reduction of wound volume by more than 50% with the use of ESWT when compared to standard treatment alone[39].

### **Stem cell therapy**

The cornerstone of available treatment options currently includes treatment of infection, surgical debridement, and revascularization[40]. Better understanding of the tissue remodeling process, which comprises inflammation, cell migration, neovascularization, and tissue proliferation, has paved the way for stem cell-based therapy to become viable for the treatment of DFU[41]. Stem cells aid wound healing by secretion of cytokines that play an important role in cell migration, angiogenesis, remodeling of extracellular matrix, and regeneration of nerves[42]. Also, stem cell capacity for differentiation into various cell types, including myofibroblasts and endothelial cells, optimizes wound healing[43].

The stem cell types that have been studied to aid in diabetic foot treatment are mainly adult stem cells (ASCs). Bone marrow-derived mesenchymal stem cells (BM-MSC) are the most extensively studied among the different ASCs; other types include adipose-derived stem cells, umbilical cord-derived mesenchymal stem cells (UC-MSC), and peripheral blood-derived mesenchymal stem cells[44] (Table 2). The use of BM-MSC in the treatment of DFU demonstrated more effective ulcer healing, with improvements in Ankle-Brachial Index (ABI), angiogenesis, and blood flow when compared to local treatment[45-47]. Even functional improvement with a decrease in rest pain and an increase in claudication distance was demonstrated. Decreased amputation when compared to conventional treatment was also seen. Furthermore, combining UC-MSC stem cell therapy with traditional angioplasty resulted in improvements in ABI, claudication distance, and skin temperature[48].

Embryonic stem cells (ESCs) are usually derived from blastocysts from the inner cell mass grown *via in vitro* fertilization[49]. The controversial ethics behind obtaining ESC and their inherent high rate of proliferation and the risks of tumor formation or immunological rejection has limited them from widespread research[50]. However, in one study using an animal model, the use of ESCs did not increase chances of tumor formation in rats[51]; however, further clinical studies are required to test the efficacy of ESC treatment in diabetic feet. Stem cell therapy shows promise as a viable therapeutic option in the treatment of DFU. Stem cells can be used alongside conventional therapies like angioplasty to achieve more desirable outcomes.

### **Systemic and local antibiotics**

The use of systemic and local antibiotics serves as a noninvasive treatment in the management of DFU. Antibiotics can be administered topically through sponge applications or through gauze wrapping, as well as with use of a circulator boot. The presence of infection is defined by the presence of more than 2

Table 2 Stem cell therapies available for diabetic foot treatment

Stem cell type	Stem cell sub-types	Administration route
Adult stem cell	(1) Bone marrow-derived mesenchymal stem cells; (2) Adipose-derived stem cells; Human umbilical cord-derived; (3) Mesenchymal stem cells; and (4) Peripheral blood-derived mesenchymal stem cells	Local: Intramuscular and subcutaneous; Systemic: Intravenous and intraarterial
Embryonic stem cell	Cell mass of blastocyst by <i>in vitro</i> fertilization	Proposed local or systemic administration

classic findings of inflammation or purulence. There are 3 classifications of infection severity: (1) Mild (superficial and limited in size and depth); (2) moderate (deeper and larger in area); and (3) severe (overexpressed and beginning to affect metabolic perturbations). Most DFUs have a microbial cause, with aerobic Gram-positive cocci and staphylococci being the most common implicated microbes. Wounds that lack signs of infection typically do not require antibiotic therapy. If the wound is infected, a post-debridement specimen must be collected for both aerobic and anaerobic cultures. Following testing and potential imaging (including radiographs and MRI, if necessary), antibiotics may be prescribed[52]. If the infection is mild or moderate, narrow-spectrum oral antibiotics may be administered. If infection severity is moderate, high, or severe, broad-spectrum parenteral antibiotics should be utilized[53].

### **Negative pressure wound therapy**

One of the most recent developments in DFU treatment is the utilization of negative pressure wound therapy (NPWT). NPWT utilizes vacuum pressure to draw fluid from the wound and increase blood flow to the affected area, thus stimulating the healing process. While primarily used in burn patients, NPWT has also recently been used in DFU patients with promising results. NPWT results in 2 primary types of tissue deformation: Macro deformation, which is exemplified by wound contraction; and micro deformation, which occurs on the microscopic level. Both deformations stimulate blood flow and promote a wound healing cascade that includes tissue granulation, vessel proliferation, neoangiogenesis, epithelialization, and excess extracellular fluid removal. NPWT also results in increased anti-inflammatory conditions in the patient. Clinical studies in DFU patients have shown that NPWT is more efficient compared to standard therapy, particularly when observing wound healing and amputation rates, without a rise in adverse events[54].

## **INVASIVE TREATMENT STRATEGIES**

### **Debridement**

Debridement is a major component in the treatment of DFU, particularly due to its ability to alter the environment of the chronic wound through the removal of necrotic and nonviable tissue and foreign debris, which impede the healing process. Debridement may not always lead to complete healing of the DFU, but it serves as an important preliminary step in the treatment. Following debridement, the wound is further analyzed and if necessary, other treatment paths are pursued[55]. Debridement is commonly used in conjunction with other treatment modalities.

### **Revascularization (angioplasty)**

When patients with DFU also have a history of peripheral arterial disease (PAD), delayed healing, higher complication rates, and an increased chance of potential amputation may be observed. Thus, when patients have both DFU and chronic limb ischemia, revascularization can serve as a promising treatment option. According to various studies, the ulcer healing rate following revascularization ranges from 46% to 91%, representing a higher rate of healing compared to PAD patients that do not undergo revascularization[56]. Revascularization options include stenting and surgical bypass if other intervention is not possible. Atherectomy, shockwave treatment for calcified lesions, and balloon revascularization (cutting, drug coated, cryoplasty) can also be used alone or with stenting[57]. In a clinical trial in which 80 patients who underwent foot revascularization procedures, promising results were also shown. All patients in this study underwent an endovascular procedure (balloon angioplasty). The patients were followed for 12 mo after the procedure, and results showed that 56.2% of the patients fully recovered, 58.7% had minor amputations, and only 16.2% required major amputations. Overall, revascularization is an effective treatment for DFU, especially when the patient is at risk of amputation [58]. However, the effectiveness of the vascular procedure differs among patients, and it also does not reduce the risk of death associated with PAD. It is important to consider the role of complex therapy (including medical management) in conjunction with revascularization in the treatment of DFU. This includes close monitoring of glucose, lipids, and blood pressure, and the use of antiplatelet therapy

**Table 3 Overview of diabetic foot management strategies**

Treatment modality	Level of evidence	Strength of recommendation
Non-invasive modalities		
Wound dressing	High	Strong recommendation
Antibiotics	Low to moderate	Strong recommendation
Total-contact casting and pressure offloading techniques	High	Strong recommendation
Maggot therapy	Low	Weak recommendation
Hyperbaric oxygen	Low	Weak recommendation
Topical growth factors	Moderate	Could be beneficial
Cell therapy	Low (more studies required)	Weak recommendation
Invasive modalities		
Debridement	Moderate to high	Strong recommendation
Skin grafting	Moderate	Could be beneficial
Revascularization	Moderate	Strong recommendation

following the surgical procedure. Compared with initial supervised exercise training (SET) alone, endovascular therapy in combination with SET is associated with significant improvements in total walking distance, ABI, and risk of future revascularization or amputation. On the other hand, endovascular therapy alone was not associated with an improvement in functional capacity[59]. It is also important to note that post-endovascular procedure patients must be started on dual antiplatelet therapy, including aspirin plus clopidogrel or ticagrelor for several months. Statin therapy has also been proven to stabilize any plaques present before and after revascularization.

### **Skin grafting**

Skin grafting may serve as a solution when DFUs become more severe, offering a chance to replace the infected skin and promote the healing process. There are a variety of skin grafting techniques that may be used, including bioengineered or artificial skin, autografts (taken from the patient), allografts (taken from another person), or xenografts (taken from animals). A review article that analyzed 17 RCTs concluded that skin grafting and tissue replacement when used in conjunction with standard treatment led to an increase in the healing rate of DFU and slightly lowered the chance of amputation. However, evidence of long-term effectiveness is uncertain[60].

### **Amputation**

Amputation represents the final management option when treating DFU and is reserved for the most chronic levels of infection or deformity that render the foot nonfunctional. Amputation can be classified as either minor or major, with minor amputation being the removal of a smaller area (*e.g.*, removal of a toe or a part of the foot). Major amputation, however, can be performed above or below a major joint such as the knee or elbow. In a clinical trial, minor amputation was performed for 38.4% and major amputation was performed for 6.8% of patients with DFU[61].

## **CONCLUSION**

DFU results in substantial morbidity and mortality in patients with diabetes. It also often leads to longer hospitalizations and associated increases in health care spending. Thus, prompt diagnosis and catered management is essential to management of this prevalent consequence of diabetes. Standard local and invasive care along with novel approaches like stem cell therapy pave the way to reduce morbidity, decrease the need for amputation, and prevent mortality due to DFU (Table 3). Further research into newer modalities that aid in prompt and effective management will further help alleviate the healthcare burden of DFU.

## **FOOTNOTES**

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