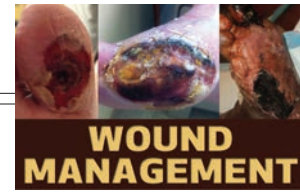

Healing Diabetic Wounds

Here's the latest on treatment options.

BY JOHN M. GIURINI, DPM

Introduction

The prevalence of diabetes worldwide was estimated to be 2.8% in 2000, and is expected to approximately double to 4.4% in 2030.[1] Since 15% of those diagnosed with diabetes will develop a foot ulceration in their lifetime,[2] it is anticipated that the number of diabetic foot ulcers (DFUs) will continue to drastically increase. The goal of healing DFUs lies in recognizing the type and nature of the wound, and thus supporting proper wound healing by providing an optimal healing environment. With the knowledge and use of topical wound care therapies, this optimal wound-healing environment can be supported and maintained.

Wound Healing Phases

Wound healing is a dynamic and evolving process. There are four main phases to wound healing, which are continuous and overlapping. These phases include rapid hemostasis, inflammation, proliferation, and remodeling.[3] The first phase consists of vasoconstriction and fibrin clot formation. The fibrin clot and surrounding wound tissues release pro-inflammatory cytokines and growth factors, such as platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and epidermal growth factor (EGF). These substances help initiate the second stage of wound healing, the inflammatory phase, by promoting chemotaxis of neutrophils, macrophages, and lymphocytes.[4]

Neutrophils are often the first responders, helping to remove invading bacteria or cellular debris. Similarly, in the early stages, macrophages help remove cellular debris, but later go on to a phenotypic transition that helps to stimulate and attract fibroblasts and keratinocytes, and initiate the process of angiogenesis.[5] While not entirely known, lymphocytes, such as T-lymphocytes, also hold an important role in the inflammatory phase. They are believed to contribute by releasing important cytokines for cell-to-cell communication, defending the wound from pathogens and regulating inflammation, thus allowing the proliferative phase to peak.[3-6]

The proliferative phase is characterized by the migration and maturation of fibroblast and endothelial cells. These cells are necessary for wound healing as they promote collagen formation, support capillary growth, lay the foundation of granulation tissue, and contribute to the formation of the extracellular matrix (ECM). As briefly described, the proliferative phase is quite robust, but eventually calms and leads to the long-term phase of remodeling. During this phase, the ECM is remodeled to help support the architecture of normal tissue, and contraction of the wound itself occurs through the aid of the myofibroblasts.[7] The remodeling phase is a slow process, and can often last years.

Factors Affecting Wound Healing

Any interruption to this dynamic healing process will lead to delayed healing or chronic wounds. Perhaps, some of the most common and devastating factors that contribute to DFUs and their chronicity include ischemia, sensory neuropathy, and infection.

Oxygen is essential to all phases of wound healing, as it is necessary for cellular metabolism and production of energy in the form of ATP. Adequate tissue oxygenation promotes angiogenesis, prevents infection, induces keratinocyte and fibroblast maturation, and proliferation. This leads to re-epithelialization and formation of collagen, which aids in wound contraction.[8]

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Peripheral vascular disease is a common complication of those afflicted with diabetes. Microvascular changes are seen in the way of capillary size reduction and basement membrane thickening.[9] This leads to a poor oxygen environment or hypoxic state of the DFU, often clinically appearing as a dry or necrotic wound.

Peripheral sensory neuropathy is another contributor to the DFU which can delay wound healing. In one study that looked at the causal pathway of DFUs, it was estimated that in 78% of the cases, peripheral sensory neuropathy was present.[10] Peripheral sensory neuropathy perhaps initiates the development of the DFU, beginning with the patient being unable to sense pain. This leads to repetitive trauma in areas of peak plantar pres-

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sures, which disrupts normal tissues or worsens existing ulcerations.[11] This propagates as a vicious cycle, often going unrecognized until significant DFUs or complications are seen.

A decrease in important chemotactic neuropeptides, including nerve growth factor, substance P, and calcitonin (a gene-related peptide) have been demonstrated in patients with neuropathy.

In addition, it has been shown that patients with peripheral sensory neuropathy also have decreased levels of lymphocyte infiltration.[12] As such, these wounds are trapped in the inflammatory phase, often leading to exudative types of wounds.

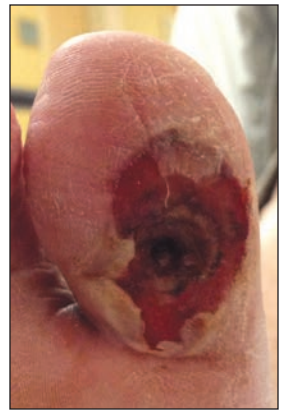

Figure 1: Deep, dry, and necrotic-appearing wound to the hallux.

After any injury or break in the skin, microorganisms can easily access deeper tissues. It is important to classify the wound as either colonized or contaminated with local infection or with deep infection. Recognizing the stage of bacterial invasion helps the physician choose proper therapy for management of infection. If the microorganisms are inadequately treated or removed from the wound, the bacteria and endotoxins produced will lead to a prolonged or indeterminate inflammatory phase. This also often leads to increased production of inflammatory cytokines, proteases, and metalloproteases which when not regulated, will lead to degradation of the ECM.[13]

Other concerns include the formation of biofilms, which are aggregates of bacteria often producing an extracellular polysaccharide matrix, which protects the bacteria from traditional antibiotic topical and systemic therapies.[14]

Topical Wound Care Therapies

While only few factors that affect wound healing are described above, one should understand that there are a significant number of causative factors. These factors do not act independently, but rather in tandem, making complex wounds challenging to evaluate and manage. As emphasis should be placed on understanding and treating the underlying pathology of the DFU, a good clinical examination of the wound should be performed to evaluate for possible topical wound care treatment.

Figure 1 shows a deep, dry wound with a necrotic appearance. Vascular perfusion and ruling out infection are important for this wound. When it comes to topical treatment of DFUs, it is helpful to categorize wounds as dry/necrotic, exudative, or infected. Depending on the type of wound, the clinician can choose appropriate topical therapy. Topical therapies ideally should be comfortable, provide protection to the wound, and create an encouraging wound-healing environment.[15]

Dry Wounds/Necrotic Wounds

DFUs that appear dry with little to no exudate, such as in Figure 2, often also have surrounding hyperkeratosis or necrotic debris within the wound. This nonviable material must be properly removed from the wound before any topical treatment can be effective. This is often accomplished by sharp debridement in the office. Once the wound bed is adequately prepared and evaluated, several topical therapies can be selected for appropriate management.

It is well known that maintaining a moist environment facilitates wound healing with several actions: prevention of tissue dehydration and cell death, accelerating angiogenesis, increasing breakdown of necrotic tissue or fibrin, and providing an environment for optimal transport of cytokines and growth factors, allowing appropriate target cell stimulation.[16] Topical therapies that help support a moist environment include non-adherents, hydrocolloids, and hydrogels. For DFUs that have significant necrotic debris, enzymatic topical therapies can be useful.

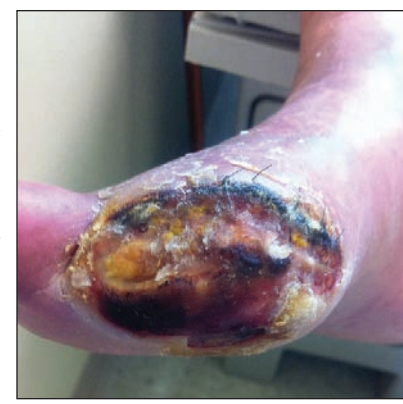

Figure 2: Dry, necrotic-appearing wound.

Non-adherents or low adherent dressings have been regarded as the standard treatment for most DFUs.[15] These are relatively simple dressings that are designed to be atraumatic and provide a moist environment. Structurally, they consist of fine mesh-type gauze that is typically impregnated with Vaseline or petroleum.[17] Other benefits to traditional non-adherents include low cost; they are relatively hypoallergenic, and they can be used in conjunction with other topical therapies. Common commercial non-adherents include Adaptic® (Johnson & Johnson, New Brunswick, NJ), Xeroform® (The Kendall Company, Mansfield, MA) and Telfa® (The Kendall Company).

Hydrocolloids, most popularly known as Duoderm® (Convactec, Skillman, NJ), are characterized as being occlusive to wound exudate, absorbent, and adherent. These types of topical therapies structurally are crossed-lined dispersions of gelatin, pectin, and carboxy-methylcellulose, along with other polymers and adhesives.[15] The polysaccharides and other polymers absorb any wound exudate, expand and create the adherent barrier, providing a moist wound environment. While a meta-analysis has shown that there is no significant difference when comparing use of a traditional non-adherent compared to a hydrocolloid, it has been recommended that the clinician choose an appropriate therapy based on wound exudate management.[18]

Hydrogels are similar in nature to hydrocolloids. They are composed of polymers of hydrophilic chains. Brand names available include Tegagel® (3M, St Paul, MN) and Curasol Hydrogel Saturated Dressing® (Healthpoint Biopharmaceuticals, Fort Worth, TX). Hence, properties of hydrogels include absorbency, moisture support, and aid in autolysis.[19] As such, they provide a similar environment to hydrocolloids but without the adhesive properties. Like most of the limited research

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on topical wound care therapies, studies have failed to show evidence that hydrogels are superior when it comes to treatment of diabetic wounds.[20] Debridement of DFUs is regarded as one of the most important aspects of diabetic wound management.[21]

Often debridement can be accomplished quickly in the office using a scalpel, or in the operating room if required for other purposes such as deep infection. However, when a wound has a large amount of non-viable tissue, use of topical enzymatic debridement therapies can be employed. DFUs that require frequent debridement of necrotic tissues also may benefit from more frequent enzymatic therapy application. Collagenase® (Healthpoint) is a well known enzymatic debridement agent that works by breaking up the peptide bonds specific to collagen, therefore avoiding healthy granular tissue.[22]

Exudative Wounds

Exudate from open wounds can help provide a moist, good wound-healing environment. However, in many situations, too much exudate is produced, which overwhelms and delays the wound-healing process. Other times, the exudate that is produced is toxic to itself and prevents proper wound-healing by interfering with or destroying healthy tissue.[23] Exudate itself is mostly composed of water, but also contains electrolytes, nutrients, inflammatory mediators, growth factors, and many different types of cells involved in the wound-healing phases as previously described.[24]

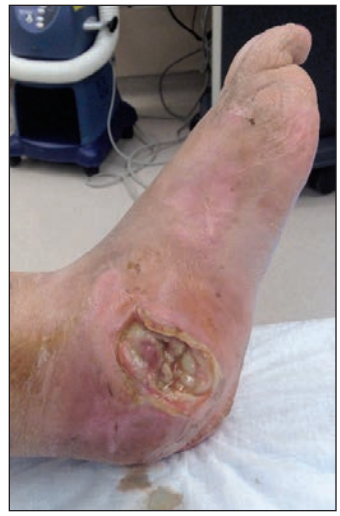

Figure 3: Highly exudative wound with peri-wound maceration.

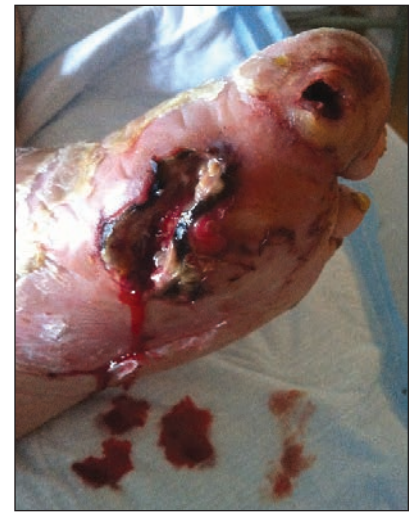

Figure 4: A deep, weeping infected wound with purulent drainage.

Signs that too much or harmful exudate is being produced include peri-wound skin changes (maceration, denudation), odor, leakage or soiling of the bandage and delayed healing. Figure 3 demonstrates a highly exudative wound with peri-wound maceration. Types of topical wound care therapies that may be indicated for highly exudative DFUs include foams and alginates.

Foams can be used for highly exudative wounds. Foams can also provide thermal insulation and they can easily conform to contours of irregular wounds to provide good protection, in addition to providing good absorbency.[25] Negative effects of foams include the ability to adhere and remove healthy tissue. They also have been reported to cause occasional dermatitis, and often the dressing itself is bulky. As previously discussed with many topical therapies, a recent meta-analysis compared the use of foam dressings to hydrocolloids, and found no significant difference.[25]

Alginate dressings are derived from natural algae and seaweed. Alginate dressings, such as Restore Calcium Alginate® (Hollister Wound Care, Libertyville, IL) are ideal topical dressings for highly exudative wounds. Calcium alginate has been shown to inhibit growth of staphylococcus aureus and limit growth of common microorganisms like pseudomonas and streptococcus pyogenes.[26] Alginate dressings can also be infused with a silver lining or other bacterial-static agents as well. Deep or irregular DFUs that are highly exudative can easily be treated with alginates as they also come in coiled or packable forms.

A recent meta-analysis compared the use of foam dressings to hydrocolloids, and found no significant difference.

Infected Wounds

As previously mentioned, wounds where infection is suspected should be classified into one of four categories: contamination, colonization, local infection, or deep infection. While colonized or contaminated wounds are often successfully treated with topical antimicrobial therapies discussed below, local or deep infections may require oral or intravenous agents in addition to the topical therapies described to maintain a good wound-healing environment.[13] Figure 4 depicts a deep wound with associated purulent and sanguinous drainage. Common topical therapies for infected wounds include silver-impregnated dressings and iodine preparations.

Silver-impregnated dressings have direct antimicrobial effects, including inducing direct inhibition of cellular respiration, inactivation of intracellular enzymes, as well as alterations to the bacterial cell membrane.[27]

Other topical therapies include silver nitrate sticks, silver sulfadiazine ointment, and other topical therapies, as previously mentioned, that are impregnated with silver. Elemental silver dressings have been shown to be more efficacious than silver nitrate sticks or silver ointment.[28]

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Iodine-based preparations are antiseptic in nature, with in vitro bactericidal rates of 0.1-1%.[29] Most commonly, iodine preparations are used for locally infected wounds in conjunction with oral or intravenous antibiotics. Iodine preparations come in many forms, including ointments, solutions, and moderately absorptive forms, making iodine useful for many types of wounds, including moderately exudative DFUs. Commonly used forms include Iodosorb® (Smith & Nephew, London, UK) and Betadine® (Purdue Pharma, Stamford, CT).

Despite its apparent usefulness, there is much debate as to whether or not iodine is effective at managing locally infected wounds.[30]

The Role of Split Thickness Skin Grafts and Biologics

The above-mentioned topical therapies, for the most part, are cost-effective, can be quickly applied, and when properly educated, patients themselves can perform dressing changes.[13] That being said, there are certain scenarios when split-thickness skin grafts (STSG) and advanced topical therapies or biologics can be employed.

Biologics are defined as medicinal preparations created by a biological or living process, hence composed of living cells or substitutes.[31] When choosing one on these therapies, as when choosing to use any topical wound care product, the patient and DFU must be properly evaluated.

Split-thickness skin grafts remain the gold standard for the reconstruction of diabetic foot wounds.

Autologous split-thickness skin grafts require a wound that has a good granular base that is well perfused.[32] It also requires a wound free of infection and is best used in non-weight-bearing areas of the foot. Donor sites for an STSG commonly are the ipsilateral thigh or calf. STSGs involve harvesting the epidermis and varying levels of thickness of the dermis with an electric dermatome.

Once the STSG is secured to the affected site, it is then often bolstered down with a negative pressure wound therapy device (NPWT). The use of STSGs has been shown to be successful over the use of free local flaps, as well as muscle flaps. STSGs remain the gold standard for the reconstruction of diabetic foot wounds.[31]

Advanced biologics are similar to

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STSGs in that they require an infection-free, healthy granular based wound. Advantages to using advanced biologics over STSGs include not having to take the patient to the operating room, and the lack of donor site morbidity.

Xenografts, such as Oasis® (Healthpoint Ltd, Fort Worth, TX) are typically derived from porcine products and contain varying thickness of dermal tissue. These have been shown to heal chronic leg ulcers faster than compression therapy alone.[33]

Commonly-used allografts include Apligraf® (Graftskin; Organogenesis, Inc, Canton, MA) and Dermagraft® (Shire), both of which contain neonatal fibroblasts as part of their components. Similarly, both products have been shown to have successful wound-healing potential.[34,35]

Conclusion

The etiology of DFUs is complex, with many of the predisposing factors inherent to the wound itself. It is essential that the clinician recognizes the potential underlying causes of the DFU and manages these appropriately. Managing blood glucose levels is perhaps one of the most important underlying factors.[36] Doing this gives the wound its best chance for healing from a systemic aspect. Equally as important, however, is a good clinical examination of the DFU, as this will help guide the physician towards the most appropriate topical therapy. Ruling out osteomyelitis or deep space infection is important as these can be a cause of non-healing wounds.[3]

There are many topical wound care products available, including products for dry/necrotic wounds, exudative wounds, and wounds that are infected. Split-thickness skin grafts and advanced biologics are also available for use when deemed appropriate. Research has shown success for the use of STSG and advanced therapies, while showing little to no benefit of one topical product over another topical product. Regardless, it is widely agreed upon that the clinician should choose a therapy based on the type of wound and its exudate.[10,25] **PM**

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