Transdermal Oxygen Delivery to Diabetic Wounds: A Report of 6 Cases
Fred Hirsh, MD; Steven J. Berlin, DPM; and Aliza Holtz, PhD

ABSTRACT
OBJECTIVE: To evaluate the use of a transdermal sustained oxygen delivery system to promote the healing of chronic lower extremity wounds in patients with diabetes.
METHODS: Six patients (5 men, 1 woman; age range, 32–77 years) with diabetes and chronic lower extremity wounds unresponsive to previous multimodal therapy were treated with transdermal sustained oxygen. The transdermal sustained oxygen delivery device (EpiFLO; Ogenix Corp, Cleveland, Ohio) delivered 100% oxygen at 3 mL/h with ambient humidity, 24 h/day, directly to the wound site, which was covered by an occlusive dressing.
RESULTS: Despite chronicity of wounds (aged 4 months to >15 years) and nonresponsiveness to previous treatments, all wounds in this case series treated with transdermal sustained oxygen therapy improved within 2 to 20 weeks, within which time 5 of the 6 wounds had healed completely. In 2 cases, scheduled amputations were prevented.
CONCLUSION: The results of the 6 cases reported here strongly support the use of transdermal sustained oxygen therapy in promoting the healing of diabetic foot and leg ulcers refractory to previous treatments. In addition, amputation was prevented in 2 cases, thus reducing prolonged costly patient care.

INTRODUCTION
According to the American Diabetes Association, the total prevalence of diabetes in the United States for all ages is 23.6 million people (7.8% of the population as a whole). Of these, an estimated 15% to 25% will develop foot ulcers during their lifetimes; 14% to 24% of diabetic foot ulcers result in amputation.

In 2004, approximately 71,000 nontraumatic lower-limb amputations were performed in people with diabetes.

In fiscal year 1995, under Diagnosis Related Groups reimbursement code 271 (skin ulcer), the average Medicare claim for inpatient care for foot ulcers was $14,641, and of the total of 402,280 Medicare beneficiaries with lower extremity wounds, 24% received inpatient care. (This does not include private insurance claims.) In a 3-year (1993–1995) retrospective cohort study of patients with diabetes in a staff-model health maintenance organization, Ramsey et al observed a cumulative incidence of foot ulcer of 5.8% and determined that, for the 2 years following diagnosis, the attributable cost for a 40- to 60-year-old man with a new foot ulcer was $27,987. The Undersea and Hyperbaric Medical Society’s 1999 Committee Report states the cost of treating nonhealing lower extremity diabetic ulcers totals more than $200 million annually. Gordois et al determined that in 2001 the mean annual cost of treating an uninfected diabetic foot ulcer was $9,306, whereas that of treating an infected foot ulcer was $24,582, and that of a foot ulcer with osteomyelitis was $45,579. In the United States, the average hospitalization cost is $31,264; average amputation cost is $40,000; estimated total (excluding rehabilitation and related medical and surgical disability care) is $71,264; and with an average of $30,000 for rehabilitation, the total cost is $101,264.

In a study of anatomic, pathophysiological, and environmental factors contributing to the development of incident diabetic foot ulcers, Reiber et al determined that the most common components of a patient’s causal pathway to foot ulcers were neuropathy (78%), minor traumatic event (77%), and foot deformity (63%), followed by edema (37%), ischemia (35%), and callus formation (30%).

Foot ulcers may become chronic, nonhealing wounds. Often painful, they always require vigilant attention to prevent infection. Because foot and leg ulcers precede amputations in most instances, the importance of promoting wound healing cannot be overstated, and the need for therapeutically effective and cost-effective measures for the prevention and treatment of diabetic foot ulcers is self-evident.

Oxygen has long been recognized as having an important role in wound healing, and much research in recent years has been aimed at elucidating this role at the cellular and molecular levels.

The development of a self-contained miniature device, EpiFLO (Ogenix Corp, Beachwood, Ohio), which delivers transdermal oxygen therapy directly to the wound bed has...
made it possible for some patients to remain ambulatory while receiving oxygen therapy at the site of the ulcer (in contrast to the confinement and intermittent exposure associated with the use of a hyperbaric oxygen chamber or being attached to an oxygen tank to get topical oxygen therapy).

The following are 6 case reports of chronic lower-limb wounds in patients with diabetes who were treated with transdermal sustained oxygen therapy (TSOT) to promote wound healing.

**METHODS**

Oxygen was delivered to the wound via the EpiFLO, which produces 100% O₂ at 3 mL/h continuously by means of a battery-driven electrochemical reaction. A sterile cannula leading from the device to the wound site (covered by an occlusive dressing) provides direct delivery of oxygen to the wound at ambient humidity 24 hours a day. The device is a single-patient, single-use, 7- or 15-day disposable apparatus.

**CASE REPORTS**

**Case 1**

A 77-year-old man with diabetes presented with a neuropathic foot ulcer (2.5 cm long, 2.5 cm wide, and 1 cm deep) of 5 months’ duration with osteomyelitis (Figure 1A). The patient had a prior history of 2 toe amputations because of wounds. Below-the-knee amputation had been planned for the patient because previous therapies, including revascularization of the area, had failed. However, 15 weeks after the initiation of TSOT with the EpiFLO, the osteomyelitis resolved, and the wound had closed completely (Figure 1B).²

**Case 2**

A 74-year-old man with type 1 diabetes with a history of renal failure was undergoing dialysis at the time of presentation. In addition to severe leg edema, he had an open weeping ulcer (72 x 80 x 2 mm) of 48 weeks’ duration on the left lower extremity (Figure 2A). The ulcer had progressed and enlarged during the previous 12 months despite multimodal treatment (silver nitrate, topical and systemic antibiotics, and an Ace wrap). Treatment with TSOT (EpiFLO) was initiated and continued until the wound closed. One week after initiation of TSOT treatment, excellent granulation tissue and early re-epithelialization were observed, and the patient reported less pain. At week 2, re-epithelialization tissue had improved significantly, and the wound dimensions had decreased. The wound was covered with Duoderm (Convatec, Skillman, New Jersey). At week 3, the EpiFLO cannula was temporarily dislodged, but this did not negatively influence the overall healing. After 4 weeks of treatment, the wound had completely closed.

**Case 3**

A 68-year-old woman with a 15-year history of diabetes had a fairly painful ulcer on the dorsum of the foot that remained open with no evidence of healing despite multimodal treatments. The lesion was nonpurulent, had no odor, and had been stable for 12 years, measuring 60 x 60 x 3 mm (Figure 3A). One week after the initiation of TSOT (EpiFLO) treatment, a large amount of exudate was noted, as was increased bleeding on debridement, but there was no change in the size of the lesion. During weeks 2 to 8, persistent drainage and a foul-smelling discharge were noted, but the...
wound never became infected. The lesion was healing slowly and steadily, measuring 40 x 40 x 2 mm at week 8. At week 9, the lesion was fully granulated, drainage was minimal, and the depth of the wound decreased to 0.5 mm. The pain had completely resolved during this period. Extensive re-epithelialization was observed at week 10, and the lesion was reduced to 10 x 15 x 0 mm (Figure 3B). The authors’ data extend through only week 10 because the patient suddenly died before the wound completely healed.

Case 4
A 32-year-old man with diabetes had an ulcer (4 x 4 x 2 mm) with 100% red granulation tissue and macerated edges on the plantar aspect of the left great toe (Figure 4A). The wound had been open for 6 months. Previous treatment included wet-to-dry therapy with iodine gel to control infection and absorb the wound exudate. One week after EpiFLO treatment, the wound was reduced to pinpoint size (1 x 1 x 0 mm), and after 2 weeks, the ulcer was completely closed and healed (Figure 4B).

Case 5
A 50-year-old woman with diabetes mellitus had 2 neuropathic ulcers that had not healed for 24 months: One was 3.5 x 1.8 x 1.5 cm on the right plantar foot, and the other 3.8 x 1.2 x 0.8 cm on the right medial foot (Figure 5A). Before presenting at the wound care clinic, the patient had been hospitalized and had received antibiotic therapy and debridement. The patient was treated with TSOT only for the wound on the right medial foot; for the next 8 weeks, dressings were changed every other day as necessary, depending on drainage, and then weekly until healed. The TSOT-treated wound healed in 8 weeks (Figure 5B). The wound on the right plantar foot did not receive TSOT but received regular dressing changes. This wound healed in 2 weeks. The TSOT treatment on the right medial foot wound may have had beneficial spillover effects on the wound on the right plantar foot.

Case 6
A 54-year-old man with diabetes and a deformed Charcot foot had a foot ulcer (8.0 x 6.0 x 0.8 cm on presentation) of 4 months’ duration on the left plantar aspect of the heel area of the left foot (Figure 6A), and another wound on the lateral distal aspect of the left foot in an area where toes had been amputated. The treatment history of the left plantar wound consisted of wet-to-dry dressings for several months before TSOT (EpiFLO). A scheduled amputation was anticipated, but delayed for a trial of TSOT. The oxygen therapy

Figure 3.
CASE 3: A CHRONIC, NONHEALING, DIABETIC FOOT ULCER WITH A VASCULAR COMPONENT THAT HAD BEEN STABLE FOR 12 YEARS (A) IN A 68-YEAR-OLD WOMAN WAS SIGNIFICANTLY REDUCED AFTER 10 WEEKS OF TREATMENT WITH EPIFLO (B).

Figure 4.
CASE 4: A DIABETIC FOOT ULCER THAT HAD NOT HEALED FOR 6 MONTHS (A) IN A 32-YEAR-OLD MAN WAS COMPLETELY CLOSED AFTER 2 WEEKS OF TREATMENT WITH EPIFLO (B).

Figure 5.
CASE 5: NONHEALING NEUROPATHIC RIGHT MEDIAL FOOT ULCER (A) IN A 50-YEAR-OLD WOMAN WITH DIABETES HEALED AFTER 8 WEEKS OF EPIFLO TREATMENT (B).
closed the chronic ulcer in 20 weeks (Figure 6B), and amputation was cancelled.

RESULTS
A summary of the 6 case reports is presented in Table 1. Despite the chronic nature of the wounds (ranging in duration from 4 months to >15 years) and their nonresponsiveness to previous treatments, all wounds in this case series treated with TSOT responded within 2 to 20 weeks, within which time 5 of the 6 wounds had healed completely. In 2 cases, scheduled amputations were cancelled. In all cases, an occlusive form of dressing was applied to enhance the oxygen therapy, and the treatment was well tolerated and without complications. Because of the nature of this therapy, none of the patients were restricted in any fashion.

DISCUSSION
The results presented in each of the 6 case reports above demonstrate the efficacy and safety of EpiFLO, a transdermal sustained oxygen delivery system, in promoting wound healing in instances of recalcitrant wounds despite previous multimodal efforts to help them heal.

In a study by Oyibo et al,10 the area of a foot ulcer at presentation was correlated with healing time and also predicted healing of the ulcer in diabetic patients with new foot ulcers. These investigators showed also that the presence of ischemia was a predictor of nonhealing, and, as would be expected, neuroischemic ulcers and infected ulcers took longer to heal than those without these confounding factors. Age, sex, type of diabetes, duration of diabetes at presentation, and site of foot ulcer did not influence the outcome of diabetic foot ulcers.

In their study of the outcomes of diabetic foot ulcers after 6 to 12 months in 194 patients who presented with new foot ulcers, Oyibo et al10 found that the median (interquartile range [IQR]) ulcer area in patients whose ulcers healed was

Table 1.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>M/F</th>
<th>Patient Age, y</th>
<th>Wound Age</th>
<th>Wound Size, cm</th>
<th>Wound Area, cm²</th>
<th>Time to Heal With EpiFLO</th>
<th>Amputation Scheduled?</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>77</td>
<td>5 mo</td>
<td>2.5 x 2.5 x 1</td>
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<td>15 wk</td>
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<td>2</td>
<td>M</td>
<td>74</td>
<td>48 wk</td>
<td>7.2 x 8.0 x 0.2</td>
<td>57.6</td>
<td>4 wk</td>
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</tr>
<tr>
<td>3</td>
<td>F</td>
<td>68</td>
<td>12 y</td>
<td>6.0 x 6.0 x 0.3</td>
<td>36</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>32</td>
<td>6 mo</td>
<td>0.4 x 0.4 x 0.2</td>
<td>0.2</td>
<td>2 wk</td>
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</tr>
<tr>
<td>5</td>
<td>F</td>
<td>50</td>
<td>24 mo</td>
<td>3.5 x 1.8 x 1.5 on right plantar foot</td>
<td>6.3</td>
<td>2 wk (dressing changes only; no EpiFLO)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.8 x 1.2 x 0.8 on right medial foot</td>
<td>4.6</td>
<td>8 wk</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>54</td>
<td>4 mo</td>
<td>8.0 x 6.0 x 0.8</td>
<td>48</td>
<td>20 wk (EpiFLO treatment from weeks 6 to 26)</td>
<td>Yes</td>
</tr>
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</table>
1.1 cm² (0.5–2.6 cm²), whereas the median (IQR) ulcer area in patients whose ulcers did not heal was 1.4 cm² (0.7–3.5 cm²). Median (IQR) ulcer areas of 3.9 cm² (1.4–5.4 cm²) were associated with amputation.

If the ulcer area according to Oyibo et al. had been used as a predictor of healing in our cases, only 1 of the 6 would have been predicted to heal, and the other 5 would have been predicted to have led to amputation. However, our cases demonstrate that sustained transdermal oxygen therapy promoted healing even in ulcers refractory to various previous therapies and with areas as large as 58 cm², and that the healing occurred within 2 to 20 weeks. In fact, amputations had been scheduled for 2 of the cases but were cancelled because of the healing. Treating physicians noted that within approximately 1 to 2 weeks of initiation of the use of EpiFLO, the wounds produced an exudate, and this was followed by the process of epithelialization.

A recent animal study demonstrated improved epithelial healing in a rabbit ear wound model using the same transdermal sustained oxygen delivery device. The results of the animal study as well as the observations noted in the current case reports suggest that transdermal sustained oxygen delivery promotes epithelial wound healing in cases of leg and foot ulcers in patients with diabetes. If further research with TSOT in diabetic and other chronic—and possibly also acute—wounds yields similar results, it is likely that the physical and economic burdens of at least some of the complications of diabetes will be mitigated.

It is reasonable to assume from the results presented here that the costs of treatment of diabetic leg ulcers in this case series were decreased with the use of EpiFLO compared with the probable costs of continued treatment of recalcitrant wounds or to the costs of amputation and follow-up care. EpiFLO can be up to 50% less costly than other advanced wound care therapies when comparing the device cost to that of other devices and treatments. Randomized controlled trials currently under way will capture health econometric data—including other costs such as nursing time, dressings, and other components—and further the cost-benefit analysis over the entire episode.

CONCLUSION
The results of the 6 cases reported here provide strong support for the use of TSOT in promoting the healing of diabetic foot and leg ulcers that were refractory to other prior treatments. Large wound areas (up to 58 cm²) that would have been predicted not to heal and amputation may have been necessary were healed within 20 weeks of initiation of TSOT, and in 2 cases, scheduled amputations were cancelled. The healing ability of a continuous oxygen therapy device (EpiFLO) has been shown to reduce the amputation potential in healing chronic wounds and has also shown that the continuous flow of oxygen has eliminated pain associated with such wounds. It is reasonable to assume that TSOT can reduce the financial burden of chronic diabetic ulcers.

References