REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Diabetic Foot Ulcers and Their Recurrence

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Complications of diabetes that affect the lower extremities are common, complex, and costly. Foot ulceration is the most frequently recognized complication. In a community-based study in the northwestern United Kingdom, the prevalence of active foot ulcers identified at screening among persons with diabetes was 1.7%, and the annual incidence was 2.2%.[1] Higher annual incidence rates have been reported in specific populations: 6.0% among Medicare beneficiaries with diabetes, 5.0% among U.S. veterans with diabetes, and 6.3% in the global population of persons with diabetes.[2-4] On the basis of 2015 prevalence data from the International Diabetes Federation,[5] it is estimated that, annually, foot ulcers develop in 9.1 million to 26.1 million people with diabetes worldwide. The proportion of persons with diabetes and a history of foot ulceration is understandably higher than the proportion with an active ulcer; 3.1 to 11.8% of persons with diabetes, or 12.9 million to 49.0 million persons worldwide and 1.0 million to 3.5 million in the United States alone, have a history of foot ulceration.[1,5-7] The lifetime incidence of foot ulcers has previously been estimated to be 15 to 25% among persons with diabetes,[8] but when additional data are considered, between 19% and 34% of persons with diabetes are likely to be affected (for the calculation, see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Natural History of Diabetic Foot Ulcers

The natural history of a diabetes-related foot ulcer is sobering. The risk of death at 5 years for a patient with a diabetic foot ulcer is 2.5 times as high as the risk for a patient with diabetes who does not have a foot ulcer.[9] More than half of diabetic ulcers become infected.[10] Approximately 20% of moderate or severe diabetic foot infections lead to some level of amputation.[11,12] Peripheral artery disease independently increases the risk of nonhealing ulcers, infection, and amputation.[13,14] Mortality after diabetes-related amputation exceeds 70% at 5 years for all patients with diabetes and 74% at 2 years for those receiving renal-replacement therapy.[15] Whether such a high mortality is due to a combination of coexisting conditions (including the risk from an amputation procedure), lack of activity, and deconditioning or to other factors is not clear. The risk of death at 10 years for a patient with diabetes who has had a foot ulcer is twice as high as the risk for a patient who has not had a foot ulcer.[16]

A recent assessment of 785 million outpatient visits by people with diabetes in the United States between 2007 and 2013 suggested that diabetic foot ulcers and associated infections constitute a powerful risk factor for emergency department visits and hospital admission.[17] The rate exceeds the rates for congestive heart

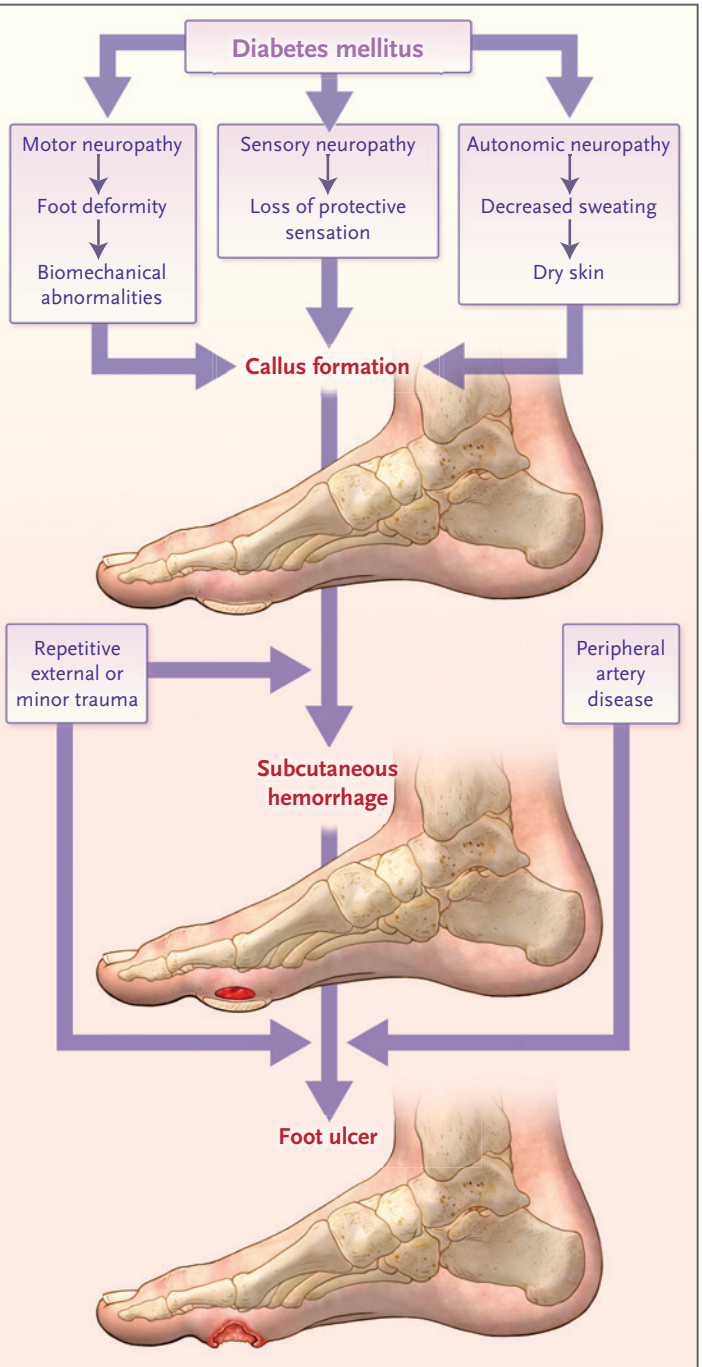

Figure 1. Common Pathway of Diabetic Foot Ulcer Occurrence and Recurrence.
Diabetic foot ulcers and their recurrences are caused by a number of factors that ultimately lead to skin breakdown. These factors include sequelae related to sensory, autonomic, and motor neuropathies.

failure, renal disease, depression, and most forms of cancer. Data from England suggest that during the 2010–2011 period, just under 10% of hospital admissions among patients with diabetes were either for ulcer care or for amputation.[18]

Similarly, the direct costs of treating diabetic foot complications exceed the treatment costs for many common cancers.[19,20] In the United States, a total of $176 billion is spent annually on direct costs for diabetes care; as much as one third of this expenditure is lower-extremity–related, constituting a substantial cost to society.[21,22]

Diabetic foot ulcers are commonly caused by repetitive stress over an area that is subject to high vertical or shear stress in patients with peripheral neuropathy.[23,24] Peripheral artery disease, when present, also contributes to the development of foot ulcers.[23] Figure 1 shows the pathogenesis of a typical diabetic foot ulcer.

ULCER HEALING

With appropriate therapy — surgical débridement, off-loading of pressure, attention to infection, and if necessary, vascular reconstruction — foot ulcers heal in many patients, and the need for amputation is averted.[25,26] On the basis of outcome data in specialized tertiary care hospitals in Europe, approximately 77% of diabetic foot ulcers heal within 1 year.[27] Factors associated with poor healing include advanced end-organ disease (congestive heart failure, peripheral artery disease, or end-stage kidney disease requiring renal-replacement therapy) and the inability to walk independently.[27]

ULCER RECURRENCE AND REMISSION

Unfortunately, even after the resolution of a foot ulcer, recurrence is common. By reviewing 19 compatible studies on incidence rates for ulcer recurrence,[28-46] we estimate that roughly 40% of patients have a recurrence within 1 year after ulcer healing, almost 60% within 3 years, and 65% within 5 years (Fig. 2). Thus, it may be more useful to think of patients who have achieved wound closure as being in remission rather than being healed. The concept of remission may also provide a better framework for allocating resources, organizing care, and communicating information about risk.[47] The number of patients in remission is, by definition, far greater than the number of patients who have active diabetes-related foot complications.[1,7,10,12] Furthermore,

for the minority of patients whose ulcers do not heal or for whom healing would pose an undue medical or social burden, a palliative approach that reduces the complexity of care and minimizes the risk of infection and the need for hospitalization may be preferable.[48]

The reasons that ulcer recurrence rates are so high appear to be biologic or behavioral or both. Many precipitating factors that led to the ulcer in the first place, such as peripheral neuropathy, foot deformity, increased plantar stress, and peripheral vascular disease, are generally not resolved after healing.[49] Although foot structure and blood supply to the foot may be improved by surgical intervention, such procedures do not resolve the profound concomitant neuropathy, which is the permissive component in the process that is triggered by repetitive stress and that leads to inflammation and ulceration.[50] Therefore, these physical factors may still conspire to cause an ulcer.

Physical factors may predominate in patients who have a history of a foot ulcer. Such patients have usually lost the "gift of pain," first described by Dr. Paul Brand in patients with leprosy.[51] Patients who lack the warning symptoms associated with pain may not take the appropriate preventive measures, such as wearing their prescribed footwear at all times.[52] The skin is normally weak just after an ulcer has healed, which is a time when patients should wear protective therapeutic footwear but might walk barefoot.[53] Moreover, after a foot ulcer has healed, many patients think that they no longer have a foot problem, an opinion that may be shared by their caregivers. Consequently, the patients may not receive the follow-up podiatric care that is required to identify warning signs of a recurrence and to provide appropriate treatment.[54] All these behavioral factors combine to increase the chance of ulcer recurrence.

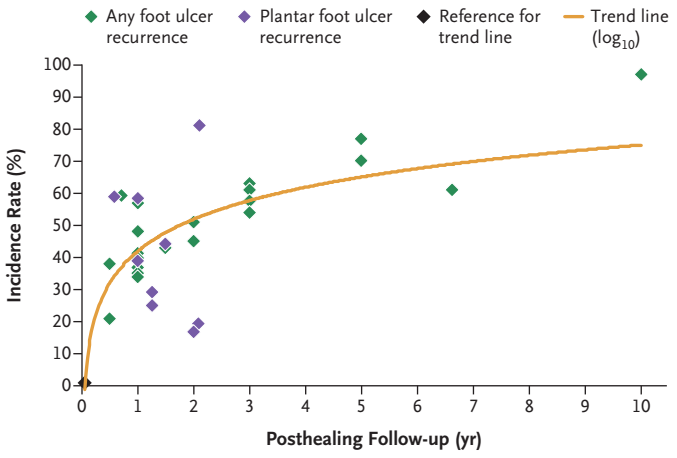

Figure 2. Incidence of Ulcer Recurrence.

Data are from nine prospective follow-up studies, one retrospective study, and the control groups (i.e., patients who received usual care) in nine randomized, controlled trials.[28-46] These studies were selected from a total of 322 reports identified from a PubMed search on September 27, 2016, with the use of "diabetes," "ulcer," and "recurrence" as the search terms. Some reports provided recurrence rates at multiple years (e.g., rates at 1, 3, and 5 years), hence the higher number of observations than studies. Only studies including at least 30 patients (in the usual-care group) were selected. An individual study with such a small sample may not have sufficient validity for drawing conclusions, but this minimum number was chosen to include enough studies for trend-line analysis, which seems valid from the 19 studies and 30 observations included. Studies could report on either all ulcers on the foot or ulcers on the plantar surface. A reference point at 0,0 has been included so that the trend line could be drawn. Ten-year recurrence data are from Morbach et al.[31]

REDUCING THE RISK OF RECURRENCE

Because of the high risk of infection, hospital admission, and amputation, prevention of ulcer recurrence is one of the most important topics in the current approach to diabetic foot disease. To guide preventive strategies, a good understanding of the factors that predict ulcer recurrence is needed. Furthermore, there are several intervention strategies that may be helpful in increasing the number of ulcer-free days for patients with a history of foot ulceration.

The strongest predictor of diabetic foot ulceration is a previous foot ulcer.[23,55] Studies involving patients with healed foot ulcers show that early signs of skin damage such as abundant callus, blistering, or hemorrhage are among the strongest predictors of ulcer recurrence (Fig. 3).[28,33,42,52,56] If these preulcerative lesions are identified in a timely manner, treating them is likely to prevent many ulcer recurrences. Biomechanical factors such as the degree of barefoot and in-shoe mechanical stress and the level of adherence to wearing prescribed footwear are also important factors in the recurrence of ulcers on the plantar foot surface (Fig. 3),[52] and in-shoe mechanical stress is a factor in the recurrence of nonplantar foot ulcers, mostly through ill-fitting footwear. Because these biomechanical factors are amendable, proper treatment may have an

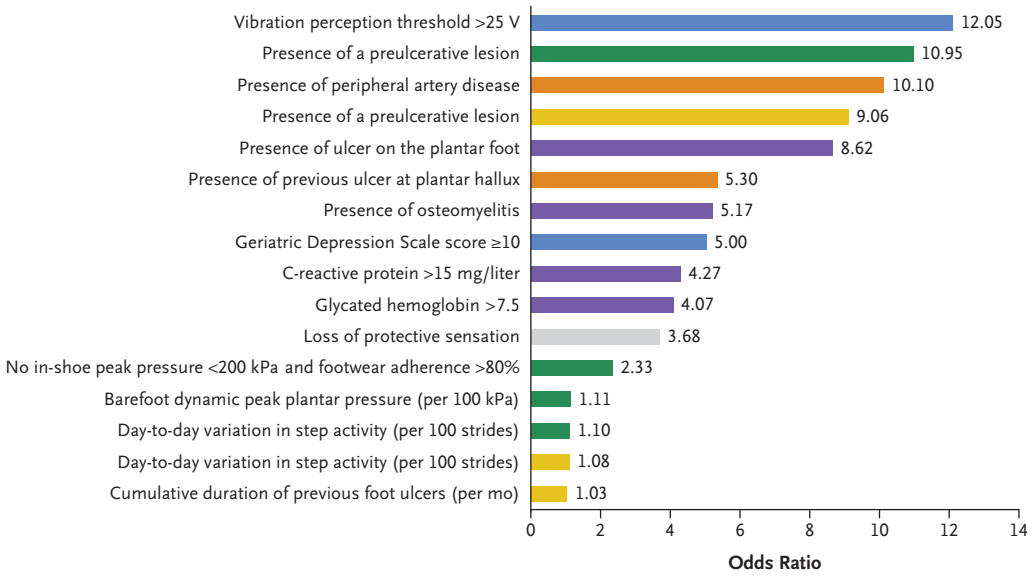

Figure 3. Risk Factors Independently Associated with Ulcer Recurrence.

Data are from five studies that reported an odds or risk ratio.[28,33,42,52,56] According to Monami et al.[42] (blue), risk factors for ulcer recurrence are a vibration perception threshold greater than 25 V and a Geriatric Depression Scale score of 10 or higher (scores range from 0 to 15, with higher scores indicating more severe depression). According to Peters et al.[56] (orange), risk factors for ulcer recurrence are the presence of peripheral artery disease and location of the previous ulcer at the plantar hallux. According to Dubský et al.[28] (purple), a plantar location of the ulcer, the presence of osteomyelitis, and elevated blood levels of C-reactive protein and glycated hemoglobin (all of which were determined at the time of study enrollment for patients with an active foot ulcer) are independent predictors of recurrence of foot ulcers. According to Reiber et al.[33] (gray), loss of protective sensation is a risk factor for recurrence of an ulcer on the plantar surface of the foot. According to Waaijman et al.,[52] risk factors for recurrence of an ulcer on the plantar surface of the foot (yellow) include the presence of a preulcerative lesion, low day-to-day variation in step activity, and a long cumulative duration of previous foot ulcers; risk factors for recurrence of a pressure-related plantar ulcer (green) include the presence of a preulcerative lesion, lack of both in-shoe peak pressure below 200 kPa and therapeutic-footwear adherence higher than 80%, high barefoot dynamic peak plantar pressure, and low day-to-day variation in step activity.

important role in preventing foot ulcer recurrence.

In 2015, the International Working Group on the Diabetic Foot systematically reviewed the medical literature on interventions for the prevention of ulcer recurrence.[24,57] Patient education is considered important and can improve patients' knowledge of diabetes-related foot problems and foot care.[36] When given in only one or two sessions, however, patient education does not effectively prevent ulcer recurrence at 6 or 12 months.[36] This apparent lack of efficacy provides an opportunity to strengthen clinician-to-patient educational efforts, through more continuous education or the use of specific educational techniques, but also to do more to promote and measure outcomes associated with clinician training in diabetic foot care and counseling. To that end, Germany and Belgium have ratified national guidelines on the certification of specialty centers for diabetic foot care. A major part of that certification focuses on clinician training, along with assessment of the training.[58]

Limited data are available on the effect of self-management. Home monitoring of foot skin temperatures, as well as appropriate foot care when the temperature difference between feet exceeds a specified threshold, can effectively reduce the incidence of recurrent plantar ulcers.[34,59,60] High-quality evidence shows that consistent use of footwear with demonstrated relief of plantar pressure, as compared with standard-of-care

Table 1. Effect Sizes in Studies of Interventions to Reduce the Risk of Foot Ulcer Recurrence.*

Intervention Category	Effect of the Intervention			Effect of Adherence to Treatment	
	No. of Studies	Mean Sample Size	Mean Effect Size†	No. of Studies	Mean Effect Size‡
		no. of patients (range)	*% (range)*		%
Integrated foot care	Four[35,61,62]§	179 (53 to 549)	30.9 (9.1 to 100)	Two[63,64]	76.7
Self-management	Four[34,59,60,65]	138 (70 to 225)	54.3 (–5.4 to 90.0)	One[34]	98.0
Patient education	Two[36,46]	152 (131 to 172)	–13.4 (–26.3 to –0.5)	Two[66,67]	85.5
Therapeutic footwear	Nine[29,30,33,37,68-72]	181 (46 to 400)	47.2 (–14.6 to 92.9)	Two[29,73]	58.1
Foot surgery	Seven[38,39,74-78]	73 (40 to 207)	61.8 (10.4 to 100)	None	—

* The five categories of preventive interventions were assessed for the 2015 systematic review of ulcer prevention performed by the International Working Group on the Diabetic Foot.[57] All studies were controlled prospective or retrospective studies (randomized trial, cohort study, or case–control study). Information about the quality of the studies can be obtained from the systematic review.[57]

† The mean effect size is expressed as the percentage reduction in the risk of recurrent foot ulcer in the intervention group as compared with the group receiving usual care (control group). Therefore, negative percentages indicate an increase in the risk of recurrent foot ulcer in the intervention group as compared with the control group.

‡ The mean effect size is expressed as the percentage reduction in the risk of recurrent foot ulcer among patients who adhered to the study treatment as compared with those who did not adhere to the study treatment.

§ A fourth study of integrated foot care, by van Putten et al., is ongoing (ISRCTN number, 50646165).

therapeutic footwear, prevents the recurrence of plantar ulcers — specifically, recurrent ulcers on the plantar surface of the metatarsal heads.[29,30] Foot surgery can effectively reduce the risk of recurrent ulcers, both plantar and nonplantar, in selected patients with an active foot ulcer that has not responded to nonsurgical treatment. In fact, foot surgery appears to be relatively more effective in preventing ulcer recurrence than in healing an active foot ulcer, but more well-designed studies are needed before definitive statements about safety and efficacy can be made.[26] Table 1 shows the effect sizes of interventions in five categories on the prevention of foot ulcer recurrence in persons with diabetes, as systematically reviewed by the International Working Group on the Diabetic Foot.[57]

ADHERENCE TO TREATMENT

Adherence to treatment has now been confirmed to play an important role in the clinical outcome.[24,57] Clinical trials of plantar ulcer healing have suggested strongly that pressure-relief devices that cannot be removed are associated with faster healing of ulcers than are removable devices.[24,26] Furthermore, seven intervention studies,[29,34,63,64,66,67,73] most of which were randomized, controlled trials, investigated the effect of adherence to specific recommendations for preventing ulcer recurrence, both plantar and nonplantar, and all these trials showed that patients who follow the recommendations (obtaining professional foot care, monitoring their foot temperatures, or wearing therapeutic footwear) have significantly better outcomes than those who do not follow the recommendations (Table 1).[57,79] Effect sizes range from 58 to 98%; the overall effects of various preventive interventions (Table 1) are dampened by the fact that large numbers of patients do not adhere to the recommended treatment.[79]

The problem of nonadherence should guide clinical practice much more than is currently the case, with a focus on identifying patients who are nonadherent or are anticipated to be nonadherent and aiming to improve adherence in conjunction with providing proper evidence-based foot care. An understanding of the reasons for nonadherence and the development of ways to improve adherence are urgently needed to help clinicians in this effort. We hypothesize that integrated wearable technologies (i.e., technologies that can provide information to the patient and clinician about whether and for how long the patient is wearing a given protective device) may be helpful in fostering this approach.

RECURRENCE OF PLANTAR AND NONPLANTAR ULCERS

Most interventions, such as specialized footwear, self-management, and most surgical procedures, focus on preventing ulcer recurrence on the plantar foot surface. Plantar ulcers account for

approximately 50% of foot ulcers seen in specialized clinics.[10] These ulcers are more difficult to prevent than nonplantar ulcers because of the weight-bearing biomechanics involved in a neuropathic limb, which is often devoid of painful feedback. Nevertheless, most nonplantar ulcers are on the dorsum or distal aspect of digits as a result of contractures and are also subject to moderate repetitive stress associated with neuropathy. Properly fitting shoes or specific surgical interventions are required to prevent recurrence of these ulcers. Several predictive factors, such as peripheral neuropathy, peripheral artery disease, and elevated glycated hemoglobin levels (Fig. 3) also contribute to nonplantar ulcers. Most studies of integrated foot care and patient education, as well as some studies of surgical intervention, focus on both plantar and nonplantar ulcers. Therefore, in discussing an overall strategy to prevent ulcer recurrence, we are referring to both plantar and nonplantar foot ulcers, unless we specify one type or the other.

STRATEGY FOR OVERALL PREVENTIVE MANAGEMENT

Knowledge of the predictors of foot ulcer recurrence (Fig. 3) that may be altered by evidence-based interventions (Table 1) can be used to develop an overall strategy for preventive management. Such management should involve an integrated approach (Table 1).[57] However, integrated approaches that have been investigated do not involve state-of-the-art interventions or interventions that have recently been shown to have a large effect size, nor do they involve specific knowledge about factors that predict ulcer recurrence.

Prevention of foot ulcer recurrence requires good diabetes control, ongoing professional foot care at intervals of 1 to 3 months, and properly fitting footwear that has a demonstrated effect on the relief of plantar pressure. Furthermore, the temperature of the skin on the foot should be monitored and additional foot care instituted if any signs of inflammation appear. A strong educational focus with a team approach may help to promote patients' adherence to treatment recommendations.[79,80] A vascular (surgical) intervention should be performed to address peripheral vascular disease. Surgery may also be required for biomechanical protection if nonsurgical treatment is not successful. Most recurrent foot ulcers are preventable when such recommendations are implemented.

Early recognition of new lesions in a patient with a previous diabetic foot ulcer is critically important for reducing the risk of complications. Callus, especially if hemorrhagic, is such a lesion; repetitive shear and vertical stress, in the absence of intervention, are likely to result in ulcer formation.[52] With the use of current techniques and technologies, the factors that lead to a preulcerative callus in the neuropathic foot can be identified and mitigated. Repetitive stress can be detected with a pressure platform and in-shoe pressure sensors.[81] Such measurements can also be used to enhance the stress-reducing properties of therapeutic footwear and lower the risk of callus development and ulcer recurrence.[29,30,82]

Before diabetic foot ulcers develop, inflammation may be detected with the use of a simple infrared thermometer. Data from three randomized, controlled trials strongly favor the use of home-based thermometry to identify preulcerative plantar inflammation, as reflected by elevated temperatures.[34,59,60] Patients can be counseled to limit their activity when such inflammation is present, just as they are instructed to modify insulin dosing after checking their blood glucose level. Such home-based and wearable or in-shoe–based strategies may facilitate home care and eliminate the need for hospital-based care. Although data strongly support the use of such strategies, implementation to date has not been widespread, ostensibly because of some key barriers, including the burden of having to check foot temperature at several locations on the foot on a daily basis over the course of a lifetime and the lack of easy access to calibrated equipment, the lack of reimbursement by insurance programs and health ministries, and the lack of industry interest in developing the technologies. A recent study suggests that use of newer-generation "smart mats" to measure temperatures may address at least some of these barriers to adoption.[83]

FUTURE PERSPECTIVES

For the patient with a foot ulcer in remission, there is a good chance of preventing a recurrent ulcer when state-of-the-art knowledge on prevention is put into practice. The International Working Group on the Diabetic Foot has provided clinicians with various evidence-based recommendations for prevention that may have a major effect in reducing the risk of ulcer recur-

rence and reducing the burden of this disease on patients and society.[26,53] New studies of the cost-effectiveness of current integrated and innovative approaches and of the efficacy of technological support and patient feedback for improving self-management and treatment adherence may foster the development of additional effective strategies for preventing ulcer recurrence. A specific focus on behavior and its role in adherence to and outcomes of therapy will also be important.

SUMMARY

Lower-extremity complications of diabetes such as foot ulcers constitute a substantial burden for people with diabetes. Once healed, foot ulcers frequently recur. This fact, coupled with demographic trends, requires a collective refocusing on prevention and a reallocation of resources from simply healing active ulcers to maximizing ulcer-free days for all patients with a history of diabetic foot ulceration. Aggressive therapy during active disease combined with a focus on improving care during remission can lead to more ulcer-free days, fewer inpatient and outpatient visits, and an improved quality of life.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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