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TOPIC HIGHLIGHT

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Literature review on the management of diabetic foot ulcer

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Abstract

Diabetic foot ulcer (DFU) is the most costly and devastating complication of diabetes mellitus, which affect 15% of diabetic patients during their lifetime. Based on National Institute for Health and Clinical Excellence strategies, early effective management of DFU can reduce the severity of complications such as preventable amputations and possible mortality, and also can improve overall quality of life. The management of DFU should be optimized by using a multidisciplinary team, due to a holistic approach to wound management is required. Based on studies, blood sugar control, wound debridement, advanced dressings and offloading modalities should always be a part of DFU management. Furthermore, surgery to heal chronic ulcer and prevent recurrence should be considered as an essential component of management in some cases. Also, hyperbaric oxygen therapy, electrical stimulation, negative pressure wound therapy, bio-engineered skin and growth factors could be used as adjunct therapies for rapid healing of DFU. So, it's suggested that with appropriate patient education encourages them to regular foot care in order to prevent DFU and its complications.

Key words: Diabetes mellitus; Wound management; Diabetic foot ulcer; Amputation; Foot care

Core tip: Diabetic foot ulcer (DFU) is the most common complication of diabetes mellitus that usually fail to heal, and leading to lower limb amputation. Early effective management of DFU as follows: education, blood sugar control, wound debridement, advanced dressing, offloading, advance therapies and in some cases surgery, can reduce the severity of complications, and also cam improve overall quality of life of patients especially by using a multidisciplinary team approach.

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INTRODUCTION

Diabetes mellitus (DM) is one of the main problems in health systems and a global public health threat that has increased dramatically over the past 2 decades[1,2]. According to epidemiological studies, the number of patients with DM increased from about 30 million cases in 1985, 177 million in 2000, 285 million in 2010, and estimated if the situation continues, more than 360 million people by 2030 will have DM[3,4].

Patients with DM are prone to multiple complications such as diabetic foot ulcer (DFU). DFU is a common complication of DM that has shown an increasing trend over previous decades[5-7]. In total, it is estimated that 15% of patients with diabetes will suffer from DFU during their lifetime[8]. Although accurate figures are difficult to obtain for the prevalence of DFU, the prevalence of this complication ranges from 4%-27%[9-11].

To date, DFU is considered as a major source of morbidity and a leading cause of hospitalization in patients with diabetes[1,5,12,13]. It is estimated that approximately 20% of hospital admissions among patients with DM are the result of DFU[14]. Indeed, DFU can lead to infection, gangrene, amputation, and even death if necessary care is not provided[14]. On the other hand, once DFU has developed, there is an increased risk of ulcer progression that may ultimately lead to amputation. Overall, the rate of lower limb amputation in patients with DM is 15 times higher than patients without diabetes[8]. It is estimated that approximately 50%-70% of all lower limb amputations are due to DFU[8]. In addition, it is reported that every 30 s one leg is amputated due to DFU in worldwide[9]. Furthermore, DFU is responsible for substantial emotional and physical distress as well as productivity and financial losses that lower the quality of life[15]. The previous literature indicates that healing of a single ulcer costs approximately $$17500 (1998 United States Dollars). In cases where lower extremity amputation is required, health care is even more expensive at $30000-33500[16]. These costs do not represent the total economic burden, because indirect costs related to losses of productivity, preventive efforts, rehabilitation, and home care should be considered. When all this is considered, 7%-20% of the total expenditure on diabetes in North America and Europe might be attributable to DFU[17].

ETIOLOGY OF DFU

Recent studies have indicated multiple risk factors associated with the development of DFU[18-21]. These risk factors are as follows: gender (male), duration of diabetes longer than 10 years, advanced age of patients, high Body Mass Index, and other comorbidities such as retinopathy, diabetic peripheral neuropathy, peripheral vascular disease, glycated hemoglobin level (HbA_1C), foot deformity, high plantar pressure, infections, and inappropriate foot self-care habits[1,12,20-22] (Figure 1).

Although the literature has identified a number of diabetes related risk factors that contribute to lower-extremity ulceration and amputation, to date most DFU has been caused by ischemic, neuropathic or combined neuroischemic abnormalities[6,17] (Figure 2). Pure ischemic ulcers probably represent only 10% of DFU and 90% are caused by neuropathy, alone or with ischemia. In recent years, the incidence of neuroischemic problems has increased and neuroischemic ulcers are the most common ulcers seen in most United Kingdom diabetic foot clinics now[23].

In total, the most common pathway to develop foot problems in patients with diabetes is peripheral sensori-motor and autonomic neuropathy that leads to high foot pressure, foot deformities, and gait instability, which increases the risks of developing ulcers[24-26]. Today, numerous investigations have shown that elevated plantar pressures are associated with foot ulceration[27-29]. Additionally, it has been demonstrated that foot deformities and gait instability increases plantar pressure, which can result in foot ulceration[24,30].

MANGMENT OF DFU

Unfortunately, often patients are in denial of their disease and fail to take ownership of their illness along with the necessary steps to prevent complication and to deal with the many challenges associated with the management of DFU. However, numerous studies have shown that proper management of DFU can greatly reduce, delay, or prevent complications such as infection, gangrene, amputation, and even death[6,31,32].

The primary management goals for DFU are to obtain wound closure as expeditiously as possible[33,34]. As diabetes is a multi-organ systemic disease, all comorbidities that affect wound healing must be managed by a multidisciplinary team for optimal outcomes with DFU[35-38]. Based on National Institute for Health and Clinical Excellence strategies, the management of DFU should be done immediately with a multidisciplinary team that consists of a general practitioner, a nurse, an educator, an orthotic specialist, a podiatrist, and consultations with other specialists such as vascular surgeons, infectious disease specialists, dermatologists, endocrinologists, dieticians, and orthopedic specialists[39]. Today, numerous studies have shown that a multidisciplinary team can reduce amputation rates, lower costs, and leads to better quality of life for patients with DFU[39-41]. The American Diabetes Association has concluded that a preventive care team, defined as a multidisciplinary team, can decrease the risks associated with DFU and amputation by 50%-85%[42]. It's suggested that with applying this approach take appropriate strategies for management of DFU to consequently reduce the severity of complications, improve overall quality of life, and increase the life expectancy of patients[36]. In this article, we review available evidence on the management of DFU as follows: education, blood sugar control, wound debridement, advanced dressing,

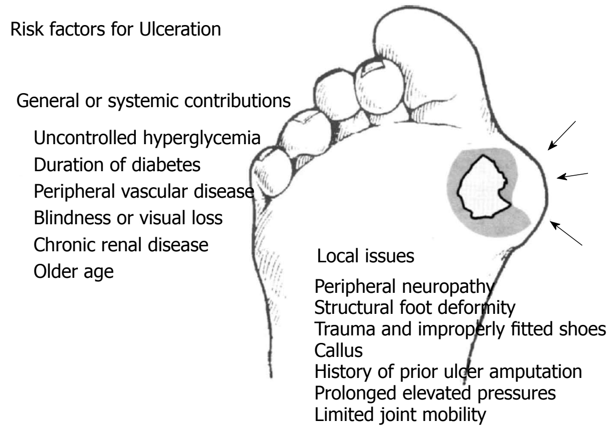

Figure 1 The risk factors for diabetic foot ulcer. Ulcers may be distinguished by general or systemic considerations *vs* those localized to the foot and its pathology. (Data adapted from Frykberg *et al*[18]).

offloading, surgery, and advanced therapies that are used clinically.

RESEARCH

In this review article, we searched for articles published between March 1, 1980 and July 28, 2014 in the following five electronic databases: PubMed, Science Direct, Embase, Web of Science, and Scopus, for both English and non-English language articles with the following keywords: "diabetic foot ulcer", "amputations", "wound management", "debridement", "advanced dressings", "offloading modalities", "hyperbaric oxygen therapy", "electrical stimulation", "negative pressure wound therapy", "bio-engineered skin", "growth factors", and "foot care" as the medical subject heading (MeSH). Study designs that were included were randomized controlled trials (RCTs), case-control studies, cohort studies, prospective and retrospective uncontrolled studies, cross-sectional studies, and review studies. Case reports and case series were excluded. We searched bibliographies for all retrieved and relevant publications to identify other studies.

Education

It has been shown that up to 50% of DFU cases can be prevented by effective education. In fact, educating patients on foot self-management is considered the cornerstone to prevent DFU[12,43-45].

Patient education programs need to emphasize patient responsibility for their own health and well-being. The ultimate aim of foot care education for people with diabetes is to prevent foot ulcers and amputation. Currently, a wide range and combinations of patient educational interventions have been evaluated for the prevention of DFU that vary from brief education to intensive education including demonstration and hands-on teaching[46]. Patients with DFU should be educated about risk factors and the importance of foot care, including the need for self-inspection, monitoring foot temperature, appropriate daily foot hygiene, use of proper footwear, and blood sugar control[47]. However, education is better when combined with other care strategies, because previous reviews on patient education has suggested that when these methods were combined with a comprehensive approach, these methods can reduce the frequency and morbidity of the limb threatening complications caused by DFU[48].

Blood sugar control

In patients with DFU, glucose control is the most important metabolic factor. In fact, it is reported inadequate control of blood sugar is the primary cause of DFU[6,49,50].

The best indicator of glucose control over a period of time is HbA_1C level. This test measures the average blood sugar concentration over a 90-d span of the average red blood cell in peripheral circulation. The higher the HbA_1C level, the more glycosylation of hemoglobin in red blood cells will occur. Studies have shown that blood glucose levels > 11.1 mmol/L (equivalent to > 310 mg/mL or an HbA_1C level of > 12) is associated with decreased neutrophil function, including leukocyte chemotaxis[50]. Indeed, a greater elevation of blood glucose level has been associated with a higher potential for suppressing inflammatory responses and decreasing host response to an infection[6]. Pomposelli *et al*[51] has indicated that a single blood glucose level > 220 mg/dL on the first postoperative day was a sensitive (87.5%) predictor of postoperative infection. Furthermore, the authors found that patients with blood glucose values > 220 mg/dL had infection rates that were 2.7 times higher than for patients with lower blood glucose values (31.3% *vs* 11.5%, respectively)[51]. In addition, it's indicated that a 1% mean reduction in HbA_1C was associated with a 25% reduction in micro vascular complications, including neuropathy[47]. Investigations have found that poor glucose control accelerated the manifestation of Peripheral Arterial Disease (PAD). It has been shown that for every 1% increase in HbA_1C, there is an increase of 25%-28% in the relative risk of PAD, which is a primary cause of DFU[52]. However, to date, no RCT has been performed to determine whether improved glucose control has benefits after a foot ulcer has developed.

Debridement

Debridement is the removal of necrotic and senescent tissues as well as foreign and infected materials from a wound, which is considered as the first and the most important therapeutic step leading to wound closure and a decrease in the possibility of limb amputation in patients with DFU[53-56]. Debridement seems to decrease bacterial counts and stimulates production of local growth factors. This method also reduces pressure, evaluates the wound bed, and facilitates wound drainage[32,57].

There are different kinds of debridement including surgical, enzymatic, autolytic, mechanical, and biological[58] (Table 1). Among these methods, surgical debridement has

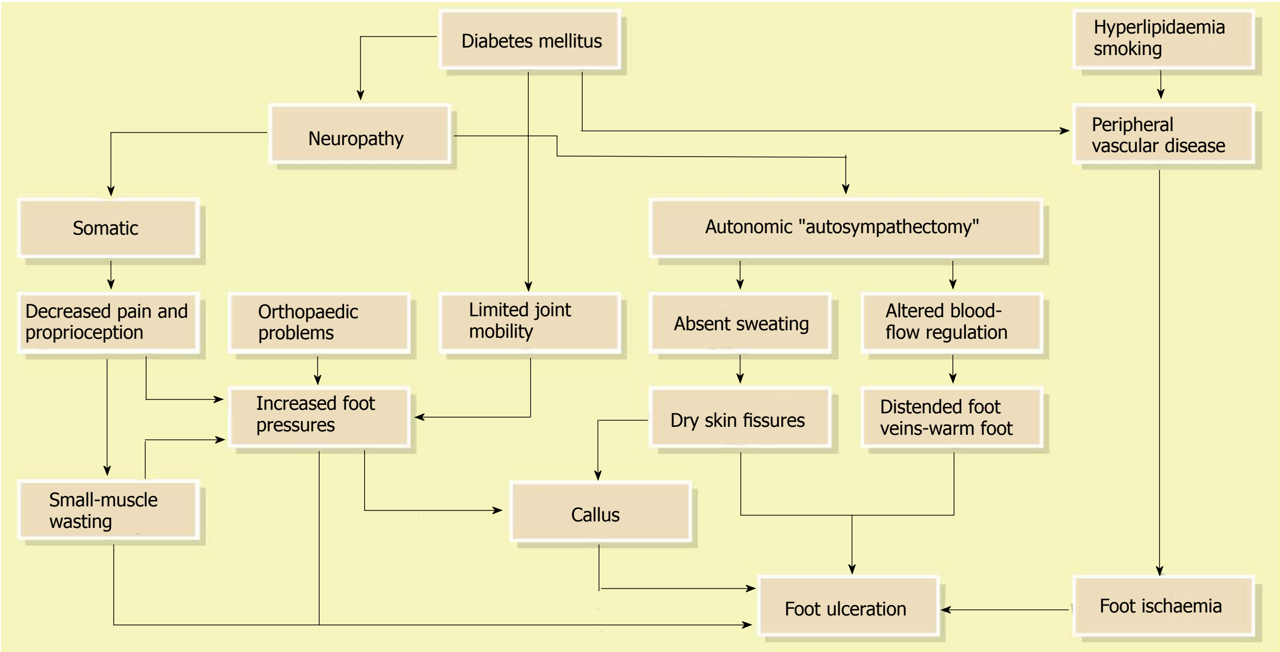

Figure 2 Etiology of diabetic foot ulcer. (Data adapted from Boulton *et al*[17]).

Table 1 Different kind of debridement for patients with diabetic foot ulcer

Method	Explanation	Advantages	Disadvantages
Surgical or Sharp	Callus and all nonviable soft tissues and bone remove from the open wound with a scalpel, tissue nippers, curettes, and curved scissors. Excision of necrotic tissues should extend as deeply and proximally as necessary until healthy, bleeding soft tissues and bone are encountered[59]	Only requires sterile scissors or a scalpel, so is cost-effective[55]	Requires a certain amount of skill to prevent enlarging the wound[55]
Mechanical	This method includes wet to dry dressings, high pressure irrigation, pulsed lavage and hydrotherapy[76], and commonly used to clean wounds prior to surgical or sharp debridement[76]	Allows removal of hardened necrosis	It is not discriminating and may remove granulating tissue It may be painful for the patients[55]
Autolytic	This method occurs naturally in a healthy, moist wound environment when arterial perfusion and venous drainage are maintained[18]	It's cost-effective[55] It is suitable for an extremely painful wound[18]	It's time consuming and may require an equivocal time for treatment[18]
Enzymatic	The only formulation available in the United Kingdom contains Streptokinase and Streptodornase (Varidase Topical® Wyeth Laboratories). This enzyme aggressively digests the proteins fibrin, collagen and elastin, which are commonly found in the necrotic exudate of a wound[77,78]	They can be applied directly into the necrotic area[55]	Streptokinase can be systemically absorbed and is therefore contraindicated in patients at risk of an MI It's expensive[55]
Biological	Sterile maggots of the green bottle fly (Lucilia sericata) are placed directly into the affected area and held in place by a close net dressing. The larvae have a ferocious appetite for necrotic material while actively avoiding newly formed healthy tissue[79,80]	They discriminate between the necrotic and the granulating tissue[79]	There may be a reluctance to use this treatment by patients and clinicians It's expensive[79,80]

been shown to be more effective in DFU healing[54,59-62]. Surgical or sharp debridement involves cutting away dead and infected tissues followed by daily application of saline moistened cotton gauze[53]. The main purpose of this type of debridement is to turn a chronic ulcer into an acute one. Surgical debridement should be repeated as often as needed if new necrotic tissue continues to form[63]. It has been reported that regular (weekly) sharp debridement is associated with the rapid healing of ulcers than for less frequent debridement[59,64-66]. In a retrospective cohort study, Wilcox *et al*[66] indicated that frequent debridement healed more wounds in a shorter time ($P < 0.001$). In fact, the more frequent the debridement, the better the healing outcome.

The method of debridement depends on characteristics, preferences, and practitioner level of expertise[54]. When surgical or sharp debridement is not indicated, then other types of debridement could be used.

An older debridement type that is categorized as biological debridement is maggot debridement therapy (MDT), which is also known as maggot therapy or larval therapy. In this method, sterile and live forms of the Lucilia sericata larvae are applied to the wound to achieve debridement, disinfection, and ultimately wound

Table 2 Common offloading techniques

Technique	Casting techniques	Footwear related techniques	Surgical offloading techniques	Other techniques
Examples	TCC (Figure 3)	Shoes or half shoes (Figure 7)	ATL	Bed rest
	iTCC (Figure 5)	Sandals	Liquid silicone injections/tissue augmentation	Crutches/Canes/Wheelchairs
	RCW (Figure 4)	Insoles	Callus debridement	Bracing (patella tendon bearing, ankle-foot orthoses)
	Scotch-cast boots (Figure 6)	In-shoe orthoses	Metatarsal head resection osteotomy/ arthroplasty/os ectomy/ exostectomy	Walkers
	Windowed casts	Socks	External fixation	Offloading dressings
	Custom splints			Felted foam/padding
				Plugs

Data adapted from Armstrong *et al*[82]. TCC: Total contact cast; iTCC: Instant TCC; RCW: Removable cast walkers; ATL: Achilles tendon lengthening.

healing[67-69]. Indeed, larvae secrete a powerful autolytic enzyme that liquefies necrotic tissues, stimulates the healing processes, and destroys bacterial biofilms[70-72]. This technique is indicated for open wounds and ulcers that contain gangrenous or necrotic tissues with or without infection[72]. To date, paucity of RCTs show efficacy of this method with DFU; however, some of retrospective[71,73]; and prospective[74] studies have shown MDT as a clinically effective treatment for DFU. These studies reported that MDT can significantly diminish wound odor and bacterial count, including *Methicillin-Resistant Staphylococcus Aurous*, prevent hospital admission, and decrease the number of outpatient visits among patients with DFU[71,73-75].

Despite the advantages of debridement, adequate debridement must always precede the application of topical wound healing agents, dressings, or wound closure procedures, which may be expensive.

Offloading

The use of offloading techniques, commonly known as pressure modulation, is considered the most important component for the management of neuropathic ulcers in patients with diabetes[81,82]. Recent studies have provided evidence indicating that proper offloading promotes DFU healing[83-85].

Although many offloading modalities are currently in use (Table 2), only a few studies describe the frequency and rate of wound healing with some of the methods frequently used clinically. The choice of these methods is determined by patient physical characteristics and abilities to comply with the treatment along with the location and severity of the ulcer[82].

The most effective offloading technique for the treatment of neuropathic DFU is total contact casts (TCC)[82,86,87]. TCC is minimally padded and molded carefully to the shape of the foot with a heel for walking (Figure 3). The cast is designed to relieve pressure from the ulcer and distribute pressure over the entire surface of the foot; thus, protecting the site of the wound[82]. Mueller *et al*[87] conducted an RCT that showed TCC healed a higher percentage of plantar ulcers at a faster rate when compared with the standard treatment. In addition, a histologic examination of ulcer specimens has shown that patients treated with TCC before debridement had better healing as indicated by angiogenesis with the formation of granulation tissue than for patients treated with debridement alone as indicated by a predominance of inflammatory elements[88]. The contributory factors to the efficacy of TCC treatment are likely to be due to pressure redistribution and offloading from the ulcer area. In addition, the patient is unable to remove the cast, which thereby forces compliance, reduces activity levels, and consequently improves wound healing[84]. However, the frequency of side effects referred to in the literature and minimal patient acceptance make this approach inappropriate for wide applications[89,90]. Fife *et al*[91] has shown that TCC is vastly underutilized for DFU wound care in the United States. Based on this study, only 16% of patients with DFU used TCC as their offloading modalities. The main disadvantage of TCC was the need for expertise in its application. Most centers do not have a physician or cast technician available with adequate training or experience to safely apply TCC. In addition, improper cast application can cause skin irritation and in some cases even frank ulceration. Also, the expense of time and materials (the device should be replaced weekly), limitations on daily activities (*e.g.*, bathing), and the potential of a rigid cast to injure the insensate neuropathic foot are considered other disadvantages. Furthermore, TCC does not allow daily assessment of the foot or wound, which is often contraindicative in cases of soft tissue or bone infections[36,32,83]. In some cases, it is suggested to use other kinds of offloading techniques such as a removable cast walker (RCW) or Instant TCC (iTCC).

An RCW is cast-like device that is easily removable to allow for self-inspection of the wound and application of topical therapies that require frequent administration[82,90] (Figure 4). The application of this method allows for bathing and comfortable sleep. In addition, because RCW is removable, they can be used for infected wounds as well as for superficial ulcers[82]. However, in a study that compared the effectiveness of TCC, RCW, and half-shoe, this method did not show equivalent healing time (mean healing time: 33.5, 50.4, and 61.1 d, respectively), and a

Figure 3 Total contact cast for patients with diabetic foot ulcer. (Data adapted from Armstrong *et al*[82]).

Figure 4 Removable cast walker (DH Walker) for patients with diabetic foot ulcer. (Data adapted from Rathur *et al*[86]).

significantly higher proportion of people with DFU were healed after 12 wk wearing a TCC compared with the two other widely used offloading modalities[81].

iTCC, which involves simply wrapping a RCW with a single layer of cohesive bandage, Elastoplast or casting tape (Figure 5), is another offloading technique that is shown to be more effective than TCC[92] and RCW[93]. This technique forces the patient to adhere to advice to immobilize the foot while allowing for ease of application and examination of the ulcer as needed. A preliminary randomized trial of TCC *vs* iTCC (Figure 6) in the management of plantar neuropathic foot ulcers has confirmed equivalent efficacy of the two devices and that iTCC is cheaper, quicker to apply, and has fewer adverse effects than traditional TCC[93]. As this device does not require a skilled technician to apply it, it could revolutionize the future management of plantar neuropathic ulcers. It has been suggested that iTCC will dramatically change the treatment of non-ischemic, neuropathic, diabetic plantar ulcers, and has the potential to replace TCC as the gold standard for offloading plantar neuropathic ulcers[92].

Regardless of the modality selected, patients should return to an unmodified shoe until complete healing of the ulcer has occurred (Figure 7). Furthermore, any shoe that resulted in the formation of an ulcer should not be worn again[94].

Figure 5 Instant total contact cast for patients with diabetic foot ulcers. The removable cast walker shown in Figure 5 has now been rendered irremovable by the application of bands of casting. (Data adapted from Rathur *et al*[86]).

Advanced dressing

A major breakthrough for DFU management over the last decades was the demonstration of novel dressings[13,95]. Ideally, dressings should confer moisture balance, protease sequestration, growth factor stimulation, antimicrobial activity, oxygen permeability, and the capacity to promote autolytic debridement that facilitates the production of granulation tissues and the re-epithelialization process. In addition, it should have a prolonged time of action, high efficiency, and improved sustained drug release in the case of medicated therapies[95,96]. Hence, no single dressing fulfills all the requirements of a diabetic patient with a foot ulcer. The choice of dressing is largely determined by the causes of DFU, wound location, depth, amount of scar or slough, exudates, condition of wound margins, presence of infection and pain, need for adhesiveness, and conformability of the dressing[13].

Wound dressing can be categorized as passive, active, or interactive[97]. Passive dressings are used as protective functions and for acute wounds because they absorb reasonable amounts of exudates and ensure good protection. Active and interactive dressings are capable of modifying the physiology of a wound by stimulating cellular activity and growth factors release. In addition, they are normally used for chronic wounds because they adapt to wounds easily and maintain a moist environment that can stimulate the healing process[95,98]. The main categories of dressings used for DFU are as follows: films, hydrogels, hydrocolloids, alginates, foams, and silver-impregnated (Table 3).

Today, all dressings are commonly used in clinical practice, while the efficacy of these products has been a challenge for researchers and clinicians, and there are controversial results regarding their use[36,99]. However, dressings are used based on DFU characteristics (Figure 8), hydrogels have been found to be the most popular choice of dressing for all DFU types[96]. Some studies dealing with the incorporation of these products show great potential in the treatment of DFU[100,101]. However, these findings do not represent a practical option since the application of these compounds is expensive and

Table 3 Classification of advanced wound dressings used for diabetic foot ulcers healing

Type	Example	Explanation	Advantages	Disadvantages
Hydrocolloids	Duoderm (Convatec) Granuflex (Convatec) Comfeel (Coloplast)	These kind of dressings usually composed of a hydrocolloid matrix bonded onto a vapor permeable film or foam backing. When in contact with the wound surface this matrix forms a gel to provide a moist environment[102]	Absorbent Can be left for several days Aid autolysis[96]	Concerns about use for infected wounds May cause maceration Unpleasant odor[96]
Hydrogels	Aquaform (Maersk Medical) Intrasite Gel (Smith and Nephew) Aquaflo (Covidien)	These dressings consist of cross-linked insoluable polymers (*i.e.*, starch or carboxymethylcellulose) and up to 96% water. These dressings are designed to absorb wound exudate or rehydrate a wound depending on the wound moisture levels. They are supplied in either flat sheets, an amorphous hydrogel or as beads[96]	Absorbent Donate liquid Aid autolysis[96]	Concerns about use for infected wounds May cause maceration using for highly exudative wounds[96]
Foams	Allevyn (Smith and Nephew) Cavicare (Smith and Nephew) Biatain (Coloplast) Tegaderm (3M)	These dressings normally contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface[103]	Highly absorbent and protective Manipulate easily[96] Can be left up to seven days Thermal insulation[96]	Occasional dermatitis with adhesive[96] Bulky[6] May macerate surrounding skin[6]
Films	Tegaderm (3M) Opsite (Smith and Nephew)	Film dressings often form part of the construction of other dressings such as hydrocolloids, foams, hydrogel sheets and composite dressings, which are made up of several materials with the film being used as the outer layer[107,108]	Cheap Manipulate easily Permeable to water vapor and oxygen but not to water microorganisms[95]	May need wetting before removal[96] Aren't suitable for infected wounds[107,108] Nonabsorbent If fluid collects under film it must be drained or the film replaced[6]
Alginates	Calcium Alginate Dressing (Smith and Nephew Inc., Australia) Kaltostat (ConvaTec) Sorbalgon (Hartman United States, Inc.l) Medihoney (Derma Sciences Inc., Canada)	The alginate forms a gel when in contact with the wound surface which can be lifted off with dressing removal or rinsed away with sterile saline. Bonding to a secondary viscose pad increases absorbency[104]	Highly absorbent Bacteriostatic Hemostatic Useful in cavities[96]	May need wetting before removal[96]
Silver-impregnated	Acticoat (Smith and Nephew) Urgosorb Silver (Urgo)	These dressing used to treat infected wounds as silver ions are thought to have antimicrobial properties[109]	Antiseptic Absorbent[96] Reduce odor Improved pain-related symptoms Decrease wound exudates Have a prolonged dressing wear time[112]	High cost[96]

Figure 6 Scotch-cast boot for off-loading pressure from the foot of a diabetic patient with foot ulcer. (Data adapted from Armstrong *et al*[82]).

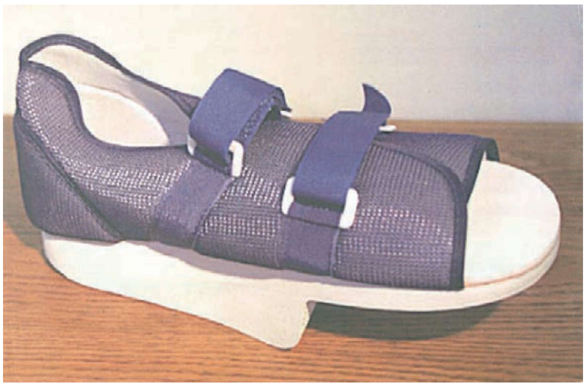

Figure 7 Half shoe for off-loading pressure from the foot of a diabetic patient with foot ulcer. (Data adapted from Armstrong *et al*[82]).

difficult to regulate[102-105]. Nevertheless, they have longer wear times, greater absorbency, may be less painful, and

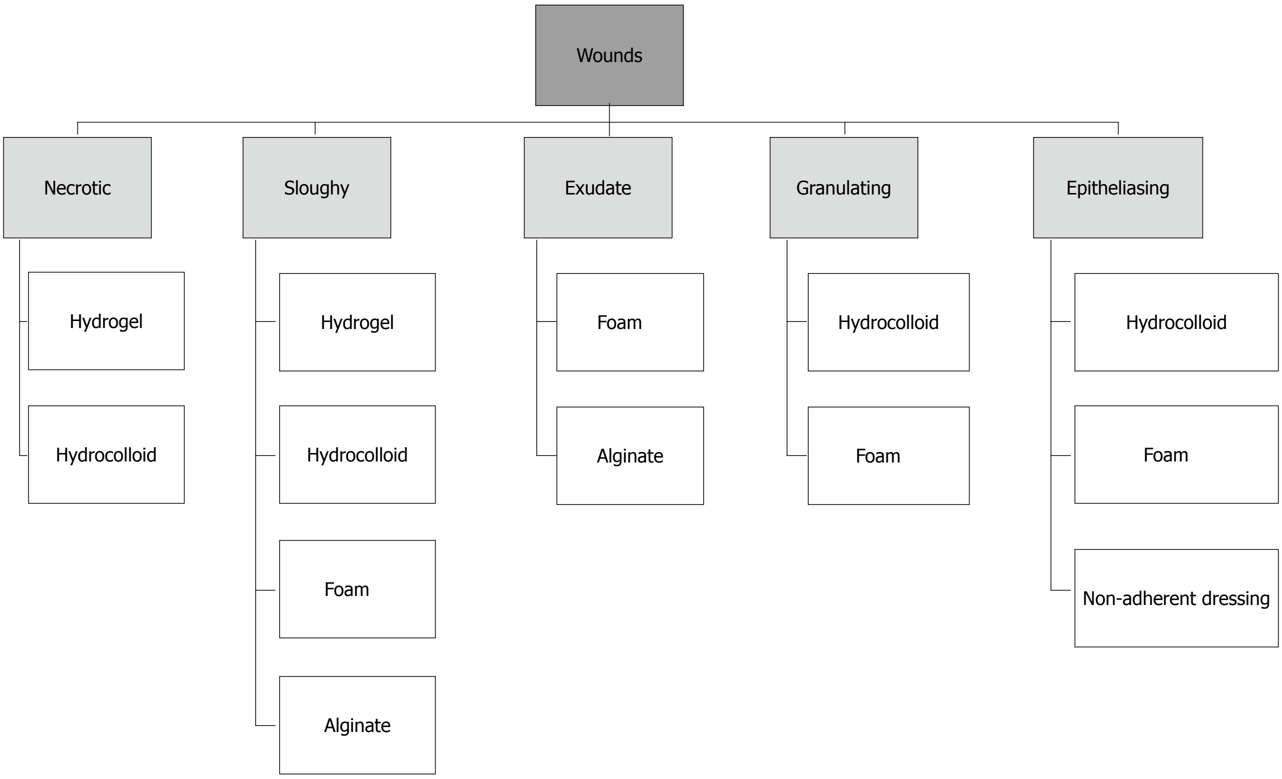

Figure 8 Classification of the different advanced dressing types usually used in diabetic foot ulcer treatment. (Data adapted from Moura *et al*[95]).

are typically less traumatic when removed. Moreover, in certain patients, they are cost effective because of the lowered frequency of dressing changes and not requiring extensive nursing time[106].

Surgery

Diabetic foot surgery plays an essential role in the prevention and management of DFU[110], and has been on the increase over the past 2 decades[111,112]. Although surgical interventions for patients with DFU are not without risk, the selective correction of persistent foot ulcers can improve outcomes[113].

In general, surgery for DFU healing includes non-vascular foot surgery, vascular foot surgery, and in some cases amputation. Nonvascular foot surgery is divided into elective, prophylactic, curative, and emergent surgeries that aim to correct deformities that increase plantar pressure[114] (Table 4). Today, a few studies have reported long-term outcomes for diabetic foot surgery in RCTs [60,115,116]. In one study conducted by Mueller *et al*[115], subjects were randomized into two groups of Achilles Tendon-Lengthening (ATL) group, who received treatment of ATL and TCC, and a group who received TCC only. Their results showed that all ulcers healed in the ATL group and the risk for ulcer recurrence was 75% less at seven months and 52% less at two years than for the TCC group[115].

Vascular foot surgery such as bypass grafts from femoral to pedal arteries and peripheral angioplasty to improve blood flow for an ischemic foot have been recently developed[117]. While studies have shown that these procedures help to heal ischemic ulcers[118-120], no RCT has been shown to reduce DFU.

While the primary goal of DFU management focuses on limb salvage, in some cases amputation may offer a better functional outcome, although this is often not clearly defined[41]. This decision is individualized and multifactorial to match patient lifestyle, medical, physical, and psychological comorbidities[121]. In general, amputation is considered as an urgent or curative surgery and should be the last resort after all other salvage techniques have been explored, and the patient must be in agreement[122]. Indications for an amputation include the removal of infected or gangrenous tissues, control of infection, and creation of a functional foot or stump that can accommodate footwear or prosthesis[123].

ADVANCED THERAPIES

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) has shown promise in the treatment of serious cases of non-healing DFU, which are resistant to other therapeutic methods[124-127]. HBOT involves intermittent administration of 100% oxygen, usually in daily sessions[128]. During each session, patients breathed pure oxygen at 1.4-3.0 absolute atmospheres during 3 periods of 30 min (overall 90 min) intercalated by 5 min intervals in a hyperbaric chamber[124,129] (Figure 9).

Today, RCTs have reported beneficial effects from HBOT in numerous studies[130-134]. A recent double-blind RCT conducted by Löndahl *et al*[134] demonstrated a significantly improved outcome in the intervention

Table 4 Different types of nonvascular diabetic foot surgery

Type	Explanation
Elective	The main goal of this surgery is to relieve the pain associated with particular deformities such as hammertoes, bunions, and bone spurs in patients without peripheral sensory neuropathy and at low risk for ulceration
Prophylactic	These procedures are indicated to prevent ulceration from occurring or recurring in patients with neuropathy, including those with a past history of ulceration (but without active ulceration)
Curative	These procedures are performed to effect healing of a non-healing ulcer or a chronically recurring ulcer when offloading and standard wound care techniques are not effective. These include multiple surgical procedures aimed at removing areas of chronically increased peak pressure as well as procedures for resecting infected bone or joints as an alternative to partial foot amputation
Emergent	These procedures are performed to arrest or limit progression of acute infection

Data adapted from Frykberg *et al*[18].

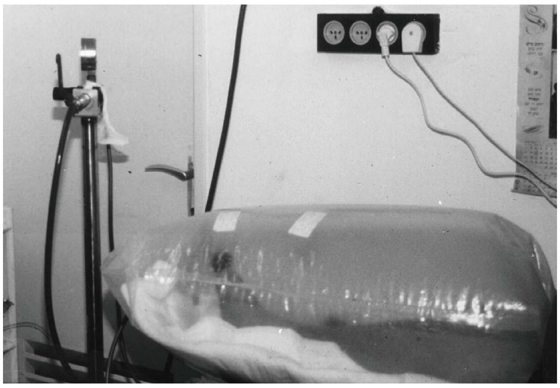

Figure 9 The polyethylene hyperbaric chamber. Oxygen in a concentration of 100% was pumped into the bag through a regular car wheel valve. The open end of the bag was sealed by an elastic bandage to the leg above the knee. Oxygen was allowed to leak around the bandage, and the pressure in the chamber was kept to between 20 and 30 mmHg (1.02-1.03 atm) above atmospheric pressure. (Data adapted from Landau[127]).

group as the treated patients were more likely to heal within 12 mo [25.48 (52%) *vs* 12.42 (29%); P = 0.03]. In addition, Kranke *et al*[135], in a systematic review, revealed that treatment with HBOT resulted in a significantly higher proportion of healed DFU when compared with treatment without HBO (relative risk, 5.20; 95%CI: 1.25-21.66; P = 0.02). However, in another systematic review conducted by O'Reilly *et al*[136], no significant effects on amputation rates were found in the RCT evidence and in the high quality studies, no difference was found between HBOT group compared to standard wound care group.

The exact mechanism of HBOT remains poorly understood. Some studies have reported that HBOT improved wound tissue hypoxia, enhanced perfusion, reduced edema, down regulated inflammatory cytokines, and promoted fibroblast proliferation, collagen production, and angiogenesis[137-140]. In addition, it was demonstrated that HBOT stimulated vasculogenic stem cell mobilization from bone marrow and recruited them to the skin wound[139].

Despite reports of increased healing rates and decreased amputation rates with using HBOT, adjuvant use of this method in DFU remains a controversial issue. HBOT does not substitute for antibiotic therapy, local humid therapy, or surgical wound debridement. Furthermore, HBOT is available in only a minority of communities as it is expensive [a full course of treatment in the United States typically costs $50000 (Medicare) to $200000 (private pay)] and is time-consuming (an average of 60 total hours in the chamber)[5,6].

Electrical stimulation

Electrical stimulation (ES) has been reported as a perfect adjunctive therapy for DFU healing in recent literature. Currently, there is a substantial body of work that supports the effectiveness of ES for DFU healing[141-144]. In a randomized, double-blind, placebo-controlled trial study conducted by Peters *et al*[141] on 40 patients with DFU, significant differences in number of healed ulcers (65% in treatment group *vs* 35% in control group) were found at 12 wk.

Based on the literature review, it is suggested that ES could improve common deficiencies that have been associated with faulty wound healing in DFU, such as poor blood flow, infection, and deficient cellular responses[141,145]. This therapy is a safe, inexpensive, and a simple intervention to improve wound healings in patients with DFU[145,146].

Negative pressure wound therapy

Negative pressure wound therapy (NPWT) is a non-invasive wound closure system that uses controlled, localized negative pressure to help heal chronic and acute wounds. This system uses latex-free and sterile polyurethane or polyvinyl alcohol foam dressing that is fitted at the bedside to the appropriate size for every wound, and then covered with an adhesive drape to create an airtight seal. Most commonly, 80-125 mmHg of negative pressure is used, either continuously or in cycles. The fluid suctioned from the wound is collected into a container in the control unit[147,148] (Figure 10).

It seems that NPWT removes edema and chronic exudate, reduces bacterial colonization, enhances formation of new blood vessels, increases cellular proliferation, and improves wound oxygenation as the result of applied mechanical force[149-151].

This method has been advocated by numerous RCTs as a safe and effective adjunctive modality in the treatment of DFU. Studies have shown that wound

Table 5 Brief description of commonly used bioengineered tissue products

Type	Explanation	Use	RCT studies
Apligraf (Advanced Biohealing Inc., La Jolla, CA)	A bilayered living-skin construct containing an outer layer of live allogeneic human keratinocytes and a second layer of live allogeneic fibroblasts on type 1 collagen dispersed in a dermal layer matrix. Both cell layers are grown from infant fore skin and looks and feels like human skin[164,165]	It's used for full-thickness neuropathic DFU of greater than 3 wk duration, resistant to standard therapy (also without tendon, muscle, capsule, or bone exposure) and is contraindicated in infected ulcers[167]	Veves *et al*[168] Falanga *et al*[169] Edmonds[170] Steinberg *et al*[171]
Dermagraft (Organogenesis Inc, Canton, Mass)	An allogeneic living-dermis equivalent and includes neonatal fibroblasts from human fore skin cultured on a polyglactin scaffold[164,165]	It's used for DFU of greater than 6 wk duration, full thickness in depth but without tendon, muscle, joint, or bone exposure and is contraindicated in infected ulcers[164,167]	Marston *et al*[172] Gentzkow *et al*[173]
Oasis (Cook Biotech, West Lafayette, IN)	An acellular biomaterial derived from porcine small intestine submucosa, contains numerous crucial dermal components including collagen, glycosaminoglycans (hyaluronic acid), proteoglycans, fibronectin, and bioactive growth factors such as fibroblast growth factor-2, transforming growth factor β1, and VEGF[164,165]	It's used for full-thickness DFU[174]	Niezgoda *et al*[174]

DFU: Diabetic foot ulcer; VEGF: Vascular endothelial growth factor.

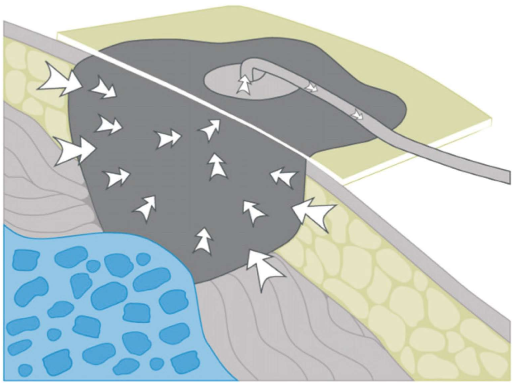

Figure 10 Schematic drawing of the negative pressure wound treatment. (Data adapted from Vikatmaa *et al*[147]).

healing with this approach results in a higher proportion of healed wounds, faster time for wound closure, a more rapid and robust granulation tissue response, and a potential trend towards reduced risk for a second amputation than for the control treatment[148,152-156]. In addition, meta-analysis studies have indicated that NPWT significantly reduces healing times and increases the number of healed wounds[147,157,158].

While the evidence for NPWT in DFU patients is promising, this method does not replace surgical wound debridement to improve blood circulation in all DFU patients. Investigations have shown that when NPWT is initiated, there must be no significant infection or gangrene in the wound[147,158]. Also, RCTs have shown significantly higher mean material expenses for wounds treated with NPWT when compared to conventional therapy (moist gauze) in the management of full-thickness wounds requiring surgical closure[159,160].

Bioengineered skin

Bio-engineered skin (BES) has been used during the last decades as a new therapeutic method to treat DFU[161-164]. This method replaces the degraded and destructive milieu of extra cellular matrix (ECM) with the introduction of a new ground substance matrix with cellular components to start a new healing trajectory[165]. Currently, three kinds of BES products approved in the United States are available to use for DFU including Derma graft (Advanced Bio healing Inc., La Jolla, CA), Apligraf (Organogenesis Inc., Canton, Mass), and, more recently, Oasis (Cook Biotech, West Lafayette, IN)[164,166]; and numerous RCT studies shown their efficacy in DFUs healing (Table 5).

BES product cells are seeded into the scaffolds and cultured *in vitro*. *In vitro* incubation establishes the cells and allows the cell-secreted ECM and growth factors to accumulate in the scaffold. The cells within live cell scaffolds are believed to accelerate DFU healing by actively secreting growth factors during the repair process[164,165]. In addition, it seems that BES can provide the cellular substrate and molecular components necessary to accelerate wound healing and angiogenesis. They act as biologic dressings and as delivery systems for growth factors and ECM components through the activity of live human fibroblasts contained in the dermal elements[162,163,170].

Despite the advantages of BES, they cannot be used in isolation to treat DFU. Peripheral ischemia, which is one of the pathological characteristics of DFU, is a critical contributing factor that affects BES transplantation. Hence, surgical revascularization and decompression as well as wound bed preparation are considered as essential prerequisites for BES applications. In addition, this method needs control of the infection[77,175]. Therefore, the above-mentioned points may result in high long-term costs and cause major concern for use of this treatment[176].

Growth factors

DFU has demonstrated the benefits from growth factors (GFs) such as platelet derived growth factor (PDGF), fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factors (IGF1, IGF2), epidermal growth factor, and transforming growth factor b[177]. Among the aforementioned GFs, only recombinant human PDGF (rhPDGF) (Becaplermin or Regranex), which is a hydrogel that contains 0.01% of PDGF-BB (rhPDGF-BB), has demonstrated increased healing rates when compared with controls in a number of clinical trials[178-181] and has shown sufficient DFU repair efficacy to earn Food and Drug Administration (FDA) approval[182]. In one randomized placebo controlled trial involving patients with full thickness DFU, Becaplermin demonstrated a 43% increase in complete closure *vs* placebo gel (50% *vs* 35%)[183]. In another randomized placebo-controlled trial, Sibbald *et al*[184] demonstrated that patients with infection-free chronic foot ulcers treated with the best clinical care and once-daily applications of 100 μg/g Becaplermin gel had a significantly greater chance of 100% ulcer closure by 20 wk than those receiving the best clinical care plus placebo (vehicle gel) alone.

GFs have been shown to stimulate chemotaxis and mitogenesis of neutrophils, fibroblasts, monocytes, and other components that form the cellular basis of wound healing[178,185]. Despite FDA approval and other reviewed studies, the clinical use of Becaplermin remains limited because of its high cost[186] and uncertain patient-specific clinical benefits[187,188]. Some studies have indicated that endogenous PDGF stimulates tumor infiltrating fibroblasts found in human melanoma cells and is overexpressed at all stages of human astrocytoma growth[164]. So, it would be biologically possible that topical administration of recombinant PDGF could promote cancer.

CONCLUSION

Foot ulcers in patients with diabetes is common, and frequently leads to lower limb amputation unless a prompt, rational, multidisciplinary approach to therapy is taken. The main components of management that can ensure successful and rapid healing of DFU include education, blood sugar control, wound debridement, advanced dressing, offloading, surgery, and advanced therapies, which are used clinically. These approaches should be used whenever feasible to reduce high morbidity and risk of serious complications resulting from foot ulcers.

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