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Non-Surgical Management of Diabetic Foot Ulcers

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Abstract

Ulcerations of the foot in diabetic patients are common, disabling and predispose to ascending infections such as gangrene and sepsis which frequently necessitate amputation of all or part of the lower extremity. Effective treatment of Diabetic Foot Ulcers (DFU) can have a major therapeutic benefit resulting in reduced morbidity, mortality and the need for surgical intervention. We review the major factors contributing to the development of these lesions and the components of an effective multidisciplinary approach to treatment with the goal of limiting major surgical intervention such as amputation when possible.

Scope of the Problem

Lower extremity ulceration in diabetic individuals is common, with a lifetime risk estimated at between 12-25% [1,2]. Presence of a DFU results in substantial patient morbidity, impairment of the quality of life, and ultimately in higher treatment costs estimated at tens-of-thousands of dollars per lesion [3,4]. Up to 85% of lower extremity amputations in diabetic individuals may be preceded by skin ulceration [5] emphasizing the need for effective preventative and therapeutic strategies in dealing with these lesions.

The etiology of DFU is usually multi-factorial with a combination of factors coalescing to result in the clinical lesion. Of the multiple etiologic factors summarized in (Table 1), the presence of neuropathy is considered the most significant [4]. Diabetes induced peripheral neuropathy results in the loss of the protective sensation of pain, while autonomic dysfunction and sympathetic denervation result in dry skin and a warm foot. Additional contributing factors may include the presence of peripheral vascular disease, callus formation, edema and deformity. These combined factors result in tissue-damaging mechanical loads applied to an insensate and poorly perfused foot which is unable to sense and prevent the impending ulceration, and impedes the tissue's ability torepair the resulting damage and defend against subsequent infection [6,7].

There are many known physiologic factors which contribute to wound healing deficiencies in diabetic individuals.

These include decreased or impaired growth factor production, angiogenic response, macrophage function, collagen accumulation, epidermal barrier function, quality of granulation tissue, keratinocyte and fibroblast migration and proliferation, number of epidermal nerves and bone healing. The imbalance of these factors impairs the cytokine and chemokine controlled migration of epithelial progenitor cells to the affected tissue [8].

Ulcer Classification

There is no universally accepted classification of DFU although several classification schemes have been proposed.

The Wagner-Meggitt classification is the traditional method of ulcer grading with six levels of wounds classified by the depth of ulceration and the extent of gangrene. Deficiency of this system is that all infections are lumped into one category limiting its clinical relevance [9]. The commonly employed University of Texas system measures ulcer depth and presence or absence of ischemia, but does not include measures of neuropathy or ulcer area [9]. Other more recently proposed classifications include the SAD and PEDIS (perfusion, extent, depth, infection severity and sensation) grading systems which incorporate multiple factors useful in comparative research studies but are cumbersome to use in clinical practice [10,11].

For clinical simplicity and utility we prefer the Infectious Diseases Society of America (IDSA) guidelines which classify infected DFU into categories of mild, moderate or severe based on relatively easily determined clinical parameters [12]. Mild infections are those defined as having two or more clinical manifestations of inflammation - purulent discharge, erythema, pain, tenderness or induration-but these changes must be limited to the skin, and the patient must lack evidence of a local complication or systemic illness. Moderate lesions are those occurring in patients who are clinically well, but exhibit evidence of more extensive cellulitis, lymphangitic streaking, or spread of infection to deeper structures (superficial fascia, deep-tissue abscess, gangrene, muscle, tendon, joint or bone)

Severe lesions are those in which evidence of systemic toxicity or metabolic instability is present. These features may include fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis,severe hyperglycemia or azotemia.

The clinical utility of this system was recently validated in a study by Lavery and colleagues [13]. In this longitudinal study of over 1600 diabetic patients, individuals with DFU lacking infection or with only mild infection rarely required repeat hospitalizations. Only 3% of these individuals required amputations during the study period.

In contrast, patients with moderate or severe infections were far more likely (46% and 78% respectively) to require amputations during the study period.

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Effect of Diabetic Control on Ulcer Healing

Improving diabetic control (along with smoking sensation) has clearly been shown to decrease the likelihood of developing DFU [14]. The prospective effect on ulcer healing is less clear. Studies commonly employ the glycosylated hemoglobin level (HgbA1C) as an indicator of glycemic control. In a meta-analysis of over 500 patients, Margolis and associates found that individuals with a lower HgbA1C at the start of management did not have an improved chance of ulcer healing [15]. However, Marston, in a study involving 245 patients treated with a bioengineered human dermal substitute, found an increased rate of ulcer healing in those individuals in which hemoglobin A1C levels decreased during the 12 week study period *versus* those in which levels increased during the same time [16].

The lack of improvement shown in most studies may be due to the short timeframe involved in ulcer treatment programs (typically several weeks). If present, improvement in ulcer healing due to improved glycemic control in the short run would most likely be related to impaired leukocyte function in chronic hyperglycemia [17]. While further studies may help clarify this discrepancy, we continue to believe that good overall medical practice demands effective glucose control in all patients with or without active DFU.

Principles of Ulcer Treatment

Predicting which ulcers will heal and which will resist therapy is difficult as many factors may contribute to wound healing. In general, wounds that are small (≤ 2 cm 2), have been present for ≤ 2 months, are relatively shallow and which are non-infected have the highest chance of healing [18].

The major principles of ulcer management can be summarized as follows

Treat any clinically evident infection

Relieve ischemia if present

Reduce mechanical pressure on the ulcer (offloading)

Perform ulcer debridement

We will examine each of these principles in turn.

Treatment of infection

Infection is typically the end result of the presence of an open skin lesion coupled with an impaired tissue defense system. The development of infection in the setting of DFU is what ultimately endangers the limb and the individual. Infections may be superficial and local, soft tissue and spreading (cellulitis), or involve deep tissues such as bone (osteomyelitis). All skin and ulcer surfaces are typically covered with bacteria, hence a routine surface culture is not sufficient for determining the presence of active infection, and the prescription of antibiotics based only on these cultures is not considered beneficial [19].

The decision to initiate antibiotic therapy should however be based on clinical grounds, with subsequent culture results guiding the ultimate choice of antibiotics. The typical signs of local infection or cellulitis-erythema, warmth, tenderness and/or purulent discharge-may be difficult to differentiate from chronic ischemic or neuropathic skin changes if present. Systemic signs such as fever or leukocytosis are infrequently present but usually indicate a more serious infectious process [20].

Infections in diabetic patients tend to be polymicrobial including gram positive, gram negative, aerobic and anaerobic species [21]. If osteomyelitis is present Staphylococcus aureus is the most likely pathogen [22], but deep (bone) cultures should still be obtained if possible. In practice, deep cultures are difficult to obtain and are often contaminated by surrounding soft tissue organisms. Treatment with broad spectrum antibiotics is therefore often empiric [22].

The presence of large quantities of colonizing bacteria or an untreated active infection can significantly impede ulcer healing [23-25]. However, it is important to note that studies have failed to demonstrate that administration of routine antibiotic treatment in the absence of a clinically active infection is effective either in advancing ulcer healing or in preventing future infections [19,26]. Given the worldwide risk of breeding resistant organisms (in large part due to overuse of antibiotics), increased cost and risk of side effects, antibiotic therapy should be reserved only for those individuals with clinically evident infections.

Relieve ischemia

A strong consistent relationship between hyperglycemia and the incidence and progression of micro vascular (diabetic retinopathy, loss of vision, and nephropathy) and macro vascular (amputation and cardiovascular disease mortality) complications in people with both Types I and II diabetes has long been noted [27]. The presence of diabetes increases the incidence of limb ischemia approximately 2-4 foldand the likelihood of lower extremity amputation by up to 20 times [28-29]. A 1% increase in Hemoglobin A1C levels increases the likelihood of peripheral arterial occlusive disease by up to 26% further emphasizing the need for primary prevention [30].

The therapy of micro vascular disease is largely preventative through good glycemic control, smoking cessation, control of hyperlipidemia and regulation of blood pressure [31]. Macro vascular disease is remediable by invasive therapies such as angioplasty or surgery and should be excluded in all patients with DFU. Findings on physical exam may be limited due to overlying edema, infection or ischemia necessitating the reliance on non-invasive vascular testing in many cases [32]. Subsequent confirmation by additional imaging studies (angiography, magnetic resonance angiography) may be required in some individuals.

Treatment is often complicated by the tendency in these patients to develop multilevel distal lesions within heavily calcified vessels. These factors as well as the frequently unsatisfactory results of non-invasive revascularization (angioplasty and the like) have long favored direct surgical intervention in diabetic patients [7]. Whereas the surgical approach to the treatment of large vessel disease is beyond the scope of this chapter, interested readers may review the consensus recommendations recently published by Norgen and colleagues [33].

Non-surgical interventions such as angioplasty, stenting, endarterectomy and sub intimal angioplasty have found increasing utility in the management of diabetic peripheral macrovascular disease. In a large Italian study, Faglia and colleagues treated 993 diabetic patients with critical limb ischemia by Peripheral Angioplasty (PTA). Only 17 individuals (1.7%) required amputations and there

Table 1: Risk factors for foot ulceration and infection.

Risk factor	Mechanism of injury or impairment
Peripheral motor neuropathy	Abnormal foot anatomy and biomechanics, with clawing of toes, high arch, and subluxed metatarsophalangeal joints leading to excess pressure, callus formation and ulcers
Peripheral sensory neuropathy	Lack of protective sensation leading to unattended minor injuries caused by excess pressure or mechanical or thermal injury
Peripheral autonomic neuropathy	Deficient sweating leading to dry cracking skin
Neuro-osteoarthopathic deformities (i.e. Charcot joint) or limited joint mobility	Abnormal anatomy and biomechanics leading to excess pressure especially in the midplantar area
Vascular (arterial) insufficiency	Impaired tissue viability, wound healing and delivery of neutrophils
Hyperglycemia and other metabolic derangements	Impaired immunologic (especially neutrophils) function and wound healing and excess collagen cross-linking
Patient disabilities	Reduced vision, limited mobility including previous amputation(s)
Maladaptive patient behaviors	Inadequate adherence to precautionary measures and foot inspection and hygiene procedures, poor compliance with medical care, inappropriate activities, excessive weight-bearing, and poor footwear
Health care system failures	Inadequate patient education and monitory of glycemic control and foot care

was only 1 death during the follow-up period. The 5-year primary patency rate was 88%, and repeat PTA was successfully performed in most cases. The authors conclude that PTA can be the first choice in diabetic patients, and does not preclude the performance of subsequent by-pass surgery if needed [34]. Impressive as these results are, the study is limited by a lack of prospective randomization and control group comparison.

Corroboration for this approach was published in the BASIL trial by Bradbury et al. In this large, prospective multicenter trial, 452 patients with critical limb ischemia were randomized to either surgery-first or angioplasty-first cohorts. In a 6 month follow-up period the results of the two groups were found to be broadly similar in regards to amputation-free survival or health-related quality of life. Significantly, no difference was seen between diabetic and non-diabetic individuals with these two approaches. The authors do note however that the first year hospital costs were about one-third higher with the surgery-first approach [35]. Taken together, these studies provide compelling evidence that angioplasty should be tried first in most cases of DFU with concomitant macro vascular occlusive disease, while open surgery should be reserved for exceptional cases or those in which angioplasty has failed.

Reduce mechanical pressure on the ulcer (offloading)

As discussed previously, the path physiologic mechanism of DFU formation is a complex process involving local trauma to an insensate, metabolically vulnerable tissue which results in a focal lesion which is difficult to heal. As would be expected from a mechanism involving trauma in the form of local pressure, any process which reduces that pressure should aid in local healing. Pressure on the DFU may be in one of two forms: direct downward pressure also called "vertical stress", and tangential movement parallel to the skin surface also called "shear". The combination of these forces results in damage to the soft tissue primarily at the ulcer edges, a process known as the "edge effect" [36].

The greatest challenge in offloading is convincing the patient of the need for offloading, and finding an effective method with which the patient will comply. Simple though somewhat draconian methods such as bed rest, wheelchair use and crutch walking should be highly effective, but are so lifestyle- altering as to be impractical for most patients. Other attempted methods including half shoes (which support only the rear and mid foot leaving the forefoot suspended above the ground), therapeutic shoes and Removable Cast Walkers (RCW) have also been tried with limited success. Although relatively easy to apply, these devices are also bulky and uncomfortable to wear, particularly at home. Easily placed they are therefore also easily removable allowing patients the option to choose their level of compliance. Unfortunately, many patients tend to use them intermittently, primarily when outside the home [37]. In one study, patient compliance with RCW averaged only 28% of their daily walking activity [38].

Whereas RCW are considered potentially highly effective in offloading, the "gold standard" for offloading DFU is the Total Contact Cast (TCC) [39]. This technique uses a well-molded, minimally padded cast that maintains contact with the entire plantar surface of the foot and lower leg. Pressure is distributed evenly over the entire plantar surface of the foot thereby relieving undue pressure on the ulcer itself. By limiting side-to-side movement it also decreased shear forces across the ulcer surface. Due to its bulky nature a side benefit of TCC is decreased walking on the affected foot further limiting pressure on the ulcer.

TCC is considered highly effective in treating non-infected, non-ischemic neuropathic plantar DFU with healing rates ranging from 72-100% in various studies [40-44]. When compared in a prospective randomized trial of 63 DFU patients, Armstrong and colleagues found a significantly higher ulcer healing rate in those individual assigned to receive offloading *via* TCC (89%) compared to those receiving RCW (65%) and half-shoes (58%) [45]. Other investigators have found similar healing rates in forefoot ulcers with alternative offloading methods (accommodative dressing, healing shoe or walking splint) compared to TCC when devices were selected based on location of the ulcer, patient age and duration of ulceration [46].

Unfortunately TCC are not effective in DFU with concomitant infection or ischemia, or when the ulcer is located on the heel area [47]. Further limitations are the difficulty in applying these devices as many centers lack the necessary experience or skilled personnel. In a study by Wu and colleagues, less than 2% of specialist's surveyed in over 900 US foot centers were found to be using TCC for treating the majority of DFU [48].

To ameliorate the problems with the TCC a new technique entitled the instant Total Contact Cast (iTCC) is currently being studied. The iTCC uses as its base a RCW that is converted into a

Table 2: Types of debridement*.

Surgical
Mechanical
Saline moistened gauze "wet-to-dry"
Saline irrigation
Autolytic
Enzymatic
Biologic

*Adapted from Steed [51].

not easily removable device by wrapping it in a plaster bandage. The advantage of this device over the TCC is that it can be easily applied by relatively unskilled practitioners [49]. In a randomized controlled trial of 50 patients, Armstrong and colleagues found these devices to be comparable to a traditional TCC with healing rates of 83% *versus* 52% in the RCW group. In addition, healing rates were also found to be significantly shorter in the iTCC *versus* the RCW-treated cohort (41 *versus* 58 days respectively) [50].

Regardless of the offloading device chosen, the importance of close patient follow-up to monitor healing and to guard against signs of ischemia or infection is mandatory.

Perform ulcer debridement

Debridement, defined as the removal of foreign matter and necrotic tissue from a wound, has a number of important benefits for ulcer healing. Active debridement accelerates the natural sloughing of necrotic tissue which allows wound granulation to begin. Since necrotic tissue also contains the highest bacterial counts, debridement provides an immediate reduction in quantitative bacterial counts, a known inhibitor of wound healing [23-25]. Exploration of the wound allows the identification of underlying osteomyelitis if present and the performance of deep cultures uncontaminated by surface colonizing bacteria [51].

Methods of debridement may be surgical, mechanical, autolytic, enzymatic or biologic, and are summarized in (Table 2). The traditional and still preferred method of ulcer debridement involves the surgical removal of necrotic tissue with a sharp instrument such as a scalpel or scissors [52]. This technique requires at least a minimum skill level and willingness on the part of the healthcare provider. Pain of the procedure is often minimal due to the insensate nature of the diabetic foot, although some individuals are hyper esthetic requiring the use of a local anesthetic or nerve block. Bleeding is typically controlled by direct pressure, topical haemostatic agents or in rare cases by electrocautery [51].

Mechanical debridement is typically performed by applying saline-moistened gauze to the wound, allowing it to dry, and then removing it. This so-called “wet-to-dry” method is simple to perform but may also cause local pain or bleeding, and may inadvertently remove newly formed epithelium. Enzymatic debridement typically employs collagenase- or papain-containing liquids to digest necrotic tissue. These agents should be applied only to the nonviable tissue within the ulcer and not to the healthy surrounding tissue. Although easy to apply, enzymatic debridement may exacerbate bacterial growth by providing a ready growth medium in the form of liquefied necrotic tissue [51]. Application of maggots (maggot debridement therapy or MDT) is the best-known example of biologic debridement and has been shown to be effective in treating diabetic ulcers. Studies are small however and patient acceptance can be problematic [53,54].

A more recent entry into the debridement/wound healing realm is the use of hydrogels in the treatment of DFU.

Hydrogels are chemically-crosslinked Glycosaminoglycan (GAG) films which are applied topically to the ulcer.

These films provide a highly hydrated, pericellular environment in which assembly of other matrix components,presentation of growth and differentiation factors, and cell migration can readily occur-processes essential for effective wound healing [55,56]. In a recent Cochrane Review of Randomized Controlled Trials (RCT), Edwards reported that hydro gels were significantly more effective in healing diabetic foot ulcers than surgical debridement or MDT. Significantly, however, this conclusion is based on a small number of studies (4 hydrogel, 1 surgical and 1 MDT) due to the lack of high quality, double blinded RCT’s for most debridement methods. Furthermore, the author notes that although hydro gels increase DFU healing, it is not clear that this effect is due to debridement [57].

In summary, the performance of ulcer debridement is widely regarded as effective, but lacking well-controlled comparison studies the preferred method is undetermined. Individual practitioner preference and experience should therefore guide the performance of ulcer debridement until better controlled trials are available.

Emerging Therapies

While the general approach to the treatment of DFU is becoming more standardized, a number of emerging therapies are being continually investigated as potential alternatives to the standard treatment principles described above. We briefly review some of the more intriguing emerging therapies undergoing investigation at this time.

Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy (HBOT) involves the systemic administration of 100% oxygen at or above one Atmosphere of Pressure (ATM) [58]. Specific treatment protocols differ between institutions and for differing indications, but most employ pressures at 2-3 times atmospheric. HBOT requires placing the patient in a specialized hyperbaric chamber either singly or in specialized multiplace chambers. Applying HBOT to a single limb is not possible asit would require sealing the proximal portion of the chamber with a tight-fitting seal, thereby creating a constricting tourniquet effect. Overall, the need for expensive hyperbaric facilities and trained personnel limits HBO’s availability, and results in a significant expense of therapy estimated at approximately $12,000 per ulcer treated [59]. Furthermore, treating every high-grade DFU with HBOT would be prohibitive, with an estimated overall cost of between $252-984 million in the US alone [59].

The rationale for HBOT is that increasing tissue oxygen tension and/or pressure within the wound site results in a number of therapeutic benefits. These include reversing tissue ischemia and edema, modulation of locally produced growth factors and tissue toxins such as nitric oxide, promotion of cellular proliferation and collagen deposition, stimulation of capillary angioneogenisis,

accelerated microbial oxidative killing and inhibition of bacterial proliferation, modulation of the immune system response, and enhancement of oxygen radical scavengers (resulting in decreased ischemia reperfusion injury) [60]. While most of these benefits occur primarily during the treatment period, many such as suppression of bacterial proliferation and immune system modulation may persist following the HBOT session [60].

Side effects of HBOT are generally mild and transitory; primarily ear and sinus barotraumas and myopia. More serious complications may include seizures, decompression sickness, fire in the hyperbaric chamber, and congestive heart failure, the latter occurring primarily in individuals with pre-existing left ventricular dysfunction [60-63].

The benefits of HBOT in the treatment of DFU have been documented in a number of clinical trials, and appear to include the acceleration of wound healing and decreasing the rate of limb amputation [64-68]. Unfortunately, most of these studies suffer from major methodological flaws including lack of randomization or blinding and absence of a control group, and the best of these, astudy by Abidia and colleagues, failed to show a reduction in amputation rate [69]. At least 3 systematic reviews including one for the Cochrane Collaboration have concluded that given the serious methodological flaws there is little evidence to support a role for HBOT in speeding ulcer healing [70-72].The limited evidence for clinical benefit and the significant cost of treatment has led some authors to suggest that HBOT should not be offered for treatment of DFU until large-scale, adequately conducted randomized controlled trials have clearly demonstrated both efficacy and cost effectiveness in ulcer healing and the prevention of major amputation [59].

Topical Oxygen Therapy

Topical Oxygen Therapy (TOT), sometimes called Topical Hyperbaric Oxygen Therapy (THOT), involves the administration of 100% oxygen at or slightly above atmospheric pressure (approximately 1.04 ATM). Fischer first proposed the technique in 1969 utilizing a chamber enclosing only the ulcerated skin sealed around its edges [73].

His first group included only two individuals with DFU and, until recently was largely ignored by the medical community. More modern adaptation involves simply enclosing the involved extremity in a disposable transparent polyethylene bag sealed proximally by an elastic bandage, and connecting it to a humidified oxygen source.

Treatment sessions are typically 1.5 hours a day, 3 times a week, and may administered in an inpatient, outpatient or home setting with minimal skill or instruction.

Though less studied than it hyperbaric cousin, TOT offers many of the same theoretical advantages but provides several additional positives such as low cost, ready availability and ease of administration. In a large uncontrolled study in our institution, an 81% healing rate of DFU was found in individuals treated with TOT in combination with low energy laser. Significantly, there was good patient tolerance and an absence of side effects [74]. Unfortunately, a smaller controlled study by Leslie and colleagues failed to show any significant benefit from TOT [75]. While further trials are ongoing we continue to recommend this simple inexpensive adjunct to our comprehensive treatment program.

Growth Factors

As described above, DFU represent complex wounds in which multiple factors interact to produce the final clinical lesion. Given the complex interaction between mechanical, neuropathic and vascular factors it is not surprising to learn the DFU like other chronic wounds do not follow an orderly and reliable progression of wound healing. Parts of the wound may be found in different stages as the ideal coordination required for rapid healing is lost. The synchronization of this complex process is brought about in large part by growth factors leading to an increased interest in their potential therapeutic role [76-78].

Of the various growth factors, Platelet-Derived Growth Factor (PDGF) is the most studied, and its human recombinant product Becaplermin is the only one licensedfor clinical use. PDGF is produced by the principal cells involved in early wound healing including platelets, macrophages, vascular endothelium, fibroblasts and keratinocytes. It is therefore felt to be an important initiator of the wound healing process [79-80]. PDGF is applied as a topical gel 100μg/g once daily, and has been assessed in a number of clinical trials in the treatment of DFU.

Wound healing has been reported in between 36 and 58% of lesions, significantly better than with placebo [81-84].

Unfortunately, these rates are comparable to healing rates achieved with conservative therapy including offloading and traditional wound care, and none of these studies addressed amputation rates. PDGF gel is expensive, and the added cost and limited documented clinical benefit *versus* traditional therapy may not justify the added expense.

Other potential growth factors under consideration include Fibroblast Growth Factor (FGF), Keratinocyte Growth Factor (KGF), Epidermal Growth Factor (EGF), Transforming Growth Factor Beta (TGFβ), Vascular Endothelial Growth Factor (VEGF), Granulocyte Colony-Stimulating Factor (G-CSF) and platelet Derived Wound Healing Factors (PDWHF)-the latter an autologous blood product containing several growth factors derived from platelet granules [77]. Of these, only a few have been tried clinically in humans with TGFβ and VEGF not having been tested at this time. KGF, FGF have been found to be effective in the healing of other chronic wounds including venous ulcers and burns, but have not yet undergone testing in DFU [85].

Aside from PDGF, the growth factors that have been assessed to various degrees in DFU include FGF, EGF, PDWHF. Richard and colleagues in a trial of FGF applied as a topical spray, failed to find any benefit *versus* placebo [86]. PDWHF has been the subject of two published trials in DFU, with results showing a significant reduction in ulcer size and increased healing rates [87-88]. Unfortunately the product is expensive and availability is limited. Recombinant human Epidermal Growth Factor (hEGF) has been tested in a double-blind randomized controlled trial conducted in Hong Kong by Tsang and colleagues. Of the 127 patients randomized the authors report a 95% healing rate in the group receiving the higher dose hEGF application (0.04% concentration). This result was significantly better than those receiving placebo or the lower 0.02% hEGF cohorts (42% and

57% respectively) [89]. Though encouraging, no additional studies incorporating this growth factor have been published to date.

Perhaps the most intriguing biologic factor is G-CSF which has been the subject of a number of clinical trials in DFU. Early reports suggested that although subcutaneous injections of G-CSF did not affect ulcer healing, it had a positive effect in decreasing infection (cellulitis) and amputation rates [90-91]. In a recent met-analysis of five randomized trials incorporating 167 patients, Cruciani and colleagues found that the addition of G-CSF did not significantly affect the resolution of infection or the healing of the DFU. However, the authors did find that G-CSF was associated with a decreased lower extremity amputation rate, and suggest that use of G-CSF should be considered especially in patients with limb-threatening infections [92]. As with other growth factors, further studies will be required to clarify the role of G-CSF in the therapy of DFU.

Topical Negative Pressure

Topical Negative Pressure (TNP) also known as Vacuum Assisted Closure (VAC) or Negative Pressure Wound Therapy (NTWP) is a technique for assisting the debridement process by continually removing fluid from the wound bed using a foam or open-pored gauze dressing connected to a vacuum device and sealed by an occlusive dressing [93]. It is believed that the negative pressure assists with removal of interstitial fluid, decreasing localized edema and increasing blood flow.This in turn decreases tissue bacterial levels. Additionally, mechanical deformation of cells is thought to result in protein and matrix molecule synthesis, which increases the rate of cell proliferation [94,95].

Over 300 articles, the majority case reports or case series, have been published on TNP therapy in various types of wounds including DFU. Two large mult icenter RCT have added to impression that NPT may play an important role in the treatment of DFU. The first by Armstrong and colleagues compared the effectiveness of NPT to standard moist wound care in 167 diabetic patients following amputation. The results showed a significantly improved healing rate in the cohort receiving NPT *versus* the control group (56% *versus* 39% respectively) [96].

The second study by Blume and associates randomly assigned 342 patients with traditional DFU to either NPT or advanced moist wound care (primarily hydrogels and alginates). This trial also demonstrated a significantly improved rate of ulcer closure in the NPT *versus* the control group (43% *versus* 29% respectively). In addition, the NPT cohort experienced a significant reduction in secondary amputations and fewer home care days with no significant increase in complications [97].

Finally, a meta-analysis published by Zhang et al pooled eight randomized controlled trials comparing NPT to standard wound care was published in 2014. Eight RCT's including a total of 669 patients was included in their analysis. Compared to standard care, NPT treated patients showed a statistically higher proportion of healed ulcers, reduction of ulcer area and a shorter time to wound healing. The NPT treated individuals also underwent significantly fewer major amputations, although their rate of minor amputations was not significantly different.

Overall the author concluded that NPT appears to be more effective for treatment of DFU compared to non-NPT wound therapy and with a similar safety profile [98].

Ozone Therapy

Ozone (O_3) is a naturally occurring molecule with broad activity against a large number of pathogens including bacteria, viruses, fungi, yeast and protozoa. In use medically since the 1800's, O_3 is also purported to have a number of beneficial effects including activation of the antioxidant and immune systems [99]. Administration is similar to TOT with enclosure of the affected limb in an air-tight bag or chamber connected to an external O_3 generator.

Unlike TOT, the O_3 generator is not generally available (nor readily portable like NPT units) limiting treatment to inpatients or those individuals sufficiently ambulatory to travel to regular outpatient therapy.

Unfortunately there is little in the form of clinical studies to support the use of O_3 in DFU. A randomized study by Martinez-Sanchez and colleagues used both topical and rectal insufflations of O_3 in 52 hospitalized patients and compared them with a cohort of inpatients assigned to antibiotic therapy. The investigators reported a significantly faster healing rate in the study group *versus* the controls, as well as improved measures of glycemic control and biochemical markers of oxidative stress [100]. Though intriguing, it is difficult to believe that rectal insufflations would be acceptable to a large number of DFU patients, and impossible to differentiate the relative contributions of the topical and rectal doses.

A smaller study by Weinstein and associates compared 61 DFU patients randomized to topical ozone-oxygen or sham therapy in an outpatient setting. In this study there was a 100% wound closure in the O_3-treated patients who completed the study protocol *versus* 50% in the control cohort [101]. Unfortunately almost half of enrolled patients did not complete the study protocol undoubtedly influencing the final statistical results.

Conclusion

The past several years have seen a dramatic increase in physician interest in the path physiology and therapy of the diabetic foot, and a resulting sea-change in the approach and therapy of affected individuals with DFU. This interest has been spurred by the recognition of the complex biology of chronic wounds, and by the devastating consequences of these lesions to the health of diabetic patients. New path physiologic understanding has led to the development of new therapies such as use of growth factors, and better use of existing therapies such as antibiotics and topical wound care. The appearance of less invasive modalities such as angioplasty and non-surgical forms of debridement has resulted in a paradigm shift, from the primarily surgical to the more integrated multispecialty-integrated approach to the diabetic foot. While much remains to be learned and more studies to be performed, there is increasing hope that new interventions and therapies will result in better outcomes for affected patients with DFU.

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