Multidisciplinary Management of Wound Healing in Diabetics

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Wound Healing in Diabetics

To understand how Diabetes causes impaired repair of injured tissue, one must first understand how wounds are repaired under normal conditions. Therefore, a brief overview of this process is included in the following paragraphs.

Regardless of the mechanism of injury, wound healing represents a complex and dynamic process involving multiple cell types, growth factors and chemical signals that mediate tissue repair. This process has traditionally been divided into 4 phases: hemostasis, inflammation, proliferation and remodeling. These phases represent a continuum and overlap usually exists at some point in the process, including interactions between different cells and the matrix—an interaction known as dynamic reciprocity [1].

When tissue injury occurs, collagen is exposed to circulating platelets, which causes them to aggregate and adhere to sites of damage, thus initiating the coagulation cascade. Fibrinogen is eventually converted to fibrin forming a fibrin plug, which induces hemostasis. This process also causes a massive release of growth factors and cytokines that initiate cell migration to the wound. As cells arrive at the site of injury, the inflammatory phase of wound repair begins. Neutrophils are usually the first cells present at wound sites where they ingest and destroy bacteria and debris through phagocytosis and the production of toxic substances such as proteases and cathepsin. Neutrophil influx lasts for 48 h and is then followed by migration of macrophages to the wound site, which produce growth factors that promote

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angiogenesis and granulation in the wound bed, and lymphocytes which help regulate the production of new tissue, like collagen and extracellular matrix, needed for wound repair [2]. Once the site of injury is clear of debris new tissue must be formed to repair the wound; this complex process is known as the proliferative phase of wound repair. From the onset of injury, multiple chemical mediators such as platelet-derived growth factor and transforming growth factor-β induce angiogenesis in the wound bed. The same mediators also attract fibroblasts that produce collagen and extracellular matrix proteins laying down what is known as granulation tissue. Fibroblasts then transform to myofibroblasts and form a complex net capable of contracting to reduce the surface area of the wound. This is important because epithelial cells must migrate from the edges of the wound to replace the lost epithelium; a process known as reepithelization. As the wound contracts, the area that must be covered by new epithelium becomes progressively smaller. Finally, the remodeling phase takes place when type 1 collagen that was laid down during the proliferative phase is replaced by stronger, more organized type 3 collagen [3, 4].

Several factors contribute to delayed wound healing in diabetic patients. Ischemia, trauma, and neuropathy, the three main abnormalities responsible for diabetic foot, are also to blame for the disruption in the healing process [5]. Additionally, other factors such as infection and chronic inflammation can also have a negative impact on wound repair. The result is a failure of the wound to successfully progress through the normal healing process [3].

Multiple microvascular abnormalities are present in patients with Diabetes such as a reduction in capillary size, thickening of the basement membrane and arteriolar hyalinosis. Furthermore, peripheral arterial disease is a common comorbidity in these patients. The resulting reduction in blood flow produces altered migration of leukocytes, misdistribution of blood flow, altered physiological exchanges, and an increased susceptibility to pressure forces in the foot. Hypoxia also produces free oxygen radicals that further delay wound repair [5].

Neuropathy in patients with Diabetes affects motor, sensory and autonomic fibers. Motor dysfunction causes abnormal gait and anatomical deformities while the absence of pain associated with sensory dysfunction is to blame for a loss of protective symptoms. Both abnormalities combined lead to constant pressure on the affected limb that is responsible for the initiation and perpetuation of the wound. Damage to autonomic nerves causes misdistribution of blood flow and altered neurovascular response leading to decrease vasodilation which, combined with micro and macrocirculatory abnormalities, lead to decreased perfusion [5].

While inflammation is necessary for wound repair, the inflammatory response in patients with Diabetes is often protracted and ineffective due mainly to altered cell function. Macrophages and neutrophils have decreased phagocytic activity, fibroblasts show decreased proliferation, and keratinocytes show decreased differentiation. At the same time, high levels of metalloproteinases in the wound lead to increased extracellular matrix destruction causing further delay in the healing process [3].

Infections are a common complication in patients with Diabetes; at least half of all diabetic foot ulcers are infected at the time the patient presents to consult. More importantly, infected foot wounds precede two-thirds of lower extremity amputations

[6]. As previously mentioned, immune cells of patients with Diabetes have decreased phagocytic ability that is further affected by varying degrees of hypoxia caused by damage to blood vessels and an impaired macro and microcirculatory system [5]. Diabetics also have impaired chemotaxis and inhibition of the complement-mediated cascade that render them susceptible to more frequent and more severe infections [7].

These factors interact to make diabetic wounds particularly difficult to treat. Given that Diabetes is a multisystem disease it seems logical that a multidisciplinary team would be best suited to elaborate a treatment plan. When faced with one of these patients it is wise to think of the patient as a whole, and not just focus on their wound so that each of these factors can be taken into account and, if possible, properly addressed. In the following sections, specific treatment recommendations for each of these factors will be discussed (see below).

Common Wounds in Diabetics

By far, the most common form of cutaneous ulceration in the diabetic is the diabetic foot ulcer (see below). However, other forms of ulceration can occur in the diabetic and the clinician must know how to properly identify them and understand their pathophysiology to be able to effectively manage the wound.

Diabetic Foot Ulcers

Any loss of continuity of the stratum corneum (SC) below the malleoli of a person with Diabetes Mellitus (DM) should be considered a diabetic foot until proven otherwise (Fig. 13.1). The reason is that, as stated above, diabetic patients are prone to complications due to a severe decrease in the ability to heal and fight-off infection.

Multiple factors should be considered when assessing a diabetic foot. As circulation is determinant on prognosis, adequate vascular examination is of the outmost importance. Evaluating the circulation can be as simple as searching for pulses or

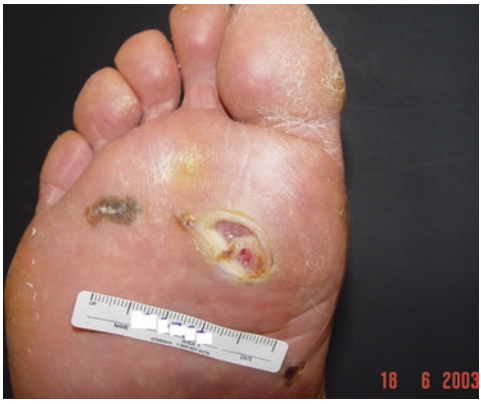

Fig. 13.1 Diabetic foot ulcer (UTex IIA)

obtaining an ankle-brachial index, or as complex as vascular laboratory testing such as angiotomography or arteriography.

The presence of infection may be obscured by delayed manifestations of inflammation caused by elevated glucose levels and leukocyte abnormalities. Infection in the diabetic foot ulcer needs to be classified into absent, mild, moderate or severe according to the criteria established by the Infectious Disease Society of America (IDSA) [8]. Increased pain, or the presence of pain in an ulcer that was anesthetic, should always be considered a sign of infection [9] and a positive probe to bone test or abnormalities in plain X-rays as signs of osteomyelitis [10].

Loss of protective sensation caused by peripheral neuropathy places diabetic patients at risk for the development of ulcers [11]. To assess for neuropathy the gold standard is the use of a biothesiometer, but this test is expensive and not readily available. To test the at-risk foot, one may use the nylon monofilament test [12] or even the simple Ipswich touch test [13]. These tests are simple methods to assess for loss of sensation in different areas of the foot and correlates with the presence of foot injuries (Fig. 13.2).

Related to the loss of protective sensation and neuropathy, patients commonly develop ulcers in pressure points such as the metatarsal heads and toes. Evaluating this continuous pressure and gait disturbances may lead to identifying areas of increased weight bearing or trauma. Since continued pressure or trauma to the ulcer leads to delayed healing, it must be addressed.

Finally, when an ulcer or skin rupture is evident, evaluation of the depth of the tissues involved is necessary since involvement of the subcutaneous fat and deeper tissues is associated with a worse prognosis [14].

Once the patient has been properly evaluated, the cutaneous ulceration must be classified. The authors prefer the University of Texas classification, provided in Table 13.1, since it has been validated and provides a logical treatment algorithm [15, 16].

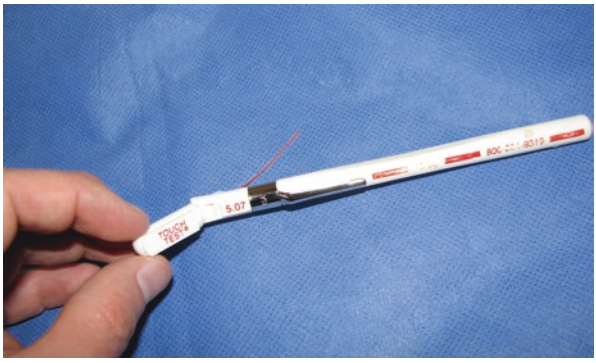

Fig. 13.2 10 g nylon monofilament test

Table 13.1 University of Texas diabetic foot classification

		Grade			
		0	I	II	III
		Pre- or post-ulcerative lesion completely epithelialized	Superficial wound down to the fascia	Wound penetrating to tendon or reaching the joint capsule	Wound penetrating to bone or joint
Stage	A	No infection or ischemia	No infection or ischemia	No infection or ischemia	No infection or ischemia
	B	Infected	Infected	Infected	Infected
	C	Ischemic	Ischemic	Ischemic	Ischemic
	D	Infected and ischemic	Infected and ischemic	Infected and ischemic	Infected and ischemic

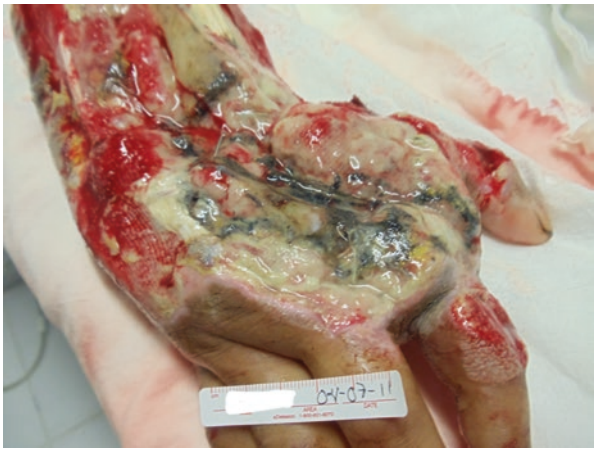

Fig. 13.3 "Diabetic hand" with severe destruction due to infection. Note active infection and the presence of slough covering the wound

"Diabetic Hand" Ulcers

Similar to the diabetic foot, hand ulcers, although much less frequent, can have devastating consequences on the patient with Diabetes (Fig. 13.3). Also known as the "Tropical Diabetic Hand Syndrome", infectious complications of wounds on the hands may lead to aggressive debridement and even amputations. In the latter, associated factors leading to it are end stage renal disease, elevated hemoglobin A1c (more than 10%) and severe peripheral neuropathy [17]. Management of these ulcers is also multidisciplinary and hyperbaric oxygen therapy has been shown to be useful [18].

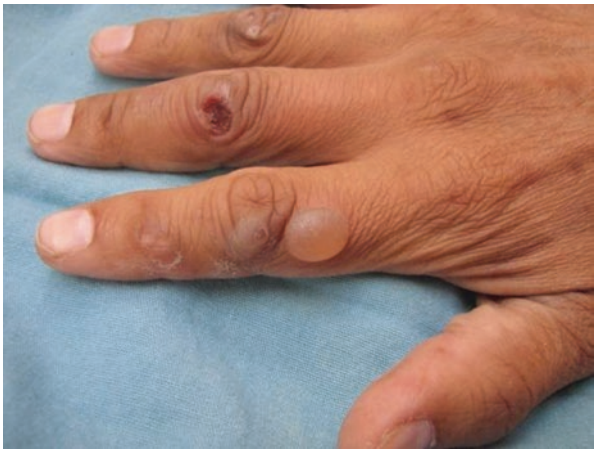

Fig. 13.4 Bullosis diabeticorum on the hand of a patient with type 2 diabetes

Bullosis Diabeticorum

This rare cutaneous marker of DM is characterized by the formation of spontaneous bullae that usually affect the skin of the lower extremities. These bullae are not associated with inflammation [19]. The etiology of this entity is still unknown but the treatment follows the basic wound care principles depicted below [20] (Fig. 13.4).

Leg Ulcers

Leg ulcers are not characteristic of the diabetic patient only, but given the co-morbidities associated with the metabolic syndrome, such as obesity and accelerated atherosclerosis, persons with Diabetes may develop chronic leg ulcers. Leg ulcers in the diabetic may be secondary to diverse conditions such as venous or arterial disease as well as more uncommon causes of leg ulceration.

Venous Leg Ulcers

Venous leg ulcers (VLU) are caused by increased resting venous pressure that may be due to valvular insufficiency, post-thrombotic syndrome or simply by affection of the ankle joint that in turn affects the "calf-muscle pump". This increased pressure leads to continuous inflammation and leakage of proteins and cells at the venous capillaries that eventually causes ulceration.

Even though venous leg ulcers are not characteristic of patients with Diabetes, they are highly prevalent in the ageing population. Furthermore, up to 20% of patients with a venous leg ulcer will have Diabetes as a co-morbid condition [21] (Fig. 13.5a).

VLU are usually located around the malleoli with cutaneous changes secondary to venous hypertension such as ochre pigmentation and the presence of varicosities.

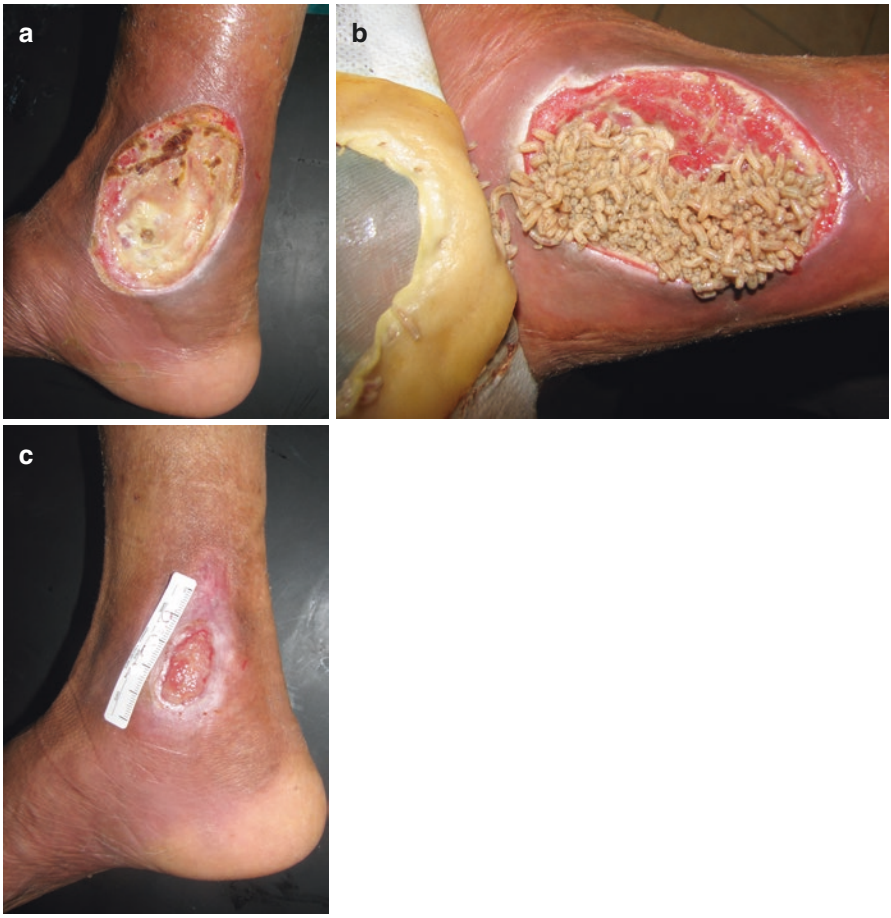

Fig. 13.5 Venous leg ulcer with necrotic tissue on the leg of a diabetic patient. (**a**) At presentation, (**b**) debridement with maggot therapy, (**c**) after moist interactive healing

The ulcer itself has a congestive wound bed, is irregularly shaped and highly exudative [22].

Arterial (Ischemic) Ulcers

Arterial or ischemic ulcers are the result of poor perfusion of the skin secondary to arterial vasocclusive disease. As Diabetes and the metabolic syndrome are associated with accelerated atherosclerosis, it is common for this type of ulcers to develop.

Arterial ulcers are characteristically covered with either necrotic eschar or pale slough. Their shape will depend on the size of the affected blood vessel. When the disease is due to the occlusion of a large vessel, very destructive deep ulcers develop while more discrete arterial disease will lead to round or wedge-shaped wounds [23] (Fig. 13.6).

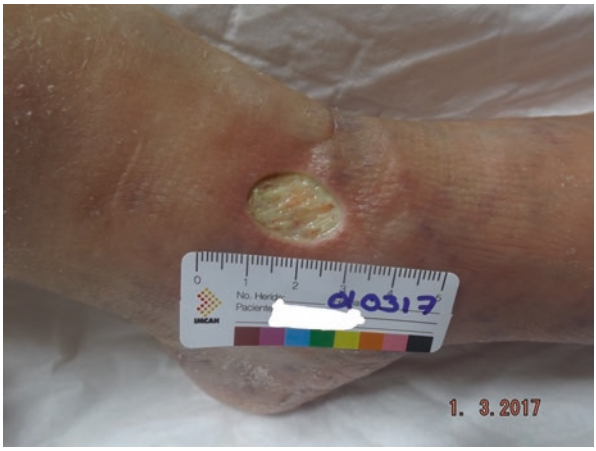

Fig. 13.6 Arterial ulcer on the ankle. Note the lack of granulation tissue and depth

Other Causes of Leg Ulceration

Necrobiosis lipoidica diabeticorum may occasionally become ulcerated. These ulcers are always located on the lower extremities and the diagnosis is relatively simple once the typical associated findings are evident. The ulcerated plaques usually have a yellowish waxy and atrophic surface with one or multiple ulcers [24]. Ulcerated necrobiosis lipoidica may even precede diabetes in as much as 30% of the cases. The cause of this cutaneous marker of DM is unknown, but it has been associated with microangiopathy, antibody-mediated vasculitis and disorders of neutrophil function (Fig. 13.7).

Other causes of leg ulceration in the diabetic are less frequent and must be ruled out whenever the clinical picture suggest them, especially the presence of atypical mycobacteria, fungi or complications of bacterial disease such as necrotizing infections.

Pressure Injuries

Pressure-related injuries or pressure ulcers are related to increased pressure between bony prominences and a surface (commonly the patient's bed) over a period of time. Pressure injury may present in any patient with decreased mobility or lack of sensitivity, both of which occur commonly in hospitalizations due to other complications of diabetes and because of neuropathy. The resulting injuries may range from small blisters or abrasions to full thickness ulcerations reaching down to the bone. As their name implies, the treatment is absolute removal of the causative factor (i.e. Pressure) and proper wound care [25] (Fig. 13.8).

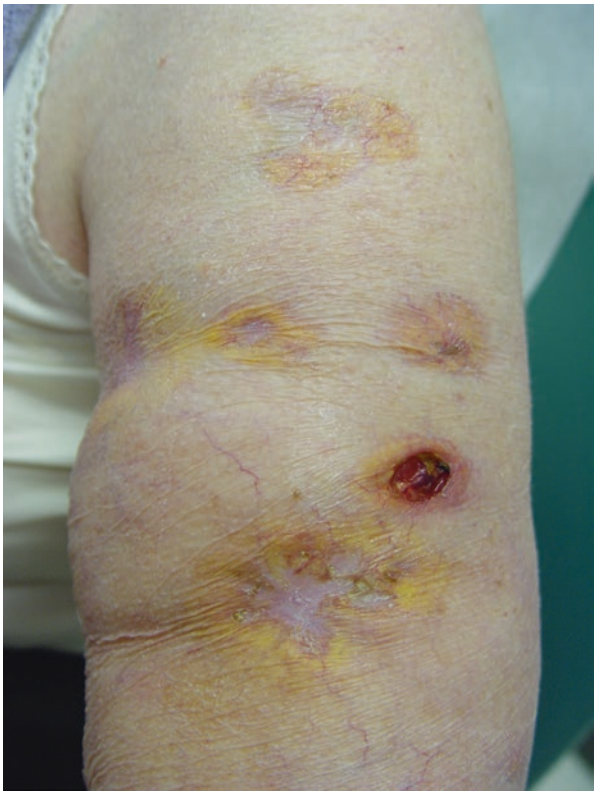

Fig. 13.7 Ulcerated necrobiosis lipoidica diabeticorum

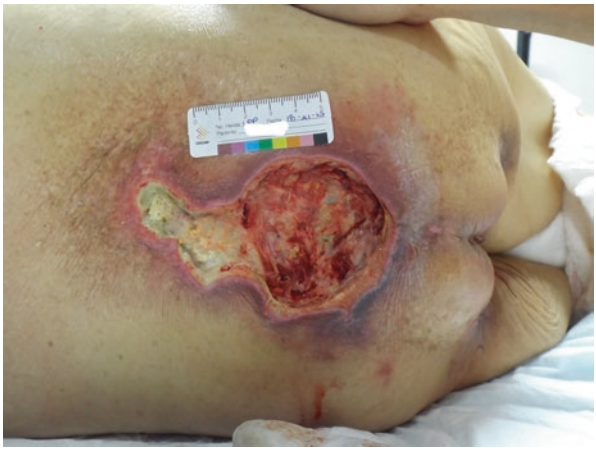

Fig. 13.8 Pressure-induced injury (pressure ulcer) on the sacral area of a diabetic patient after hospitalization

Wound Care in Diabetic Patients

Advances in the understanding of wound healing in the past century have led to new treatment paradigms and technological improvements. Since 1962, when Winter showed [26] that allowing a wound to dry is definitely not beneficial to the healing process, and the later work by Hinman in 1963 [27] confirming this conclusion in humans, wound care has become almost a new specialty where scientific evidence and new exciting research has led to better outcomes. In the following sections, we will analyze some of these developments. A general approach to wound care in the diabetic is depicted in Fig. 13.9.

Wound Evaluation, Diagnosis and Treatment Goals

Whenever a patient presents to the clinic with a wound, the first step in their care is to perform an adequate evaluation. The dermatologist is able not only to properly diagnose an ulcer based on its location and morphology, but also to assess the condition of the surrounding skin, the associated possible complications (e.g. contact dermatitis) and any additional cutaneous signs that the patient may have (e.g. necrobiosis lipoidica). Full evaluation of a cutaneous ulcer includes wound measurement, assessment of the wound bed, borders, exudate, and the skin [28].

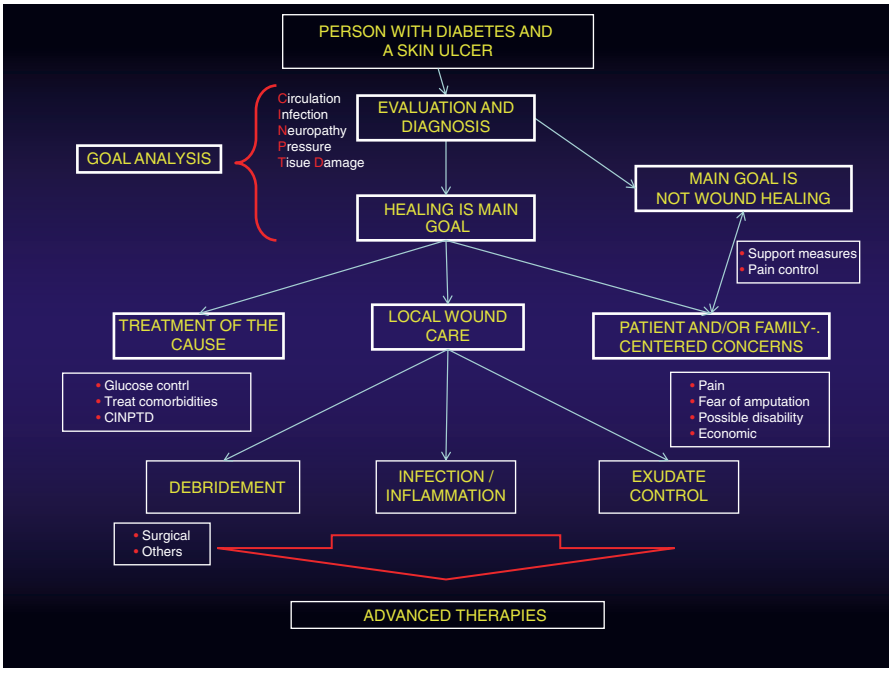

Fig. 13.9 General treatment algorithm for a person with diabetes and a cutaneous ulcer

Once the ulcer has been examined, a history of the present illness must be obtained. This includes asking when was the last time the patient had healthy skin on the area, how the ulcer began, past treatments, symptoms associated with the ulcer and relevant past medical history.

Proper assessment is key in obtaining an adequate diagnosis of the cause of the ulcer. Without an adequate diagnosis, one may not provide an ideal treatment plan, which should always, ideally, be driven by the patient's needs and desires and not solely on the clinician's.

The goals of treatment must take into consideration whether healing an ulcer is likely (e.g. critical ischemia), whether the patient is beyond treatment or if delaying a radical treatment (e.g. an amputation) may endanger his life or increase the risk of a higher amputation. Also, the physician must understand what the patient's main concern is (e.g. sometimes pain relief or odor control becomes more important than treating the wound itself).

Severe or Critical Ischemia Recommendations

One of the main factors affecting wound healing in the diabetic is cutaneous perfusion [29]. Ischemia leads to shortage of oxygen and nutrients necessary for wound healing, it affects the ability of the host to establish a proper immune response, and when severe enough, it will not allow for medications and antibiotics to reach the affected area. Therefore, reestablishing circulation is of paramount importance.

Unfortunately, sometimes this is not possible due to very advanced atherosclerosis or to a lack of human and economic resources to achieve successful revascularization, which is common in developing countries. When a cutaneous ulcer in a diabetic patient falls into this group, quality of life and avoiding further deterioration of the patient is the most important goal. To achieve the former, one must establish a close relationship with the patient, and take any possible measures to control the patient's pain; always taking into consideration that kidney function may be impaired. Pain may be due to associated ischemia, infection, or a combination of both. Therefore, the cause of the pain and any aggravating factors should be addressed.

Further deterioration of the wound, and of the patient's health, must be avoided. Although progressive ischemia may lead to deterioration, it is usually infection the main reason why these wounds become unstable. To avoid it, aggressive debridement is contraindicated (i.e. avoid removing necrotic tissue that is strongly adhered to the wound bed) since it will lead to a larger wound that will not heal anyway. In this scenario, moist healing (see below) is contraindicated for increasing humidity will also increase bacterial proliferation. The wound must be dried to allow for eschar formation and in some cases "mummification". Systemic antibiotics will be necessary in some cases to drive infection back while getting the patient in control [30, 31] (Fig. 13.10).

Finally, as stated before, if the pain becomes unbearable, the patient becomes unstable and there is risk of sepsis or the need for a higher level of amputation, or whenever the patient requests it, radical surgery by means of an amputation may be indicated.

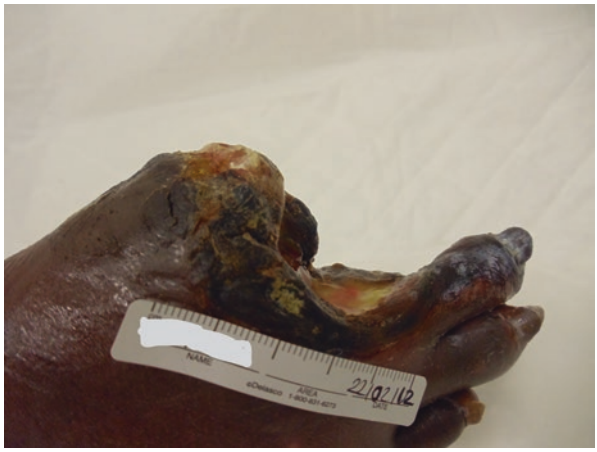

Fig. 13.10 Crtilical limb ischemia

Patient-Centered Concerns

More and more, quality of life and listening to the patient's worries, beliefs, and expectations have become a marker of good healthcare. Especially when treating persons with Diabetes and cutaneous ulcers these aspects of care need to be taken into consideration. Fear of amputation is very common in diabetics who have ulcers. After evaluating the wound, the clinician should discuss the goals of treatment and listen to the patient's understanding of the plan and expectations.

The economic aspects of treatment should also be discussed since advanced wound care modalities, and the healthcare team that needs to be involved in their care, can become costly. Therapies should then be selected based on the ability of the patient or health care system to pay for them. Furthermore, many patients become incapacitated by their wounds, so occupational, and work-related issues should be discussed. Centering care around the patient will identify these as well as other issues related to adherence to treatment, and will aid in establishing a good relationship between physician and patient [32, 33].

Treating the Cause

Once the patient has been properly evaluated, the diagnosis has been established, and goals and expectations of treatment have been discussed with the patient, the single most important measure into achieving wound improvement is treating the cause.

Treatment of the cause will correct, whenever possible, the underlying factors leading to poor healing.

General treatment of the cause in Diabetes focuses directly on optimal glucose control. One must remember that whenever infection or a wound ensues, this may cause glucose levels to vary wildly. Therefore, one must team up with the internist

Table 13.2 Frequent causes of ulcers in the diabetic patient and treatment of the causative factors

Wound	Cause	Treatment
Diabetic foot and hand	Ischemia Infection Pressure	Revascularization Antimicrobial therapy Offloading [34]
Venous leg ulcer	Venous hypertension	Compression therapy [35]
Arterial	Ischemia	Revascularization [36]
Pressure	Pressure	Offloading (pressure shifting) [37, 38] Special surfaces [39]
Other		Treat specific cause

or diabetic care expert to keep glucose under control. Also, Diabetes may co-exist with several comorbidities that affect healing such as lack of circulation, hypertension or hypercholesterolemia. All these should be controlled should also be addressed.

Some of the most common types of ulcers found in diabetics, as well as their cause and specific treatment, are listed in Table 13.2.

Unfortunately, treatment of the cause is not always possible due mainly to either the patient's general condition, or because the cause is still unknown. In these cases, proper wound care preparation will optimize the local conditions to improve the chances of healing.

Principles of Wound Bed Preparation

A concept introduced to the wound care literature first by plastic surgeons, and later adopted by wound care clinicians, wound bed preparation is an organized series of steps or conditions that need to be addressed to optimize wound healing [40]. This approach deals with adequate tissue debridement, diagnosis and treatment of infection, and providing adequate moisture to the wound to allow cell migration and healing. If these aspects have been addressed and the wound is still not healing, the use of advanced wound care modalities may be indicated.

Tissue Debridement

The first step in managing the wound is to remove necrotic tissue from the wound bed, also known as debridement. When dry, necrotic tissue is usually black or brown and easily distinguished from healthy tissues underneath. However, when moist, it becomes a white, stringy, adherent substance known as slough that should not be confused with viable tissue and should be readily removed (Fig. 13.3).

Debridement is vital to preparing the wound for closure. The presence of necrotic tissue in the wound bed causes delays in its repair in several ways. First, it acts as a mechanical barrier that blocks the migration of keratinocytes from the edges of the wound as well wound contraction. Second, it is a constant stimulus for the already chronic inflammatory process that diabetics are especially prone to have. Third, it

promotes bacterial infections. Removing necrotic tissue will allow the clinician to properly measure the wound, evaluate for signs of infection and, more importantly, it stimulates the wound to begin the repair process, turning a chronic wound into an acute one [41].

A few conditions must be met before debridement. Patients must be evaluated and treated for conditions that may affect the outcome of the procedure such as hyperglycemia. It is important to remember that diabetics usually have some degree of vascular damage; in order to avoid creating a larger wound that is more prone to infection, the area to be treated should be evaluated for adequate blood supply (see above) [41]. Finally, consider using some kind of analgesic or anesthetic, whether it be topical or systemic. The fact that patients have neuropathy does not mean they may not require pain control during the procedure.

There are several modalities that may be used for tissue debridement. The most common ones are surgical (sharp), mechanical, biosurgical, enzymatic, and autolytic.

Surgical debridement uses sharp instruments such as scalpels, scissors, or curettes to remove necrotic tissue. It is the fastest method and will remove large amounts of necrotic tissue that may involve deeper structures as bone and tendons. Sharp debridement will also reduce bacterial burden effectively so it is indicated whenever a wound is severely infected. The cost may vary greatly depending on whether or not the patient requires the use of an operating room and anesthesia. It also has the advantage of stimulating the wound bed which makes it the method of choice for diabetic wounds [41]. Drawbacks to surgical debridement include a higher risk of bleeding, pain and the fact that it requires the clinician to distinguish devitalized from healthy tissue making it a non-selective method of debridement. Hydrosurgical debridement uses a high-pressure water jet to cut through tissue. It hasn't been shown to be more effective than other options and costs significantly limits its use in daily practice [42].

Mechanical debridement involves the forceful removal of tissue from the wound bed. This can be achieved by several methods and may range from the simple rubbing of gauze on the surface of the wound, to the infamous wet-to-dry. Wet-to-dry debridement consists on applying wet gauze on the wound bed and allowing it to dry. The gauze is then pulled and removed together with necrotic tissue. Wound cleansing debridement involves using a continuous flow of fluid at high pressures to force devitalized tissue out of the wound bed. In whirlpool debridement, the patient is submerged in a whirlpool where water jets help loosens necrotic tissue and bacteria from the wound. These methods are also non-selective and can cause significant pain to the patient which is why they should be avoided if possible [43].

Maggot debridement therapy, also called biosurgery, is the use of medical-grade larvae of the blowfly *Lucilia sericata* to remove necrotic tissue from the wound base. Basically, the larvae are "caged" over the area to be cleaned where they will selectively remove devitalized material while avoiding healthy, viable tissue. Additionally, they have been shown to produce antiseptic substances that may help decrease bacterial load and fight off infection. Advantages of biosurgical debridement include its high selectivity for unviable tissue, low risk, and high effectiveness

(Fig. 13.5a–c). Disadvantages include the need to procure the larvae, which must be bred in a sterile environment, and patient compliance [44].

Wounds can be debrided by applying topical enzymes such as papain, streptokinase and fibrinolysin to devitalized tissue until the wound is completely cleaned; this is known as enzymatic debridement. Since papain may cause cross-sensitivity with latex, the only available enzymatic debridement is through the use of collagenase. Autolytic debridement involves keeping wounds moist with hydrogels, or occlusive dressings to cause naturally occurring enzymes to break down devitalized tissue. These are painless and selective methods; however, if used alone, it can take a long time to clean the wound completely.

The choice between the different types of debridement depends on several factors such as the physician's skill, the conditions of the patient and the wound, availability and costs [45]. Another important factor to consider is the amount of tissue that needs to be removed. Wounds with large amounts of devitalized tissue may take too long to debride with enzymatic or autolytic methods and surgical debridement may represent a better option. Over the course of treatment most patients will require maintenance debriding of small quantities of tissue to maintain the wound bed in optimal conditions; in these cases, less invasive methods such as enzymatic debridement may be considered. Most patients will probably benefit from a combination of methods that maximizes the removal of devitalized tissue and minimized the loss of viable tissue.

Table 13.3 summarizes advantages and disadvantages of different methods of debridement (Table 13.3).

Infection

Host resistance is one of the most important factors in wound infection. Infection occurs whenever the host's ability to counteract bacteria in the wound is surpassed

Table 13.3 Advantages and disadvantages of some of the existing methods for wound debridement

Debridement method	Advantages	Disadvantages
Surgical	– Fast – Allows removal of large quantities of tissue – Reduces bacterial burden – Stimulates wound bed – Variable costs	– Higher risk of bleeding – Pain – Non-selective (depends on clinician's skill)
Mechanical	– Low cost (wet-to-dry and physical) – High cost (pressurized water)	– Non-selective – Pain
Biosurgical	– Selective – May decrease bacterial load – Effective	– Patient compliance – Availability of larvae is limited – May be painful
Enzymatic/ Autolytic	– Selective – Painless	– Slow

[46]. In diabetics, this is particularly important since uncontrolled Diabetes leads to a poor immune response. Furthermore, typical signs of inflammation may not be evident for some time and therefore infections tend to be more severe at the time of diagnosis.

The diagnosis of infection in a wound should always be based on clinical signs. Unfortunately, there is great variability in the available evidence on how to diagnose infection given that complex interactions exist between the host and the bacteria present in the wound.

Whenever a patient develops and ulcer, bacteria will enter deeper tissues and will begin to replicate and invade them. If the host can fight back the bacteria, the bacteria will be eliminated, the wound bed will granulate and eventually the wound edges will advance and heal the wound. Unfortunately, diabetics are prone to infections given the previously discussed alterations caused by chronic abnormal glucose levels. Furthermore, the patient will present for evaluation later, given that most of the time neuropathy will affect the ability to feel pain. Hence, most wounds in diabetics will already have polymicrobial infections.

Signs of local infection or "critical colonization" will include a wound that stalls or wound edges that fail to advance. The wound odor and exudate may increase or even new areas of slough will form. All these signs should warn the clinician that bacterial burden has increased to the point of not allowing the wound to heal [47, 48]. Biofilm formation may ensue and cause increased levels of chronic inflammatory mediators in the wound and repeated acute infections [49].

Deep infection will show the classical signs of inflammation: erythema, increased temperature, edema, loss of function and pain. Increased pain or the appearance of pain in a non-painful wound has been shown to be the best predictor of wound infection [9]. Infection would then need to be classified into mild, moderate or severe according to specific criteria and systemic involvement [50].

Osteomyelitis is a common concern in diabetic patients; in the case of diabetic foot ulcers, research has shown that positive plain x-rays or a positive probe-to-bone test may be enough to diagnose bone involvement [10, 51]. Imaging modalities like MRI or nuclear medicine may be necessary in cases of suspected osteomyelitis associated with other types of ulcers.

Cultures should be obtained whenever infection is suspected to guide proper antimicrobial therapy. Although tissue cultures from the wound bed are ideal, properly obtained swabs have shown to be a good alternative [52]. These swabs should be taken from the deeper part of the wound after debridement of all necrotic tissue. Lately, a new method of molecular bacterial identification, has led to new discoveries on the most common bacteria found in all chronic wounds and may substitute common cultures in the future [53].

Treatment of infection will depend on whether infection is limited to the surface of the wound or bacteria are causing deep infection. As stated above, infection in the diabetic can be lethal and therefore it is important to consider prompt hospitalization and therapy when a severe or even moderate infection is diagnosed. Prompt debridement and adequate antimicrobial therapy should be started immediately after diagnosis and cultures.

Several antimicrobial dressings are now available to treat increased bacterial burden in the wounds. The advantages of these dressings over common materials are that they will deliver the antimicrobial agent continuously in steady concentrations while controlling exudate and minimizing chances of resistance or sensitizations. The most common of these antimicrobials are silver, iodine or polyhexamethylene (PHMB) [54–65]. Briefly, silver may be found in numerous dressings ranging from hydrocolloids to alginates or pure carboxymethylcellulose; ionic silver is slowly released into the wound bed. Cadexomer iodine, a slow-release iodine compound, has been shown to increase wound healing in leg ulcers and diabetic ulcers. Finally, PHMB is a wide-spectrum polymerized biguanide with no reported bacterial resistance. It denatures bacterial proteins causing membrane pores that will destroy bacteria in the wound. This compound may be found in cleansing solutions and dressings as well. It is important to remember that these dressings will only treat the surface of the wound and therefore, if deeper infection is suspected, systemic antibiotics will be necessary. Recently published data indicates that osteomyelitis can be treated with antibiotics alone, challenging the traditional belief that it should always be treated with surgery and antibiotics [66, 67].

Treating increased bacterial burden and infection will lead to better chances of healing and formation of granulation tissue and wound closure. Once granulation tissue begins to appear, one may consider switching to regular advanced wound care dressings that are not impregnated with antimicrobials, but this will depend on the host's ability to fight off infection.

Moisture Balance

For many years, and following Hippocrates' teachings, it was believed that in order for a wound to heal, it should be dried and allowed to form a scab. This concept prevailed for centuries until Winter proved that allowing a wound to dry would slow the healing process [26]. Hinman later corroborated these findings on the arms of healthy volunteers where the use of occlusion with a polyurethane film helped wounds to heal faster and better [27]. The concept of moist healing was then introduced to the medical literature.

Moisture in the wound should be balanced. Uncontrolled exudate usually follows increased inflammation, and may cause maceration of the borders, new ulcer formation and loss of protein and growth factors. Therefore, achieving moisture balance by absorbing excess exudate and providing a moist environment is a goal of therapy.

For this reason, advanced dressings materials were developed to substitute for common cotton gauze that has limited absorbing capabilities and may adhere to the wound, leave residue or allow the wound to dry.

A full list of all the available dressings would be too lengthy for this chapter, but the most commonly used dressings are:

Hydrogels. Previously mentioned in the debridement section, these are gels with high amounts of water that will provide moisture to dry wounds. It may be amorphous or come in wafers.

Polyurethane films. These were the dressings first used by Winter and Hinman. Films will not allow the wound to dry and act mainly by allowing water vapor through without absorbing any fluid. This makes them ideal for wounds with very little exudate, for large amounts of exudate will cause maceration.

Hydrocolloids. Different mixtures of carboxymethyl cellulose, gelatin and pectin create a colloid that may be found in several shapes and sizes. This dressing will form a gel in contact with the exudate (the gel may have a characteristic odor and consistency) that will provide for some exudate absorption while maintaining active autolytic debridement (Fig. 13.11).

Foams. These dressings may range from high-grade polyurethane foams to some hydropolymers that absorb and lock-in exudate. They may hold large quantities of exudate according to their design and may even be used under compression. Foams may also be used as adjuvant therapy to prevent ulcer formation in patients at risk of friction or pressure (Fig. 13.12).

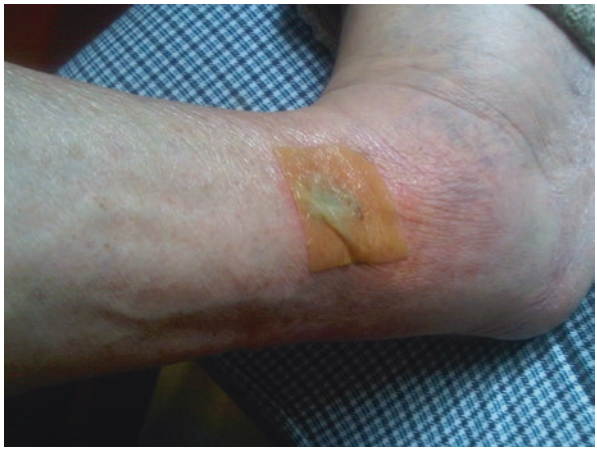

Fig. 13.11 Hydrocolloid dressing after 48 h on a lightly exudative ulcer

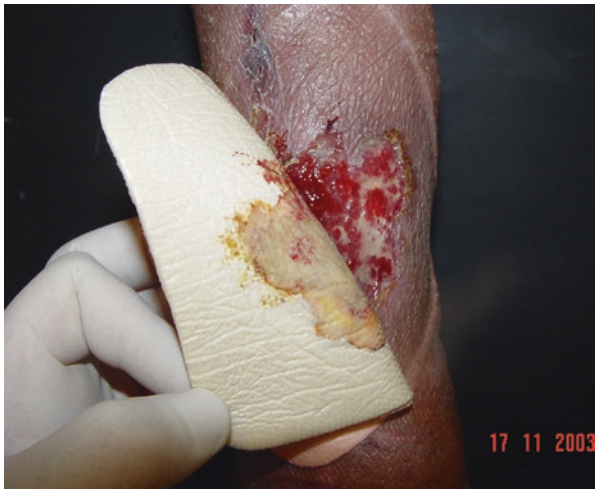

Fig. 13.12 Foam dressing on an ulcer leg

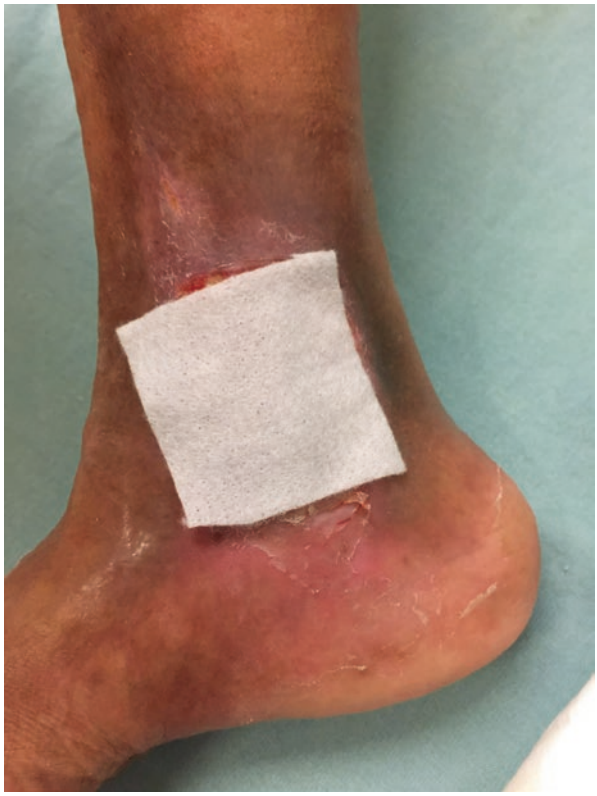

Fig. 13.13 Hydrofiber dressing applied on a wound with moderate to high exudate

Alginates. Calcium alginate is a highly absorbing soft material that is used in wounds with heavy exudate. This compound is degradable and may be used to pack wounds safely, especially those with large amounts of drainage.

Pure carboxymethyl cellulose fibers. These dressings are also soft and highly absorbent. Their main advantage besides their absorption is that they will not diffuse the exudate beyond the border of the ulcer and are particularly helpful in preventing maceration (Fig. 13.13).

Exudate may also be controlled using devices such as negative pressure wound therapy (see below).

The use of these materials will depend on the amount of exudate, the goals of therapy and the clinician's experience. Once the properties and general principles of these dressings are understood, the clinician may either change the dressings to a less or more absorbing material or increase or decrease the number of days between dressing changes to achieve optimum moisture balance [68, 69].

Advanced Wound Care Modalities

Most wounds will heal after correcting the cause and achieve proper debridement, control of infection and inflammation and providing moist healing. However close to 10% of wounds will take much longer to heal or will require advanced wound

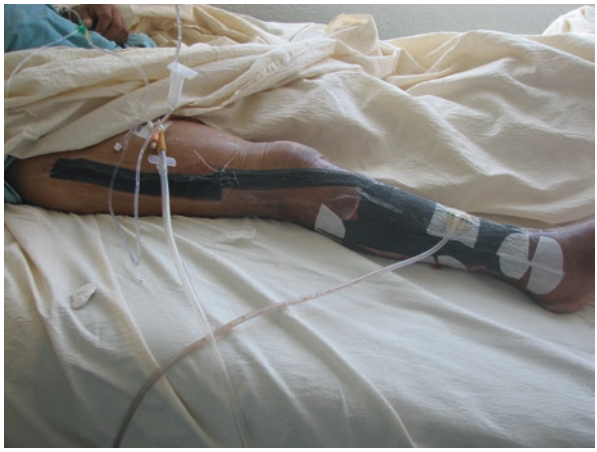

Fig. 13.14 Negative pressure wound therapy on a patient with diabetes who developed fasciitis

care modalities. Most of these therapies have been developed over the last 20 years and are costly, but some of them have proven to shorten healing times and are backed by strong evidence.

Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) is the transmission of vacuum to the surface of the ulcer by means of an interphase (that may be foam or special gauze) and an advanced pump that can graduate the amount of negative pressure to be delivered. NPWT has been shown to provide many advantages on the wound bed. By creating negative pressure, it will help the wound contract towards the center of the ulcer. Granulation tissue is then stimulated through increased cell replication. Since all the exudate is collected in a canister, it will also control moisture by removing excess fluid. This removal of fluid improves local circulation and rids the wound of local lymphatic congestion and edema. Silver interphase foams are available when additional antimicrobial activity is needed [70].

Negative pressure wound therapy has shown to decrease healing times and decrease the number of complications and amputations in diabetic patients [71] (Fig. 13.14).

Hyperbaric Oxygen Therapy

Although initial hypoxia in the wound acts as a potent initiator of healing, oxygen is necessary for the synthesis of collagen and for immune cells to effectively fight back infection. Therefore, wounds that are not properly perfused will not heal, in part, due to lack of oxygenation.

Hyperbaric oxygen therapy (HBOT) is defined as "an intervention in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute, or ATA)" [72]. By increasing the pressure, gases become more soluble and therefore oxygen concentrations in the blood and plasma will increase 1000-fold allowing for underperfused tissues to become oxygenated.

Due to the large variability of the study quality regarding HBOT, and the fact that the therapy is used for unapproved indications, controversy exists regarding its efficacy. However, recent studies have shown that the use of this modality of therapy is well indicated in diabetic foot ulcers and will improve the chances that a wound will heal [73].

Growth Factors

During the healing process, inflammatory cells will produce several growth factors to stimulate collagen synthesis, recruitment and migration of cells necessary to produce new tissue. These growth factors have several effects on the ulcer itself.

With this knowledge, recombinant growth factors have been synthesized to stimulate the wound bed to healing [74, 75]. The first product to be approved for this purpose was becaplermin, a recombinant platelet-derived growth factor. Becaplermin increases healing rate in diabetic foot ulcers and has proven to be cost-effective, however a recent black box warning by the FDA indicates that patients who underwent this therapy may have a higher risk of developing cancer.

Another growth factor that has been used in the treatment of cutaneous ulcers is recombinant epidermal growth factor. In a double-blind comparative trial using this factor, more ulcers healed in the study group than in the control group. Furthermore, recent systematic reviews have shown that this therapy is more efficacious than standard care [76].

Other growth factors have been investigated but their efficacy remains to be proven.

An old therapy that has regained some popularity is platelet-rich plasma where a gel containing activated platelets and growth factors is either injected or applied topically to the wound. Unfortunately, not enough evidence exists to regard it as useful in chronic wounds [77].

Although much more research is needed in these novel therapies, especially in the combined use of several growth factors, some of them have shown promising results.

Cutaneous Substitutes

Cutaneous substitutes are bioengineered dressings that are meant to provide temporary (or permanent) wound coverage while healing takes place. Multiple new dressings have been devised in recent years with this purpose ranging from those without living cells that act as scaffolding in the healing process and inhibit metalloproteases, to skin constructs that look and function as normal skin would [78].

Wound matrices are dressings made of substances commonly found in the dermis such as collagen, fibrin, hyaluronic acid or other components of the granulation tissue. These dressings will act as a temporary dermis allowing for cells to migrate into the matrix and create new tissue and blood vessels. These dressings may range from cadaveric dermis from donors specially prepared to become acellular to complex compounds of these molecules that may even be specifically tailored to a particular wound.

Skin constructs or substitutes consist of bio-dressings containing living cells. These living cells may be of dermal origin, such as fibroblasts, or epidermal

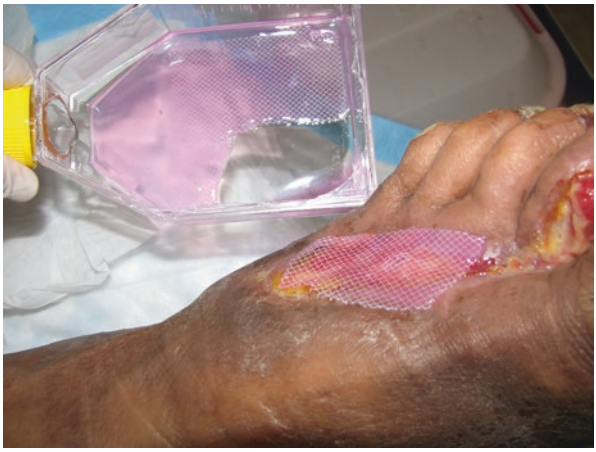

Fig. 13.15 Multi-layer fibroblast construct on a patient with a diabetic foot ulcer

consisting of keratinocytes. The origin of these living cells may be autologous or more commonly from healthy skin donors. Therefore, most of these dressings will not become incorporated, but the living cells within will produce cytokines and growth factors that will stimulate healing while providing a temporary cover for the wound (Fig. 13.15).

Conclusions

Wound healing is a complex process that involves cellular recruitment, matrix synthesis and interactions between the host and the microbiome within the wound. In persons with Diabetes this process may become stalled due to abnormalities caused by increase blood glucose.

Given that amputations in diabetics usually follow a poorly-treated ulcer, it is important to properly assess and readily treat these patients through a multidisciplinary team.

Advanced wound care modalities have allowed to provide the best care to optimize healing, as long as the cause of the ulcer can be treated and the patient and health care team are committed to the treatment.

New technologies are becoming available that will allow for better treatment outcomes for diabetics in the future.

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