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REVIEW

Management of Diabetic Foot Ulcers

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ABSTRACT

Diabetic foot is a serious complication of diabetes which aggravates the patient's condition whilst also having significant socioeconomic impact. The aim of the present review is to summarize the causes and pathogenetic mechanisms leading to diabetic foot, and to focus on the management of this important health issue. Increasing physicians' awareness and hence their ability to identify the "foot at risk," along with proper foot care, may prevent diabetic foot ulceration and thus reduce the risk of amputation.

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INTRODUCTION

Diabetic foot is one of the most significant and devastating complications of diabetes, and is defined as a foot affected by ulceration that is associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes. The prevalence of diabetic foot ulceration in the diabetic population is 4–10%; the condition is more frequent in older patients [1–3]. It is estimated that about 5% of all patients with diabetes present with a history of foot ulceration, while the lifetime risk of diabetic patients developing this complication is 15% [1–3].

The majority (60–80%) of foot ulcers will heal, while 10–15% of them will remain active, and 5–24% of them will finally lead to limb amputation within a period of 6–18 months after the first evaluation. Neuropathic wounds are more likely to heal over a period of 20 weeks, while neuroischemic ulcers take longer and will

more often lead to limb amputation [4]. It has been found that 40–70% of all nontraumatic amputations of the lower limbs occur in patients with diabetes [5]. Furthermore, many studies have reported that foot ulcers precede approximately 85% of all amputations performed in diabetic patients [5].

The risk of foot ulceration and limb amputation increases with age and the duration of diabetes [6, 7]. The prevention of diabetic foot is crucial, considering the negative impact on a patient's quality of life and the associated economic burden on the healthcare system [8].

Diabetic foot ulceration is a major health problem and its management involves a multidisciplinary approach. This review aims to provide a synopsis of the current management strategies of diabetic foot ulcers, from prevention to the options for treatment. The authors believe that it may be useful to primary care physicians, nurses, podiatrists, diabetologists, and vascular surgeons, as well as all healthcare providers involved in the prevention or management of diabetic foot ulcers.

PATHOGENESIS

The most significant risk factors for foot ulceration are diabetic neuropathy, peripheral arterial disease, and consequent traumas of the foot.

Diabetic neuropathy is the common factor in almost 90% of diabetic foot ulcers [9, 10]. Nerve damage in diabetes affects the motor, sensory, and autonomic fibers. Motor neuropathy causes muscle weakness, atrophy, and paresis. Sensory neuropathy leads to loss of the protective sensation of pain, pressure, and heat. Autonomic dysfunction causes vasodilation and decreased sweating [11], resulting in a loss of skin integrity, providing a site vulnerable to microbial infection [12].

Peripheral arterial disease is 2–8 times more common in patients with diabetes, starting at an earlier age, progressing more rapidly, and usually being more severe than in the general population. It commonly affects the segments between the knee and the ankle. It has been proven to be an independent risk factor for cardiovascular disease as well as a predictor of the outcome of foot ulceration [13]. Even minor injuries, especially when complicated by infection, increase the demand for blood in the foot, and an inadequate blood supply may result in foot ulceration, potentially leading to limb amputation [14]. The majority of foot ulcers are of mixed etiology (neuroischemic), particularly in older patients [15].

In patients with peripheral diabetic neuropathy, loss of sensation in the feet leads to repetitive minor injuries from internal (calluses, nails, foot deformities) or external causes (shoes, burns, foreign bodies) that are undetected at the time and may consequently lead to foot ulceration. This may be followed by infection of the ulcer, which may ultimately lead to foot amputation, especially in patients with peripheral arterial disease.

Structural foot deformities and abnormalities, such as flatfoot, hallux valgus, claw toes, Charcot neuroarthropathy, and hammer foot, play an important role in the pathway of diabetic foot ulcers since they contribute to abnormal plantar pressures and therefore predispose to ulceration.

Other risk factors for foot ulceration include a previous history of foot ulceration or amputation, visual impairment, diabetic nephropathy, poor glycemic control, and cigarette smoking. Some studies have shown that foot ulceration is more common in men with diabetes than in women [14, 16].

Social factors, such as low socioeconomic status, poor access to healthcare services, and poor education are also proven to be related to more frequent foot ulceration [14, 16].

ASSESSMENT AND CLASSIFICATION

Physical examination of the diabetic foot is based on assessment of the skin and of the vascular, neurological, and musculoskeletal systems.

The dermatological examination includes a visual inspection of the skin of the legs and feet, particularly the dorsal, plantar, medial, lateral, and posterior surfaces, as well as a close examination of each toenail [17]. Other observations to be noted include the presence of peeling skin and maceration or fissuring of the interdigital skin. The visual inspection may discover signs of autonomic neuropathy and sudomotor dysfunction [17].

People with diabetes are at high risk of developing peripheral vascular disease; therefore, the palpation of pulses bilaterally in the dorsalis pedis, posterior tibial, popliteal, and superficial femoral arteries is necessary for assessment of the blood circulation in the lower limbs. Inadequate perfusion of a limb, due to peripheral vascular disease, may crucially affect the progress of the healing of an ulcer, often resulting in chronic unhealed ulcers that are susceptible to infection [15]. A relatively simple method to confirm the clinical suspicion of arterial occlusive disease is to measure the resting systolic blood pressure in the ankles and arms. This is performed by measuring the systolic blood pressure (using a Doppler probe) in the brachial, posterior tibial, and dorsalis pedis arteries [17]. The highest of the four measurements in the ankles and feet is divided by the higher of the two brachial measurements. This ratio is referred to as the ankle–brachial index (ABI). Normal ABI values range from 1.0 to 1.3, since the pressure is higher in the ankle than in the arm. Values over 1.3 suggest a noncompressible calcified vessel. An ABI of less than 0.9 is indicative of peripheral vascular disease and is associated with 50% or more stenosis in one or more major vessels. An ABI of 0.4–0.9 suggests a degree of arterial obstruction associated with claudication. An ABI of less than 0.4 or an ankle systolic pressure of less than 50 mmHg represents advanced ischemia [18]. The ABI correlates with clinical measures of lower extremity function, such as walking distance, velocity, balance, and overall physical activity. In addition, a low ABI has been associated with a higher risk of coronary heart disease, stroke, transient ischemic attack, progressive renal insufficiency, and all-cause mortality [19]. A potential limitation of the ABI is that calcified vessels may not compress normally, possibly resulting in falsely elevated Doppler signals. Thus, an ABI of over 1.3 is suggestive of calcified vessels. In such patients, an accurate pressure may be obtained by measuring the blood pressure in the toe and calculating the toe–brachial index [19]. If ABIs are normal at rest but symptoms strongly suggest claudication, ABIs and segmental pressures should be obtained before and after exercise on a treadmill. This may unmask a hemodynamically significant stenosis that is subclinical at rest but significant on exertion.

The physician should also assess skin temperature with the back of the hand. Normal skin temperature ranges from warm at the tibia to cool at the distal toes [20]. Foot-skin temperature can be measured with a handheld infrared thermometer on the plantar aspect of the foot at the level of the first metatarsal head.

Elevated temperature is reported to be associated with sudomotor dysfunction and a higher risk for foot ulceration [21, 22].

The presence of diabetic neuropathy can be established from an abbreviated medical history and physical examination. Symptoms such as a burning sensation; pins and needles; shooting, sharp, or stabbing pains; and muscle cramps, which are distributed symmetrically in both limbs ("stocking and glove distribution"), and often worse at night, are usually present in peripheral neuropathy. Diabetic peripheral neuropathy may also be evaluated using the Neuropathy Symptom Score (NSS), which is a validated symptom score with a high predictive value to screen for peripheral neuropathy in diabetes [23, 24] (Table 1).

The physical examination of the foot assesses the perception of superficial pain (pinprick), temperature sensation (using a two-metal rod), light sensation (using the edge of a cotton-wool twist), and pressure (using the Semmes–Weinstein 5.07 monofilament). Additionally, the physician should examine the vibration perception using a tuning fork and/or a biothesiometer. The examination of position sense (proprioception) and deep tendon reflexes (Achilles tendon, patellar) is also essential [4].

Neuropathic deficits in the feet can be determined using the Neuropathy Disability Score (NDS), which is derived from the inability to detect pinprick sensation (using a neurological examination pin), vibration (using a 128-Hz tuning fork), or differences in temperature sensation (using warm and cool rods), and loss or reduction of the Achilles reflex (using a tendon hammer) [1] (Table 1). According to the American Diabetes Association, a foot that has lost its protective sensation is considered to be a "foot at risk" for ulceration. The diagnosis of a foot at risk is confirmed by a positive

Table 1 Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS)

	Score
NSS	
Description	
Fatigue/cramping/aching	1
Burning/numbness/tingling	2
Location	
Thighs	0
Legs	1
Feet	2
Pain exacerbation:	
Daytime only	0
Day and night	1
Night	2
Have the symptoms ever woken the patient from sleep?	
No	0
Yes	1
Could any maneuver reduce the symptoms?	
Sitting or lying	0
Standing	1
Walking	2
NSS: …/9	
NDS	
Big toe	
Right	
Normal	0
Abnormal	1
Left	
Normal	0
Abnormal	1
Vibration perception	
Right	
Normal	0

Table 1 continued

	Score
Abnormal	1
Left	
Normal	0
Abnormal	1
Dorsal foot area	
Temperature sensation	
Right	
Normal	0
Abnormal	1
Left	
Normal	0
Abnormal	1
Achilles reflex	
Right	
Normal	0
Increased	1
Abnormal	2
Left	
Normal	0
Increased	1
Abnormal	2
NDS: …/10	

Peripheral neuropathy is present if there are moderate signs (NDS > 6) with or without symptoms (any NSS), or mild signs (NDS 3–5) with moderate symptoms (NSS > 5)[a]

[a]NSS	NDS
3–4: mild symptoms	3–5: mild neuropathic signs
5–6: moderate symptoms	6–8: moderate
7–9: severe	9–10: severe

5.07/10-g monofilament test, plus one of the following tests: vibration test (using 128-Hz tuning fork or a biothesiometer), pinprick sensation, or ankle reflexes [25].

Table 2 Meggitt–Wagner classification of foot ulcers

Grade	Description of the ulcer
0	Pre- or postulcerative lesion completely epithelialized
1	Superficial, full-thickness ulcer limited to the dermis, not extending to the subcutis
2	Ulcer of the skin extending through the subcutis with exposed tendon or bone and without osteomyelitis or abscess formation
3	Deep ulcers with osteomyelitis or abscess formation
4	Localized gangrene of the toes or the forefoot
5	Foot with extensive gangrene

The above tests have been reported to have a positive predictive value of 46% and a negative predictive value of 87% for the risk of incident neuropathy [26].

Diabetic foot ulcers are defined as: neuropathic in the presence of peripheral diabetic neuropathy and absence of ischemia; ischemic if the patient presents peripheral artery disease but no diabetic peripheral neuropathy; and neuroischemic if neuropathy and ischemia coexist. Apart from this rather crude classification, many efforts have been made to categorize foot ulcers according to extent, size and depth, location, presence of infection, and ischemia. The Meggitt–Wagner classification is one of the most popular validated classifications for the foot ulcers (Table 2). Other classification systems for diabetic foot ulcers have also been proposed and validated [27].

Whatever method is used for the diabetic foot ulcer evaluation, all classification systems should aim at facilitating the correct choice of treatment and reliable monitoring of the healing progress of the ulcer, while at the same time serving as a communication tool across specialties.

TREATMENT

The gold standard for diabetic foot ulcer treatment includes debridement of the wound, management of any infection, revascularization procedures when indicated, and off-loading of the ulcer [28]. Other methods have also been suggested to be beneficial as add-on therapies, such as hyperbaric oxygen therapy, use of advanced wound care products, and negative-pressure wound therapy (NPWT) [29]. However, data so far have not provided adequate evidence of the efficacy and cost-effectiveness of these add-on treatment methods.

Debridement

Debridement should be carried out in all chronic wounds to remove surface debris and necrotic tissues. It improves healing by promoting the production of granulation tissue and can be achieved surgically, enzymatically, biologically, and through autolysis.

Surgical debridement, known also as the "sharp method," is performed by scalpels, and is rapid and effective in removing hyperkeratosis and dead tissue. Particular care should be taken to protect healthy tissue, which has a red or deep pink (granulation tissue) appearance [30]. Using a scalpel blade with the tip pointed at a 45° angle, all nonviable tissue must be removed until a healthy bleeding ulcer bed is produced with saucerization of the wound edges. If severe ischemia is suspected, aggressive debridement should be postponed until a vascular examination has been carried out and, if necessary, a revascularization procedure performed.

Enzymatic debridement can be achieved using a variety of enzymatic agents, including crab-derived collagenase, collagen from krill, papain, a combination of streptokinase and streptodornase, and dextrans. These are able to remove necrotic tissue without damaging the healthy tissue. Although expensive, enzymatic debridement is indicated for ischemic ulcers because surgical debridement is extremely painful in these cases [31].

Biological debridement has been applied recently using sterile maggots. Maggots have the ability to digest surface debris, bacteria, and necrotic tissues only, leaving healthy tissue intact. Recent reports suggest that this method is also effective in the elimination of drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus*, from wound surfaces [32].

Autolytic debridement involves the use of dressings that create a moist wound environment so that host defense mechanisms (neutrophils, macrophages) can clear devitalized tissue using the body's enzymes. Autolysis is enhanced by the use of proper dressings, such as hydrocolloids, hydrogels, and films. Autolysis is highly selective, avoiding damage to the surrounding skin [33].

In conclusion, debridement, especially the "sharp method," is one of the gold standards in wound healing management, significantly contributing to the healing process of the wound, including the diabetic ulcer [34, 35].

Off-loading

Off-loading of the ulcer area is extremely important for the healing of plantar ulcers. Retrospective and prospective studies have shown that elevated plantar pressures significantly contribute to the development of plantar ulcers in diabetic patients [36–38]. In addition, any existing foot deformities may increase the possibility of ulceration, especially in the presence of diabetic peripheral neuropathy and inadequate off-loading.

Furthermore, inadequate off-loading of the ulcer has been proven to be a significant reason for the delay of ulcer healing even in an adequately perfused limb [30]. The value of ulcer off-loading is increasing, as it has been reported that the risk of recurrence of a healed foot ulcer is high if the foot is not properly off-loaded (in the high-pressure areas), even after closure of the ulcer [39].

The most effective method of off-loading, which is also considered to be the gold standard, is the nonremovable total-contact cast (TCC). It is made of plaster or fast-setting fiberglass cast materials, has relatively low costs, and permits restricted activity [40]. Nonremovable TCCs are indicated for the effective off-loading of ulcers located at the forefoot or midfoot. Severe foot ischemia, a deep abscess, osteomyelitis, and poor skin quality are absolute contraindications to the use of a nonremovable TCC. Nonremovable TCCs work by distributing the plantar pressures from the forefoot and midfoot to the heel. They allow complete rest of the foot whilst also permitting restricted activity. Nonremovable TCCs also reduce edema, and compliance with treatment is necessarily high [40].

There are a number of removable cast walkers (RCW), which usually have a lightweight, semirigid shell that helps support the limb whilst also providing full-cell protection (Fig. 1). The sole is of a rocker type, offering off-loading of the forefoot during standing and walking. The foot base is wide and there is enough room for dressings. In some RCWs, overlapping air cells provide intermittent pneumatic compression for edema reduction. In other RCWs, there are additional layers of foam or other soft material, offering total contact [41].

A modification of RCWs is an instant total-contact cast (ITCC), where there is a wrapping layer of cohesive tape or plaster bandage around the RCW [42]. The aim of the ITCC is to combine the efficacy of a TCC with the easy application of a RCW.

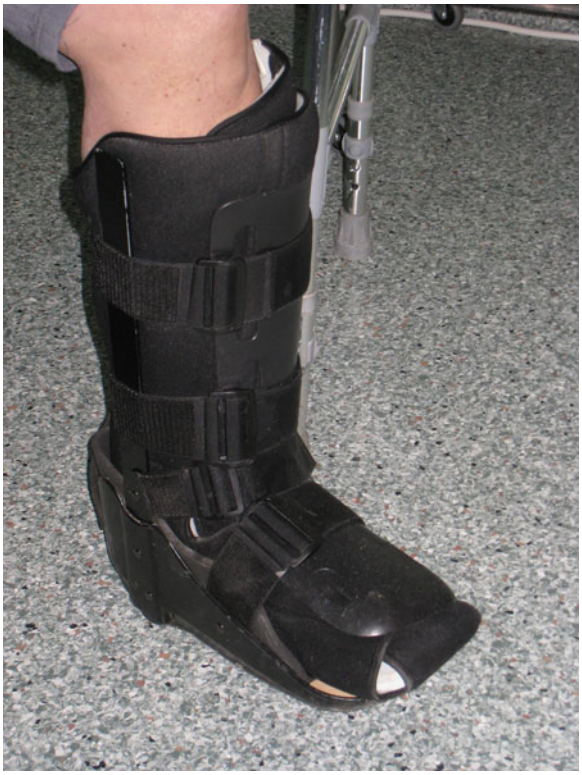

Fig. 1 Removable cast walker

Half shoes are another solution for patients who cannot tolerate other methods of off-loading, although they provide less pressure relief than a cast boot and are difficult to walk in. Therapeutic shoes, custom insoles, and the use of felted foam (Fig. 2) are alternative methods to off-load wounds located on the forefoot, and can reduce pressure at the site of ulceration by 4–50% [43].

Dressings

Ulcers heal more quickly and are often less complicated by infection when in a moist environment. The only exception is

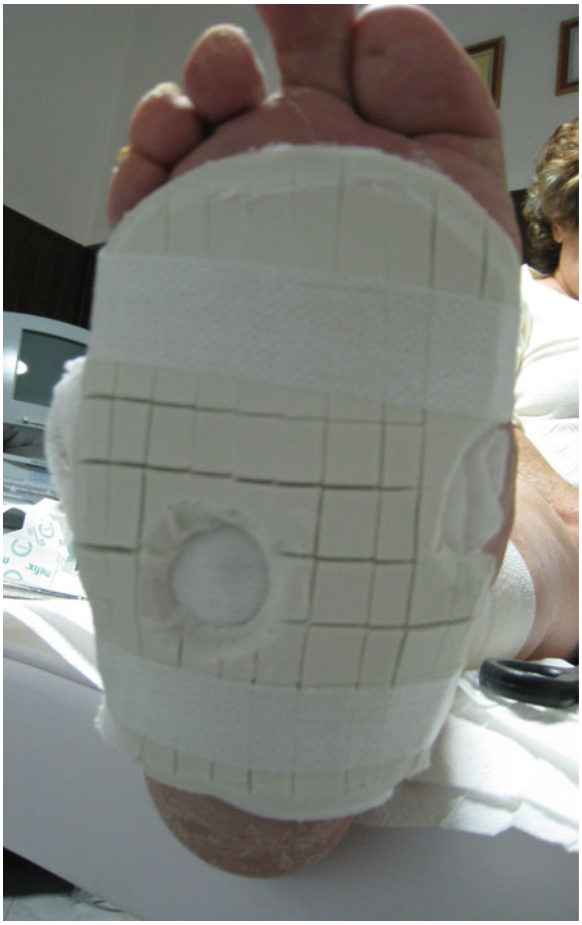

Fig. 2 Off-loading of a diabetic foot ulcer with felted foam

dry gangrene, where the necrotic area should be kept dry in order to avoid infection and conversion to wet gangrene. A wound's exudate is rich in cytokines, platelets, white blood cells, growth factors, matrix metalloproteinases (MMPs), and other enzymes. Most of these factors promote healing via fibroblast and keratinocyte proliferation and angiogenesis, while others, such as leukocytes and toxins produced by bacteria, inhibit the healing process. Moreover, it has been reported that local concentrations of growth factors [platelet-derived growth factor-beta (PDGF-beta), transforming growth factor-beta] are low in patients with chronic ulcers [44]. The ideal dressing should be free from contaminants, be able to remove excess exudates and toxic components, maintain a moist environment at the wound-dressing interface, be impermeable to microorganisms, allow gaseous exchange, and, finally, should be easily removed and cost-effective [45]. Various dressings are available that are intended to prevent infection and enhance wound healing, and several studies support their effectiveness for this purpose [46, 47]. However, most of these studies were performed in wounds and not in diabetic ulcers [44, 46, 47]. Available data on their use in diabetes are scarce [35], and therefore further randomized clinical trials are needed to support the existing evidence for their benefit in diabetic ulcers.

Growth Factors

PDGF-beta (becaplermin; available as Regranex®; Ortho-McNeil Pharmaceutical, Inc., Titusville, NJ, USA; and Janssen-Cilag International NV, Beerse, Belgium) has been developed as a topical therapy for the treatment of noninfected diabetic foot ulcers. It is applied in the form of a once-daily gel along with debridement on a weekly basis [48]. Initial studies have indicated a significant positive effect of becaplermin [49, 50] on ulcer healing; however, more recent studies have reported an increased incidence of cancer in patients treated with becaplermin, especially at high doses [48]. Consequently, the US Food and Drug Administration has published a warning of an increased risk of cancer if more than three tubes of becaplermin are used [51]. Further studies are necessary in order to explore the benefit-to-risk ratio, as well as the cost effectiveness of this therapy.

Platelet-rich plasma (PRP) is an autologous product, extracted from the patient's plasma, which includes a high platelet concentration in

a fibrin clot that can be easily applied to the ulcer area. The fibrin clot is absorbed during wound healing within days to weeks following its application [52]. There are a few studies reporting a shorter closure time and higher healing percentage in patients using PRP and platelet-derived products [53, 54]. However, further studies are required to support the possible beneficial effect of this method in ulcer healing.

The results of the subcutaneous administration of granulocyte colony-stimulating factor (GCFS) in patients with infected foot ulcers vary, with some studies indicating faster resolution of the infection and faster healing [55, 56], while others did not report any significant difference [57, 58]. Basic fibroblast growth factor (bFGF) is known to be beneficial in the formation of granulation tissue and normal healing [59]; however, one small study failed to prove any significant difference between the intervention and the control group [60]. Epidermal growth factor (EGF) acts on epithelial cells, fibroblasts, and smooth muscle cells to promote healing [61]. Evidence for the use of EGF in diabetic ulcers is limited, with only a small amount of data reporting a significantly higher rate of ulcer healing with EGF use compared with placebo [62].

Bioengineered Skin Substitutes

Tissue-engineered skin substitutes are classified into allogenic cell-containing (Apligraf® Graftskin, Organogenesis Inc., Canton, MA, USA; Dermagraft®, Advanced Biohealing Westport, CT, USA; OrCell®, Ortec International Inc., New York, NY, USA), autologous cell-containing (Hyalograft® 3D, Fidia Advanced BioPolymers, Abano Terme, Italy; Laserskin®, Fidia Advanced BioPolymers, Abano Terme, Italy; TranCell®, CellTran Ltd., Sheffield, UK), and acellular (OASIS®, Cook Biotech, West Lafayette, IN, USA; GRAFTJACKET®, Wright Medical Group Inc., Arlington, TN, USA; AlloDerm®, LifeCell Corporation, Branchburg, NJ, USA) matrices. The first two types of matrix contain living cells, such as keratinocytes or fibroblasts, in a matrix, while acellular matrices are free of cells and act by releasing growth factors to stimulate neovascularization and wound healing.

Accumulating evidence shows that bioengineered skin substitutes may be a promising therapeutic adjunct therapy to the standard wound care for the management of noninfected diabetic foot ulcers. Nevertheless, more studies need to be conducted in the future in order to confirm these results [63–69].

Extracellular Matrix Proteins

Hyaff® (Fidia Farmaceutici, Abano Terme, Italy) is a semisynthetic ester of hyaluronic acid which facilitates the growth and movement of fibroblasts, and controls hydration [70].

Other available products contain lyophilized collagen from various sources (bovine, porcine), alone or in combination with alginates, cellulose (Promogran®, Johnson & Johnson, New Brunswick, NJ, USA), or antibiotics. Collagen seems to induce the production of endogenous collagen and to promote platelet adhesion and aggregation. It has been reported to be safe and effective as an adjunctive therapy in the management of foot ulceration; however, evidence is still limited [71].

MMP Modulators

Matrix metalloproteinases regulate the extracellular matrix components. During normal wound healing, there is a balance between the construction and the destruction

of the extracellular matrix. In chronic wounds, a high expression of MMP-2 in fibroblasts and the endothelium is detected and is believed to favor destruction. Thus, downregulation of MMP-2 expression may enhance the healing process [72].

DerMax® (Tyco Healthcare Group Lp, North Haven, CT, USA) is a dressing containing metal ions and citric acid, and its topical application is associated with a lower expression of MMP-2 by fibroblasts and endothelial cells. Metal ions inhibit the production of reactive oxygen species by polymorphonuclear cells, and citric acid acts as a scavenger of superoxide anions [72]. One pilot study provided encouraging results [73]. Certainly, randomized trials are necessary in order to establish the role of DerMax in the treatment of diabetic ulcers.

Negative-Pressure Wound Therapy

Negative-pressure wound therapy (NPWT) has emerged as a new treatment for diabetic foot ulcers. It involves the use of intermittent or continuous subatmospheric pressure through a special pump (vacuum-assisted closure) connected to a resilient open-celled foam surface dressing covered with an adhesive drape to maintain a closed environment. The pump is connected to a canister to collect wound discharge and exudate. Experimental data suggest that NPWT optimizes blood flow, decreases tissue edema, and removes exudate, proinflammatory cytokines, and bacteria from the wound area [74]. It should be performed after debridement and continued until the formation of healthy granulation tissue at the surface of the ulcer. Currently, NPWT is indicated for complex diabetic foot wounds [74]; however, it is contraindicated for patients with an active bleeding ulcer. Two small studies [75, 76] and one larger study [77] provide some encouraging data concerning the possible benefit of NPWT in the healing rate and time of diabetic foot ulcers. However, more randomized trials are needed in order to confirm these results.

Hyperbaric Oxygen

There is strong evidence that fibroblasts, endothelial cells, and keratinocytes are replicated at higher rates in an oxygen-rich environment [78, 79]. Moreover, leukocytes kill bacteria more effectively when supplied by oxygen. It is also known that fibroblasts from diabetic individuals show diminished cell turnover in comparison with those from nondiabetic persons. Based on these data, the idea was that the administration of oxygen at high concentrations might accelerate wound healing in diabetes [78]. Treatment with hyperbaric oxygen therapy involves the intermittent administration of 100% oxygen at a pressure greater than that at sea level. It is performed in a chamber with the patient breathing 100% oxygen intermittently while the atmospheric pressure is increased to 2–3 atmospheres for a duration of 1–2 h. A full course involves 30–40 sessions. A small amount of data suggests significant reduction of the ulcer area [79] as well as reduction of the risk for major amputation [80]. Hyperbaric oxygen can be applied as an adjunctive therapy for patients with severe soft-tissue foot infections and osteomyelitis who have not responded to conventional treatment. Adverse effects include barotrauma to the ears and sinuses, pneumothorax, transient changes in visual acuity, and seizures [81]. Furthermore, a recent systematic review by the National Institute for Health and Clinical Excellence (NICE) Guidelines Development Group in the UK concluded that the available data are

insufficient to demonstrate that hyperbaric oxygen therapy is cost-effective [82].

CONCLUSION

The management of diabetic foot ulcers remains a major therapeutic challenge which implies an urgent need to review strategies and treatments in order to achieve the goals and reduce the burden of care in an efficient and cost-effective way. Questions remain as to which types of intervention, technology, and dressing are suitable to promote healing, and whether all therapies are necessary and cost-effective as adjunctive therapies. The International Working Group on the Diabetic Foot has conducted two systematic reviews [35, 83] of the evidence and effectiveness of interventions to enhance the healing of chronic diabetic foot ulcers. The preliminary results are promising, but large randomized controlled trials are necessary in order to establish the cost-effectiveness of the new therapies.

Prevention of diabetic foot ulceration is critical in order to reduce the associated high morbidity and mortality rates, and the danger of amputation. It is essential to identify the "foot at risk," through careful inspection and physical examination of the foot followed by neuropathy and vascular tests.

Regular foot examination, patient education, simple hygienic practices, provision of appropriate footwear, and prompt treatment of minor injuries can decrease ulcer occurrence by 50% and eliminate the need for major amputation in nonischemic limbs [84, 85]. Diabetic foot ulcers should be carefully evaluated and the gold-standard treatments should be strictly applied in order to prevent amputation. Further clinical studies are needed to support the existing evidence regarding the clinical benefit of new approaches for the treatment of diabetic ulcers, and these approaches should be used only as add-on therapies to the gold-standard wound care.

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