A Review of the Pathophysiology, Classification, and Treatment of Foot Ulcers in Diabetic Patients

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The number of people with diabetes worldwide was estimated at 131 million in 2000; it is projected to increase to 366 million by 2030.[1] Previous studies have indicated that diabetic patients have up to a 25% lifetime risk of developing a foot ulcer.[2] The annual incidence of diabetic foot ulcers is ~ 3%, and the reported incidence in U.S. and U.K. studies ranges as high as 10%.[3]

Once an ulcer has developed, there is an increased risk of wound progression that may ultimately lead to amputation; diabetic ulceration has been shown to precede amputation in up to 85% of cases.[3] At least 40% of amputations in diabetic patients can be prevented with a team approach to wound care.[4] The purpose of this review is to describe the causes of lower-extremity ulceration in diabetic patients and to identify common methods of classification and treatment to aid primary care providers in determining appropriate treatment approaches for their patients.

Pathogenesis of Ulceration

Diabetic foot ulcers result from the simultaneous action of multiple contributing causes.[5,6] The major underlying causes are noted to be peripheral neuropathy and ischemia from peripheral vascular disease.[7]

Neuropathy

More than 60% of diabetic foot ulcers are the result of underlying neuropathy.[7,8] The development of neuropathy in affected patients has been shown in animal and in vitro models to be a result of hyperglycemia-induced metabolic abnormalities.[9–11] One of the more commonly described mechanisms of action is the polyol pathway.[10] In the development of neuropathy, the hyperglycemic state leads to an increase in action of the enzymes aldose reductase and sorbitol dehydrogenase. This results in the conversion of intracellular glucose to sorbitol and fructose.

The accumulation of these sugar products results in a decrease in the synthesis of nerve cell myoinositol, required for normal neuron conduction. Additionally, the chemical conversion of glucose results in a depletion of nicotinamide adenine dinucleotide phosphate stores, which are necessary for the detoxification of reactive oxygen species and for the synthesis of the vasodilator nitric oxide. There is a resultant increase in oxidative stress on the nerve cell and an increase in vasoconstriction leading to ischemia, which will promote nerve cell injury and death. Hyperglycemia and oxidative stress also contribute to the abnormal glycation of nerve cell proteins and the inappropriate activation of protein kinase C, resulting in further nerve dysfunction and ischemia.

Neuropathy in diabetic patients is manifested in the motor, autonomic, and sensory components of the nervous system.[7] Damage to the innervations of the intrinsic foot muscles leads to an imbalance between flexion and extension of the affected foot. This produces anatomic foot deformities that create abnormal bony prominences and pressure points, which gradually cause skin breakdown and ulceration.

Autonomic neuropathy leads to a diminution in sweat and oil gland functionality. As a result, the foot loses its natural ability to moisturize the overlying skin and becomes dry and increasingly susceptible to tears and the subsequent development of infection.

The loss of sensation as a part of peripheral neuropathy exacerbates the development of ulcerations. As trauma occurs at the affected site, patients are often unable to detect the insult to their lower extremities. As a result, many wounds go unnoticed and progressively worsen as the affected area is continuously subjected to repetitive pressure and shear forces from ambulation and weight bearing.

IN BRIEF

The development of lower extremity ulcers is a well known potential complication for patients with diabetes. This article reviews the common causes of diabetic foot ulceration and discusses methods for assessment and treatment to aid providers in developing appropriate strategies for foot care in individuals with diabetes

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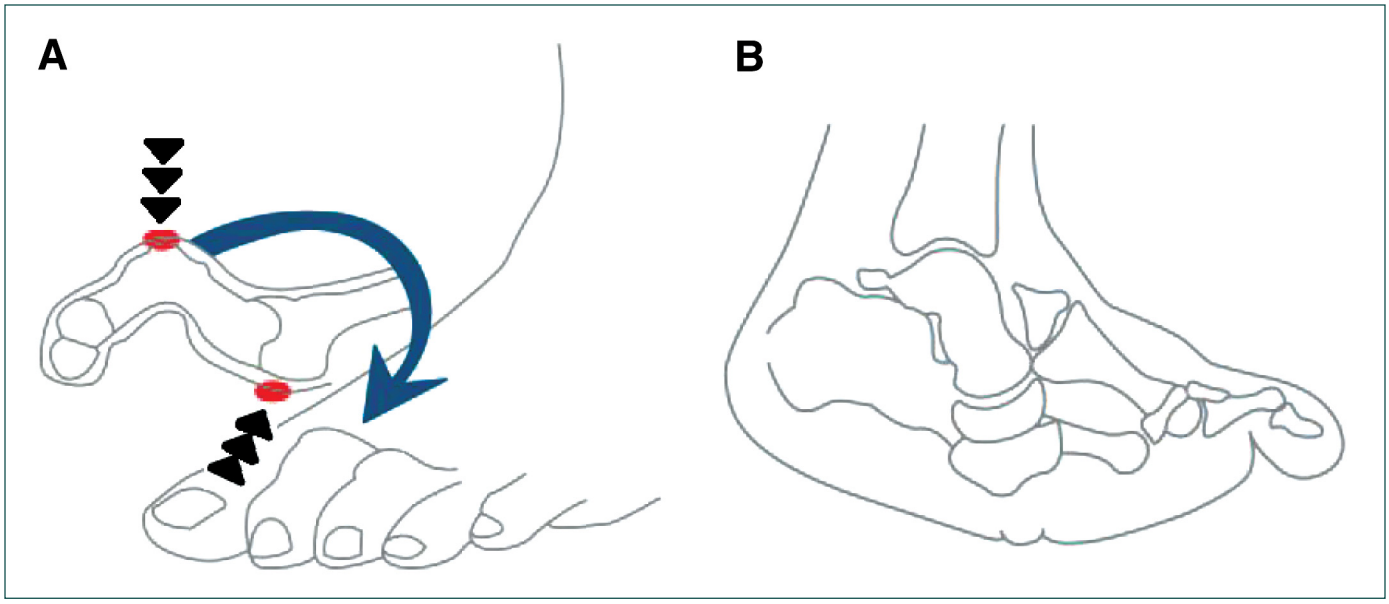

Figure 1. Common foot deformities resulting from diabetes complications: A) claw toe deformity (increased pressure is placed on the dorsal and plantar aspects of the deformity as indicated by the triple arrows); and B) Charcot arthropathy (the rocker-bottom deformity leads to increased pressure on the plantar midfoot). Adapted from Ref. 13.

Vascular Disease

Peripheral arterial disease (PAD) is a contributing factor to the development of foot ulcers in up to 50% of cases.[12,13] It commonly affects the tibial and peroneal arteries of the calf. Endothelial cell dysfunction and smooth cell abnormalities develop in peripheral arteries as a consequence of the persistent hyperglycemic state.[9] There is a resultant decrease in endothelium-derived vasodilators leading to constriction. Further, the hyperglycemia in diabetes is associated with an increase in thromboxane A2, a vasoconstrictor and platelet aggregation agonist, which leads to an increased risk for plasma hypercoagulability.[14] There is also the potential for alterations in the vascular extracellular matrix leading to stenosis of the arterial lumen.[14] Moreover, smoking, hypertension, and hyperlipidemia are other factors that are common in diabetic patients and contribute to the development of PAD.[5] Cumulatively, this leads to occlusive arterial disease that results in ischemia in the lower extremity and an increased risk of ulceration in diabetic patients.

Assessment of Diabetic Foot Ulcers

A task force of the Foot Care Interest Group of the American Diabetes Association (ADA) released a 2008 report that specifies recommended components of foot examinations for patients with diabetes.[13] Providers should take a history that takes into consideration previous ulceration or amputation. The history should also include any neuropathic symptoms or symptoms that are suggestive of peripheral vascular disease. Further, providers should inquire about other complications of diabetes, including vision impairment suggestive of retinopathy and nephropathy, especially dialysis or renal transplantation. Finally, patients should be questioned regarding smoking because smoking is linked to the development of neuropathic and vascular disease. A complete history will aid in assessing the risk for foot ulceration.[13]

In examining the foot, visual inspection of the bare foot should be performed in a well-lit room. The examination should include an assessment of the shoes; inappropriate footwear can be a contributing factor to the development of foot ulceration. In the visual inspection of the foot, the evaluator should check between the toes for the presence of ulceration or signs of infection. The presence of callus or nail abnormalities should be noted. Additionally, a temperature difference between feet is suggestive of vascular disease.

The foot should also be examined for deformities. The imbalance in the innervations of the foot muscles from neuropathic damage can lead to the development of common deformities seen in affected patients. Hyperextension of the metatarsal-phalangeal joint with interphalangeal or distal phalangeal joint flexion leads to hammer toe and claw toe deformities, respectively. The Charcot arthropathy is another commonly mentioned deformity found in some affected diabetic patients. It is the result of a combination of motor, autonomic, and sensory neuropathies in which there is muscle and joint laxity that lead to changes in the arches of the foot. Further, the autonomic denervation

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leads to bone demineralization via the impairment of vascular smooth muscle, which leads to an increase in blood flow to the bone with a consequential osteolysis. An illustration of some commonly described abnormalities is shown in Figure 1.

In examining for vascular abnormalities of the foot, the dorsalis pedis and posterior tibial pulses should be palpated and characterized as present or absent.[15] Claudication, loss of hair, and the presence of pale, thin, shiny, or cool skin are physical findings suggestive of potential ischemia. If vascular disease is a concern, measuring the ankle brachial index (ABI) can be used in the outpatient setting for determining the extent of vascular disease and need for referral to a vascular specialist. The ABI is obtained by measuring the systolic blood pressures in the ankles (dorsalis pedis and posterior tibial arteries) and arms (brachial artery) using a handheld Doppler and then calculating a ratio. Ratios below 0.91 are suggestive of obstruction. However, in patients with calcified, poorly compressible vessels or aortoiliac stenosis, the results of the ABI can be complicated.[16] If there is a strong suspicion of vascular disease, the patient should undergo vascular imaging as an alternate method of testing to determine the extent of disease and possible ischemia.[5]

The loss of pressure sensation in the foot has been identified as a significant predictive factor for the likelihood of ulceration. A screening tool in the examination of the diabetic foot is the 10-gauge monofilament. The monofilament is tested on various sites along the plantar aspect of the toes, the ball of the foot, and between the great and second toe. The test is considered reflective of an ulcer risk if the patient is unable to sense the monofilament when it is pressed against the foot with enough pressure to bend it.[17] Areas of callus should not be tested.[13]

Table 1. Wagner Ulcer Classification System

Grade	Lesion
1	Superficial diabetic ulcer
2	Ulcer extension involving ligament, tendon, joint capsule, or fascia with no abscess or osteomyelitis
3	Deep ulcer with abscess or osteomyelitis
4	Gangrene to portion of forefoot
5	Extensive gangrene of foot

Table 2. University of Texas Wound Classification System

Stages	Description
Stage A	No infection or ischemia
Stage B	Infection present
Stage C	Ischemia present
Stage D	Infection and ischemia present
Grading	**Description**
Grade 0	Epithelialized wound
Grade 1	Superficial wound
Grade 2	Wound penetrates to tendon or capsule
Grade 3	Wound penetrates to bone or joint

Classification of Diabetic Foot Ulcers

The results of the foot evaluation should aid in developing an appropriate management plan.[18] If an ulcer is discovered, the description should include characteristics of the ulcer, including size, depth, appearance, and location.[19] There are many classification systems used to depict ulcers that can aid in developing a standardized method of description. These classification systems are based on a variety of physical findings.

One of the most popular systems of classification is the Wagner Ulcer Classification System, which is based on wound depth and the extent of tissue necrosis (Table 1).[20] Several authors have noted a disadvantage of this system in that it only accounts for wound depth and appearance and does not consider the presence of ischemia or infection.[13,21]

The University of Texas system is another classification system that addresses ulcer depth and includes the presence of infection and ischemia (Table 2).[22] Wounds of increasing grade and stage are less likely to heal without vascular repair or amputation.[21]

Treatment Modalities

The management of diabetic foot ulcers includes several facets of care. Offloading and debridement are considered vital to the healing process for diabetic foot wounds.[23] The goal of offloading is to redistribute force from ulcers sites and pressure points at risk to a wider area of contact. There are multiple methods of pressure relief, including total contact casting, half shoes, removable cast walkers,

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wheelchairs, and crutches. There are advantages and disadvantages to each modality, and factors such as overall wound condition, required frequency for assessment, presence of infection, and the likelihood for patient compliance should be considered in determining which modality would be most beneficial to the patient.[24]

The open diabetic foot ulcer may require debridement if necrotic or unhealthy tissue is present. The debridement of the wound will include the removal of surrounding callus and will aid in decreasing pressure points at callused sites on the foot. Additionally, the removal of unhealthy tissue can aid in removing colonizing bacteria in the wound. It will also facilitate the collection of appropriate specimens for culture and permit examination for the involvement of deep tissues in the ulceration.[25]

The selection of wound dressings is also an important component of diabetic wound care management. There are a number of available dressing types to consider in the course of wound care. Although there is a dearth of published trials to support the use of one type of dressing compared to another,[26] the characteristics of specific dressing types can prove beneficial depending on the characteristics of the individual wound. Saline-soaked gauze dressings, for example, are inexpensive, well tolerated, and contribute to an atraumatic, moist wound environment. Foam and alginate dressings are highly absorbent and can aid in decreasing the risk for maceration in wounds with heavy exudates. A complete discussion of the various classes of wound dressings is beyond the scope of this review; however, an ideal dressing should contribute to a moist wound environment, absorb excessive exudates, and not increase the risk for infections.[27] Dressing changes and wound inspection should occur on a daily basis.[26]

If infection is suspected in the wound, the selection of appropriate treatments should be based on the results of a wound culture. Tissue curettage from the base of the ulcer after debridement will reveal more accurate results than a superficial wound swab.[28] In the case of deep tissue infections, specimens obtained aseptically during surgery provide optimal results.[28]

Gram-positive cocci are typically the most common pathogens isolated. However, chronic or previously treated wounds often show polymicrobial growth, including gram-negative rods or anaerobes. Pseudomonas, for example, is often cultured from wounds that have been soaked or treated with wet dressings. Anaerobic bacteria are often cultured from ulcers with ischemic necrosis or deep tissue involvement. Antibiotic-resistant organisms such as methicillin-resistant staphylococcus aureus are frequently found in patients previously treated with antibiotic therapy or patients with a recent history of hospitalization or residence in a long-term care facility.

The selection of appropriate antimicrobial therapy, including the agent, route of administration, and need for inpatient or outpatient treatment will be determined in part by the severity of the infection. Clinical signs of purulent drainage, inflammatory signs of increased warmth, erythema, pain and induration, or systemic signs such as fever or leukocytosis should be considered. Patients with systemic signs of severe infection should be admitted for supportive care and intravenous antibiotic therapy; additionally, a surgical evaluation is warranted to evaluate for a deep occult infection.[29] Inpatient care is also suggested for patients who are not able to provide proper self-care or comply with antibiotic therapy or who need close monitoring for treatment response.[28]

In the absence of serious signs, patients can be treated with outpatient therapy and frequent follow-up.[30] Although a detailed discussion of the range of antibiotic therapy is beyond the scope of this review, common classes of agents used include cephalosporins, fluoroquinolones, and penicillin/B-lactamase inhibitors. Information about specific agents that have shown clinical effectiveness and suggested treatment schemes based on infection severity has been published elsewhere.[25,28]

The possibility of underlying osteomyelitis should be considered with the presence of exposed bone or bone that can be palpated with a blunt probe. If osteomyelitis is diagnosed, the patient may undergo surgical excision of the affected bone or an extensive course of antibiotic therapy.[5]

Consideration is also given to the presence of underlying ischemia because an adequate arterial blood supply is necessary to facilitate wound healing and to resolve underlying infections. Patients with evidence of decreased distal blood flow or ulceration that does not progress toward healing with appropriate therapy should be referred to a vascular specialist. Upon determination of the patient's anatomy and a vascular route amenable to restoration, the patient may undergo arterial revascularization.

Surgical bypass is a common method of treatment for ischemic limbs, and favorable long-term results have been reported.[31] Up to a 90% 10-year limb-salvage rate has been demonstrated with surgical bypass procedures of the lower extremity.[32] In cases in which there are multiple levels of occlusion, revascularization at each point is necessary to restore arterial blood

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flow and increase the chance for limb salvage.[31] Transluminal angioplasty of the iliac arteries in conjunction with surgical bypass in the distal extremity may be implemented, and efficacy has been demonstrated in diabetic patients.[33]

A number of adjunctive wound care treatments are under investigation and in practice for treating diabetic foot ulcers. The use of human skin equivalents has been shown to promote wound healing in diabetic ulcers via the action of cytokines and dermal matrix components that stimulate tissue growth and wound closure.[34,35] A recombinant platelet-derived growth factor is also currently in use and has been shown to stimulate wound healing.[36] However, the present data for most of these modalities are not considered sufficient for routine implementation in the treatment of diabetic wounds.[25]

Two of the more popular adjunctive therapies in use are hyperbaric oxygen therapy (HBOT) and the use of granulocyte colony stimulating factors (G-CSF). HBOT is the delivery of oxygen to patients at higher than normal atmospheric pressures. This results in an increase in the concentration of oxygen in the blood and an increase in the diffusion capacity to the tissues. The partial pressure of oxygen in the tissues is increased, which stimulates neovascularization and fibroblast replication and increases phagocytosis and leukocyte-mediated killing of bacterial pathogens in the wound.

Presently, there are conflicting data regarding the efficacy of this therapy. Although small randomized studies have demonstrated an improvement in the rate of wound healing and a decrease in the number of amputations,[37,38] other studies contest these data. The quality of the studies to date has been poor, and their findings have not been confirmed in a large, blinded, and adequately powered randomized trial.[39]

However, the Center for Medicare & Medicaid Services has approved reimbursement of HBOT for 14 conditions, including diabetic ulcers. Diabetic wounds that meet the appropriate criteria are classified as Wagner Grade 3 wounds that have failed to resolve after a 30-day course of standard treatment.

The use of G-CSF is another new adjunctive therapy under investigation. G-CSF has been found to enhance the activity of neutrophils in diabetic patients.[40] A small number of studies have investigated the use of G-CSF as an adjunctive therapy. A meta-analysis of these studies[41] revealed that, although the use of G-CSF did not significantly accelerate the resolution of infection in diabetic wounds, there was a decreased likelihood of amputation

Table 3. Risk Classification System of the Task Force of the Foot Care Interest Group of the ADA

Risk Category	Definition	Treatment Recommendations	Suggested Follow-up
0	No LOPS, no PAD, no deformity	Consider patient education on foot care, including information on appropriate footwear.	Annually (by generalist and/or specialist)
1	LOPS ± deformity	Consider prescriptive or accommodative footwear. Consider prophylactic surgery if deformity is not able to be safely accommodated in shoes. Continue patient education.	Every 3–6 months (by generalist or specialist)
2	PAD ± LOPS	Consider the use of accommodative footwear. Consider a vascular consultation for combined follow-up.	Every 2–3 months (by specialist)
3	History of ulcer or amputation	Consider patient education on foot care. Consider vascular consultation for combined follow-up if PAD present.	Every 1–2 months (by specialist)

LOPS, loss of protective sensation; PAD, peripheral arterial disease. Adapted from Ref. 13.

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and the need for other surgical therapies in treated wounds.

Prevention

Early detection of potential risk factors for ulceration can decrease the frequency of wound development. It is recommended that all patients with diabetes undergo foot examinations at least annually to determine predisposing conditions to ulceration.[13] Patients should be educated regarding the importance of maintaining good glycemic control, wearing appropriate footwear, avoiding trauma, and performing frequent self-examinations.[25]

A risk classification scheme has been created in the report of the task force of the Foot Care Interest Group of the ADA[13] that is reportedly designed to make basic recommendations regarding the need for specialist referral and the frequency of follow-up by primary providers and specialists (Table 3). Patients in the lowest risk category are recommended to receive education on general foot care and annual follow-up. Increasing risk categories require more components of care and are more likely to benefit from specialist care and follow-up. A recommended frequency of follow-up for each risk category is also included in the table; follow-up increases in frequency with an increase in risk category.

Conclusion

Patients with diabetes are at an increased risk for developing foot ulcerations. The consequences of persistent and poorly controlled hyperglycemia lead to neuropathic and vascular abnormalities that cause foot deformities and ulceration. The feet of diabetic patients should be examined at least annually to determine predisposing conditions to ulceration. Treatment plans should be based on examination findings and the individual risk for ulceration.

If ulcers are present, the treatment strategy should include offloading, debridement, and appropriate dressings. Further, the presence of infections should be determined by clinical findings and appropriate wound cultures and treated based on the culture results. If evidence for ischemia is present, revascularization may be indicated to restore arterial blood flow and increase the chance for limb salvage. There are adjunctive therapies available that can also contribute to the overall healing process of the wounds in affected patients.

By conducting a periodic foot survey in diabetic patients and incorporating the appropriate basic and specialized care as warranted, the risk of ulceration and its associated morbidities can be reduced.

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