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Nonsurgical Management of Chronic Wounds in Patients With Diabetes

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Background

Diabetes mellitus increases the risk for disorders that result in more frequent hospitalizations, longer in-patient stays, and increased morbidity and mortality. The incidence and severity of coronary artery disease, cerebrovascular disease, and peripheral artery macrovascular and microvascular diseases are greater in diabetics than in nondiabetics. Diabetic foot wounds are the single greatest cause of nontraumatic amputations. Unfortunately, in both inpatient and outpatient settings, diabetes management is often a secondary consideration when compared with the presenting condition or problem.[1]

It is well known that diabetics are more susceptible to infection than are nondiabetics[2] secondary to hyperglycemia-induced phagocyte dysfunction. These defects include impairment of phagocyte adherence, chemotaxis, phagocytosis, and bacterial killing.[2–18] The defects are at least partially reversible once blood glucose levels are controlled.[12,15] *In vitro* studies suggest that blood glucose levels greater than 200 mg/dl are sufficient to cause leukocyte dysfunction.[13,14,16] Clearly, hyperglycemia causes immunosuppression. Reduction of serum glucose restores immune functions.

Hyperglycemia is also causally linked to a variety of vascular problems, including hypertension[19–21] and thrombosis.[22–26] However, the hyperglycemic impairment of microvascular blood flow and microvascular responses to injury are large contributors to the development of chronic ulcers in patients with diabetes and to overall resistance to healing of even noninfected wounds. Diabetic microangiopathy and foot ulcer development are the result of a spectrum of factors that include continuous trauma, neuropathy, immunosuppression, arterial occlusive disease, and capillary perfusion and permeability dysfunction.[27–33] Diabetic microangiopathy is a type of high perfusion angiopathy that can mimic chronic venous insufficiency[27–35] and is associated with the development of stasis-related increases in capillary pressure.[29–44] Furthermore, diabetes disrupts the autonomic pathways of regulation of skin perfusion, even before development of the regional sensory loss, or neuropathy, that is common in patients with diabetes.[45] Diabetic sensory neuropathy also affects the neurally mediated vasodilatory response normally associated with increased local cutaneous pressure.[46–49] In patients with diabetes, cutaneous blood flow is decreased in proportion to the increased local pressure. Skin temperature and microcirculatory flow are closely related,[50] and it is likely that the aberrant, pressure-induced decrease in skin blood flow is exacerbated by the typically low skin temperature in patients with diabetes. The inability of skin microcirculation in diabetics to respond appropriately to injury is an important factor leading to chronic wounds and diabetic ulcer development. The similarly abnormal responses of skin capillary beds in diabetics to warm water immersion and cold water immersion challenges suggest enhanced arteriovenous anastomotic blood flow resulting in reduced nutritional blood flow.[51]

Diabetic Foot Ulcers

Among diabetics, the prevalence of foot ulcers is estimated at 4% to 10%, the annual incidence is 1% to 4% and the lifetime incidence can approach 25%.[52] These ulcers frequently are infected, cause great morbidity, result in huge costs, and often lead to lower-extremity amputation.[52] Diabetic foot ulcers require early, aggressive, rational treatment strategies to minimize morbidity, avoid amputation, and achieve healing. Factors that must be vigorously and effectively addressed include metabolic control, the presence of tissue ischemia, infection and ongoing trauma.[53] The frequently encountered combination of infection with multiple drug-resistant organisms, diabetic immunosuppression, and ischemia-induced tissue necrosis in diabetic foot ulcers often results in adverse treatment outcomes.[53] Treatment strategies are varied but nearly all are based on the principles of offloading or other means of extramural pressure reduction, antibiosis, and improved local perfusion. The latter may require macrovascular intervention to correct blood flow obstructions in proximal arteries via angioplasty, atherectomy or arterial bypass surgery. At the local level, however, the use of wound care products containing stabilized, superoxidized water (Dermacyn Wound

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Care. Oculus Innovative Sciences, Petaluma, CA) will often improve wound bed vascularity via increased capillary perfusion and acceleration of the development of neovascularity (Figures 1–3). The same superoxidized solutions kill most single-cell organisms within seconds of contact,[54] thus dramatically reducing bacterial bioburden. Both of these effects result in the significant acceleration of the granulation and epithelialization processes with complete healing occurring in less than 4 weeks on average. Of course, these results cannot be obtained without concomitant assertion of glycemic control, offloading, nutritional amendment and, whenever possible, smoking cessation. Documented improvements in $TcPO_2$, as seen in Figures 1–3, are all measured within 1 cm of the ulcer and are sustained for at least 36 hours without additional exposure to superoxidized water. The visibly improved tissue oxygenation and blood flow is likely caused by dilation of precapillary arterioles, which reduces or eliminates the microvascular arteriovenous shunting that occurs in diabetic tissue beds. Unfortunately, smoking will immediately return $TcPO_2$ and microvascular perfusion to pretreatment levels. The failure to sustain tissue oxygen improvement greatly retards ulcer healing in diabetic smokers.

Leg Ulcers

Leg ulcers are caused by circulatory impairment. In brief, a venous ulcer occurs when venous valves are damaged thus producing venous reflux, pooling and increased venous pressure. The increased pressure causes fluid to leak into surrounding tissues and this prevents local tissue oxygenation resulting in tissue necrosis and an open ulcer. Such wounds can be heavily exudative, malodorous and painful. Venous leg ulcers are the most common type of chronic wound with an annual incidence of 2.5 million.[55]

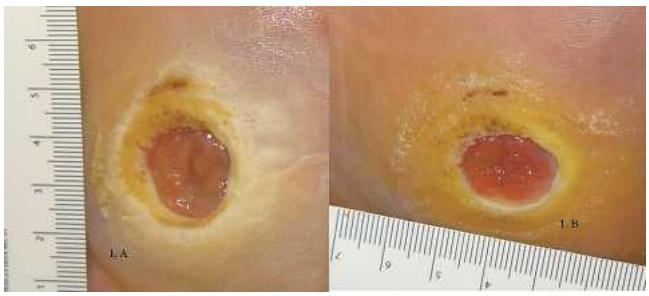

Figure 1

A 68-year-old woman with type II diabetes is shown with a fairly typical diabetic plantar ulcer that is circumscribed, invested with a thick layer of brittle callus and some macerated tissue. At the time of presentation (A,) the ulcer had been present for 13 months. This lesion was underlying the left second metatarsal head. The ulcer bed in (A) is dusky and cyanotic. $TcPO_2$ measured 5 mm lateral to the ulcer was 35 mmHg. The photo in (B) was obtained 36 hr after a single, 60-sec exposure to superoxidized water. Note the improved color of the ulcer itself and the surrounding tissue. $TcPO_2$ measured at the same site, i.e., 5 mm lateral to the ulcer, was 89 mmHg.

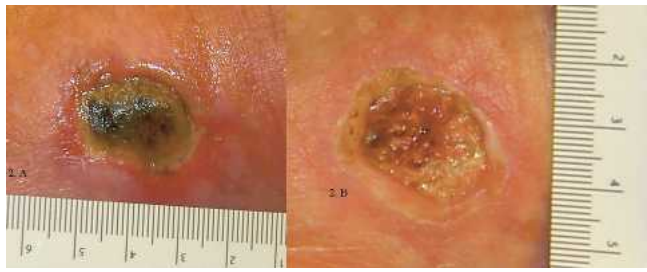

Figure 2

A 56-year old woman with type II diabetes, who has a 40 pack-year smoking history, is shown. (A) depicts a necrotic wound that developed on the dorsolateral aspect of the left foot when the patient wore a new pair of shoes. At this time, the wound had been present for 4 months. Purulent exudate was cultured and found to be positive for a very resistant strain of Escherichia coli. *$TcPO_2$ measured 1 cm medial to the lesion was 41 mmHg. (B) was obtained 72 hr after a single, 2-min exposure of the wound to superoxidized water. The patient reported that she had refrained from smoking for the 72-hr period as well. $TcPO_2$ measured at the same site, i.e., 1 cm medial to the ulcer was 78 mmHg. Note that necrotic material has sloughed leaving a clean, partially granulated wound bed that is free of purulent exudate. The lesion went on to heal completely by day 10.*

An arterial ulcer results from arterial flow obstruction, resulting in tissue ischemia. These lesions are more common in diabetics than in nondiabetics and are usually extremely painful. Occasionally, leg ulcers may arise from a combination of both arterial and venous pathologies. Without restoration of tissue oxygenation and nutrition via improved capillary function, such wounds are very painful and are notoriously difficult to heal. Severe infection of such lesions is common. As with diabetic foot ulcers, the use of superoxidized water in the treatment of these lesions results in rapid and dramatic improvement.

Pressure Ulcers

Pressure ulcers occur over bony prominences when a person is immobilized. Sustained pressure reduces cutaneous blood flow resulting in tissue ischemia, necrosis, and ulcer formation. Pressure ulcers can be small or large and can involve skin, muscle, and bone. More than 2 million pressure ulcers occur each year. Older individuals are particularly vulnerable to pressure ulcer development as are patients with hip fractures, people undergoing prolonged surgical procedures or hospitalizations, spinal cord injury patients, and patients who, for any reason, experience long periods of immobility. It can be argued that diabetic foot ulcers are, in fact, a form of pressure ulcer.

Any form of pressure ulcer in a diabetic patient requires aggressive and persistent treatment aimed at relieving the pressure (offloading), instituting glycemic control, eliminating infection and improving circulation to the region. Local, noninvasive monitoring of skin blood flow via laser Doppler flowmetry and/or $TcPO_2$ provide reliable documentation of the vascular status of wound tissues and can serve as predictors of wound healing.

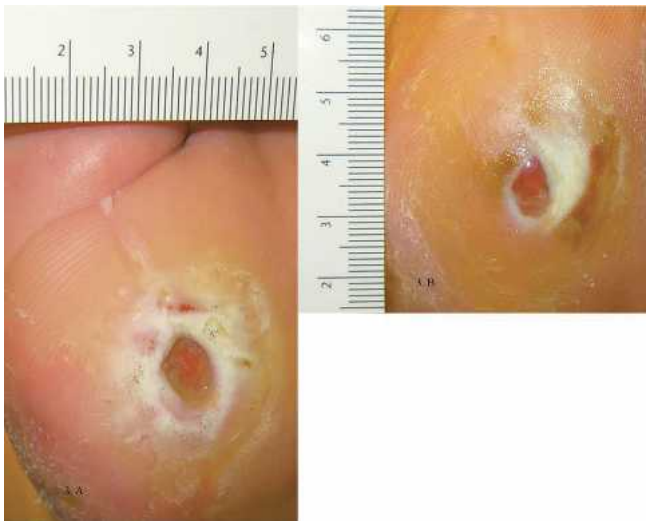

Figure 3

A 46-year-old woman with type II diabetes is shown. (A) shows a diabetic plantar ulcer underlying the right first metatarsal head. This wound had been present for a year. The second, fourth, and fifth toes had been amputated previously. At the time of presentation, the patient had already received 30 days of intravenous vancomycin for the methicillin-resistant Staphylococcus aureus *infection present in the ulcer. Cultures obtained after presentation to the wound clinic were positive for vancomycin-resistant* S. aureus. *$TcPO_2$ obtained 1 cm medial to the ulcer was 23 mmHg. In (B), the ulcer is shown 48 hr after a single, 60-sec exposure to superoxidized water. Note the expansion of granulation tissue, reduction of surrounding maceration, absence of exudates, and reduction of ulcer diameter (8 mm diameter in A, 6-mm diameter in B). $TcPO_2$ obtained at this time was 80 mmHg.*

Burns

In the United States alone, more than one million burn cases occur each year.[56] When burns occur in diabetic patients, healing is delayed by the vascular insufficiency caused by diabetes *per se* as well as the immunosuppression and insulin deficiency of this disease.[57] The circulatory impairment affects the peripheral arteries and results in tissue hypoxia. The inhibition of phagocytosis cased by hyperglycemia leaves the diabetic burn victim particularly susceptible to infection. Insulin deficiency negatively affects fibroblasts, thus reducing protein synthesis and glucose absorption.[58]

In a recent study, Shalom et al.[59] noted that diabetic burn patients were older, underwent more surgical procedures, and had a greater rate of mortality than their matched, nondiabetic burn patient counterparts. Furthermore, diabetics had a higher incidence of scald burns to the legs and feet than did the nondiabetic group, and this scenario is likely the result of diabetic sensory neuropathy.

The diabetic burn patient has several unique requirements.[59] The prevalence of burns to the legs and feet is associated with elevated infection rates, prolonged hospitalization, and increased need for skin grafting. The older age of diabetic burn patients carries with it an increased rate of morbidity and mortality secondary to the comorbidities that are common to diabetics of long standing. The combination of poor wound healing and diabetic immunosuppression increases the incidence of cellulitis and sepsis. Burn injury in diabetics exacerbates insulin resistance thus requiring rigid glucose control. The decreased vascularity in the legs and feet of diabetics leads to further tissue hypoxia and necrosis.

Accelerated development of clean granulation tissue and neovascularity, facilitated by use of superoxidized water, predispose burned areas to readily accept skin grafts. Close monitoring of adjacent skin perfusion, via $TcPO_2$ and/or laser Doppler flowmetry is a valuable tool in the estimation of healing potential. The profound antibiotic capability of superoxidized water, the lack of mammalian tissue toxicity and positive microvascular effects make this agent uniquely appropriate for facilitating healing in diabetic burn patients.

Summary

Wounds fail to heal in a timely and orderly manner when regional blood flow is impaired, when infections are present and host immune mechanisms are damaged, and when invading flora are multidrug resistant. In the diabetic patient, the impact of all of these factors is commonly present and can have devastating effects, including limb loss and death. Key to healing wounds in diabetics is the resolution of metabolic issues, restoration of blood flow to ischemic and hypoxic tissues, and elimination of infection. None of these goals is simple, but all are necessary to reduce the staggering economic and social costs of wound care in diabetics. New wound treatment options, including superoxidized water and negative pressure devices,[60] antibacterial dressing materials, etc are having a positive effect on healing outcomes in general. New agents for ameliorating diabetes itself are increasingly available and will, hopefully, allow the patient to disrupt the downward spiral so common to the development, and retarded healing, of chronic wounds that occur in patients with diabetes.

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