Wound healing and diabetes mellitus

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One of the leading causes of impaired wound healing is diabetes mellitus. Unlike other causes of altered tissue repair, there are multiple factors that contribute to the impairment. The impact of the altered healing is enormous, considering the number of diabetic patients that exist. Patients with diabetes may present with relatively minor wounds such as minor trauma after trimming a toenail or walking on a pebble. Minor wounds often lead to chronic, nonhealing ulcers that are predisposed to infection. It is not uncommon for the infection to lead to gangrene and, ultimately, the need for amputation. Indeed, diabetic patients have the highest amputation rate of any type of chronic wound. To expand the significance of the problem, one estimate suggested that admissions for foot infections constituted 20% of hospitalizations for patients with diabetes, and led to 50% of all nontraumatic lower limb amputations. In their lifetime, 25% of patients with diabetes mellitus are expected to have severe foot problems [1].

The purpose of this review is to describe the classic clinical presentations of chronic wounds in diabetes. The multiple reasons why diabetes mellitus contributes to altered tissue repair, including the latest in research, are covered. The ultimate goal is to use these factors to develop techniques that may help augment the healing of wounds in diabetes. Fortunately, the pharmaceutical world is aware of this problem and currently the only commercially available growth factor on the market in the United States is approved for treating diabetes mellitus. In addition, biologic products are also approved for the treatment of these wounds. It is hoped that some day it will be possible to prevent the terrible wound complications of this disease.

Clinical presentation

Most chronic wound problems in diabetes mellitus involve the feet. Other areas may be involved, but for many reasons that are discussed later, feet are the most commonly affected area [2,3]. The classic chronic ulcer in diabetes mellitus is a relatively small, punctate wound that lies on the plantar surface beneath a deformed metatarsal head. This site is most often affected because of neuropathy and anatomic changes in the arch. Because of insensitivity, pressure is a major contributor to these wounds. In addition, the tips of the toes may develop pressure-related ulcers due to clawing, and the toes may develop gangrene from microvascular disease or microemboli. These problems are related to the diabetic’s predisposition to atherosclerosis. Ill-fitting shoes may lead to wounds in other areas of the foot.

Once a wound develops, it often remains open for prolonged periods. The ulcer develops a rim of raised epithelium with some pale granulation tissue in the center. There is often callus formation around the ulcer. It is not uncommon for the wound to develop surrounding cellulitis, because there tends to be reduced ability to control local colonization of bacteria. Unfortunately, there is also a tendency for the wound infection to “invade” inside the foot and travel along plantar fascial planes. For instance, a
relatively small metatarsal wound may track well inside the foot. A plantar ulcer may track all the way through the foot to the dorsal side. In a similar fashion, a patient may present with a gangrenous toe that requires amputation. After the amputation, the wound between the remaining toes fails to close. Later, the patient may develop cellulitis and probing the wound reveals a wound that dissected well into the foot. The next procedure is a transmetatarsal amputation that also does not close. Finally, the patient requires a below-knee or even an above-knee amputation. The reasons for these dismal outcomes are discussed in the next section.

Factors contributing to altered healing

There are many factors that contribute to the altered tissue repair of diabetes mellitus [1–6]. Some factors are related to a diabetic patient’s predisposition to diseases such as atherosclerosis or renal failure. Another factor is related to the predisposition to the development of neuropathy. The reduced ability to deal with infection is another contributing factor. Finally, there are cellular, metabolic, and biochemical factors that have been found to contribute to altered tissue repair in diabetes mellitus. There is predisposition for both macrovascular and microvascular diseases in diabetes mellitus. The incidence of atherosclerosis is increased in diabetes, so wound problems related to major vascular stenosis or occlusion are not uncommon. Atherosclerosis can lead to emboli from proximal vessels that usually lead to the damage of toes. Decreased blood flow may result in insufficient oxygen delivery that makes healing impossible unless angioplasty or vascular bypass is performed. Therefore, it is important to check for insufficient oxygen delivery to the wound as an early cause of impaired healing. The atherosclerosis of diabetes also tends to have some differences compared with the manifestations in nondiabetic patients. Frequently, there is a palpable pulse because calcification makes the arteries inflexible. This problem makes using the ankle-brachial (AB) index difficult. The transthecutaneous monitor, however, is useful to ensure that there is enough local oxygen delivery to begin healing the wound.

Another contributing factor is microvascular disease. At the capillary level, there is a tendency to develop a thickened perivascular basement membrane. The consequence of this thickening is not quite clear. It may contribute to altered delivery of micronutrients, but some studies suggest that there is a tendency for increased vascular permeability [7]. Edema is a factor that impairs healing in diabetes and in venous stasis disease. The basement membrane thickening may also make leukocyte migration more difficult. This extracellular matrix deposition may “trap” inflammatory cells and may contribute to the increased tendency for infection.

Uremia is another factor that alters healing. Patients with diabetes mellitus are prone to silent or overt renal disease. Increased urinary protein loss in these diseases predisposes the patient to edema, which, as stated before, contributes to impaired tissue repair. In addition, uremia is another factor that independently contributes to altered healing [8].

A major contributor to the development of problem wounds in diabetes mellitus is the propensity for developing neuropathy. A discussion of the pathogenesis of diabetic neuropathy is not appropriate for this article, but more information can be found elsewhere [4,9]. People with diabetes mellitus are predisposed to develop neuropathy of the lower extremities. The neuropathy involves all nerve types. The most obvious consequence of neuropathy is the loss of protective reflexes. Because pain is not felt, diabetic patients will walk on wounds without knowing that they are present. For instance, if a shoe does not fit well, the resulting pressure or rubbing is not felt and may continue until a wound develops. Cutting toenails is another case in which minor wounds may be missed, left untreated, and ultimately become infected. The true pathogenesis of many of these wounds is the same as for any other person with loss of sensation—pressure necrosis. Without sensory input, the pain of pressure is ignored and ultimately leads to ischemic death of the involved area. As for any patient with neuropathy, prevention is the key to preventing these problems. Diabetic patients need to be careful with their selection of shoes and with their trimming toenails. Simple routine inspection of the feet may prevent amputations in the future.

The reason why diabetic patients tend to develop plantar ulcers over the metatarsal heads is also related to neuropathy. In addition to a sensory defect, diabetic neuropathy involves the destruction of motor and sympathetic nerve function. The muscles that control the arch of the foot lose the feedback as to their normal positioning. Therefore, diabetic patients tend to lose the normal position of the arch and more pressure is placed over the metatarsal heads. Combined with the lack of sensation, pressure necrosis results from this increased pressure that occurs most commonly over the second metatarsal head. The protective callus that is produced tends to increase the chance for pressure. The loss of sympathetic nerve supply tends to lead to a foot that does not sweat. This lack of moisture causes...
cracking of the skin and further increases the risk of wounds. Obviously, the preventative issues discussed above are essential for preservation of the lower limbs in diabetes mellitus.

Another key issue with diabetes mellitus is the preponderance for the development of infection. The causes of the impaired resistance to infection are multifactorial. The tendency for the skin to crack leads to increased areas for bacteria to colonize. The altered sweating described above may also alter the bacterial flora. Lack of glucose control is a factor that increases the risk for infection. Hyperglycemia may increase available nutrients for bacteria, and may also impair local defenses. Leukocytes have different forms of impaired function in a hyperglycemic environment. In addition, other factors contribute to impaired immune function in diabetes mellitus.

Animal models have shown that there are specific cellular changes that contribute to impaired tissue repair in diabetes mellitus. In the 1990s, a great deal of research focused on the potential use of recombinant growth factors in accelerating healing in the diabetic population. Investigators first discovered that there were beneficial effects on healing after the application of growth factors to wounds in diabetic animals [10–12]. Later, they tried to understand what the problems were and how growth factors worked. One hypothesis was that wounds in diabetic animals did not produce enough growth factors [13]. In other words, if the wound did not synthesize enough growth factors, then the stimuli for normal healing would be lacking. The finding that treatment with growth factors was effective also lent support to the growth factor deficiency hypothesis. Using molecular detection techniques, investigators have found that there is a decrease in the expression of mRNA and protein of several growth factors (insulin-like growth factor (IGF-I), IGF-II, keratinocyte growth factor (KGF), plus others) in diabetic animals compared with control animals [14–16].

Another hypothesis was that there was increased destruction of growth factors in the wound environment of diabetic animals and patients. This hypothesis was supported by studies in chronic pressure ulcers in which increased levels of matrix metalloproteinases (MMPs) were found in chronic wound fluid as compared with acute wound fluid (from mastectomy drains) [17]. Soon, similar results were found in the wounds of diabetic animals. Using the genetically diabetic mouse model, Neely et al [18] found that several MMPs were increased in the diabetic wounds when compared with non-diabetic controls. It appears, therefore, that both decreased growth factor production and increased proteolytic activity (destruction of growth factors) are involved in the pathogenesis of impaired healing in diabetes mellitus.

It has been proven that poor glucose control contributes to the altered healing in diabetic wounds [3]. Along the same lines, prevention of hyperglycemia improves healing in animals made diabetic by destruction of the islets of Langerhans [3]. Understanding how altered glucose control leads to altered healing would help with the development of treatments for impaired tissue repair. There are three possible ways that hyperglycemia contributes to the metabolic pathophysiology of diabetes-related complications. (Several excellent reviews [1–7] provide details about the potential causes of complications in diabetes mellitus.)

The first hypothesis is that abnormal glucose levels alter the actual control of cellular Na⁺/K⁺ ATPase activity [6,19,20]. Hyperglycemia leads to increased polyol pathway activity, which leads to a depletion of myo-inositol stores. This involves the biochemical pathway in which glucose is converted to sorbitol by aldose reductase. Because the conversion of sorbitol to fructose (by sorbitol dehydrogenase) is slow, sorbitol tends to collect in the cell. The end-product of the sorbitol to fructose conversion is NADH. The increased conversion to fructose leads to decreased NADPH and increased risk for oxidative stress. The increased levels of sorbitol may increase the osmotic load in the cells. Sorbitol inhibits myo-inositol uptake, which, in turn, leads to the alteration in Na⁺/K⁺ ATPase activity. Inhibitors of aldose reductase have demonstrated some promise for reducing the complications of diabetes mellitus [21]. A second metabolic abnormality that results from hyperglycemia may be related to the activity of protein kinase C (PKC) [22]. Diabetes appears to increase the synthesis of diacylglycerol, which, in turn, leads to increased PKC activity. PKC is a key signaling receptor for many cellular activities including proliferation, contraction, calcium influx, and others.

Hyperglycemia also leads to the production of pathologic by-products. Hyperglycemia leads to “advanced glycosylation end products” (AGEs), which are large aggregates of aldoses covalently bound to reactive amino groups [23]. AGEs may lead to increased oxidative stress and may activate a key transcription factor, nuclear factor (NF)-κB [24]. NF-κB is involved in many cytokine-related cell responses. For instance, AGEs appear to induce the production of platelet-derived growth factor (PDGF), tumor necrosis factor-α, and interleukin-1α [25,26]. AGEs may also lead to collagen cross-linking [27] and inhibit normal collagen degradation [28]. The
agent aminoguanidine may be a therapeutic option to reduce the effects of AGEs [29,30].

**Treatment of diabetic wound problems**

Once a diabetic patient develops an ulcer in a lower extremity, adequate care should be instituted to prevent infection and ultimately, amputation. The outcome for routine care of diabetic foot ulcers has been well documented and is actually quite discouraging (see Table 1). Oyibo et al [31] followed 194 patients with diabetic foot ulcers for 1 year. These patients were treated with routine saline soaked dressing changes. The mean age of the patients was 56.6 years, and the duration of diabetes was 15.4 years. Sixty-seven percent of the ulcers were neuropathic and 77.8% involved the forefoot. The mean ulcer size was 1.5 (0.6–4.0) cm². After 1 year, 65% healed, 15% required amputations, 16% failed to heal, and 4% died. The size of the ulcer determined whether or not it would heal (3.9 cm² for amputations versus 1.2 cm² for those that healed). In a similar kind of study, Edelman et al [32] followed 64 patients with 78 ulcers for 6 months. In half a year, 47% healed, 22% required amputations, 22% failed to heal, and 13% of the patients died. Margolis et al [33] collected “control” patients from 10 wound healing trials and found that in the six trials that followed patients for 20 weeks, 31% healed. For the four trials that followed patients for 12 weeks 24% of the control patients healed. The rates of healing stayed quite consistent for all of the trials.

Several trials have performed analyses that examined factors that might predict outcome. Margolis et al [34] performed a meta-analysis study that looked at

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Results of different trials for the treatment of diabetic foot ulcers</th>
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<tr>
<td>Treatment</td>
<td>Control</td>
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<tr>
<td>Standard care</td>
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<tr>
<td>Oyibo et al [31]</td>
<td>N = 194, 65% in 1 year</td>
</tr>
<tr>
<td>Edelman et al [32]</td>
<td>N = 64, 47% in 1/2 year</td>
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<tr>
<td>Margolis et al [33]</td>
<td>Six trials, 31% in 20 weeks</td>
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<tr>
<td>Offloading</td>
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<tr>
<td>Armstrong et al [39]</td>
<td>N = 63, 12 weeks</td>
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<tr>
<td>Removal cast walker, 65%</td>
<td>Total contact cast, 89.5%</td>
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<td>Half shoe, 58%</td>
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<tr>
<td>Platelet releasates</td>
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<tr>
<td>Margolis et al [44]</td>
<td>Relative risk for healing: 1.14–1.59</td>
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<tr>
<td>Artificial skins</td>
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<tr>
<td>Dermagraft (Smith &amp; Nephew Inc., Largo, FL), Gentzkow et al [49]</td>
<td>N = 12, 50% in 12 weeks</td>
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<td>Graftskin</td>
<td>N = 208, 38% in 12 weeks</td>
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<td>(Novartis Pharmaceuticals Corp., East Hanover, NJ), Veves et al [51]</td>
<td>56% in 12 weeks</td>
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<td>Pham et al [59]</td>
<td>N = 33, 41% in 12 weeks</td>
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<td>75% in 12 weeks</td>
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<tr>
<td>Regranex (Ortho-McNeil Pharmaceutical, Raritan, NJ)</td>
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<tr>
<td>Steed et al [55]</td>
<td>N = 57, 25% in 20 weeks</td>
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<tr>
<td>Wieman et al [56]</td>
<td>N = 127, 35% in 20 weeks</td>
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<tr>
<td>d’Hemecourt et al [52]</td>
<td>N = 68, 22% (good care)</td>
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<tr>
<td>N = 70, 36% (placebo gel)</td>
<td>N = 34, 44% (100 μg) (20 weeks)</td>
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<tr>
<td>Zagari et al [57]</td>
<td>N = 122, 35% in 20 weeks</td>
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<tr>
<td>Embil et al [53]</td>
<td>No control</td>
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<tr>
<td>N = 134, 57% in 20 weeks</td>
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Values reveal the percentage healed at the indicated time point.
the factors that increased the likelihood of healing a neuropathic diabetic foot ulcer. The three factors that were important predictors were smaller ulcer size, shorter duration of the presence of the wound, and being nonwhite. Others have confirmed that ulcer size does predict outcome. Edelman et al [32] showed that univariate predictors of healing included age less than 65 years, diagnosis of diabetes mellitus less than 15 years, painless ulcer, palpable ankle pulse, AB index greater than 0.5, and physician’s assessment of the likelihood of osteomyelitis. When multivariate analysis was performed, the presence of a Doppler pulse and painless ulcer were the only predictors. Of diagnostic tests, transcutaneous pO2 levels less than 25–30 mm Hg were also predictive of failure to heal. Other assessments of vascular function, such as toe blood pressure and AB index, have not been as predictive [35,36].

The treatment of diabetic wounds begins with preventative measures that include both controlling hyperglycemia and preventative foot maintenance [37]. It is essential that the patient be on an aggressive program to produce tight control of glucose levels. Those patients who have poor control have more problems. For patients with neuropathy, the feet should be inspected daily for any signs of breakdown. Special care should be taken when cutting toenails. In addition, great care should be taken to ensure that good-fitting footwear is obtained. Simple prevention may obviate the need for future amputations.

Once a diabetic ulcer has developed, aggressive wound care is essential. First, other factors that might play a role in the pathogenesis of the impaired healing should be sought after. The foot should be checked for any signs of vascular insufficiency. Simple checking for pulses and the AB index should be performed, but are not always reliable. A good indicator of adequate vascularity is the transcutaneous monitor. A vascular workup should be instituted if there are signs of impaired oxygenation. Dialysis should also be instituted if the patient is uremic. Renal transplantation may improve the healing abnormalities.

The patient should eliminate pressure on ulcers that develop on the plantar surface. Although it is easy to tell patients to stay off their feet, it is frequently difficult for patients not to walk. One treatment is to use “total contact” casts that produce even pressure throughout the foot and “off-load” the pressure on the ulcer [38]. Armstrong et al [39] performed a randomized trial of different types of “off-loading.” Sixty-three patients were randomized to treatment with a total contact cast, removable cast walker, or “half shoes.” At 12 weeks, patients treated with a total contact cast healed 89.5% of the time. This healing rate was significantly better when compared with 65% for removable cast walkers, and 58.3% for “half shoes.” One contributing factor was that patients with total contact casts were significantly less active than were patients in the other two groups.

Debridement of necrotic tissue and elimination of surrounding callus also improves healing. The effectiveness of simple debridement became evident in a clinical trial that examined the efficacy of Regranex (Becaplermin; Ortho-McNeil Pharmaceutical, Raritan, NJ) in diabetic ulcers. Wounds that were aggressively debrided to clean tissue healed better than did those that were left alone, irrespective of treatment [40]. Wounds should be checked frequently for signs of infection, and aggressive treatment should be instituted if found. Infections are usually polymicrobial, and therefore antibiotics should be chosen appropriately. One study involving 84 patients with “severe” diabetic wound infections [35] demonstrated that ciprofloxacin and clindamycin led to a 95% response rate with 55% cured, 24% improved, and a 21% failure rate. The prognosis in these patients was worse with a transcutaneous pO2 value of less than 30 mm Hg.

Another treatment modality that is often used is hyperbaric oxygen treatment. The use of hyperbaric oxygen is somewhat controversial. Bakker [41] reviewed the literature on the use of this treatment and stated that there are several theoretic reasons for choosing hyperbaric oxygen. It increases O2 delivery to the tissues, increases killing by leukocytes, and increases anaerobic bacterial killing in the wound. He found, however, that most of the clinical studies were anecdotal and retrospective, and that there were many methodological problems with the prospective trials. Wunderlich and Lavery [42] reviewed the literature on the use of this treatment and found that five (two randomized) had no controls. The numbers of patients in those trials that did have controls averaged 28 for hyperbaric oxygen and 16.2 for the controls. Most studies had bias and four of the seven were from one center (in Milan). Both Bakker and Wunderlich and Lavery stressed the urgent need for collaborative, multi-institutional, randomized, prospective trials.

The clinical trials testing the efficacy of growth factors have been relatively well designed. Growth factors are given to the wounds by platelet releasates, bioengineered tissues (cultured cells or composite skins), or recombinant growth factors. The first trials focused on platelet releasates. The patient’s own platelets are collected and stimulated to release proteins from their alpha granules. The alpha granules contain numerous growth factors that have been found to accelerate tissue repair [43]. These “relea-
sates” are then applied over the patient’s wounds. This technology is performed at proprietary “wound care centers.” The best evaluation was by Margolis et al [44], who performed a retrospective cohort study controlling for treatment selection bias using logistic regression-derived propensity scores. They found that healing in diabetic neuropathic ulcers after the use of a platelet releasate was more effective than “standard care.” The relative risk for a wound to heal by platelet releasate treatment when compared with standard care ranged between 1.14 (95% confidence interval [CI] 1.03–1.27) and 1.59 (95% CI 1.49–1.70). The benefit was greatest in patients with the most severe (larger and deeper) wounds. These authors completed the evaluation by noting that severe wounds have not been evaluated by prospective, randomized trials [44].

Another “natural” source of growth factors is from cultured cells and bioengineered tissues. The first cells to be tested were cultured keratinocytes. Preliminary and uncontrolled trials suggested that they would be useful for the treatment of all sorts of chronic dermal wounds [45–47]. These cells are now available commercially and can be used for these problem wounds. Another option is to utilize fibroblasts cultured in “dermal” matrices for the treatment of chronic wounds. Mansbridge et al [48] described the potential use of a commercially available live dermal product for diabetic foot ulcers [35]. According to the manufacturer, Dermagraft (Smith & Nephew Inc., Largo, FL) is a “three-dimensional, allogeneic, human neontal dermal fibroblast culture grown on a biodegradable scaffold that is cryopreserved.” The product is applied over the wound to stimulate healing. The clinical trials suggested “optimal healing within a range of metabolic activity.” One clinical trial suggested that the “neodermis” could improve healing in chronic wounds of diabetic patients [49].

Both keratinocytes and fibroblasts produce a variety of cytokines and growth factors. The combination of the two cell types leads to a synergistic increase in growth factor production [50]. It makes sense, then, that the use of composite skins consisting of both keratinocytes and fibroblasts should enhance healing. In 2001, Veves et al [51] performed a randomized prospective of the effectiveness of Graftskin (Aplicra; Novartis Pharmaceuticals Corp., East Hanover, NJ), a “living skin equivalent” consisting of a dermis (with fibroblasts) and keratinocytes, on the healing of noninfected, nonischemic chronic plantar diabetic foot ulcers. Twenty-four centers in the United States entered 208 patients into the study. Patients were randomized to treatment with Graftskin or control (saline-moistened gauze). All patients had “standard state-of-the-art adjunctive therapy,” including extensive debridement and adequate foot off-loading. Graftskin was applied at the start of the study and reapplied weekly for a maximum of five applications. The main outcome of complete healing was assessed by intention to treat at 12 weeks. At 12 weeks, 63 (56%) of the patients treated with Graftskin achieved complete healing compared with 36 (38%) of the control wounds \( (P = 0.0042) \). The Kaplan-Meier median time until complete closure was 65 days for Graftskin versus 90 days for the controls \( (P = 0.0026) \). The odds ratio for complete healing for the Graftskin treatment group was 2.14 (95% CI 1.23–3.74). There was a higher rate of osteomyelitis and lower limb amputations for the control group. There were no other differences in adverse events. These results suggest that the use of the “skin equivalent” is superior to the standard care. Because the cost of the Graftskin is over $1000 per sheet, the cost-effectiveness needs to be determined. Unfortunately this product was recently removed from the market.

Another option for treating diabetic foot ulcers is the use of recombinant growth factors. Although there was a great deal of interest in the development of these products in the past, their popularity has faded in the last several years. As of now, only one of the dozens of growth factors is available for the treatment of chronic wounds. Regranex, which is recombinant human platelet-derived growth factor (rhPDGF-BB), has been approved by the Food and Drug Administration for the treatment of chronic diabetic wounds. The growth factor has not, however, been approved for any other type of wound. Several well-designed, prospective, randomized trials have been performed and suggest that Regranex is effective in accelerating healing in diabetic foot ulcers [52–57]. Steed et al [55] published the first study to show that Regranex significantly improved healing in diabetic ulcers. The growth factor was applied once a day and dressings were changed twice a day. Results showed that the rate of healing was increased after treatment. Embil et al [53] performed an open-label study to determine whether once-a-day dressings and Regranex application were effective. The 134 patients were treated for 20 weeks and evaluated at 6 months. Complete healing was observed in 57%, with a mean time until closure of 63 days. These findings were consistent with the Steed et al [55] trial.

Another novel approach was presented by Margolis et al [58]. They performed a phase I trial to evaluate the safety of H5.020CMV.PDGF-B for the treatment of insensitive diabetic foot ulcers. The trial was designed to utilize the recently developed gene therapy techniques. H5.020CMV.PDGF-B uses a viral
delivery system to introduce the gene for the B chain of PDGF into the wound. The trial involved injecting the gene product into the ulcers of insensate diabetic feet. Because it was a phase I trial, definitive findings were not the goal. Safety and potential feasibility of using the gene therapy technique were demonstrated. The use of gene therapy for the delivery of growth factors has been used extensively in preclinical models. Their potential for clinical applicability needs to be proven, but has great potential.

Summary

Diabetes mellitus is one of the major contributors to chronic wound healing problems. When diabetic patients develop an ulcer, they become at high risk for major complications, including infection and amputation. The pathophysiologic relationship between diabetes and impaired healing is complex. Vascular, neuropathic, immune function, and biochemical abnormalities each contribute to the altered tissue repair. Despite treatment of these chronic wounds, which involves tight glucose control and meticulous wound care, the prognosis for their healing is quite poor. Newer modalities that deliver natural or engineered growth factors show a great deal of promise. All of the studies clearly show the continued need for well-controlled clinical trials.

References


[54] Wieman J, Smiell J, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor BB (becaplermin) in patients

