CME

Pathogenesis and management of diabetic foot ulcers

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ABSTRACT

Diabetic foot ulcers are a devastating component of diabetes progression and are caused by loss of glycemic control, peripheral neuropathy, peripheral vascular disease, and immunosuppression. An estimated 15% of patients with diabetes have diabetic foot ulcers. This article describes the pathogenesis, diagnosis, clinical management, and advances in wound treatment for diabetic foot ulcers.

Keywords: diabetes, foot ulcers, amputation, peripheral neuropathy, glycemic control, peripheral arterial disease

Learning objectives

- List the risk factors and classifications of wound infections and ulcers.
- Develop management plans for patients with diabetic foot ulcers based on their relative risk categories.
- Describe steps in the pharmacologic and nonpharmacologic management of patients with uninfected and infected diabetic foot ulcers.

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Diabetic foot ulcers are one of several serious complications of diabetes progression. Major contributing causes to diabetic foot ulcers are peripheral neuropathy, peripheral arterial disease, and immunosuppression.[1-3] Up to 15% of patients with diabetes have diabetic foot ulcers, and these ulcers lead to more than 80,000 amputations per year in the United States.[4,5] The lifetime risk of diabetic foot ulcers for patients with diabetes may reach up to 68 per 1,000 persons as reported by some studies.[6] As a diabetic foot ulcer progresses, the patient's risk for amputation increases; in nearly 84% of patients who have a lower limb amputation secondary to diabetes, the amputation is preceded by a diabetic foot ulcer.[7] Peripheral neuropathy secondary to diabetes is an etiologic factor of diabetic foot ulcers and is estimated to affect 5.5 million people in the United States.[8] The estimated annual cost of treating peripheral neuropathy in patients with diabetes is $10.91 billion.[8] These collective findings indicate that diabetic foot ulcers lead to serious disability, serious reduction in patient quality of life, and high financial costs for society.[9] With increased vigilance on risk assessment, diagnosis, and management of diabetic foot ulcers, clinicians can improve patient outcomes and reduce healthcare costs.

RISK FACTORS

Risk factors for foot ulcers in patients with diabetes include:

- previous lower extremity amputation
- history of a foot ulcer
- anatomic foot deformity
- peripheral vascular disease
- diabetic nephropathy in those on dialysis
- poor glycemic control
- smoking.[10]

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Key points

- Diabetic foot ulcers are a devastating component of diabetes progression and affect about 15% of patients with diabetes.
- The pathophysiology of diabetic foot ulcers has neuropathic, vascular, and immune system components, all related to hyperglycemia.
- Patients with diabetes should be assessed regularly for arterial insufficiency and neuropathic disease.
- Provide patient education and assess glycemic control in low-risk patients.
- Refer high-risk patients with open ulcers to an orthopedic practice for appropriate surgical management.

TABLE 1. University of Texas Diabetic Wound Classification[11]

Stage	
A	no infection or ischemia
B	infection present
C	ischemia present
D	infection and ischemia present
Grade	
0	epithelialized wound
1	superficial wound
2	wound penetrates to tendon or capsule
3	wound penetrates to bone or joint

PATHOPHYSIOLOGY

The pathophysiology of diabetic foot ulcers has neuropathic, vascular, and immune system components, which all show a base relationship with the hyperglycemic state of diabetes.[11,12] Hyperglycemia produces oxidative stress on nerve cells and leads to neuropathy.[11] Additional nerve dysfunction follows from glycosylation of nerve cell proteins, leading to further ischemia. These cellular changes manifest in motor, autonomic, and sensory components of neuropathic foot ulcers. Damage to motor neurons of the foot musculature may lead to an imbalance of flexors and extensors, anatomic deformities, and eventual skin ulcerations. Damage to autonomic nerves impairs sweat gland function, and the foot may develop decreased ability to moisturize skin, leading to epidermal cracks and skin breakdown. Lastly, patients may not notice foot wounds because of decreased peripheral sensation. Because the blood supply required to heal a diabetic foot ulcer is greater than that needed to maintain intact skin, chronic ulceration can develop.[9]

Vascular changes that lead to diabetic foot ulcers correlate with hyperglycemia-induced changes in the peripheral arteries of the foot and begin on the cellular level.[11] Endothelial cell dysfunction leads to a decrease in vasodilators; also, plasma thromboxane A2 levels become elevated.[13] The result is vasoconstriction and plasma hypercoagulation in peripheral arteries leading to ischemia and increased risk of ulceration.

Immune changes include reduced healing response in diabetic foot ulcers. Increased T lymphocyte apoptosis, which inhibits healing, has been observed in patients with diabetic foot ulcers.[14]

ASSESSMENT AND DIAGNOSIS

Patients with diabetes should be assessed for arterial insufficiency and neuropathic disease on a structured schedule based on defined risk factors.[9] Assess the patient's temperature, respirations, heart rate, and BP in both extremities and document any abnormalities.[9] Fever, tachycardia, or tachypnea may indicate an infected ulcer. Evaluate the patient's vascular status by palpating all peripheral pulses and assessing the appearance and temperature of the patient's extremities. Measure the arterial-brachial index (ABI); a result of 1 to 1.2 is normal, and a result below 0.6 indicates claudication. For patients with medial sclerosis, a toe-brachial index (TBI) may be preferred; a result of 0.6 or less indicates a need for vascular intervention.

Arterial insufficiency is characterized by intermittent claudication or limb ischemia; dry, shiny, hairless skin on the affected limb; brittle nails; and skin that is cool to the touch. A patient with arterial insufficiency also may have a history of erectile dysfunction or cardiovascular disease. Assess arterial flow by elevating the limb above the level of the heart, letting pooled blood drain. A normal limb will remain pink; one with arterial insufficiency becomes pallid.

Symptoms of neuropathic disease include numbness, paresthesia, and burning sensations. All patients with diabetes should be assessed regularly for loss of protective sensation; any of the following five tests may be used.[15]

- *The 10-g monofilament test* determines a patient's sensitivity to touch. With the patient's eyes closed, touch the monofilament to one or more anatomic sites, including reference sites to verify sensation detection; inability to detect this touch at the test site indicates loss of large nerve fiber function. Test the first, third, and fifth metatarsal heads and the plantar surface of the distal hallux.
- *A 128-Hz tuning fork* used to detect vibratory sensation. This test uses a tuning fork held bilaterally over the toes to elicit vibratory sensation. Have the patient close his or her eyes. To conduct the test, touch the base of a vibrating 128-Hz tuning fork to a bony surface of each bare toe in succession, and ask the patient to acknowledge when the vibration is felt and when it is removed.
- *A pinprick test* is administered just proximal to the toenail of the dorsal aspect of the hallux. Inability to detect the pinprick is an abnormal result and indicates neuropathy.
- *The ankle reflexes test* of the Achilles tendon is done with the patient sitting in a chair or on an examination table.

TABLE 2. Classifying wound infection[16]

The Infectious Diseases Society of America (IDSA) defines infection as the presence of at least two of the following: Local swelling or induration; erythema >0.5 cm around ulcer in any direction; local tenderness or pain; local warmth; purulent discharge, and no other causes of an inflammatory response such as fracture, trauma, or thrombosis.

Clinical classification (IDSA)	International Working Group on Diabetic Foot grade	Description
Uninfected	1	No systemic or local signs or symptoms of infection
Mild infection	2	Infection involving the skin or subcutaneous tissue only or erythema extending <2 cm in any direction from the wound. No systemic signs or symptoms of infection.
Moderate infection	3	Infection involving structures deeper than the skin and subcutaneous tissues or erythema extending >2 cm from the wound margin. No systemic signs or symptoms of infection.
Severe infection	4	Any foot infection with two or more of the following signs of a systemic inflammatory response syndrome: • Temperature >38° C (100.4° F) or <36° C (96.8° F) • Heart rate >90 beats/minute • Respiratory rate >20 breaths or $Paco_2$ <32 mm Hg • White blood cell count >12,000 or <4,000 cells/mm or 10% immature forms

Place the foot in a neutral position, slightly stretching the Achilles tendon. Strike the tendon with a tendon hammer. If no tendon response occurs, ask the patient to lock his or her fingers together and pull; then retest the tendon reflex. Absence of an ankle reflex is an abnormal result that may indicate peripheral neuropathy.

• *The vibration perception threshold test* uses a biothesiometer to make a semiquantitative assessment of the patient's vibration perception threshold (VPT). With the patient lying supine, a VPT is measured at a proximal control site by placing the instrument stylet on the skin and increasing the amplitude until vibration is detected. VPT measurement is then conducted at each hallux using the mean of three measurements for each. A VPT greater than 25 V has been correlated with later development of diabetic foot ulcers.[15]

If the patient has soft-tissue wounds on the feet, inspect, palpate, and probe them on initial presentation and in follow-up to evaluate and track the extent of soft-tissue damage and to assess for bone involvement (osteomyelitis).[16]

Diabetic foot ulcers can be classified by wound depth and by level of infection (**Tables 1, 2,** and **3**).[11,16]

OSTEOMYELITIS

Suspect osteomyelitis if the patient's ulcer is over a bony prominence and fails to heal with adequate pressure-reduction. Diagnostic tests for osteomyelitis include probe to bone and erythrocyte sedimentation rate (ESR). In the probe-to-bone test, a blunt sterile probe is inserted into the wound; a hard, gritty feel is a positive finding (**Figure 1**). An ESR of greater than 70 mm/hour suggests osteomyelitis in a patient with a diabetic foot ulcer (normal range is 0 to 22 mm/hour for men and 0 to 29 mm/hour for women).[16]

Plain radiographs also can support a diagnosis of osteomyelitis. Depending on when radiographs are taken, they are 28% to 75% sensitive and 64% specific for osteomyelitis.[16] Patients with longer term diabetic foot ulcers are more likely to show bone abnormality changes in plain radiographs.[16] Serial radiographs have a higher predictive value.[16] MRI has been shown to have a sensitivity of 77% to 100% and specificity of 40% to 100% for detecting osteomyelitis.[17] MRI also provides significant soft-tissue detail on edema, fluid accumulation, and bone changes associated with osteomyelitis. Limited studies suggest that CT, in combination with positron emission tomography (PET), is highly sensitive (81%), specific (93%), and accurate (90%) for diagnosing osteomyelitis.[16] Although CT/PET is an attractive option for diagnosing osteomyelitis, this test may not be practical or economical. If the clinician suspects osteomyelitis, front-line tests such as radiographs and MRI should be used first before considering tests that may have limited availability. A leukocyte or antigranulocyte scan, in conjunction with a bone scan, is a recommended alternative diagnostic imaging approach for osteomyelitis in a diabetic foot ulcer if MRI is unavailable or contraindicated.[10]

If imaging results strongly suggest osteomyelitis, the diagnosis may be confirmed by bone biopsy. Microbiology

TABLE 3. Wagner Ulcer Classification System[11]

- Grade 1—superficial diabetic ulcer
- Grade 2—ulcer extension involving ligament, tendon, joint capsule, or fascia with no abscess or osteomyelitis
- Grade 3—deep ulcer with abscess or osteomyelitis
- Grade 4—extensive gangrene of the foot

and histology cultures of the bone can identify pathogens and their antibiotic susceptibility.[10,17] However, false-positives may result if bone biopsies are obtained through the ulcer; samples should instead be taken through clinically uninvolved skin or after careful wound debridement. Similarly, soft-tissue cultures should be taken at the deep base of a diabetic foot ulcer via curettage and aspiration and after debridement; this provides the most reliable results for guiding treatment.[16]

CLINICAL MANAGEMENT

Primary care providers are likely to identify diabetic foot ulcers in patients under their care, and can manage these patients with appropriate interdisciplinary support such as wound care specialists. Based on the patient's history, physical examination, and diagnosis, determine the patient's risk category and initiate an appropriate treatment plan (**Table 4**). Refer high-risk patients with open ulcers to orthopedic practices for appropriate surgical management.

> Infected diabetic foot ulcers often are polymicrobial in nature.

Low-risk patients without anatomic foot deformities should receive patient education on foot care, appropriate footwear recommendations to reduce pressure points, and a careful assessment of glycemic control. Monitor and optimize blood glucose levels, aiming for a hemoglobin A1C level of 7% or less to reduce the patient's risk of microvascular disease.[9]

For patients in higher risk classifications, who may have anatomic foot deformities or active ulcers, surgical intervention may be necessary.

- *Ulcer debridement* (**Figure 2**) removes necrotic tissue, foreign material such as bacteria, and hyperkeratosis that may surround the wound.[10] Sharp debridement using a scalpel cleans the wounds, excises the margins, and exposes a healthy tissue granulation base for epithelial layer regeneration; specimens also may be taken at this time for culture.[9,15,16] Selective sharp debridement followed by saline-moistened gauze has been used widely in managing diabetic foot ulcers.[18] Superficial ulcer debridement can usually be carried out in the clinic or at the bedside using local anesthesia, where necessary. Local anesthesia may not be required with more advanced manifestations of peripheral neuropathy. Advanced ulcers requiring deep tissue debridement require surgery in the OR so that appropriate specimens for culture can be obtained.[10]

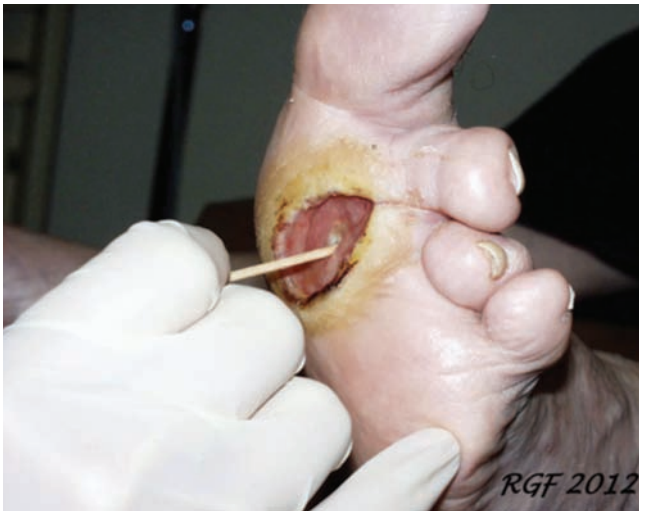

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FIGURE 1. Bone probe test.

Chemical debridement is an alternative to sharp or mechanical debridement. Clostridial collagenase ointment debridement has been shown to provide improved healing of diabetic foot ulcers.[18] A study by Tallis and colleagues found that clostridial collagenase ointment debridement reduced mean wound area significantly compared with selective sharp debridement followed by saline-moistened gauze.[18] In addition, economic analysis indicated that clostridial collagenase ointment is cost-effective in multiple care settings.

Other debridement methods include hydrocolloid and hydrogel dressings, which facilitate autolysis of necrotic wound tissue but cannot be used on infected wounds. Alginate and silver-impregnated dressings and maggot debridement therapy also may be appropriate.[19] However, there is no substitute for adequate wound debridement, appropriate systemic antibiotic therapy, and daily dressing changes and wound inspection.[20]

Patients with infected diabetic foot ulcers should be prescribed a targeted antibiotic regimen based on the wound culture results.[9] Inspect the wound regularly to assess the patient's response to antibiotic therapy. Mild infections call for 2 weeks of antibiotic treatment; deep infections may require up to 2 months of therapy.[9] A prospective study by Manisha and colleagues found that the major microorganisms were *Pseudomonas aeruginosa* (30.57%), *Klebsiella* (22.29%), *Escherischia coli* (16.56%), and *Staphylococcus aureus* (12.74%).[21] Methicillin resistance was detected in 55% of the *S. aureus* cultures. Gram-negative isolates were

TABLE 4. Risk classification of diabetic foot ulcers[15]

Risk category	Definition	Treatment recommendation	Suggested follow-up
0	No loss of protective sensation or peripheral arterial disease, no anatomic deformity	• Patient education on foot care, including information on appropriate footwear	Annually by generalist and/or specialist
1	Loss of protective sensation, with or without anatomic deformity	• Prescriptive or accommodative footwear • Prophylactic surgery if deformity cannot be safely accommodated in shoes • Continue patient education.	Every 3-6 months by generalist and/or specialist
2	Peripheral arterial disease, with or without loss of protective sensation	• Accommodative footwear • Consider a vascular consultation for combined follow-up.	Every 2-3 months by specialist
3	History of ulcer or amputation	• Patient education on foot care • Consider vascular consultation for combined follow-up if patient also has peripheral arterial disease.	Every 1-2 months by specialist

found to be susceptible to ampicillin plus sulfobactam, cefepime plus tazobactam, and ceftriaxone plus tazobactam. Gram-positive isolates were found to be sensitive to teicoplanin, minocycline, and amoxicillin plus clavulanic acid. Appropriate antibiotic empirical treatment was identified as cefepime plus tazobactam, imipenem, and amikacin. The study also confirmed that infected diabetic foot ulcers are polymicrobial in nature and that these mixed infections show multidrug resistance, which creates a serious risk factor in infection management.[21]

Sotto and colleagues found marked differences between infected and uninfected ulcers.[22] The presence of two methicillin-sensitive *S. aureus* clonal complexes was associated with a favorable outcome in uninfected wounds; 86% of the uninfected wound isolates contained these two clonal complexes. In addition, a virulence marker gene was identified with 96.5% sensitivity as a differentiation tool for uninfected and infected diabetic foot ulcers. The identified clonal complexes and virulence marker present potent prognostic tools for managing diabetic foot ulcers, and may lead to more judicious use of antibiotics.

Pressure-reducing strategies and negative-pressure wound therapy can help improve wound healing; negative-pressure wound therapy stimulates angiogenesis and increases granulation tissue.[23,24] Driver and colleagues compared the outcomes of wound treatment with transdermal continuous oxygen therapy (treatment group) to standard debridement, offloading, and moisture therapy (control group).[25] Weekly wound measurements were taken and wound fluid collected over 14 to 20 months. Biomarker levels of proinflammatory cytokines, proteases, and macrophages were analyzed in the fluid samples. Patients in the treatment group had significantly higher levels of interleukin-8 and interleukin-6, and significantly lower levels of macrophages, indicating that transdermal continuous oxygen therapy resolves inflammation and helps restore tissue turnover and healing.

• *Vascular grafts or bypasses* may be indicated in patients with peripheral arterial disease. Adequate peripheral circulation is key to fighting infection and promoting wound healing. To determine the patient's need for revascularization, evaluate the patient's vascular status, looking for flow-limiting vascular leg lesions. Vascular assessment methods include Doppler ultrasound, ABI, TBI, duplex ultrasound, MRI angiography, CT angiography, and contrast angiography.[9,26] Because patients may have adverse reactions to contrast media, consider baseline tests such as ABI, TBI, plain radiography, and Doppler ultrasound before ordering studies such as MRI and CT angiography and contrast arteriography.

Proceeding with revascularization depends on many factors, mainly operative risk, arteriographic results, and available graft material. Candidates for revascularization surgery include patients with acceptable surgical risk, suitable life expectancy, and lesions technically unsuitable to endovascular repair or that have failed endovascular repair. Contraindications to revascularization include foot sepsis, extensive foot gangrene, and a nonambulatory status.[9] The operative risk of revascularization depends on the method used, which can include surgical arterial bypass, endovascular angioplasty stenting, endovascular subintimal angioplasty, and endovascular artherectomy.[9]

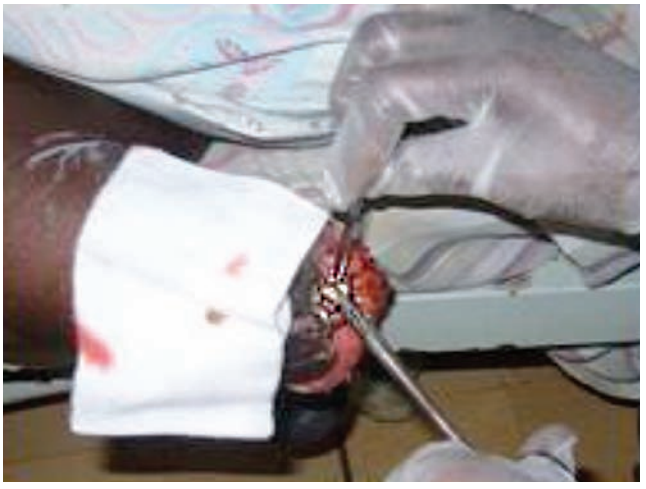

FIGURE 2. Sharp debridement.

Endovascular repair techniques have shown high success in patients with claudication.[27] Comprehensive arteriographic studies help clinicians identify flow-limiting lesions and determine the repair procedure.[28] Revascularization using a saphenous vein bypass graft is the gold standard in lower extremity revascularization.[9] However, in patients without a suitable saphenous vein for grafting, polytetrafluoroethylene conduit material is a viable substitute. Revascularization surgery should be undertaken as soon as possible to avoid losing healthy limb tissue and reduce the risk of foot amputation.

Patients in higher risk categories, and those with infections including osteomyelitis, may need surgical resection or amputation. If debridement, antibiotic therapy, or resection fails and life-threatening infection develops, the patient will need foot amputation and, if appropriate, should be considered for a prosthesis.[16]

WHAT PATIENTS NEED TO KNOW

Patients must understand and adhere to optimal wound care for good outcomes in diabetic foot ulcers. The first step is to reduce repetitive pressure on the foot that caused the ulcer. Various pressure-reducing devices and shoe modifications may be used.[9] Explain to patients that addressing causes of limb ischemia will require many office visits. Where appropriate, encourage patients to stop smoking and to gain control of hyperglycemia.[11] Patients also must adhere to antibiotic therapy (which may be adjusted periodically) to control wound infection.[16] Patients also must change wound dressings daily to encourage formation of healthy granulation tissue and wound healing.[16,18]

CONCLUSION

Patients with poorly controlled diabetes are at high risk for diabetic foot ulcers, and need appropriate medical care to reduce the risk of foot amputation. Patients who present with advanced diabetic foot ulcers may also have infected ulcers, greater tissue necrosis, and osteomyelitis (**Figure 3**).

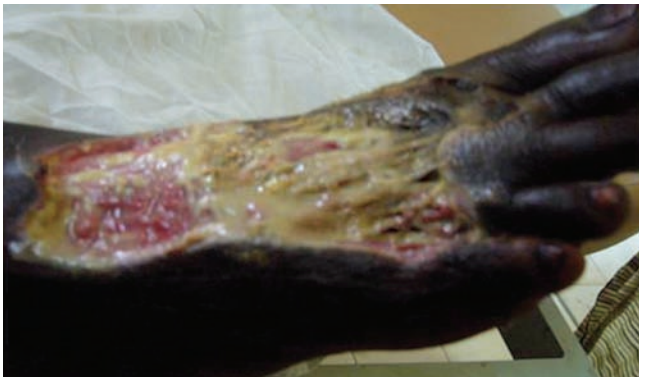

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FIGURE 3. Wagner grade 4 diabetic foot ulcer.

These high-risk patients should be referred to an appropriate orthopedic office for immediate evaluation and management.

A full vascular evaluation of the affected limb and treatment of ischemia should be performed before debridement, to ensure sufficient peripheral circulation for resolving the infection and healing the ulcer. Early, consistent patient education about managing blood glucose may help patients avoid peripheral arterial disease, peripheral neuropathy, and diabetic foot ulcers. **JAAPA**

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