



## How Wound Healing Abnormalities Impact Clinical Care

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### Abstract

One of the greatest clinical challenges faced by plastic surgeons is that of the chronic non-healing wound. In this review, we provide a brief overview of the molecular biology of wound healing, discussing the three overlapping phases: reactive, proliferative and maturational. We also discuss the most commonly encountered deterrents to physiologic wound healing, including hypoxia, infection, diabetes, malnutrition, and medications. Moreover, we describe the most common chronic wounds: pressure ulcers, diabetic foot ulcers, and venous stasis wounds. A variety of treatment modalities is available to solve these difficult problems, such as hyperbaric oxygen therapy and regenerative medicine treatments. Due to the complex natural history of chronic wounds, they are best approached in an inter-disciplinary manner.

**Keywords:** Wound healing; Diabetic foot ulcers; Inflammation

### Introduction

Chronic, non-healing wounds pose a formidable clinical challenge for plastic and reconstructive surgeons. A thorough understanding of the underlying physiology of wound healing is required to optimize patient outcomes and understand the complex and ever-expanding armamentarium of therapeutic options used to treat chronic wounds. This review provides a brief overview of the molecular biology of wound healing, deterrents to physiologic wound healing, types of chronic wounds commonly encountered by plastic surgeons, current treatment modalities, and future therapeutic horizons for treating patients with chronic wounds.

### Normal Wound Healing

Wound healing is a complex process, which is classically divided into three overlapping phases: reactive, proliferative, and maturational (Figure 1,2) [1].

#### I. Reactive phase

**A) Hemostasis:** Following tissue injury, exposed subendothelial collagen activates platelets and the intrinsic clotting cascade. Activated platelets adhere to one another to form a hemostatic plug, activate the extrinsic clotting cascade, and release a myriad of soluble factors, which promote coagulation and inflammation.

**B) Inflammation:** Leukocytes are recruited to the area of injury by soluble mediators released from activated platelets and endothelial cells. Neutrophils are the first cells to arrive in the wound, often appearing within 24-48 hours of the time of injury. Neutrophils enter the wound site through diapedesis and subsequently work to clear necrotic debris, foreign material, and bacteria through the generation of reactive oxygen species. Subsequently, macrophages enter the wound at roughly 48-96 hours post-injury to phagocytose bacteria, digest extracellular debris, and secrete several soluble mediators, which coordinate later stages of the wound-healing cascade including angiogenesis, fibroblast activation/proliferation, and collagen production/maturation. Lymphocytes are the last class of leukocytes to enter the wound site, often arriving within 5-7 days of injury. Lymphocytes primarily function to sustain the inflammatory response through the release of cytokines and promotion of long-term immunity to pathogens encountered in the wound.

#### II. Proliferation

The proliferative phase of wound healing results in granulation tissue formation. In response to hypoxia, epithelial cells release vascular endothelial growth factor (VEGF) which stimulates angiogenesis. Endothelial cells coalesce to form rudimentary blood vessels, which subsequently undergo maturation and stabilization. Simultaneously, fibroblasts begin to migrate and proliferate within the wound bed and function to synthesize collagen and other components of the new

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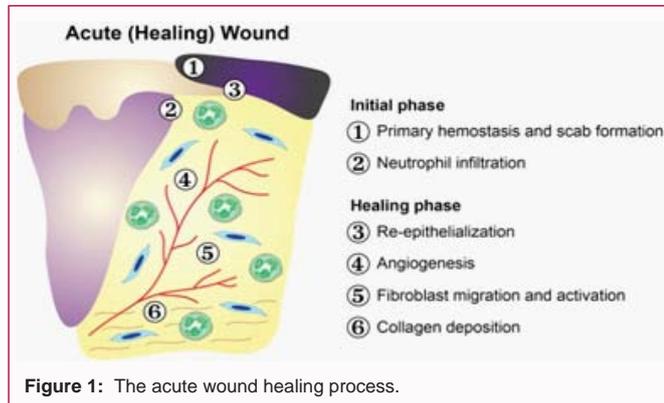


Figure 1: The acute wound healing process.

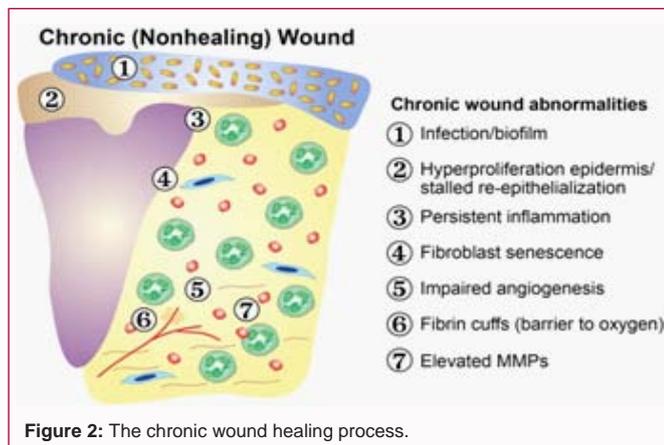


Figure 2: The chronic wound healing process.

extracellular matrix.

### III. Maturation

Wound contraction and collagen remodeling mark the maturation phase of wound healing. Wound contraction is mediated by myofibroblasts, which utilize specialized actin-myosin appendages to contract the surrounding extracellular matrix. Over time, equilibrium between collagen synthesis and degradation occurs. Type I collagen is gradually replaced by type III collagen and extensive cross-links develop to enhance the tensile strength of the scar to a maximum value of 80% of non-wounded skin.

## Deterrents to Physiologic Wound Healing

Several clinical factors affect the healing wound and can impede or disrupt the wound-healing cascade. Important considerations include hypoxia, infection, diabetes, malnutrition, and medications.

### I. Hypoxia

Adequate tissue oxygenation is essential to physiologic wound healing [2]. The wound-healing cascade will not proceed effectively with tissue oxygen levels below 35 mmHg [3]. When tissue oxygen levels fall below this critical value, the replication of fibroblasts is impaired, ultimately resulting in deficient collagen production. Furthermore, post-translational collagen hydroxylation is dependent on molecular oxygen [2]. Numerous factors can result in tissue hypoxia, including occlusive arterial disease, vasospastic disease, vasculitis, hematologic disorders, and external compression of the wound bed.

### II. Infection

Bacterial contamination poses a significant impediment to

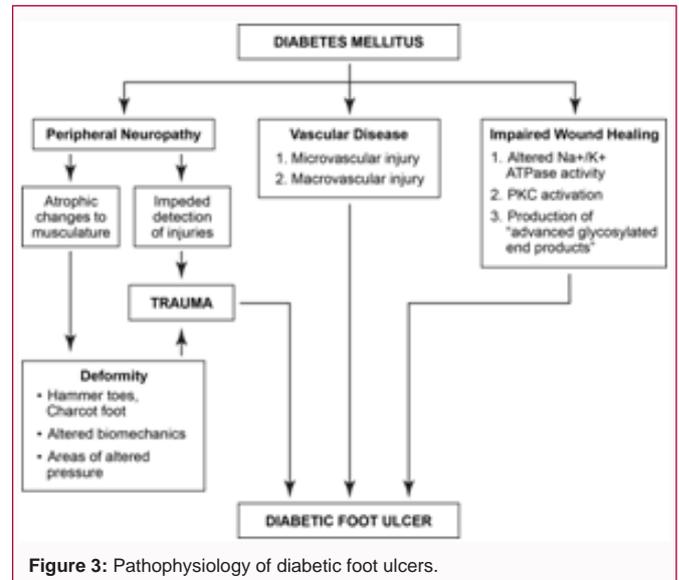


Figure 3: Pathophysiology of diabetic foot ulcers.

wound healing. Bacteria provide a constant antigenic stimulus, which prolongs the inflammatory phase of wound healing. Chronic inflammation results in the up-regulation of proteases, which degrade growth factors and collagen within the local microenvironment and inhibit further deposition of collagen, epithelialization, and contraction of the wound [4].

### III. Diabetes

The relationship between diabetes and impaired wound healing is complex and research on that topic continues to evolve. Many factors contribute to the altered wound healing seen in diabetic patients. These include, but are not limited to, predisposition to other systemic diseases such as atherosclerosis, renal failure with concomitant uremia, peripheral arterial disease, and coagulopathy.

Uncontrolled hyperglycemia is thought to impede wound healing on the molecular level in several different ways. Three hypotheses seek to explain this phenomenon (Figure 3). The first hypothesis involves the alteration of Na<sup>+</sup>/K<sup>+</sup> ATPase activity [5]. Hyperglycemia up-regulates the enzyme aldose reductase, which is responsible for converting glucose to sorbitol via the polyol pathway. In this pathway, sorbitol is then converted to fructose, resulting in the generation of NADH. However, this enzymatic reaction is slow, thereby resulting in a build-up of sorbitol within the cell. As an effective osmole, this increases the osmotic stress on the cell and promotes swelling. In addition, the increased conversion of sorbitol to fructose ultimately causes reduction in NADPH levels, which makes the cells more susceptible to oxidative stress. This is especially augmented by the fact that chronic wounds have elevated levels of reactive oxidative species. The second hypothesis involves activation of protein kinase C (PKC) by hyperglycemia [6]. Diacyl-glycerol synthesis is elevated by hyperglycemia, which, in turn, causes PKC activity to increase. PKC is an important signaling molecule and alterations in its expression can have detrimental effects on cellular proliferation, thereby impeding wound healing. The third mechanism involves the production of "advanced glycosylation end products" (AGEs) [7,8]. AGEs are large aggregates of aldolases bound to reactive amino groups by covalent bonds. These molecules are thought to activate NF-κB, a key transcription factor involved in many cytokine-related cell responses. AGEs may induce PDGF, TNF-α, and IL-1α and inhibit normal collagen degradation.

#### IV. Malnutrition

Insufficient protein intake and vitamin/mineral deficiencies can have profound consequences on wound healing. Dietary proteins are the fundamental building blocks of collagen. Furthermore, protein plays a key role in capillary formation, fibroblast proliferation, and proteoglycan synthesis (GUO). While most agree that the normal wound-healing cascade cannot precede with albumin levels less than 2 g/dL, impaired wound healing has been reported with albumin levels less than 3.5 g/dL [9]. Protein replacement and supplementation can reverse this process, hence the importance of early enteral feeds rich in protein.

The most important vitamins for wound-healing are vitamins A, C, E, and K. Vitamin A plays a fundamental role in the activation of monocytes [10]. Vitamin C serves as a cofactor in the hydroxylation of collagen residues and promotes proper immune function [11]. Vitamin E is the major anti-oxidant in skin and functions primarily to stabilize cell membranes from reactive intermediates [4]. Vitamin K is essential for the production of clotting factors necessary for hemostasis (Factors VII, IX, X, prothrombin, Protein C, and Protein S). In addition to vitamins, there are several important trace minerals that are essential for proper wound healing, including zinc, iron, copper, and magnesium. These elements are predominantly utilized as cofactors for enzymatic reactions.

#### V. Medications

Numerous drugs impair the wound-healing process. While the list continues to increase, chemotherapeutic agents, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely studied drugs that affect wound healing. Although different in their respective mechanisms of action, these therapeutics ultimately exert their detrimental effects on wound healing by hampering the inflammatory response. Impaired fibroblast proliferation results in decreased collagen production, thereby preventing granulation tissue formation and wound closure.

### Common Chronic Wounds

#### I. Pressure ulcers

Pressure ulcers occur when a sustained mechanical force compresses soft tissue for a prolonged period of time. The mechanism of injury is complex and not completely understood, there is evidence though that many factors come into play, including ischemia, reperfusion injury, and impaired lymphatic drainage.

When an externally applied pressure, usually on a prominent body surface, exceeds the capillary pressure within the tissue, ischemia occurs. During ischemia, the cellular metabolism transitions from aerobic to anaerobic, with deleterious effect to the function of intracellular organelles and cell membrane. That leads to cellular damage and promotes cellular necrosis. When the cause of pressure is reversed, reperfusion of ischemic tissue can result in the formation of reactive oxygen and nitrogen species, which further damage surrounding tissue. Neutrophils are recruited to the previously ischemic area and damage the surrounding tissue via the release of inflammatory mediators, such as superoxide, hydroxyl radicals, and peroxynitrite. Additionally, during periods of ischemia, endothelial cells become activated to secrete pro-inflammatory cytokines and increase the expression of adhesion molecules. All of these components interact and eventually lead to tissue injury, which becomes more extensive with repeated cycles of ischemia-reperfusion [12].

Another mechanism, often underestimated, is the obstruction of lymphatic drainage as a result of local pressure that leads to inadequate removal of harmful waste products from the interstitial space surrounding cells [13]. Lymph stasis has also been shown to contribute to inflammation, fibrosis, and localized cell death, which suggests that impaired lymphatic drainage plays a central role in the pathophysiology of pressure ulcers.

Pressure ulcers, like all chronic wounds, undergo a prolonged inflammatory phase. Microbial contamination is one of the main factors contributing to that. A biofilm often develops, which consistently activates the immune system. Chemotactic factors such as IL-1 and TNF- $\alpha$  are produced, attracting immune cells including macrophages, neutrophils, and mast cells. Reactive oxygen species (ROS), neutrophil elastase, and matrix metalloproteinases (MMPs) are subsequently produced. The protective glycocalyx of the biofilm prevents penetration of bactericidal molecules, protecting the underlying bacteria and perpetuating the chronic contamination and potentially infection of the wound, preventing proper wound healing. The function of fibroblasts is also impaired secondary to altered response to growth factors, which has a detrimental effect on the proliferative phase of wound healing. Moreover, inhibition of signaling pathways responsible for keratinocyte migration, lead to impaired keratinocyte translocation from the wound edges, which further impairs wound healing.

From a clinical perspective, most pressure ulcers occur in patients who demonstrate a number of intrinsic risk factors including advanced age, medications (i.e., corticosteroids, vasoactive agents), comorbid diseases (cancer, cardiovascular disease, peripheral vascular disease, diabetes), anemia, low systolic or mean blood pressure, body mass index (BMI) less than 18.5 or greater than 40, poor nutritional status and low albumin levels. These factors affect the ability of the skin to respond to extrinsic risk factors that include shear, friction, moisture and pressure.

A full physical exam and history is important for evaluation of patients with pressure ulcers. Important considerations include social history, spasms management, and bladder and bowel habits. Control of spasms is critical as they can lead to shearing forces that impair wound healing. They can be managed either medically (e.g., Botox, Baclofen, Diazepam, Dantrolene, Gabapentin, Tizanidine) or surgically (e.g., Baclofen pumps, spinal electric stimulation therapy, nerve blocks, surgical rhizotomy, joint releases). Additionally, optimization of patient's nutrition and medical condition is very important. For diabetic patients, it is critical to achieve tight blood glucose control with HbA1c below 7%. All pressure sores are considered colonized since they are open wounds; however, it is critical to determine the evidence of active and invasive infection. Imaging studies, such as CT scan, bone scan, MRI, can be helpful, but the gold standard to assess for soft tissue infection is tissue biopsy with quantitative culture. Bacterial count greater than  $10^5$  is considered diagnostic for invasive infection and needs to be addressed in order to increase the chances of a successful reconstruction. If infection of the bone is suspected, bone biopsy is required to rule out osteomyelitis. Occasionally, pulmonary and urinary sources cause transient bacteremia and seeding of the bloodstream with potential subsequent infection of the pressure ulcers. Treatment of any other sources of infection is equally important to treating the pressure wound infection. For incontinent patients, any pelvic, gluteal or lower back wounds are potentially continuously exposed to urine and/or feces,



**Figure 4:** Lower back, lumbar area pressure ulcer with complete re-epithelialization after medical optimization and appropriate wound care.



**Figure 5:** Sacral pressure ulcer, stage IV; clear wound edges with no drainage or sign of infection, presence of granulation tissue at the base of the wound.

which can make management of these wounds more challenging. Discussion with the patient for potential diverting colostomy may be recommended, as it significantly increases the chances of successful pressure sore treatment.

Depending on the depth of the ulcer and the level of involvement, pressure sores are classified in 4 stages. In stage I ulcers, the skin is intact with areas of non-blanchable erythema. In stage II ulcers, there is evidence of partial-thickness skin loss with exposed dermis. The wound bed is viable, pink or red and moist. They may appear as intact or ruptured serum-filled blisters. Adipose and deeper tissues are not visible and granulation tissue, slough and eschar are not present. In stage III ulcers, there is full-thickness loss of skin with exposed subcutaneous adipose tissue and evidence of granulation tissue and epibole (rolled wound edges). Finally, in stage IV ulcers there is full-thickness skin and tissue loss with exposed fascia, muscle, tendon, ligament, cartilage and/or bone. Slough, eschar, epibole, undermining and/or tunneling may be present. If slough or eschar is covering the wound and obscures the extent of tissue loss, this is defined as unstageable pressure ulcer. Representative images of pressure sores are shown in Figures 4-6.

The size and depth of the wound, presence of exposed structures, especially tendons, bursa or bone, neurovascular structures, and the



**Figure 6:** Trochanteric pressure ulcer stage IV; moderate amount of drainage and fibrinous tissue covering part of the wound but no signs of infection, evidence of granulation tissue with small amount of epibole at the wound edges.

relationship of the wound to underlying or adjacent bony prominences, as well as the rectum and urethra, should be assessed thoroughly. Pressure ulcers can be treated non-operatively by promoting secondary intention healing. A combination of interventions is utilized, including turning the patient every 2 hours, keeping bed linens clean, dry and wrinkle free, using soft cushions between knees and bony prominences to avoid direct contact, moving immobile patient with caution. In addition, cleaning and protecting the skin surrounding the pressure sore to prevent further break down, relieving pressure, friction, shear, and moisture, supplementing patient's diet with multivitamin, zinc sulfate, and Vitamin C, using low air loss mattress and performing appropriate dressing changes. Split or full thickness skin grafts are alternative reconstruction modalities when secondary healing is unlikely to achieve complete closure of the wound in a timely fashion. In case major reconstruction is indicated, local flaps can be considered, although fasciocutaneous or myocutaneous flaps are the gold standard for treatment of non-healing, large wounds that involve deeper structures, such as bone, bursa, muscle or tendons.

## II. Diabetic foot ulcers

Diabetic foot ulcers are one of the most serious manifestations of uncontrolled diabetes with a reported incidence of 4 to 10% [14]. Diabetic foot ulcers are a source of considerable morbidity and mortality, including discomfort, decreased quality of life, need for health care provider visits, wound care, and need for surgical intervention [15].

Diabetic foot ulcers are the culmination of several distinct underlying pathophysiological processes. Previous studies have shown that the majority of patients with diabetic foot ulcers have a critical triad of peripheral neuropathy, deformity, and trauma (Figure 3) [16]. Peripheral neuropathy is considered the earliest feature in the development of diabetic foot ulcers [15]. Motor neuropathy promotes atrophic changes of the foot musculature, ultimately resulting in characteristic deformities of the feet, including hammertoes and Charcot arthropathy. The altered biomechanics of the foot create focal areas of pressure that are prone to injury. Furthermore, altered sensation secondary to neuropathy impedes the initial detection of injuries and allows progression of the wounds when they occur. Coexisting peripheral vascular disease also



**Figure 7:** Diabetic ulcer of the foot; full thickness defect with evidence of granulation tissue and small area of fibrinous exudate.



**Figure 8:** Diabetic ulcer of the 2<sup>nd</sup> toe; healing wound with granulation tissue and no evidence of infection.

contributes to the pathogenesis of diabetic foot ulcers. Over time, non-enzymatic glycosylation of the endothelium causes sclerosis of the vessel wall. Diminished perfusion contributes to hypoxia and ischemic necrosis of the affected tissue. Uncontrolled hyperglycemia results in impaired leukocyte chemotaxis, phagocytosis, and killing, thus increasing susceptibility to microbial infection. Furthermore, the relative immunodeficiency impedes the inflammatory phase of wound healing and diminishes the regenerative capacity of the tissue.

The clinical evaluation of diabetic foot ulcers begins with a complete history and physical, including a systematic assessment of the lower extremities. Vascular status should be assessed by the palpation of the dorsalis pedis and posterior tibial pulses. Neurological assessment should be conducted using a monofilament. Inability to detect a 10-g monofilament has been shown to convey a 2.2-fold to 18-fold risk of ulceration [16]. Further neurological testing includes assessment of deep tendon reflexes at the ankle. The foot should then be inspected for gross deformity. The patient’s footwear should be examined. Important considerations include excessively worn shoes, shoes with obvious weakness in the sole, and the presence of stitches or seams around the toes [17]. The location of the ulcers should be noted and assessed for diameter and depth. Given the impaired immunologic



**Figure 9:** Diabetic ulcer of the plantar surface of the foot; full thickness wound with evidence of granulation tissue and significant amount of hyperkeratosis, pictures before and after local wound care and limited bedside debridement.

**Table 1:** Wagner system for classification of diabetic foot wounds.

Grade 0	Skin lesions absent, hyperkeratosis below or above bony prominences
Grade 1	Skin and immediate subcutaneous tissue area ulcerated
Grade 2	Lesions are deep and may penetrate to tendon, bone or joint capsule
Grade 3	Deep tissues are always involved, osteomyelitis may be present
Grade 4	Gangrene of some portion of the toes or forefoot
Grade 5	The entire foot is gangrenous

With permission of The American Academy of Orthopaedic Surgeons: [18].

function of diabetic patients with uncontrolled hyperglycemia, the wounds may lack the characteristic signs of infection such as warmth, redness, and swelling. Wounds, which extend all the way down to the bone, have a high predictive value for underlying osteomyelitis, even without acute signs of infection (Figure. 7-9) [16].

There are currently several clinically utilized classification systems for diabetic foot ulcers. The two most commonly used classification systems include the Wagner system and the University of Texas system [14,18-20]. The Wagner system assesses the depth of the diabetic foot ulcer and the presence of osteomyelitis and gangrene (Table 1) [18,19]. The University of Texas system assesses ulcer depth, the presence of wound infection, and the presence of clinical signs of ischemia [19,20]. Recently, a new diabetic foot ulcer assessment scale (DFUAS) was developed in Indonesia. This newly developed system consists of 11 evaluation components (depth, size, size score, inflammation/infection, proportion of granulation tissue, type of necrotic tissue, proportion of necrotic tissue, proportion of slough, maceration, type of wound edge, and tunneling) which are assessed to yield an overall score ranging from 0 to 98, with higher scores corresponding to more severe wounds [14]. Using this system, the authors of the study determined that a cutoff score of 12 could accurately predict whether a wound would heal within 4 weeks [14].

The clinical management of diabetic foot ulcers should begin with patient education. Patients should be taught about the underlying pathology of diabetic foot ulcers in terms that are comprehensible for their corresponding level of education. The importance of glycemic control should be emphasized. Conservative management options include rest, elevation, and pressure off-loading of the ulcer. Off-loading the ulcer can be accomplished in several different ways, including changing the patient’s footwear, creating a complex molded device, or utilizing an aircast boot [17]. Total contact casts have been regarded as a superior standard therapy in neuropathic ulcers due to the purported ability to redistribute pressure, decrease patient activity



**Figure 10:** Venous stasis ulcers; evidence of pitting edema, hyperpigmentation and full thickness wounds with granulation tissue and small amount of exudate.

levels, and increase adherence to the off-loading regiment [16]. Debridement is the mainstay of ulcer therapy. Callus surrounding the foot ulcer impedes wound healing by preventing epithelial migration across the bed of the wound [17]. Necrotic tissue is no longer viable and serves as a nidus for infection. Thus, these tissues should be removed in order to promote physiologic wound healing. Tissue samples should be taken and sent for further pathologic and infectious work-up. Antibiotics should be administered to combat infection when present and tailored to the infective organism. It is imperative to keep the affected area clean with sterile and nonadhesive dressings. In cases refractory to conservative management, more extensive surgical debridement, including potential amputation, should be considered.

### III. Venous ulcers

Ulceration secondary to chronic venous insufficiency is a common problem in the United States, with an estimated prevalence of 1-2% in the adult population [21]. Chronic venous insufficiency is more common among those who are obese, pregnant, and sedentary, have incurred trauma to the vasculature secondary to prior injury or surgery, or have a family history of varicose veins.

Venous insufficiency is multifactorial in nature and can result from several different causes, including; valvular incompetence, outflow obstruction, congenital weakness of the vasculature, or ineffective pumping of the surrounding musculature [21]. Regardless of the underlying cause, this ultimately results in pooling of blood within the venous system. The resulting hypertension leads to extravasation of multiple blood proteins, most notably hemosiderin and fibrinogen. Hemosiderin deposition results in the hyperpigmentation of the overlying skin. Fibrinogen is believed to polymerize into fibrin cuffs, which impede oxygen diffusion and entrap growth factors, thereby promoting ischemic necrosis and ulceration of the overlying skin.

Patients with venous stasis commonly present with complaints of a dull ache or pain in the affected area [22]. On physical exam, the skin will often have a characteristic dark pigmentation resulting from hemosiderin deposition. Other associated skin findings include lipodermatosclerosis, reticular or varicose veins, atrophic blanche, telangiectasia, and stasis eczema [23]. Ulcers often form above the medial malleolus and tend to be superficial with poorly defined margins (Figure 10,11) [23].

Non-operative treatment of venous ulcers is centered on compression therapy and dressing changes to prevent concomitant infection. There are several different clinically available options for compression therapy, including bandages, stockings, and boots [24]. In addition to standard wound care; several pharmacological



**Figure 11:** Venous stasis ulcer at the medial malleolus; pictures before and after split thickness skin graft placement.

therapies are available to attenuate the inflammation associated with venous ulceration. Examples of such therapies include pentoxifylline, an inhibitor of adenylate cyclase, and micronized purified flavonoid fraction (MPFF). Artificial skin substitutes and autologous skin grafting can be used in cases refractory to medical management.

### Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is another modality used in the treatment of specific types of wounds. The patient is placed in a chamber that has the ability to deliver up to 100% oxygen. That increases the delivery of oxygen to areas with poor perfusion or increased metabolic demand because of inflammation and/or infection, improving the wound healing process. HBOT is currently indicated for the treatment of chronic diabetic and radiation wounds, as well as chronic wounds with evidence of osteomyelitis [25-27]. Potential complications, such as barotrauma, oxygen toxicity and visual changes, need to be carefully considered. Additionally, it is important to mention that the cost of HBOT is high, requiring expensive equipment and specialized staff. However, there is literature that supports the cost-effectiveness of HBOT in a multidisciplinary wound care center setting with appropriate utilization of the available resources [25,26].

### Future Horizons for Healing of Chronic Wounds

Advances in the field of regenerative medicine have led to the development of novel therapeutic modalities, which seek to accelerate physiologic wound healing and improve cosmetic outcomes. Many of these therapies aim to augment and manipulate factors within the wound bed in order to favor a pro-regenerative microenvironment.

The extracellular matrix is critically important to the physiologic

healing of wounds and has been a target of substantial scientific investigation. Both natural and synthetic biomaterials are currently being developed to guide wound regeneration. Ideally, these materials will guide the production of new host extracellular matrix while being simultaneously degraded into non-toxic byproducts. Current options include acellular dermal matrix (ADM) and polyesters made of polycaprolactone, polyglycolide, and polylactic acid [28].

Acellular dermal matrices are composed of several different components, including collagen, glycoproteins, glycosaminoglycans, adhesion molecules, growth factors, chemokines, and cytokines. The complex architecture of the acellular dermal matrix helps to guide regeneration in part by promoting a phenotypic change of M1-like, pro-inflammatory macrophages to M2-like pro-healing macrophages [29]. Furthermore, because ADM is natural, it is metabolized into non-toxic degradation products which have been shown to promote wound regeneration and facilitate cellular recruitment [27]. The efficacy of acellular dermal matrices has been verified in a randomized control trial for both diabetic foot ulcers [30].

Synthetic polymers offer the additional benefits of being able to alter the physiochemical properties of the biomaterial as well as load the material with bioactive molecules, which promote regeneration. Synthetic scaffolds can be produced by several different manufacturing processes, including electrospinning to produce nano-fiber scaffolds, salt-leaching to produce porous scaffolds, and lithography to produce three-dimensional scaffold [28]. By altering the chemical composition of the polymer, one can augment the degradation kinetics, mechanical strength, stiffness, porosity, and permeability. Moreover, there have been several studies, which demonstrate that loading these polymers with cytokines, growth factors, siRNA, and genes can promote a pro-regenerative environment [31-36].

Stem cells provide another potential therapeutic strategy to improve cutaneous wound healing. Through self-renewal and daughter cell differentiation, stem cells replenish damaged tissues directly through proliferation and by secreting a host of pro-regenerative factors. Although there are several different types of stem cells that can be utilized for wound healing applications, adipose derived stem cells tend to be the preferred subtype given the ease at which adipose tissue can be harvested and the relative density of stem cells within this tissue. Although the efficacy of utilizing adipose-stem cells to enhance wound healing has been documented in several studies, this technology has yet to be translated clinically [37,38].

## Multidisciplinary Approach in Wound Care

The increasing need for care of non-healing wounds, combined with the great advances in the science of wound care have led to the development of specialized multidisciplinary teams and centers. These teams usually comprise of physicians, nurses and technicians from different specialties, including plastic surgery, vascular surgery, general surgery, podiatry, dermatology and hyperbaric medicine. It has been shown that multidisciplinary approach can improve the healing rates of chronic wounds, decrease hospitalizations and reduce the rate of complications related to non-healing wounds [39,40]. For instance, our institution's wound care center provides advanced conventional wound care, such as application of specialized dressings and wound debridement, compression therapy for venous stasis ulcers, surgical and non-surgical techniques for wound closure, including vacuum-assisted technology, tissue replacement with skin grafts or flaps, skin substitutes or scaffolds and HBOT. More evidence-

based research is required in order to develop validated guidelines for the function of multidisciplinary wound care centers [41].

## Conclusion

Healing chronic wounds presents a formidable challenge to the field of plastic and reconstructive surgery. Patients with non-healing wounds often have multiple comorbidities, which further complicate their medical care. A thorough understanding of the underlying principles of wound healing and available treatment modalities is essential to optimizing the care of these patients. Future efforts will further expand on the clinical armamentarium available to reconstructive surgeons to help rebuild and restore the wounds and lives of the patients we serve.

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