

Management of Diabetic Foot Ulcers: A Review

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Early diagnosis and a multidisciplinary team approach to managing comorbidities are essential in treating foot ulcerations.

The prevalence of diabetes mellitus (DM) is growing at epidemic proportions in the U.S. and has been reported as the most common reason for hospital admissions in western countries.¹ There continues to be an alarmingly steady increase in the incidence of type 2 DM (T2DM), especially among the young and obese. Long-term diabetes-related complications also are likely to rise in prevalence. In particular, the diabetic foot is associated with morbidity and disability, leading to a significant impairment of quality of life.² People with DM develop foot ulcers because of neuropathy (sensory, motor, and autonomic deficits), ischemia, or both.³ The initiating injury may be from acute mechanical or thermal trauma or from repetitively or continuously applied mechanical stress.⁴

From foot ulcerations to neuropathy to peripheral vascular disease, the challenges are significant and can result in amputations and even premature death. To address these challenges, early diagnosis and a multidisciplinary team approach should be employed. Managing the

numerous comorbidities is essential for treatment.^{1,2,5}

Due to the longevity of patients with DM, diabetes-associated complications are expected to rise in prevalence.⁶ The American Diabetes Association recently reported that T2DM accounts for about 90% to 95% of all persons with DM.^{7,8} Today, many hospitalizations for patients with DM are for lower extremity conditions, such as ulceration, infection, or gangrene. Diabetic foot ulcerations (DFUs) are painful and costly for both the patient and the health care system. Every year, more than 1 million people with DM worldwide lose a leg as a consequence of this disease.⁹ Most DM-related amputations are preceded by a foot ulcer.

Diabetic foot ulcerations are the most common foot condition leading to lower extremity amputation (Figure 1).¹⁰ About 14 million individuals in the U.S. with diagnosed and undiagnosed DM will experience pathologic changes of their lower extremities that, when combined with minor trauma and infection, may lead to serious foot problems.¹¹ Although the triad of vasculopathy, neuropathy, and susceptibility to infection are the primary permissive factors in its pathogenesis, DFU can also be attributed to other important risk factors. The presence of peripheral neuropathy and periph-

eral arterial disease (PAD) are considered to be the most significant risk factors for all types of diabetic foot complications.¹²

Optimal care of foot ulceration depends on the treating physician's understanding of the pathophysiology involved, familiarity with accepted principles of treatment, and the knowledge that a coordinated, multidisciplinary team approach will best accomplish the goal of limb salvage. All efforts should be made to prevent foot lesions, and when present, existing ulcers should be treated promptly and aggressively, which can often prevent an exacerbation of the problem and decrease the incidence of amputations. Even when ulcers have healed, patients with DM and a history of a lower extremity ulcer should consider it a lifelong condition that requires monitoring to prevent recurrence.^{13,14}

This review provides a brief overview of DFU, including etiology, evaluation, treatment, and prevention, to provide clinicians with the clinical markers, evidence, and DFU treatment recommendations.

ETIOLOGIES

Multiple risk factors contribute to the development and pathogenesis of DFUs.^{5,6,15,16} Neuropathy and PAD are major factors in the pathogenesis of diabetic foot ulcers.¹⁷ However, there

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are several additional factors leading to the occurrence of foot complications. Reiber and colleagues have determined that 63% of their patients' ulcers were attributed to the critical triad of peripheral sensory neuropathy, trauma, and deformity.¹⁵

Other factors also implicated in the causal pathway to ulceration were ischemia, callus, and edema. Infection was rarely implicated in the etiology of these lesions, although once an ulcer has developed, infection and PAD were found to be the major causes for amputation.^{10,18,19} Many of the risk factors for foot ulcer are also predisposing factors for amputation, because ulcers are primary antecedent events leading to amputation.²⁰⁻²³

Other contributing causes for ulceration that have been identified are gender (male), duration of DM longer than 10 years, advanced age, high body mass index, prior ulceration, and other comorbidities, such as retinopathy, glycated hemoglobin level, limited joint mobility, foot deformity (Charcot foot, prior partial foot amputation, etc), high plantar pressures, and inappropriate foot self-care habits (Table 1).^{3-6,22,24,25}

EVALUATION

The clinical evaluation must include a thorough and systematic lower extremity examination when starting DFU treatment. It is important to have a thorough assessment of the ulcer's size and depth, and the evaluation should include a description of its appearance and measurement of its diameter at each visit. Evaluation for the presence of local and systemic infection and potential for osteomyelitis, using a small sterile blunt probe, is critical in determining depth of penetration and tracking along tendon sheaths (Figure 2). Directly probing to bone (positive probe to bone test) has a high

Figure 1. Neuropathic Foot Ulcer



predictive value for underlying osteomyelitis even without acute signs of infection.²⁶ In addition, inspecting the wound for gangrene, necrosis, cellulitis, or infection and inspection of shoes for proper fit, foreign objects, and wear patterns can provide insight into other complications and underlying issues.

Peripheral arterial disease is directly linked to lower extremity disorders, such as intermittent claudication, pain on exertion, pain at rest, and, in severe cases, critical limb ischemia and gangrene.¹ Bilateral lower extremity pulses should routinely be palpated. When dorsalis pedis or posterior tibial artery pulses are absent or diminished, Doppler segmental pressures to the toes, pulse volume recording, skin perfusion pressure, or transcutaneous oxygen evaluation is indicated, and vascular consultation should be sought.³

Figure 2. Probe to Bone Test in an Infected Ulcer



Ischemia is caused by peripheral arterial occlusive disease of larger vessels, not by microangiopathy.¹³ Poor arterial inflow is associated not only with impaired ulcer healing, but also subsequent infection, gangrene, and amputation.¹³

Diabetic peripheral neuropathy is characterized by loss of protective sensation, allowing ulceration in areas of high pressure. Peripheral sensory neuropathy as measured by vibration perception thresholds can impart a 3.4-fold to 32-fold risk of ulceration.^{19,21} Patients insensitive to a 10-g monofilament, commonly used to assess peripheral neuropathy, has been shown in several studies to convey a 2.2-fold to 18-fold risk of ulceration.^{6,19,27,28} In the large, population-based North-West Diabetes Foot Care Study, loss of protective sensation to the 10-g monofilament increased the risk of ulceration

Table 1. Risk Factors for Ulceration

- Peripheral neuropathy (sensory, motor, autonomic)
- Foot deformity (hammer toe, bunion, Charcot, etc)
- Trauma
- Improperly fitted shoes
- Peripheral arterial disease
- Callus
- History of prior ulcers/amputations
- High plantar foot pressures
- Limited joint mobility (cheiroarthropathy)
- Uncontrolled hyperglycemia
- Chronic renal insufficiency
- Diabetes duration
- Blindness/partial sight
- Older age
- Poor knowledge of diabetes

80%, whereas abnormal ankle reflexes increased this risk 55%.²⁹

Peripheral neuropathy has been demonstrated as a strong risk factor for foot ulceration in many cross-sectional studies and is present in > 80% of affected patients.²⁹ Recent studies suggested that impaired sensation makes the foot increasingly vulnerable to damage caused by mechanical, thermal, or pressure-related injury.³⁰ Autonomic neuropathy by virtue of subsequent anhidrosis causes dryness of the skin and, therefore, vulnerability to fissuring.¹³

Unhealed cracks in the skin can easily lead to infection, especially in the presence of PAD. Neuropathy has an insidious and nonhomogeneous manifestation, making it difficult to identify its onset and a challenge for patients and clinicians.^{31,32}

Sacco and colleagues reviewed current literature and the International Consensus on the Diabetic Foot recommendation and concluded that most attention is given to patients with imminent foot ulceration rather than attempting to

develop and improve assessment techniques that detect early impairments.^{31,33} They propose that effort should be made that detect patients at risk of developing diabetic polyneuropathy. Although the 10-g monofilament pressure perception threshold is a common screening technique for early detection, tests of the vibration perception threshold may be more sensitive.

The authors propose that different monofilament sizes could probably better help determine the disease status, as the vibration tests do. In addition to the considerable subjectivity of both methods of assessing sensitivity, they are unquestionably clinical resources that can contribute to early detection of DPN. Future studies should focus on developing assessment strategies and tools that better detect early neuropathic changes. Early diagnosis of impending problems will aid in preventing further limb-threatening complications.

TREATMENT

The management of diabetic foot disease is focused primarily on avoiding lower extremity amputation and should be carried out through 3 main strategies: identification of the at risk foot, treatment of the acutely diseased foot, and prevention of further complications.³⁴ The primary goal in the treatment of DFUs is to obtain wound closure. Prompt, aggressive treatment of DFUs can often prevent an exacerbation of the problem and the potential need for amputation. The aim of therapy, therefore, should be early intervention to allow prompt healing of the lesion and, once healed, prevent its recurrence.^{3,20,25,35}

Management of the foot ulcer is largely determined by its severity (grade), vascularity, and presence of infection.^{3,14,36} A multidisciplinary

team approach should be used due to the multifaceted nature of foot ulcers, as well as for managing the numerous comorbidities attendant with these patients. The choice of treatment methods is determined by patient and ulcer characteristics. Equally important is the ability of patients to comply with the treatment as well as with the location and severity of the ulcer.⁴

Rest, elevation, and removal of pressure (off-loading) are essential components of treatment and should be initiated at first presentation. Recent studies provided evidence that indicated proper off-loading promotes more rapid DFU healing.^{37,38} Ill-fitting footwear should be discarded and replaced with an appropriate off-loading device for mitigating pressure at the site of the ulceration. Although many off-loading modalities are currently in use, only a few studies describe the frequency and rate of wound healing associated with their use.

The total contact cast (TCC) is considered the superior standard therapy in management for neuropathic ulcers due to its proven ability to redistribute pressure, thereby promoting expeditious wound closure. Another inherent benefit is to ensure patient adherence with off-loading as well as reducing activity levels.^{24,39} Previous randomized controlled trials have demonstrated that patients treated with TCC healed a higher percentage of plantar ulcers at a faster rate than did patients in the control groups. One unique study demonstrated histologic evidence of more rapid angiogenesis with formation of granulation tissue in the casted group compared with the standard treatment group.^{40,41}

Potential disadvantages of the TCC include the need for expertise in its proper application, the need

Table 2. Classification of Advanced Wound Dressings Used for Diabetic Foot Ulcers Healing²⁴

Type	Example	Explanation	Advantages	Disadvantages
Hydrocolloids	Duoderm Granuflex Comfeel	Dressings usually composed of a hydrocolloid matrix bonded onto a vapor permeable film or foam backing. When in contact with the wound surface, this matrix forms a gel to provide a moist environment.	Absorbent; can be left for several days; aids autolysis	Concerns about use for infected wounds; may cause maceration; unpleasant odor
Hydrogels	Aquaform Intrasite Gel Aquaflor	These dressings consist of cross-linked insoluble polymers (ie, starch or carboxymethylcellulose) and up to 96% water. They are designed to absorb wound exudate or rehydrate a wound, depending on the wound moisture levels. They are supplied in flat sheets, an amorphous hydrogel, or as beads.	Absorbent; donate liquid; aid autolysis	Concerns about use for infected wounds; may cause maceration; using for highly exudative wounds
Foams	Allevyn Cavicare Biatain Tegaderm	These dressings normally contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface.	Highly absorbent and protective; manipulate easily; can be left up to 7 days; thermal insulation	Occasional dermatitis with adhesive; bulky; may cause maceration
Films	Tegaderm Opsite	Film dressings often form part of the construction of other dressings, such as hydrocolloids, foams, hydrogel sheets, and composite dressings, which are made of several materials with film being used as outer layer.	Cheap; easily manipulated; permeable to water vapor and oxygen but not to water microorganisms	May need wetting before removal; not suitable for infected wounds; nonabsorbent; if fluid collects under film it must be drained or the film replaced
Alginates	Calcium alginate dressing Kaltostat Sorbalgon Medihoney	The alginate forms a gel when in contact with the wound surface, which can be lifted off with dressing removal or rinsed away with sterile saline; bonding to a secondary viscose pad increases absorbency	Highly absorbent; bacteriostatic; hemostatic; useful in cavities	May need wetting before removal
Silver-impregnated	Acticoat Urgosorb Silver	These dressing are used to treat infected wounds, as silver ions are thought to have antimicrobial properties.	Antiseptic; absorbent; reduce odor; improved pain-related symptoms; decrease wound exudates; prolonged dressing wear time	High cost

Source: Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. *World J Diabetes*. 2015;6(1):37-53. Reprinted with permission.

for weekly cast changes, and related costs.^{24,35} Although a number of new devices have been introduced as alternatives to the TCC, only several clinical studies demonstrating their efficacy have been published.^{5,14,25,36} If nonweight bearing with crutches, wheelchair, or more effective devices are not feasible, even a pressure-attenuating insert can be used in a

simple postoperative shoe until specialty referral is made.

Debridement of necrotic, callus, fibrous, and senescent tissues is a mainstay of ulcer therapy.^{42,43} It is considered the first and the most important therapeutic step leading to wound closure in patients with DFU.⁴²⁻⁴⁴ Unhealthy tissue must be sharply debrided back to bleeding tis-

sue to fully visualize the extent of the ulcer as well as to detect any underlying abscesses or sinuses. It has been reported that regular (weekly) sharp debridement is associated with more rapid healing of ulcers compared with less frequent debridement.⁴⁵⁻⁴⁷ Wilcox and colleagues indicated that frequent debridement healed more wounds in a shorter time

Table 3. Wound Care Technologies

Negative pressure wound therapy
Standard electrically powered
Mechanically powered
Hyperbaric oxygen therapy
Topical oxygen therapy
Biophysical
Electrical stimulation, diathermy, pulsed electromagnetic fields
Pulsed radio-frequency energy
Low-frequency noncontact ultrasound
Extracorporeal shock-wave therapy
Growth factors
Becaplermin: platelet-derived growth factor
Fibroblast growth factor
Epidermal growth factor
Platelet rich plasma
Acellular matrix tissues
Xenograft dermis
bovine neonatal dermis
bovine collagen
bovine dermis
Xenograft acellular matrices
small intestine submucosa
porcine urinary bladder matrix
ovine forestomach
equine pericardium
Human dermis
Graftjacket
dCELL
DermACELL
TheraSkin
Human pericardium
Placental tissues
Amniotic tissues/amniotic fluid
Umbilical cord
Dehydrated human amnion chorion
Bioengineered allogeneic cellular therapies
Bilayered skin equivalent
Dermal replacement therapy
Stem cell therapies
Autogenous: bone marrow-derived stem cells
Allogeneic: amniotic matrix with mesenchymal stem cells
Miscellaneous
Hyalomatrix

($P < .001$).⁴⁶ The more frequent the debridement, the better the healing outcome. There are different types of debridement methods, including surgical, enzymatic, autolytic, mechanical, and biologic.⁴⁸ Surgical or sharp debridement can convert a chronic ulcer into an acute wound that is more likely to heal.²⁴ Adequate debridement must always precede the application of topical wound healing agents, dressings, or wound closure procedures.²⁴ Conversely, a wound that does not receive the necessary debridement is one that has not been adequately treated.

There are numerous types of dressings that have been developed over the past decade that promote wound healing. Few have undergone any formal clinical studies to determine efficacy or effectiveness to help guide clinicians in their use.

Yazdanpanah and colleagues argued that dressings should confer moisture balance, protease sequestration, growth factor stimulation, antimicrobial activity, oxygen permeability, and the capacity to promote autolytic debridement to facilitate the production of granulation tissues and the re-epithelialization process.²⁴ In addition, it should have a prolonged time of action, high efficiency, and protection against contamination or infection.¹⁷ The group noted that no single dressing fulfills all the requirements of a diabetic patient with a foot ulcer. The choice of dressing is largely determined by the causes of DFU, wound location, depth, amount of scar or slough, exudates, condition of wound margins, presence of infection and pain, need for adhesiveness, and conformability of the dressing (Table 2).

ADVANCED THERAPIES

In 2003, Sheehan and colleagues reported that a 50% change in foot

ulcer area after 4 weeks of observation is a robust predictor of healing at 12 weeks.⁴⁹ In addition, wounds failing to achieve a 50% reduction in area after 4 weeks need to be reassessed and considered for advanced treatment modalities if there are no otherwise identified impediments to wound healing.^{6,9,38} These findings have served as a pivotal clinical decision point in the care of DFUs over the past several years for early identification of patients who may not respond to the standard of care. Today, most wound care protocols advocate use of standard therapies for at least 4 weeks before advanced therapies are considered.

Significant improvements have been achieved in the treatment of ulcerations, and today clinicians have several advanced therapeutic options for management of chronic DFUs. These new technologies have been shown to increase the probability of complete wound closure in difficult-to-heal foot ulcerations in patients with diabetes. Among these are recombinant platelet-derived growth factors, a human living skin equivalent, and a human fibroblast-derived dermal substitute.⁴⁹⁻⁵¹ Tissue-engineered skin equivalent (Apligraf) and human dermis (Dermagraft) are types of biologically active dressings that are derived from fibroblasts of neonatal foreskins.

The most recent advancements for wound care therapies is that of stem cell therapies, primarily bone marrow-derived and, most recently, placental-derived stem cells, including dehydrated human amnion chorion (Epifix) and amniotic matrix with mesenchymal stem cells (Grafix).^{52,53} Because of the expense of these products, they cannot be used universally in the treatment of DFUs but rather are used and re-

served for difficult-to-heal wounds. In addition, negative pressure therapy has assumed a major role in the management of traumatic, acute, and chronic wounds and has shown efficacy in healing DFUs.⁵⁴⁻⁵⁷ Hyperbaric oxygen therapy and several biophysical modalities have been studied and found to be efficacious in healing a wide variety of chronic wounds over the past decade as well, although results vary by study, and no advanced modality has become universal in its application.⁵⁸⁻⁶⁴

Table 3 lists most of the wound care technologies commonly used in current clinical practice. Although randomized controlled trials have been published supporting the use of most of these modalities, a lack of strong data proving efficacy for use of such treatment options remains.

Treatment of any underlying ischemia is critical in achieving a successful outcome. Vascular surgical consultation should be obtained on presentation of an ischemic wound and in cases where ulcers show no sign of progress despite appropriate management.^{4,13} Revascularization is commonly performed in patients with critical limb ischemia and DFUs but is also performed in patients with less severe arteriopathy. The goal is to restore a palpable pulse on the affected foot.⁶⁵ The postrevascularization ulcer-healing rate ranges from 46% to 91% at 1 year and seems to be improved in those patients with distal arterial reconstruction and restoration of pulsatile flow.⁶⁶

Endovascular approaches are becoming increasingly common in patients whose arterial disease is more limited or morbidity is a significant concern.^{67,68} Studies report that the exact role of isolated endovascular procedures is still to be determined, although such interventions are frequently performed in concert with

angiography preceding vascular reconstructive procedures.^{69,70} However, in many such studies, healing was often a secondary criterion, and there was no description of the initial wound or its management.⁷¹

CHALLENGES

Within the VA setting there is a wide range of patient comorbidities that frequently present clinicians with unique challenges. Often these patients are older with many social and mental health conditions, including self-abuse, drug-abuse, nonadherence, psychological issues and lack of financial and/or educational resources or support. Many of these patients have comorbidities associated with diabetes that can delay healing of their ulcerations.

Systemwide VA mandates have implemented multidisciplinary foot care teams. The teams identify veterans at risk for lower limb complications; provide preventive care; track high-risk foot care across the continuum of outpatient, inpatient, and rehabilitative care; and provide education, orthoses, and social support.^{72,73} In the late 1990s, the VHA implemented a national program of foot risk screening and referral, conducted largely in primary care.²⁹ By 1998 as determined from medical record reviews, 95% of veterans had a visual examination, 84% had palpation of pulses, and 78% had undergone a sensory examination. In addition, about 83% of patients had a monofilament examination, and 85% of individuals with risk factors were referred to foot specialists in 2004.^{72,74} Veterans at higher risk for lower extremity complications routinely receive subsequent preventive foot care, such as education or prescription of therapeutic shoes in the VHA.

Tseng and colleagues evaluated

risk-adjusted trends in amputations among veterans with diabetes during a 5-year period and reported a decrease in amputation rates observed for all types of lower extremity amputations (LEA) and among all racial groups.⁷⁴ Implementation of such universal programs for foot screening, tracked through performance measures, may have contributed to a decrease in LEAs and improved outcomes in the VA patient population.

PREVENTION

A healthy, intact diabetic foot is best maintained by a consistent and recurrent preventive treatment strategy. Prevention of ulcer recurrence remains to be a major clinical challenge. Andrews and colleagues demonstrated that recurrence rates range from 28% at 12 months to 100% at 40 months.⁷⁵ They report that the highest incidence of reulceration is in the site of a previous ulceration, noting that a newly healed ulcer is covered with fragile skin and after complete healing, there is an area of higher density tissue (scar). Shearing between the different tissue densities often contributes to new ulcers.

After the ulcer heals, the patient and their caregivers must incorporate preventative measures in care plans to reduce the risk of wound reoccurrence. A study reported by Barshes and colleagues demonstrated that a majority of people with diabetes do not receive guideline-recommended foot care, including regular foot examinations.⁷⁶ Identifying the patients with diabetes at risk for ulceration requires foot examination, including the vascular and neurologic systems, skin conditions, and foot structure.⁷⁷ Among the complications of diabetes, lower limb amputation is considered to be preventable.^{78,79} Because there is a great beneficial

effect of patient education on reducing LEAs, a flexible schedule for diabetes education, that offers education at any time for the maximum convenience of patients rather than focusing on health care provider's convenience is critical.^{79,80} Conservative management of foot problems also has reduced the risk of amputation by simple procedures, such as appropriate foot wear, cleanliness, aggressive surgical debridement, and evidence-based ulcer management.³⁴ This is best accomplished through a multidisciplinary approach involving a team of specialists and personnel who provide a coordinated process of care, including a patient motivated to ensure its success.⁶

CONCLUSIONS

The authors have described the components of assessment and treatment that can help ensure successful healing of foot ulcers in diabetic patients. These approaches should be used whenever feasible to reduce the high morbidity and risk of serious complications resulting from foot ulcers. Advances in treating chronic diabetic wounds are promising; however, the intrinsic pathophysiologic abnormalities that lead to ulcers in the first place cannot be ignored. No known therapy will be effective without concomitant management of ischemia, infection, and adequate off-loading.^{6,75}

Not all diabetic foot complications can be prevented, but it is possible to dramatically reduce their incidence through appropriate management and prevention programs. The multidisciplinary team approach that combines the expertise of many types of health care providers for diabetic foot disorders has been demonstrated as the optimal method to achieve favorable rates of limb salvage in the high-risk diabetic patient. ●

Author disclosures

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