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Modern Wound Healing Technologies for Managing Diabetic Foot Ulcers

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Introduction

Foot complications in people with diabetes have been long recognized as a major health issue, even since before the advent of insulin in the early 1980s.[1] Because diabetic ulcers precede most non-traumatic amputations in people with diabetes, it is essential to optimize healing of the ulcer. In addition to addressing surgical and systemic factors underlying a diabetic foot ulcer (DFU), early topical intervention with appropriate advanced active wound therapies is recommended to help promote granulation tissue formation and DFU closure.[1;2]

Presence of granulation tissue is critical to determining further changes in therapeutic approach and the ability to close the wound by primary intention, skin graft, or bioengineered autologous/heterologous tissues.[3] V.A.C.® Therapy and PRO-MOGRAN® Matrix dressings are two wound management products that help manage the wound environment and have been reported to help promote the formation of granulation tissue in DFUs. In addition, a new automated epidermal harvesting system (CelluTome™ Epidermal Harvesting System) is now available to harvest viable autologous epidermal micrografts with minimal to no donor site morbidity to cover superficial chronic wounds. Optimized use of each of these technologies may positively affect closure of DFUs.

Prevalence and Incidence of DFUs

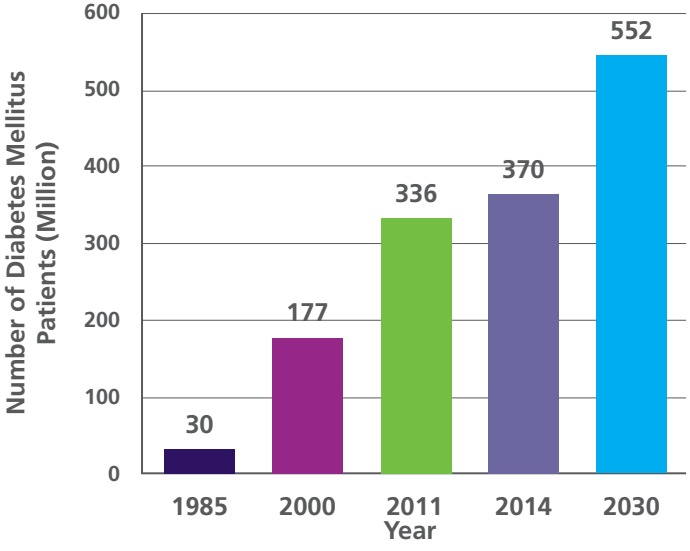
Diabetes is a global health threat that has increased drastically over the past two decades (Figure 1).[4] Diabetic patients have a lifetime risk between 15% and 25% of developing a DFU.[5;6] The cost per ulcer episode varies widely according to ulcer depth, with an average cost estimated at $13,179.[7] Patients with DFUs require more frequent emergency department visits, are more commonly admitted to hospital, and require longer in-patient length of stay.[1] DFUs may also be responsible for substantial emotional and physical distress as well as productivity and financial losses that lower the quality of life.[8]

Threat of Amputation

Foot ulcers are a major public health challenge in patients with diabetes mellitus because they frequently progress to infections of surrounding tissue and result in amputations.[5] More than 15% of all DFUs may result in amputation,[10] and at least 80% of non-traumatic amputations are preceded by an ulcer.[1] Every hour, approximately 10 Americans undergo an amputation as a result of diabetes.[11]

Consequences of these amputations are devastating and include increased morbidity and mortality (especially for major amputations),[6] reduced quality of life[1] and high health care costs.[12] The cost of a lower extremity amputation has been estimated to be $30,000 to $60,000, with an additional $43,000 to $60,000 for subsequent care for 3 years.[12]

Figure 1. Actual and projected worldwide growth of numbers of people with diabetes mellitus (adapted from literature[4;9])



Etiology of DFUs

DFUs are a consequence of many factors, including loss of protective sensation due to peripheral neuropathy as well as arterial insufficiency.[13;14]

The most common pathway to developing foot problems in patients with diabetes is peripheral sensori-motor and autonomic neuropathy that lead to high foot pressure, foot deformities, and gait instability, which increases the risks of developing ulcers.[15-17] These progressive additive effects of neuropathy, minor trauma, ulceration, faulty healing, ischemia and infection leading to amputation were first characterized in 1990.[18] Risk factors for developing a DFU are summarized in Table 1.

Table 1. DFU risk factors[14;19-21]

Systemic risk factors	Local risk factors
Gender (male)	Foot deformity
Duration of diabetes longer than 10 years	Peripheral neuropathy
Older age	Trauma and improperly fitted shoes
High body mass index	Callus
Uncontrolled hyperglycemia	High plantar pressure
Poor nutrition	Infections
Retinopathy	Limited joint mobility
Peripheral vascular disease	Inappropriate personal foot care habits

Importance of DFU Prevention

According to Driver and colleagues, extensive patient education, early assessment, and aggressive treatment by a multidisciplinary team represent the best approach to managing high-risk patients with diabetes.[1] Patient education programs on foot self-management that emphasize patient responsibility for his/her own health and well-being are considered a cornerstone in preventing DFUs and their complications.[22;23] It has been reported that educational intervention, a multidisciplinary approach, and therapeutic footwear coverage could avoid 72%, 47% and 53% of amputations, respectively.[24]

Holistic Care for DFUs

Wound healing is far more likely to be optimal in the setting of good diabetes management and ulcer care. Fundamentals of good clinical care are listed in Table 2.

Table 2. Fundamentals of good clinical care for treating DFUs[25;26]

• Early assessment and treatment of patient comorbidities	• Moist wound care
• Definitive diagnosis	• Infection management
• Surgical corrective action when appropriate	• Pressure management
• Restoring circulation	• Cushioned, protective footwear
• Sharp debridement	• Use of various offloading techniques

Treatment of the Whole Patient

Examining the patient as a whole is important in evaluating and correcting causes of tissue damage and includes factors such as systemic diseases, medications, nutrition, and tissue perfusion/oxygenation.[27] Treatment of peripheral vascular disease, infection and pathological plantar pressure plays a significant role in the global management of complex DFUs; glucose control is the most important metabolic factor.[28;29] Appropriate offloading (eg, total contact casts and therapeutic shoes) is also a key component of the multidisciplinary approach to managing DFUs and providing the best outcomes for patients.[30]

Wound-Related Concerns: Debridement and Infection Management

Debridement

Concerning the wound itself, debridement of necrotic tissue and non-viable tissue may be considered the first and most important therapeutic step leading to wound closure and decreased chance of limb amputation, as wounds do not heal in the presence of non-viable tissue, debris, or critical colonization.[27] The main purpose of surgical debridement is to convert a chronic ulcer into an acute ulcer, and debridement should be repeated as often as appropriate if new necrotic tissue continues to form.[31] V.A.C.® Therapy, as well as other wound healing technologies, can be utilized to work in conjunction with debridement as a foundation upon which the wound healing process can begin.[32]

Infection Management

Wound exudate is naturally bactericidal and can inhibit the spread of surface contamination from becoming a deep wound infection. However, when hyperglycemia, wound ischemia or systemic immune compromise supervenes, pathogenic microorganisms multiply until an excessive concentration of bacteria in the wound precludes healing.[33] This constitutes infection, a major risk factor in amputation.

It is important to understand distinctions among colonization, critical colonization, and infection and to treat each appropriately.[34;35] Systemic wound infection requires surgical debridement and appropriate systemic antibiotic therapy.[36] Critical colonization occurs when bacteria damage tissue and delay or prevent healing; in addition to moisture balance and autolytic debridement, topical antibacterials should be considered if critical colonization is suspected.[2;35]

Modern Wound Care Therapies to Treat DFUs—When to Switch?

While some DFUs may be superficial and can heal with conservative treatment, they are often notoriously slow to resolve, taking up to several months to heal. Indeed, one meta-analysis showed that less than 25% of DFUs heal with conservative care within 3 months.[37] Based on suggested guidelines for the treatment of diabetic ulcers of the lower extremity, patients who fail to show a 40%-50% reduction in ulcer size after 4 weeks of a given therapy should be reevaluated, and other therapies should be considered.[13;38-42]

Similarly, results of one study suggest clinicians can calculate the percentage of wound area reduction (PWAR) of a wound even as early as one week into treatment to predict the likelihood of healing at 16 weeks. In a study that evaluated the probability of chronic, diabetic foot wound healing at 1 and 4 weeks following partial foot amputation, Lavery and colleagues determined that wounds that reached ≥15% PWAR at 1 week or ≥60% PWAR at 4 weeks had a 68 and 77% (respectively) probability of healing versus a 31 and 30% probability if these wound area reductions were not achieved. This calculation might assist in identifying a rationale to reevaluate the wound and change wound therapies.[43]

Use of V.A.C.® Therapy in Treating DFUs

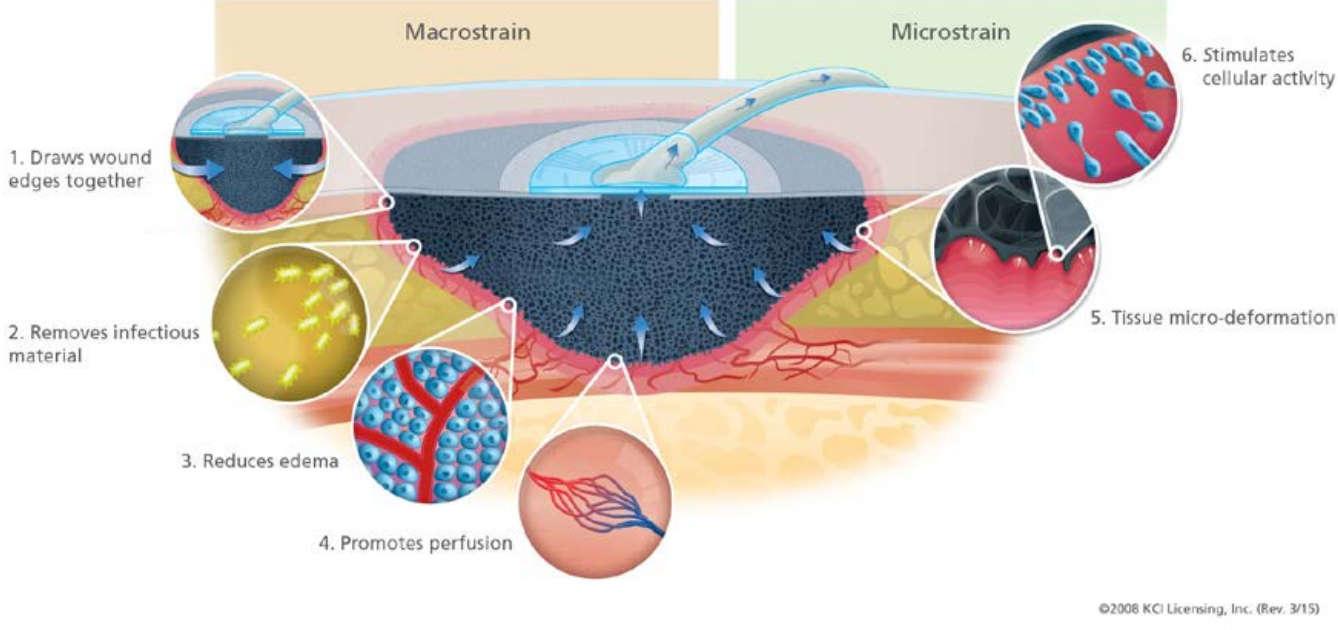
Over the past decade, use of the V.A.C.® Therapy System (Figure 2) to help manage diabetic foot wounds has increased exponentially. V.A.C.® Therapy is applied negative pressure that helps promote wound healing through a variety of mechanisms, including drawing wound edges together; removing infectious materials and wound fluids; promoting perfusion; maintaining a closed, moist wound-healing environment; and stimulating cellular activity via cell stretch under negative pressure, which promotes granulation tissue formation (Figure 3).[26;32]

According to a systematic review performed by Xie and colleagues of 7 published RCTs on the effects of V.A.C.® Therapy on DFUs, there is consistent evidence of the potential benefits of V.A.C.® Therapy compared with control treatments.[44] These authors concluded that there is now sufficient evidence showing that V.A.C.® Therapy can be used in the treatment of diabetes-associated ulcers.[44]

Numerous controlled studies have been published regarding the effects of V.A.C.® Therapy on closure of amputation stumps and DFUs, reduction of secondary amputations, split-thickness graft take, overall costs and quality of life for diabetic patients. Controlled clinical studies that best demonstrate the benefits of V.A.C.® Therapy for patients with DFUs are summarized in Table 3.

Figure 2. V.A.C.Ulta™ Therapy Unit, ActiV.A.C.® Therapy Unit, and a V.A.C.® GranuFoam™ Bridge Dressing

Figure 3. V.A.C.® Therapy applied to a wound



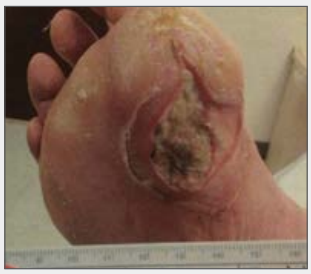
Clinical Case Study

As with any case study, results and outcomes should not be interpreted as a guarantee or warranty of similar results. Individual results may vary, depending on patient circumstances and conditions.

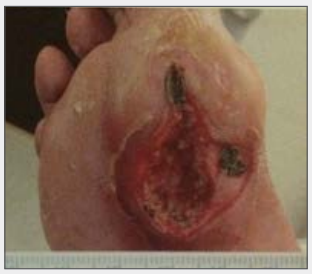
Progressing a DFU to Closure with V.A.C.® Therapy and Epidermal Skin Grafting

Patient was a 59-year-old male who presented to the wound clinic with a wound on the plantar surface of the right foot. There was periwound erythema with significant slough and necrotic tissue present on the wound base. Patient had been seen by other physicians 3 weeks prior with past treatments of antibiotics, debridements, and standard gauze dressings. Patient medical history reported atrial fibrillation, hyperlipidemia, hypertension, colitis, diabetes, hypothyroidism, and bladder cancer. After examination at the wound clinic, diagnosis was a Wagner grade 2 DFU located on the plantar surface of the right foot (Figure 4A). Extensive debridement was performed using scissors, forceps, and a curette to remove slough, subcutaneous tissue and necrotic tissue (Figure 4B). V.A.C.® Therapy using a V.A.C.® GranuFoam™ Dressing was initiated at -125 mmHg continuous pressure. After 1 week, granulation tissue was present in the wound (Figure 4C) and continued to increase after 4 weeks of V.A.C.® Therapy (Figure 4D). At 10 weeks, V.A.C.® Therapy was discontinued, and wound was fully granulated (Figure 4E). Two weeks later, wound was prepared for epidermal graft application (Figure 4F). At 1-week post application, epidermal buds were present within the wound (Figure 4G). At 2-weeks post application, epithelialization was noted (Figure 4H). At 3-weeks post application, epithelialization was increased (Figure 4I). At 4-weeks post application, DFU was closed (Figure 4J).

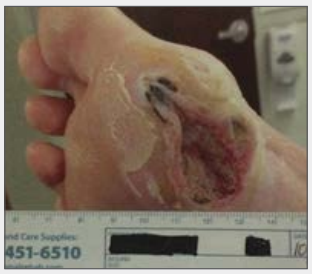
Information and photos provided by Mark Shaw, DO, FACEP, Mount Nittany Wound Center, State College, PA.



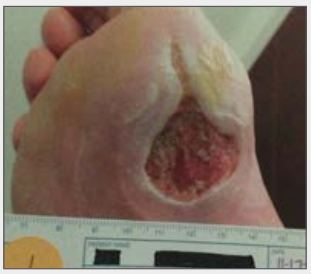
4A. Initial presentation.



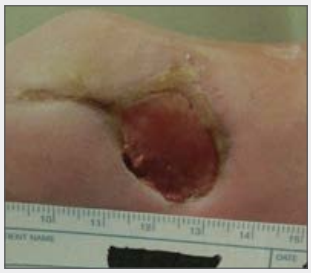
4B. Postoperative foot following debridement; V.A.C.® Therapy with V.A.C.® GranuFoam™ Dressing is applied postoperatively over foot ulcer for 10 weeks.



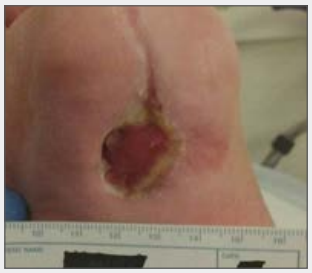
4C. At 1 week post V.A.C.® Therapy, granulation tissue is present in the wound.



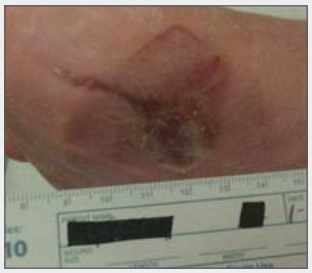
4D. At 4 weeks post V.A.C.® Therapy, increase in granulation tissue in wound.



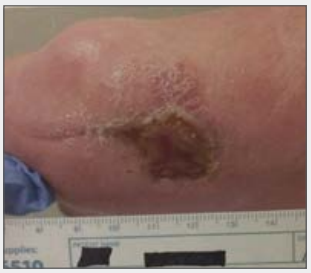
4E. At 10 weeks, wound fully granulated and V.A.C.® Therapy discontinued.



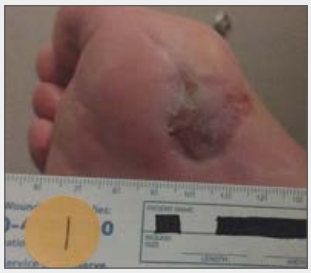
4F. Wound prepared for epidermal graft application.



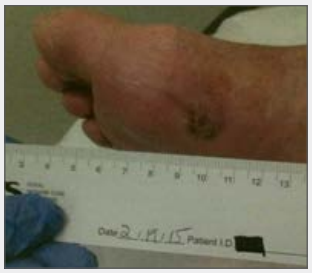
4G. At 1 week post application, epidermal buds were present within the wound.



4H. At 2 weeks post application, wound was epithelializing from edges.



4I. At 3 weeks post application, wound was nearly fully re-epithelialized.



4J. At 4 weeks post application, DFU was closed.

Table 3. Controlled studies supporting V.A.C.® Therapy treatment of DFUs

Study Reference	Therapy	Design	Results/Conclusions	Demonstrated Benefits of V.A.C.® Therapy
SPLIT-THICKNESS GRAFT TAKE				
Dalla Paola et al. 2010;[3] Use of vacuum assisted closure therapy in the treatment of diabetic foot wounds.	V.A.C.® Therapy (n=35) vs non adherent gauze (n=35) placed over STSGs of diabetic foot and ankle ulcers	Parallel, randomized controlled trial (RCT)	Graft take rate was better in the V.A.C.® Therapy versus gauze bolster group (80% vs. 68%; p=0.05).	In this study, successful STSG graft take occurred with V.A.C.® Therapy as bolster.
HEALING OF AMPUTATION STUMPS				
Dalla Paola et al. 2010;[3] Use of vacuum assisted closure therapy in the treatment of diabetic foot wounds.	Surgical debridement and V.A.C.® Therapy (n=65) vs surgical debridement and semi-occlusive silver dressing (Control; n=65) over infected DFUs, open amputations, and surgical dehiscence after foot surgery	Parallel RCT	Significantly more rapid development of granulation tissue covering exposed bone with V.A.C.® Therapy versus silver dressing (41±8 vs 59±18 [p = 0.03] and 65±16 vs 98±45 days [p = 0.005]). Better and more rapid control of infections with V.A.C.® Therapy versus silver dressing (10±8 vs 19±13 days; p = 0.05). Significantly reduced time to complete closure of the DFU with V.A.C.® Therapy vs silver dressing (65±16 vs 98±45 days; p = 0.005). Significantly reduced total time required for surgical procedures in the V.A.C.® Therapy group vs silver dressing (2.5 vs 6.0 hours; p = 0.02).	In this study, V.A.C.® Therapy patients showed a more rapid development of well-vascularized granulation tissue over exposed bones and tendons and a reduced time to closure as compared to Control patients.
Armstrong and Lavery 2005;[45] Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial.	V.A.C.® Therapy (n=77) vs standard moist wound care (n=85) over partial foot amputation wounds of patients with diabetes	RCT	Treatment with V.A.C.® Therapy resulted in a significantly higher proportion of wounds that healed (43 [56%] vs 33 [39%]; p=0.040), faster healing rates (p=0.005), and faster rate of granulation tissue formation (p=0.002). Authors concluded that there were potentially fewer re-amputations with V.A.C.® Therapy compared with standard moist wound care.	In this study, V.A.C.® Therapy patients had a higher proportion of wounds that healed, greater rate of healing, and a greater rate of granulation tissue formation compared to standard moist wound care patients.
INCIDENCE OF AMPUTATIONS				
Frykberg and Williams 2007;[19] Negative-pressure wound therapy and diabetic foot amputations: a retrospective study of payer claims data.	Review of administrative claims records submitted by commercial payers or Medicare for DFU patients who received V.A.C.® Therapy (n=200) versus traditional therapy (n=200)	Retrospective record analysis	There was a 34% reduced incidence of lower-extremity amputations in patients who received V.A.C.® Therapy versus traditional therapy (Control) in commercial payer sample; 35% reduced incidence in the Medicare sample (15.1% versus 21.4%; P = .0951 and 10.8% versus 16.6%; P = .0077). The authors noted that in this study, V.A.C.® Therapy was equally effective in reducing amputation rates in shallow and deep wounds, in contrast to traditional therapy.	In this study, V.A.C.® Therapy was associated with a reduced incidence of lower extremity amputations, regardless of wound depth, compared to traditional therapy.
HEALING OF DFUs				
Blume et al. 2008;[46] Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial.	V.A.C.® Therapy (n=169) vs advanced moist wound care (n=166) over DFUs	RCT	A significantly greater proportion of foot ulcers achieved complete closure with V.A.C.® Therapy (73/169, 43.2%) than with advanced moist wound therapy (48/166, 28.9%) within the 112-day active treatment phase (P = 0.007). V.A.C.® Therapy patients experienced significantly fewer secondary amputations (p=0.035).	In this study, V.A.C.® Therapy patients had a higher rate of ulcer closure and fewer secondary amputations compared to advanced moist wound care.
COST EFFECTIVENESS				
Driver and Blume 2008;[47] Evaluation of wound care and health-care use costs in patients with diabetic foot ulcers treated with negative pressure wound therapy versus advanced moist wound therapy.	Records of DFU patients treated with V.A.C.® Therapy (n=162) vs advanced moist wound therapy (AMWT; n=162) as basis of calculations	Post-hoc retrospective cost analysis of an RCT	Greater cost effectiveness with V.A.C.® Therapy versus AMWT in recalcitrant wounds that didn't close during 12 week period, due to lower expenditures on procedures and use of healthcare resources. Median cost to close 1 cm^2 of DFU was lower for V.A.C.® Therapy patients compared to AMWT, regardless of closure status, suggesting that V.A.C.® Therapy may be more cost effective in terms of wound progression toward closure.	In this study, V.A.C.® Therapy was associated with lower expenditures on procedures and use of healthcare resources and showed a lower median cost to close 1 cm^2 of DFU as compared to AMWT.

Study Reference	Therapy	Design	Results/Conclusions	Demonstrated Benefits of V.A.C.® Therapy
Apelqvist et al. 2008;[48] Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds.	Records of patients with post-amputation wounds treated with V.A.C.® Therapy (n=77) vs advanced moist wound therapy (n=85) as basis of calculations	Post-hoc retrospective cost analysis of RCT	Average direct cost per patient treated for 8 weeks or longer (independent of clinical outcome) was $27,270 and $36,096 in the V.A.C.® Therapy and standard moist wound therapy groups, respectively. Average total cost to achieve healing was $25,954 for patients treated with V.A.C.® Therapy compared with $38,806 for the moist wound therapy group.	In this study, V.A.C.® Therapy was associated with lower overall patient cost of care compared to standard care for post-amputation stumps.
QUALITY OF LIFE				
Karatepe et al. 2011;[49] Vacuum assisted closure improves the quality of life in patients with diabetic foot.	Analysis of Short-Form Health Survey results of patients with DFUs treated with V.A.C.® Therapy (n=30) vs standard wound care dressing (n=37)	Retrospective analysis	All 8 scaled scores of SF-36 health survey improved remarkably after V.A.C.® Therapy. V.A.C.® Therapy treatment indicated a significantly positive effect on both mental (p=0.0287) and physical (p=0.004) health, compared to conventional wound dressing.	In this study, V.A.C.® Therapy was associated with improved patient quality of life scores compared to standard wound care dressings.

Use of PROMOGRAN®/PROMOGRAN PRISMA® Matrix Dressings in Managing DFUs

PROMOGRAN® Matrix is an absorbent open-pored, sterile, freeze-dried matrix that is composed of 45% oxidized regenerated cellulose (ORC) and 55% collagen (Figure 5). These are both naturally-derived, non-cytotoxic materials that are readily broken down when placed in the wound. Chemically, ORC is classified as polysaccharides—sugar molecules linked together to form a polymer. In the case of ORC, which has undergone chemical modification through oxidation, the main components are glucose and glucuronic acid. When ORC fibers absorb fluid, such as saline solution or wound exudate, they swell, become a gel, and break into their basic components (sugars), which can be completely absorbed.[50;51] PROMOGRAN PRISMA® Matrix is comprised of a sterile, freeze dried composite of 44% ORC, 55% collagen, and 1% silver-ORC. Silver-ORC contains 25% w/w ionically bound silver, a well-known antimicrobial agent.[52] The dressing provides an effective antimicrobial barrier as demonstrated by the *in vitro* reduction of bacterial growth with common wound pathogens such as, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Eschericia coli* and *Streptococcus pyogenes*. Reduction of bacterial bioburden in the dressing may result in reduced risk of infection. Also, compared to PROMOGRAN®, PROMOGRAN PRISMA® has an increased concentration of collagen and ORC, which increases the overall density, and depending on wound exudate levels, extends the time taken for collagen and ORC to biodegrade in the wound.

PROMOGRAN®/PROMOGRAN PRISMA® Matrix dressings can be used to manage DFUs that have shown little change in size or in appearance of wound bed or edges. These dressings are generally recommended for ulcers that have failed to proceed through an orderly and timely reparative process towards healing.

Science Supporting Silver-ORC/ORC/Collagen in Wound Healing

The biochemical aspects of collagen and its role in wound management are increasingly well understood.[53;54] When the silver-ORC/ORC/collagen matrix comes into contact with fluid/exudate in the wound, it absorbs the liquid to form a soft gel, which allows the dressing to conform to the shape of the wound and to contact all areas of the wound. This type of matrix maintains a physiologically moist microenvironment at the wound surface, which is conducive to granulation tissue formation, epithelialization and rapid wound healing. ORC has also been shown to have a positive role in wound management—both for promoting cell proliferation and helping to manage bacterial bioburden.[55-57]

Results from an *in vitro* study using chronic wound fluid suggested that the combination of ORC and collagen is more effective at reducing protease levels in wound fluid than either component alone.[58] These results are supported by clinical findings from a single-blinded RCT that measured wound size reduction and biochemistry (wound fluid) in DFU patients (n=33) over an 8-day period. In addition to the reduction in wound size of patients managed with PROMOGRAN®, wound fluid biochemistry data also indicated a more favorable moist wound environment in wounds to which PROMOGRAN® was allocated versus the Control (good standard of wound care).[59] Additional *in vitro* studies have demonstrated the ability of ORC-silver/collagen to reduce bacterial bioburden and growth, further supporting a moist wound environment conducive to healing.[60;61]

Clinical Evidence Supporting the use of PROMOGRAN®/PROMOGRAN PRISMA® Matrix Dressings for Managing DFUs

The efficacy of PROMOGRAN® and PROMOGRAN PRISMA® Matrix dressings is supported by a large body of clinical evidence, including 6 published RCTs in DFUs. A 12-week multicentre RCT involving DFU patients (n=276) reported more wounds achieved complete healing in the PROMOGRAN® group than in the Control group (standard of care – saline moistened gauze). The

difference was significant in wounds <6 months duration (45% vs 33%, p=0.056).[53] In a different 14-week RCT comparing PROMOGRAN PRISMA® (n=25) with Control (best standard of care, n=15), significantly more wounds (DFUs) responded (achieved a greater than 50% reduction in wound area as measured by the Margolis Index) vs Control at week 4 (79% vs 43%, p=0.035). Also, the number of wounds withdrawn from the study due to infection was significantly less with PROMOGRAN PRISMA® as compared to Control (0% vs 31%, respectively; p=0.012). At week 14, the number of wounds completely healed was 52% vs 31%, respectively. Results from all 6 RCTs are summarized in Table 4.

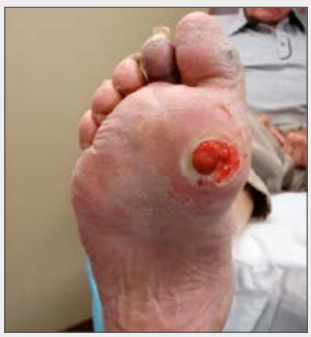
Figure 5. PROMOGRAN PRISMA® Matrix Dressing

Clinical Case Study

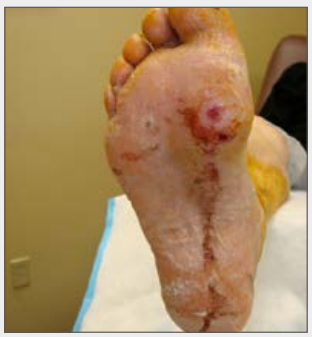
As with any case study, the results and outcomes should not be interpreted as a guarantee or warranty of similar results. Individual results may vary, depending on patient circumstances and conditions.

Application of PROMOGRAN PRISMA® in Chronic, Non-Healing DFU

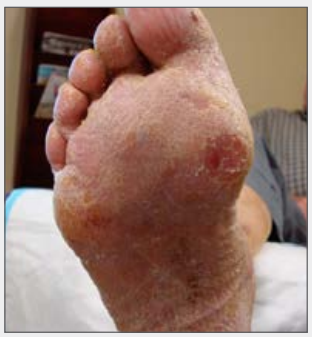
Patient was a 70-year-old white male with a history of long standing diabetes mellitus and diabetic peripheral neuropathy who presented with a chronic, non-healing DFU on the right foot (Figure 6A). Multiple treatments, debridements and antibiotic topical therapy were provided by other physicians but with no success. The DFU remained a non-infected full-thickness wound with hypergranulation on the first submetatarsal head with minimal exudate drainage. There was no gross deformity or bony involvement. A gastrocnemius equinus contracture was noted on patient's right lower extremity that increased the forefoot pressures. Upon vascular examination, patient had intact pedal pulses with adequate ankle brachial index and digital pressures, but there was loss of protective sensation. Management consisted of a full-thickness, sharp excisional debridement into and through the subcutaneous tissue, which removed any fibrotic tissue. Wound was debrided down to a healthy pink granular base, followed by application of PROMOGRAN PRISMA®. An offloading boot was also provided to reduce the forefoot pressures. At 3 and 7 weeks post initiation of PROMOGRAN PRISMA® (Figures 6B and 6C), DFU continued to heal. At 3 months, DFU was fully closed (Figure 6D).



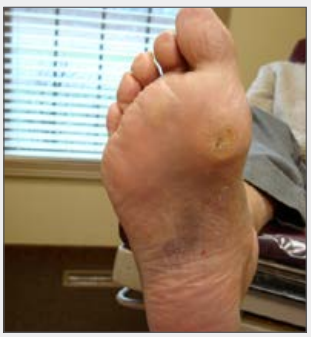
6A. DFU at presentation.



6B. 3 weeks post sharp excisional debridement and initiation of PROMOGRAN Prisma® dressings, wound size was notably decreased.



6C. At 7 weeks, DFU was nearly re-epithelialized.



6D. After 3 months of PROMOGRAN Prisma® and offloading, DFU was closed.

Table 4. Clinical Evidence Supporting Use of PROMOGRAN®/PROMOGRAN PRISMA® Matrix Dressings in Managing DFUs

Study Reference	Therapy	Design	Results/Conclusions	Demonstrated benefits of PROMOGRAN®/ PROMOGRAN PRISMA® Matrix Dressings
Lazaro-Martinez et al. 2007;[62] Randomized comparative trial of a collagen/oxidized regenerated cellulose dressing in the treatment of neuropathic diabetic foot ulcers.	PROMOGRAN® (n=20) vs Control (moist wound healing – standard wound care protocol; n=20)	Single-center, randomized, prospective, controlled, longitudinal clinical trial over a 6-week period	Significantly more wounds achieved complete healing with PROMOGRAN® versus Control (63% vs 15%; p<0.03). Mean time to achieve healing was 23.3 days in the PROMOGRAN® group compared with 40 days in the Control group (p<0.01).	Reduced healing time
Veves et al. 2002;[53] A randomized controlled trial of a collagen/oxidised regenerated cellulose dressing vs standard treatment in the management of diabetic foot ulcers.	PROMOGRAN® (n=138) vs saline-moistened gauze (n=138)	Multi-center (11 sites) Randomized, prospective, controlled clinical trial over a 12-week period	More wounds achieved complete healing with PROMOGRAN®, especially in wounds <6 months duration (45% vs 33%, p=0.056).	Greater number of wounds healed
Gottrup et al. 2013;[63] Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment.	PROMOGRAN PRISMA® (n=24) vs Control (best standard of care; n=15)	Multi-center (2 sites) Randomized, prospective, controlled clinical trial Duration of study & follow-up: 14 weeks	Significantly more responders (≥50% reduction in wound area measured by the Margolis index) in the PROMOGRAN PRISMA® group compared with the Control group (79% vs. 43%, p = 0.035) at week 4. Significantly fewer withdrawals from the study because of infection in the PROMOGRAN PRISMA® group compared with the Control group (0% vs. 31%, p = 0.012). At week 14, the number of wounds completely healed was 52% vs 31%.	Reduced wound size Reduced rate of infection
Lobmann et al. 2002;[64] Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia 2002;45:1011–1016.	PROMOGRAN® (n=18) vs Control (good standard of wound care; n=15	Randomized, controlled clinical research measuring healing and wound biochemistry over an 8 day period	Clinical data showed 16% vs 1.65% reduction in wound size in 8 days with PROMOGRAN® vs Control. Wound fluid biochemistry data also indicated a more favorable moist wound environments in wounds to which PROMOGRAN® was allocated.	Reduced wound size More favorable moist wound environment
Kakagia et al. 2007;[65] Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial.	PROMOGRAN® (n=17) vs autologous growth factors (n=17) vs combination (PROMOGRAN® + autologous growth factors) (n=17)	Randomized, prospective clinical trial over an 8 week period	PROMOGRAN® was more effective at reducing ulcer size than autologous growth factors; however, the combination was significantly better than either of the other groups (p<0.001).	Reduced wound size
Ulrich D et al. 2011;[66] Effect of oxidized regenerated cellulose/collagen matrix on proteases in wound exudate of patients with diabetic foot ulcers.	Promogran® (n=22) vs Control (Hydrocolloid dressing) in DFU patients Wagner Status 2-4	Randomized controlled trial over a 12-week period	There were significant differences (p<0.05) in wound area reduction on days 14 and 28 in the PROMOGRAN® group vs Control. Wound fluid biochemistry data also indicated a more favorable moist wound environment in wounds to which PROMOGRAN® was allocated.	Reduced wound size More favorable moist wound environment

Use of Epidermal Skin Grafts in Treating DFUs

Skin graft coverage of diabetic foot wounds can be exceptionally challenging, especially when donor sites are limited. Advances such as engineered artificial skin provide a quick, but costly, approach to achieve wound coverage in the absence of suitable donor skin. Epidermal skin grafts provide a viable option for wound coverage. Only the epidermal skin layer is removed at the donor site, resulting in minimal to no bleeding, minimal scarring and donor site pain, and no need for anesthesia.[67]

An automated epidermal harvesting system, CelluTome™ Epidermal Harvesting System, is now commercially available for harvesting epidermal skin grafts in an office or outpatient setting. This new technology in epidermal harvesting offers a simple, low-risk option that can be performed by a non-surgically trained clinician in an outpatient setting. The CelluTome™ Epidermal Harvesting System consists of a reusable control unit, reusable vacuum head, and disposable harvester (Figure 7). Heat and suction are applied concurrently to normal skin to induce epidermal microdome formation.

Epidermal grafts are harvested by activating a handle that sets the harvester blade in motion, and a transparent thin film dressing is used to collect and transfer epidermal grafts onto the recipient site. Up to 128 epidermal microdomes can be harvested with CelluTome™ Epidermal Harvesting System within 30 to 45 minutes, and no surgical training is needed.[68] In a study of 15 healthy human subjects, the automated epidermal harvesting tool has been shown to harvest uniformly viable autologous micrografts at the dermal-epidermal junction with minimal pain and superficial donor site wound healing within one to three weeks.[69;70]

Science Supporting Epidermal Skin Grafts

In order for re-epithelialization and re-pigmentation to occur, each epidermal skin graft must produce epidermal basal cell outgrowth from the graft edges to close the 2 mm distance between grafts. A KCI *in vitro* examination of epidermal grafts harvested with this automated system from 12 healthy human subjects showed that migratory basal layer keratinocytes and melanocytes were proliferative.[70] Examination of intact microdome roofs from 3 healthy human samples demonstrated that viable basal cells actively secreted key growth factors important for modulating wound healing responses, including VEGF, HGF, G-CSF, PDGF, and TGF-α.[70]

While suction blister epidermal grafting (SBEG) has been successfully used for many decades in managing stable vitiligo and other secondary leukodermas, reports of its application over acute and chronic wounds, most notably in burns, pyoderma gangrenosum and lower extremity ulcers, are more recent.[71-73] One comparative study of 38 patients has demonstrated favorable results observed with SBEG versus standard local wound care in managing intractable diabetic foot ulcers.[74] DFUs without exposed bone (n=10) managed with epidermal grafts had significantly shorter healing times compared to patients (n=8) who received standard therapy (4.3 ±0.6 vs. 11.6 ±3.4 weeks, respectively; p=0.042). There were no significant differences in healing times between DFUs with exposed bone (n=11) managed with epidermal grafts and those DFUs (n=9) that received standard therapy (5.1 ±0.7 vs. 6.2 ±2.5 weeks, respectively; p=0.860). Interestingly, the amputation rate of patients with DFUs with exposed bone who received epidermal grafting was 0/11 versus 8/9 for standard therapy (p <0.0001).[74]

However, use of conventional SBEG methods that achieve dermo-epidermal separation has been limited in clinical practice due to lack of a reliable and automated method for harvesting patient epidermal skin.[75] Historically, epidermal blisters have been created using a variety of techniques including syringes, portable suction pump and suction cups, as well as temperature controlled cutaneous suction chambers. However, these techniques have been described as time consuming and tedious.[76-78] Compared to other existing SBEG harvesting techniques, the CelluTome™ Epidermal Harvesting System simplifies the harvesting process and facilitates uniform, reproducible microdome formation and distribution.[69]

Preliminary Evidence

Preliminary evidence evaluating the use of epidermal skin grafts harvested with the CelluTome™ Epidermal Harvesting System over DFUs is promising. In a case series of 6 patients with multiple comorbidities, patients received an epidermal skin graft over their chronic DFU, which assisted in wound coverage and healing. Average time to complete epithelialization was 10.5 weeks. Five of six (83.3%) wounds achieved full re-epithelialization during the study period, and all donor sites healed without complications.[79] Successful use of epidermal grafts obtained with the CelluTome™ Epidermal Harvesting System has also been described in coverage of pyoderma gangrenosum ulcers (n=5), lower extremity wounds (n=7), and acute wounds (n=4).[80-82]

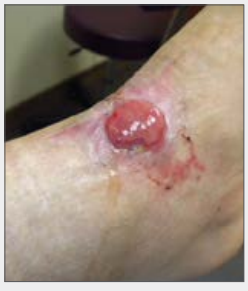
Figure 7. CelluTome™ Epidermal Harvesting System: reusable control unit, reusable vacuum head, and disposable harvester

Clinical Case Study

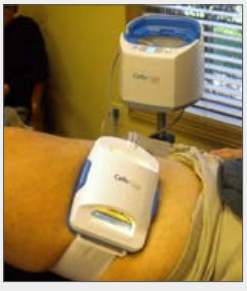
As with any case study, the results and outcomes should not be interpreted as a guarantee or warranty of similar results. Individual results may vary, depending on patient circumstances and conditions.

Epidermal Graft Coverage of DFU

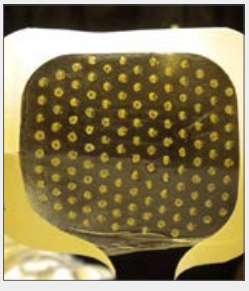
A 65-year-old diabetic white male presented with a DFU on the dorsum of the right ankle that was caused by a complication from a previous surgery. Patient had a history of peripheral vascular disease. Standard wound care was initially performed with a CAM boot, but with no success (Figure 8A). Therefore, silver nitrate was used to treat the hypergranulation tissue, followed by coverage of the DFU with epidermal grafts harvested from the patient's right thigh using the CelluTome™ Epidermal Harvesting System (Figure 8B). Hair was removed from the donor site, and skin was prepped with isopropyl alcohol. No anesthesia was required for the procedure. The epidermal grafts were transferred using an adhesive film dressing (Figure 8C) and applied over the DFU (Figure 8D). A bolster dressing was applied over the grafts. At 1 week, the film dressing was removed, and a non-adhering dressing was placed over the wound. By approximately 3 weeks post epidermal grafting, the DFU was re-epithelialized with no complications (Figure 8E).



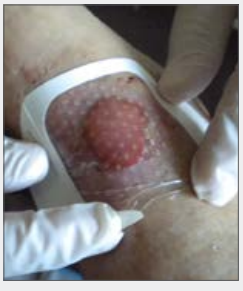
8A. DFU at presentation.



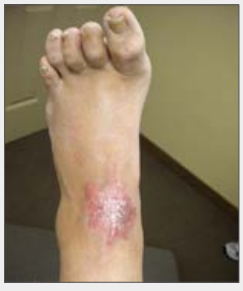
8B. Epidermal grafts were harvested from patient's right thigh.



8C. Epidermal grafts were transferred using an adhesive film dressing.



8D. Epidermal grafts were applied over the DFU.



8E. Healed DFU at 3 weeks post epidermal grafting.

Conclusion

DFUs are a major health issue because they may be associated with amputations and high healthcare system expenditures.[1] Extensive patient education, early assessment, and aggressive treatment by a multidisciplinary team represent the best approach to managing high-risk patients with diabetes.[1] Debridement, infection management, and treatment of underlying causes are paramount to healing success of diabetic ulcers. While some DFUs may be superficial and can heal with conservative treatment, some diabetic ulcers require advanced, modern wound care technologies to progress to healing.[37]

V.A.C.® Therapy, PROMOGRAN® Matrix dressings, and epidermal grafts harvested with the CelluTome™ System are viable advanced wound care modalities that may be considered for adjunctive management of DFUs. V.A.C.® Therapy has been reported to help promote closure of DFUs and amputation stump wounds, bolster split-thickness skin grafts, and limit secondary amputations, compared to controls. PROMOGRAN® Matrix has been shown to help create an environment conducive to granulation tissue formation, epithelialization, and wound healing. In addition, the CelluTome™ Epidermal Harvesting System allows automated harvest of uniformly viable autologous micrografts that can be performed by a non-surgically trained clinician in an outpatient setting to produce epidermal grafts that can assist in re-epithelialization of superficial DFUs. Understanding mechanisms of these devices and their role in the wound healing armamentarium can benefit wound care clinicians and patients in achieving definitive goals of wound healing.

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