Supplement to:

DIABETIC FOOT DISORDERS: A CLINICAL PRACTICE GUIDELINE (2006 revision)

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ABSTRACT: The prevalence of diabetes mellitus is growing at epidemic proportions in the United States and worldwide. Most alarming is the steady increase in type 2 diabetes, especially among young and obese persons. An estimated 7% of the US population has diabetes, and because of the increased longevity of this population, diabetes-associated complications are expected to rise in prevalence.

Foot ulcerations, infections, Charcot neuroarthropathy, and peripheral arterial disease frequently result in gangrene and lower limb amputation. Consequently, foot disorders are leading causes of hospitalization for persons with diabetes and account for billion-dollar expenditures annually in the US. Although not all foot complications can be prevented, dramatic reductions in frequency have been achieved by taking a multidisciplinary approach to patient management. Using this concept, the authors present a clinical practice guideline for diabetic foot disorders based on currently available evidence, committee consensus, and current clinical practice. The pathophysiology and treatment of diabetic foot ulcers, infections, and the diabetic Charcot foot are reviewed. While these guidelines cannot and should not dictate the care of all affected patients, they provide evidence-based guidance for general patterns of practice. If these concepts are embraced and incorporated into patient management protocols, a major reduction in diabetic limb amputations is certainly an attainable goal.

This clinical practice guideline (CPG) is based on the consensus of current clinical practice and review of the clinical literature. This guideline was developed by the Clinical Practice Guideline Diabetes Panel of the American College of Foot and Ankle Surgeons.

INTRODUCTION

The prevalence of diabetes mellitus is growing at epidemic proportions in the United States and worldwide (1). Most alarming is the steady increase in type 2 diabetes, especially among young and obese persons. An estimated 7% of Americans are afflicted with diabetes, and with the longevity of this population increasing, the prevalence of diabetes-related complications will continue to rise.

Foot disorders are a major source of morbidity and a leading cause of hospitalization for persons with diabetes. Ulceration, infection, gangrene, and amputation are significant complications of the disease, estimated to cost billions of dollars each year. Charcot foot, which of itself can lead to limb-threatening disorders, is another serious complication of long-standing diabetes. In addition to improving the management of ulcers—the leading precursor to lower extremity amputation in diabetic patients (2)—clinicians must determine how to more effectively prevent ulceration. Although not all diabetic foot disorders can be prevented, it is possible to effect dramatic reductions in their incidence and morbidity through appropriate evidence-based prevention and management protocols.

Taking a multidisciplinary approach to diabetic foot disorders, many centers from around the world have noted consistent improvement in limb salvage rates. With this premise as our central theme, the authors present this clinical practice guideline based on currently available evidence. Three major pedal complications of diabetes are reviewed: diabetic foot ulcers, diabetic foot infections, and the diabetic Charcot foot. These guidelines are intended to provide evidence-based guidance for general patterns of practice and do not necessarily dictate the care of a particular patient.
Diabetes is one of the foremost causes of death in many countries and a leading cause of blindness, renal failure, and nontraumatic amputation. Global prevalence of diabetes in 2003 was estimated to be 194 million (3). By 2030, this figure is predicted to rise to 366 million due to longer life expectancy and changing dietary habits (4).

The estimated incidence of diabetes in the US exceeds 1.5 million new cases annually, with an overall prevalence of 20.8 million people or 7% of the nation’s population (5). An estimated 14.6 million persons are currently diagnosed with the disease, while an additional 6.2 million people who have diabetes remain undiagnosed; this represents a sixfold increase in the number of persons with diabetes over the past four decades (6). A higher incidence of diabetes occurs among non-Hispanic blacks, Hispanic/Latino Americans, and Native Americans compared with non-Hispanic whites (7). Diagnosed diabetes is most prevalent in middle-aged and elderly populations, with the highest rates occurring in persons aged 65 years and older (8-10). As the sixth leading cause of death in the US, diabetes contributes to more than 224,000 deaths per year (5).

**Table 1** Classification of Diabetes Mellitus *

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>absolute insulin deficiency</th>
</tr>
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<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>insulin resistant +/- insulin deficiency</td>
</tr>
<tr>
<td>Other types</td>
<td>genetic defects of β-cell function or insulin action endocrinopathies drug or chemical infections</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td></td>
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</tbody>
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Four categories of diabetes are recognized (Table 1). Type 1, formerly insulin-dependent diabetes mellitus (IDDM), is an autoimmune disease affecting the pancreas. Individuals with type 1 diabetes are prone to ketosis and unable to produce endogenous insulin. Type 2, formerly non-insulin dependent diabetes mellitus (NIDDM), accounts for 90% to 95% of cases diagnosed. Type 2 diabetes is characterized by hyperglycemia in the presence of hyperinsulinemia due to peripheral insulin resistance. Gestational as well as genetic defects and endocrinopathies are recognized as other types of diabetes (11). Diabetes is associated with numerous complications related to microvascular, macrovascular, and metabolic etiologies. These include cerebrovascular, cardiovascular, and peripheral arterial disease; retinopathy; neuropathy; and nephropathy. Currently, cardiovascular complications are the most common cause of premature death among patients with diabetes (9, 12). Rates of heart disease and stroke are 2 to 4 times higher among diabetic adults compared with nondiabetic adults, accounting for about 65% of deaths in people with diabetes (5). Estimated total (direct and indirect) annual expenditures for diabetes management in 2002 was $132 billion, representing 1 of every 10 health care dollars spent in the US (13).

One of the most common complications of diabetes in the lower extremity is the diabetic foot ulcer. An estimated 15% of patients with diabetes will develop a lower extremity ulcer during the course of their disease (14-17). Several population-based studies indicate a 0.5% to 3% annual cumulative incidence of diabetic foot ulcers (18-21). According to one large British study of neuropathic patients, the 1-year incidence of initial foot ulcer was 7% (22). The prevalence of foot ulcers reported for a variety of populations ranges from 2% to 10% (16, 18, 22, 23). Neuropathy, deformity, high plantar pressure, poor glucose control, duration of diabetes, and male gender are all contributory factors for foot ulceration (see the following section: “Risk for Ulceration”) (24-27). National hospital discharge data indicate that the average hospital length of stay (LOS) for diabetic patients with ulcer diagnoses was 59% longer than for diabetic patients without ulcers (16). While 7% to 20% of patients with foot ulcers will subsequently require an amputation, foot ulceration is the precursor to approximately 85% of lower extremity of amputations in persons with diabetes (28-31).

Diabetes continues to be the most common underlying cause of nontraumatic lower extremity amputations (LEAs) in the US and Europe (1, 32). More than 60% of LEAs in the US occur in people with diabetes, averaging 82,000 per year (5, 10). While the number of diabetes-related hospital discharges has progressively increased from 33,000 in 1980 to 84,000 in 1997, this number seems to have leveled off during the present decade. In 2002, there were 82,000 diabetes-related LEA discharges, accounting for 911,000 days of hospital stay with an average LOS of 11.2 days (10). The age-adjusted rate of amputation for that year was 5.2 per 1,000 persons with diabetes, a notable decrease from the highest rate of 8.1 per 1,000 in 1996.

In terms of level of diabetes-related lower limb amputations, toe amputations comprise the majority of procedures. The age-adjusted LEA rate in 2002 among persons with diabetes was highest for toe LEA (2.6 per 1,000 persons), followed by below-knee LEA (1.6 per 1,000 persons). For foot LEA and above-knee LEA, the age-adjusted rate was 0.8 per 1,000 persons. These trends in amputation level have essentially remained the same since 1993 (10). Generally, the LEA rate is 15 to 40 times higher in the diabetic versus...
nondiabetic populations, and the rate is at least 50% higher in men versus women (8, 10, 12, 33). In 2002, the age-adjusted LEA rate among men was 7.0 per 1,000 persons with diabetes compared with to the rate among women reported at 3.3 per 1000 persons with diabetes (10).

Several ethnic differences occur in the frequency of diabetes-related amputations. Mexican (Hispanic) Americans, Native Americans, and African Americans each have at least a 1.5- to 2-fold greater risk for diabetes-related amputation than age-matched diabetic Caucasians (8, 10, 16, 17, 34, 35). When LEA risk is compared between diabetic and nondiabetic populations worldwide, it is apparent that both diabetes and ethnicity have profound implications on rates of lower limb amputation (1, 17).

Survival rates after amputation are generally lower for diabetic versus nondiabetic patients (16, 17, 29). The 3- and 5-year survival rates are about 50% and 40%, respectively, with cardiovascular disease being the major cause of death (8). Although mortality rates following major amputation are high among both diabetic and nondiabetic patients, a recent study reported no significant difference between these two populations. The mean survival was approximately 6.5 years, with a 68% mortality after 9 years regardless of diabetes status (36). An earlier study from Sweden reported a 5-year mortality rate of 68% after lower limb amputation, with survival rates lower among patients who underwent higher levels of amputation (29). Similar trends were found in a review of amputations within the Veterans Affairs system, but worse survival outcomes were observed for older patients, those with renal disease, and those with peripheral arterial disease (37). Researchers have reported a 50% incidence of serious contralateral foot lesion (ie, ulcer) following an LEA, and a 50% incidence of contralateral amputation within 2 to 5 years of an LEA (16, 29).

Total (direct and indirect) annual health care costs for persons with diabetes were estimated to be $132 billion in 2002. Direct medical expenditures, including hospitalization, medical care, and supplies, accounted for $91.8 billion (13). The estimated cost for foot ulcer care in the US ranges from $4,595 per ulcer episode to nearly $28,000 for the 2 years after diagnosis (19, 38). One report estimates 800,000 prevalent ulcer cases in the US, with costs averaging $5,457 per year per patient or total national annual costs of $5 billion (39). A study of Medicare claims data found that expenditures for patients with lower extremity ulcers averaged 3 times higher than expenditures for Medicare beneficiaries in general. With 24% of their total costs allocated to ulcer-related expenses, lower extremity ulcer patients cost the Medicare system $1.5 billion in 1995 (40). According to a large prospective study of diabetic patients with foot ulcers, about 7% will subsequently require a lower extremity amputation (31). While hospital LOSs for diabetes-related LEA have progressively decreased in the US, the overall direct costs remain high (10, 16). Direct and indirect costs of LEA—which range from $20,000 to $40,000 per event—vary by year, payer, level of amputation, LOS, and attendant comorbidities (16). If the lower figure is applied to the 82,000 amputations performed in 2002, estimated total costs of LEA might exceed $1.6 billion annually. When outpatient costs for ulcer care preceding these amputations is added, the estimated total costs in the US for diabetic foot disease can easily approach or exceed $6 billion annually.

Risk for Ulceration

Foot ulceration is the most common single precursor to lower extremity amputations among persons with diabetes (28-30). Treatment of infected foot wounds comprises up to one quarter of all diabetic hospital admissions in the US and Britain, making this the most common reason for diabetes-related hospitalization in these countries (41-43). The multifactorial nature of diabetic foot ulceration has been elucidated by numerous observational studies (16, 22, 24, 26, 27, 44-48). Risk factors identified include peripheral neuropathy, vascular disease, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, a history of ulceration or amputation, and impaired visual acuity (25, 49, 50). These and other putative causative factors are shown in Figure 1.

Peripheral sensory neuropathy in the face of unperceived trauma is the primary factor leading to diabetic foot ulcerations (24, 27, 46, 49). Approximately 45% to 60% of all diabetic ulcerations are purely neuropathic, while up to 45% have neuropathic and ischemic components (24, 51). According to an important prospective multicenter study, sensory neuropathy was the most frequent component in the causal sequence to ulceration in diabetic patients (24).

Other forms of neuropathy may also play a role in foot ulceration. Motor neuropathy resulting in anterior crural muscle atrophy or intrinsic muscle wasting can lead to foot deformities such as foot drop, equinus, hammertoe, and prominent plantar metatarsal heads (25, 26, 52-54). Ankle equinus with restricted dorsiflexory range of motion is fairly common in patients with diabetic neuropathy and can be a consequence of anterior crural muscle atrophy (55-60). The decreased ankle motion, which confers higher-than-normal plantar pressures at the forefoot, has been implicated as a contributory cause of ulceration as well as recurrence or recalcitrance of existing ulcers (57, 58, 60, 61).

Autonomic neuropathy often results in dry skin with cracking and fissuring, creating a portal of entry for bacte-
Risk Factors for Ulceration

General or Systemic Contributions
- Uncontrolled hyperglycemia
- Duration of diabetes
- Peripheral vascular disease
- Blindness or visual loss
- Chronic renal disease
- Older age

Local Issues
- Peripheral neuropathy
- Structural foot deformity
- Trauma and improperly fitted shoes
- Callus
- History of prior ulcer amputation
- Prolonged elevated pressures
- Limited joint mobility

The risk factors for ulceration may be distinguished by general or systemic considerations versus those localized to the foot and its pathology.

Foot deformities resulting from neuropathy, abnormal biomechanics, congenital disorders, or prior surgical intervention may result in high focal foot pressures and increased risk of ulceration (24, 48, 50, 57, 68-71). The effects of motor neuropathy occur relatively early and lead to foot muscle atrophy with consequent development of hammertoes, fat pad displacement, and associated increases in plantar forefoot pressures (53, 72-75). Although most deformities cause high plantar pressures and plantar foot ulcerations, medial and dorsal ulcerations may develop as a result of footwear irritation. Common deformities might include prior partial foot amputations, prominent metatarsal heads, hammertoes, Charcot arthropathy, or hallux valgus (69, 76-79). A large prospective population-based study found that elevated plantar foot pressures are significantly associated with neuropathic ulceration and amputation (80). The study also revealed a trend for increased foot pressures as the number of pedal deformities increased.

Trauma to the foot in the presence of sensory neuropathy is an important component cause of ulceration (24). While trauma may include puncture wounds and blunt injury, a common injury leading to ulceration is moderate repetitive stress associated with walking or day-to-day activity (69, 76, 81). This is often manifested by callus formation under the metatarsal heads (48, 82, 83). A recent report suggests that even with moderate activity, ulceration may be precipitated by a higher degree of variability in activity or periodic “bursts” of activity (84). Shoe-related trauma has also been identified as a frequent precursor to foot ulceration (28, 51, 54, 85, 86).

Peripheral arterial disease (PAD) rarely leads to foot ulcerations directly. However, once ulceration develops, arterial insufficiency will result in prolonged healing, imparting an elevated risk of amputation (28, 87, 88). Additionally, attempts to resolve any infection will be impaired due to lack of oxygenation and difficulty in delivering antibiotics to the infection site. Therefore, early recognition and aggressive treatment of lower extremity ischemia are vital to lower limb salvage (30, 52, 89-91).

Limited joint mobility has also been described as a potential risk factor for ulceration (92-94). Glycosylation of collagen as a result of longstanding diabetes may lead to stiffening of capsular structures and ligaments (cheiroarthropathy) (95). The subsequent reduction in ankle, subtalar, and first metatarsophalangeal (MTP) joint mobility has been shown to result in high focal plantar pressures with increased ulceration risk in patients with neuropathy (92, 96, 97). Several reports also attribute glycosylation and altered arrangement of Achilles tendon collagen to the propensity for diabetic patients to develop ankle equinus (98, 99).

Other factors frequently associated with heightened ulceration risk include nephropathy, poor diabetes control, duration of diabetes, visual loss, and advanced age (48, 69,
Soft tissue changes (other than cheiroarthropathy) in the feet of diabetic patients might also contribute to ulceration through the pathway of altered pressure distributions through the sole of the foot. Such alterations include a reported increased thickness of the plantar fascia with associated limitation of hallux dorsiflexion, decreased thickness of plantar soft tissue, accentuated hardness/stiffness of the skin, and a propensity to develop calluses (82, 96, 101-105). While these changes are presumably caused by glycosylation of collagen, their sum effect is to enhance plantar pressures in gait. In the presence of neuropathy, the accentuated plantar pressures can be implicated in the development of ulceration (70, 80, 92, 106).

Mechanisms of Injury

The multifactorial etiology of diabetic foot ulcers is evidenced by the numerous pathophysiologic pathways that can potentially lead to this disorder (24, 43, 54, 62, 90, 107). Among these are two common mechanisms by which foot deformity and neuropathy may induce skin breakdown in persons with diabetes (69, 108, 109).

The first mechanism of injury refers to prolonged low pressure over a bony prominence (ie, bunion or hammertoe deformity). This generally causes wounds over the medial, lateral, and dorsal aspects of the forefoot and is associated with tight or ill-fitting shoes. Shoe trauma, in concert with loss of protective sensation and concomitant foot deformity, is the leading event precipitating foot ulceration in persons with diabetes (24, 28, 57, 85).
Regions of high pedal pressure are frequently associated with foot deformity (68, 73, 76, 77, 106, 107). When an abnormal focus of pressure is coupled with lack of protective sensation, the result can be development of a callus, blister, and ulcer (110). The other common mechanism of ulceration involves prolonged repetitive moderate stress (108). This normally occurs on the sole of the foot and is related to prominent metatarsal heads, atrophied or anteriorly displaced fat pads, structural deformity of the lower extremity, and prolonged walking. Rigid deformities such as hallux valgus, hallux rigidus, hammertoe, Charcot arthropathy, and limited range of motion of the ankle (equinus), subtalar, and MTP joints have been linked to the development of diabetic foot ulcers (27, 57, 71, 80, 94, 96). Numerous studies support the significant association between high plantar pressures and foot ulceration (26, 70, 80, 92, 106, 111, 112). Other biomechanical perturbations, including partial foot amputations, have the same adverse effects (57, 68, 80, 113).

Figure 2 summarizes the various pathways and contributing factors leading to diabetic foot complications.

Risk for Infection

Infections are common in diabetic patients and are often more severe than infections found in nondiabetic patients. Persons with diabetes have an increased risk for developing an infection of any kind and a several-fold risk for developing osteomyelitis (114). With an incidence of 36.5 per 1,000 persons per year, foot infections are among the most common lower extremity complications in the diabetic population (excluding neuropathy), second only to foot ulcers in frequency (115).

It is well documented that diabetic foot infections are frequently polymicrobial in nature (30, 116-121). Hyperglycemia, impaired immunologic responses, neuropathy, and peripheral arterial disease are the major predisposing factors leading to limb-threatening diabetic foot infections (122-124). Uncontrolled diabetes results in impaired ability of host leukocytes to fight bacterial pathogens, and ischemia also affects the ability to fight infections because delivery of antibiotics to the site of infection is impaired. Consequently, infection can develop, spread rapidly, and produce significant and irreversible tissue damage (125). Even in the presence of adequate arterial perfusion, underlying peripheral sensory neuropathy will often allow the progression of infection through continued walking or delay in recognition (126, 127).

Risk for Charcot Joint Disease

It has been estimated that less than 1% of persons with diabetes will develop Charcot joint disease (128-130). Data on the true incidence of neuroarthropathy in diabetes are limited by the paucity of prospective or population-based studies in the literature. One large population-based prospective study found an incidence of about 8.5 per 1,000 persons with diabetes per year (115); this equates to 0.85% per year and is probably the most reliable figure currently available. Much of the data clinicians rely upon have been extracted from retrospective studies of small, single-center cohorts. The incidence of reported Charcot cases is likely to be underestimated because many cases go undetected, especially in the early stages (131-134).

Primary risk factors for this potentially limb-threatening deformity are the presence of dense peripheral sensory neuropathy, normal circulation, and history of preceding trauma (often minor in nature) (50, 135, 136). Trauma is not limited to injuries such as sprains or contusions. Foot deformities, prior amputations, joint infections, or surgical trauma may result in sufficient stress that can lead to Charcot joint disease (137-140).

Risk for Amputation

The reported risk of lower extremity amputations in diabetic patients ranges from 2% to 16%, depending on study design and the populations studied (19, 21, 32, 115, 141-144). LEA rates can be 15 to 40 times higher among the diabetic versus nondiabetic populations (8, 16, 34, 35). Although one author suggests that amputation may be a marker not only for disease severity but also for disease management, it is clear that amputation remains a global problem for all persons with diabetes (32, 143). The same risk factors that predispose to ulceration can also generally be considered contributing causes of amputation, albeit with several modifications (Fig 3).

While peripheral arterial disease may not always be an independent risk factor for ulceration when controlling for neuropathy, it can be a significant risk factor for amputation (24, 28, 88, 142, 145, 146). PAD affecting the feet and legs is present in 8% of adult diabetic patients at diagnosis and in 45% after 20 years (147, 148). The incidence of amputation is 4 to 7 times greater for diabetic men and women than for their nondiabetic counterparts. Impairment of arterial perfusion may be an isolated cause for amputation and a predisposing factor for gangrene. Early diagnosis, control of risk factors, and medical management as well as timely revascularization may aid in avoiding limb loss (30, 52, 77, 88, 149).
While infection is not often implicated in the pathway leading to ulceration, it is a significant risk factor in the causal pathway to amputation (24, 28). Lack of wound healing, systemic sepsis, or unresolved infection can lead to extensive tissue necrosis and gangrene, requiring amputation to prevent more proximal limb loss. This includes soft tissue infection with severe tissue destruction, deep space abscess, or osteomyelitis. Adequate debridement may require amputation at some level as a means of removing all infected material (77, 123, 150, 151).

Another frequently described risk factor for amputation is chronic hyperglycemia. Results of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) support the long-held theory that chronic poor control of diabetes is associated with a host of systemic complications (152, 153). The link between degree of glucose control and incidence or progression of numerous diabetic complications has been well established by these and other studies (154, 155). Such complications include peripheral neuropathy, microangiopathy, microcirculatory disturbances, impaired leukocyte phagocytosis, and glycosylation of tissue proteins. Each has adverse effects on the diabetic foot: They can contribute to the etiology of foot ulceration, delay normal wound healing, and subsequently lead to amputation (25, 30, 48, 50, 72). Several studies have reported a significant correlation between elevated glucose and LEA (21, 141, 156-161). Amputation has also been associated with other diabetes-related comorbidities such as nephropathy, retinopathy, and cardiovascular disease (21, 48, 144). Aggressive glucose control, management of associated comorbidities, and appropriate lower extremity care coordinated in a team environment may indeed lower overall risk for amputation (30, 90, 162-166).

The best predictor of amputation is a history of previous amputation. A past history of a lower extremity ulceration or amputation increases the risk for further ulceration, infection, and subsequent amputation (29, 142, 157, 167). It may also be inferred that patients with previous ulceration possess all the risk factors for developing another ulceration, having demonstrated that they already have the component elements in the causal pathway (24, 27, 28, 57). Up to 34% of patients develop another ulcer within 1 year after healing an index wound, and the 5-year rate of developing a new ulcer is 70% (164, 168). The recurrence rate is higher for patients with a previous amputation because of abnormal distribution of plantar pressures and altered osseous architecture. The cumulative risks of neuropathy, deformity, high plantar pressure, poor glucose control, and male gender are all additive factors for pedal ulceration in these diabetic patients (26, 46, 50, 57, 111). Re-amputation can be attributed to disease progression, nonhealing wounds, and additional risk factors for limb loss that develop as a result of the first amputation. Tragically, the 5-year survival rate