

How CDO Works

This is a summary overview of how Continuous Diffusion of Oxygen (CDO) therapy works, how it differs from intermittent oxygen therapies & the most recent supporting clinical evidence (refer to eo2.com for updates). Detailed information follows this introductory page. Additional evidence as to how oxygen is effective in wound healing can be found in the EO2 guidance document “How Oxygen Works in Wound Healing”.¹

How Oxygen Penetrates Wounds



Moist Wounds “Breathe” Similar to Alveoli in Lungs – By Diffusion

- Oxygen diffuses into moist tissue in the same way it penetrates alveoli during breathing (external respiration), or at the cellular level (internal respiration)
- Topically applied oxygen penetrates tissues directly, not reliant on good local blood flow



Using Pure Oxygen Increases Tissue Levels

- Henry’s Law - concentration in tissue is proportional to concentration above tissue²
- Pure oxygen results in fast four-fold increase at 2 mm depth in tissue in 4 min³



Process is Rapid

- As evidenced during breathing, oxygen diffuses into the moist tissues rapidly
- Results in moist tissues show rapid and deep penetration³

How CDO Differs from Topical (TO, TWO) and Hyperbaric Oxygen (HBO) Therapies^{4,5}



Silent, Wearable & Discreet

- CDO is small & lightweight, others are not



Continuous Treatment

- CDO treats continuously (24/7), others are only 90 minutes per day (~5% of CDO time)



Cost Effective⁶

- CDO is a fraction of the cost of others (\$1800 less than MWT, \$14,000 less than HBO)

Clinical Evidence Supporting CDO

Fully Blinded



Fully-Blinded RCT with Sham/Placebo in Diabetic Foot Ulcers: 146 Patients^{7,8,9}

- CDO significantly accelerates closure (2x to 4.6x; P = .02 to .002)
- CDO works better as wounds become more chronic, larger, weight bearing & are debrided
- CDO results in significantly faster time to closure (P < 0.001)



Prospective Trial on Growth Factors, Cytokines & Perfusion in 20 Patients¹⁰

- 280% to 820% significant increases in growth factors and cytokines in one week

Prospective Trial of Pain Reduction: 20 Patients¹¹

- 75% reduction in pain relief by the first follow-up visit (median of 4 days)
- Over 90% had noticeable pain reduction (>25%) by the first follow-up visit



Retrospective Review Chronic Toe Ulcers: 20 Patients¹²

- 74% full closure on ulcers that were unresponsive to other treatments
- High degree of patient compliance with therapy (95%)

Retrospective Review of Ulcers in Veterans Healthcare: 25 Patients¹³

- 68% full closure on ulcers that were unresponsive to other treatments
- Demonstrated adjunctive use with advanced tissue / skin substitutes



Prospective RCT with MWT Control Group: 9 CDO & 8 MWT Patients¹⁴

- 87% volume reduction in 4 weeks vs. 46% with MWT (P < .05)

Prospective RCT with MWT Control Group in DFUs: 9 CDO & 9 MWT Patients¹⁵

- 90% closure in 8 weeks vs. 30% with MWT



Case Report of Pain Reduction and Wound Closure in Venous Ulcer¹⁶

- Patient served as own control, pain reduced from 10 to 2 in 3 days

Pain Reduction in Uncontrolled Study of Venous Ulcers: 10 Patients¹⁷

- Significant (P < .009) pain reduction during six weeks with 58.9% size reduction



Case Series Review of Severe, Painful Wounds: 4 Patients¹⁸

- Significant pain reduction in all cases and all closed fully

Case Series Review of Painful Lower Extremity Wounds: 6 Patients¹⁹

- Significant pain reduction in all cases

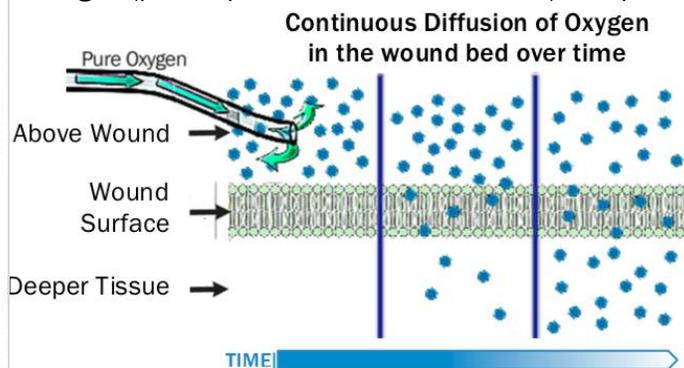
How CDO Works

How Oxygen Penetrates Wounds

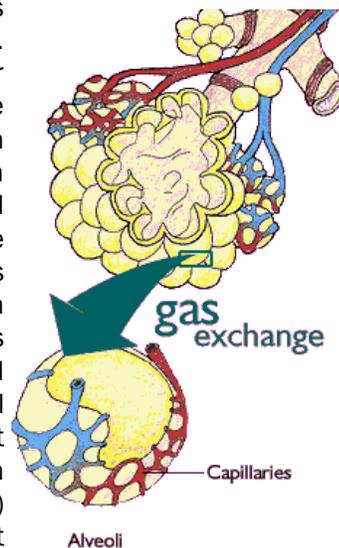


Moist Wounds “Breathe” Similar to Alveoli in Lungs – By Diffusion

Oxygen transport into a clean, moist wound occurs via the same transport processes that govern oxygen absorption into the alveoli in lungs during breathing: diffusion. Oxygen is transported from the surrounding air to cells in a clean, moist wound (or alveoli) via the physical driving force of diffusion. In diffusion, gases (or liquids) move from an area of high concentration (partial pressure) to areas of low concentration (partial pressure). If there is a mixture of gases in a container, the pressure of each gas (partial pressure or concentration) is equal to the pressure that each gas would



produce if it occupied the container alone. This applies equally well to the concentration of a gas in a liquid. If a gas (oxygen) is present above a liquid (open moist wound), the gas will diffuse into the liquid until it reaches equilibrium in concentration (partial pressure) in the liquid in proportion to that present in the gas above it.



Using Pure Oxygen Increases Tissue Levels

Henry's law states that at a constant temperature, the amount of a gas that dissolves in a liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid. Oxygen in water obeys Henry's law rather well; the solubility is roughly proportional to the partial pressure of oxygen in the air: $pO_2 = K_{O_2} \cdot x_{O_2}$, where pO_2 is the partial pressure of oxygen in Torr, x_{O_2} is the mole fraction of oxygen in oxygen-saturated water, and K_{O_2} is the Henry's law constant for oxygen in water (about 3.30×10^7 K/Torr at 298 K).²

Potential 20x or Greater pO_2 Increase in Ischemic Tissues

In human tissue, oxygen levels contain approximately 50 mmHg pO_2 at 3-4 mm below the wound for moist wounds exposed to air which has 21% oxygen ($pO_2 = 159$ mmHg). By increasing the oxygen concentration above the wound from 21% ($pO_2 = 159$ mmHg) to 100% ($pO_2 = 760$ mmHg), as is the case with CDO, the resulting oxygen levels in the tissue can increase to as high as 250 mmHg pO_2 . These levels have been found experimentally to be optimal for many of the enzymatic pathways involved in fibroblast proliferation, collagen synthesis, phagocytic (antibacterial) activity, angiogenesis (new blood vessel formation) and growth factor signaling transduction in wound repair. For more information, refer to the “How Oxygen Works in Wound Healing” guidance document.¹



Supplemental Oxygen Rapidly Raises Tissue Oxygen Levels

Oxygen therapies have been shown to rapidly raise oxygen levels in the wound bed, in both clinical and preclinical settings, when pure oxygen is applied directly to the surface of a moist wound at near-atmospheric pressures (not hyperbaric). Preclinically, pure oxygen applied to an open wound has been shown to increase the pO_2 of the superficial wound tissue in pigs³. In this study, an increase of pO_2 from less than 10 mmHg to 40 mmHg at a depth of 2 mm in the center of the wound bed was observed in as little as 4 minutes using an implanted probe.

4x pO_2 Level Increase within 4 minutes at 2 mm Depth

How CDO Works

How CDO Differs from Topical (TO, TWO) and Hyperbaric Oxygen (HBO)

There are three primary different methods of oxygen-based therapies that are used to treat wounds: Hyperbaric Oxygen, Topical Oxygen and Continuous Diffusion of Oxygen.⁴ All three technologies are similar in that they use pure oxygen as an aid to wound healing. Hyperbaric Oxygen Therapy is used to treat a patient systemically with pure oxygen at elevated pressures. Topical Oxygen Therapy is used to treat an area directly surrounding a patient's wound using pure oxygen at pressures slightly above atmospheric. Both **HBO & TO are intermittent**, only providing treatment for a relatively short period of time (typically **90 minutes per day**, 4 or 5 days per week), which means that the wound only receives supplemental oxygen for a few hours a day. Furthermore, neither of these technologies allows for patient mobility during treatment and can require significant time and expense associated with travel and preparation time for the patient.

CDO Therapy offers several breakthroughs in oxygen therapy in that it:



Provides continuous oxygen therapy, which is about 25x the therapy time of competing intermittent technologies



Is lightweight (six ounces)



Is wearable, which enables full patient mobility and restoration of lifestyle



Is rechargeable



Is silent



Incorporates continuous monitoring of oxygen flow rates and pressures to ensure efficacious delivery of oxygen

Table 1. Advantages of CDO

| Modality | Continuous Diffusion of Oxygen Therapy (CDO) | Topical Oxygen Therapy ^A (TO) | Hyperbaric Oxygen Therapy (HBO) |
|---------------------------------|----------------------------------------------|------------------------------------------|---------------------------------|
| Treatment at Home | YES | Yes ^B | No (travel to facility) |
| Wearable, 24/7 Patient Mobility | YES | No (patient immobile 90 min) | No (patient immobile 90 min) |
| Complete System with Dressings | YES | No (additional \$\$) | No (additional \$\$) |
| Direct Wound Oxygenation | YES | Yes ^C | No (min TCOM req'd) |
| Continuous Wound Oxygenation | YES | No (only ~90 min/day) | No (only ~90 min/day) |
| Absence of Fire Hazard | YES | No (high flow oxygen) | No (high flow oxygen) |
| Battery Operated | YES | No (uses 600-1300W, heat) | No (high power) |

Notes: A - also referred to as Topical Hyperbaric Oxygen Therapy (THOT) or Topical Wound Oxygen (TWO) therapy

B - can be treated at home, yet patient immobile for an hour and a half during treatment

C - treatment typically treats portion of limb, not just wound: limb may be constricted

CDO



TOT



HBO



CDO Therapy continuously diffuses pure oxygen into an oxygen-compromised wound to significantly accelerate wound healing while maintaining a moist wound healing environment, maintaining patient mobility and significantly reducing costs. CDO is essentially moist wound therapy with the added benefit of a continuous supply of oxygen directly to the tissue.

How CDO Works

Evidence Supporting CDO

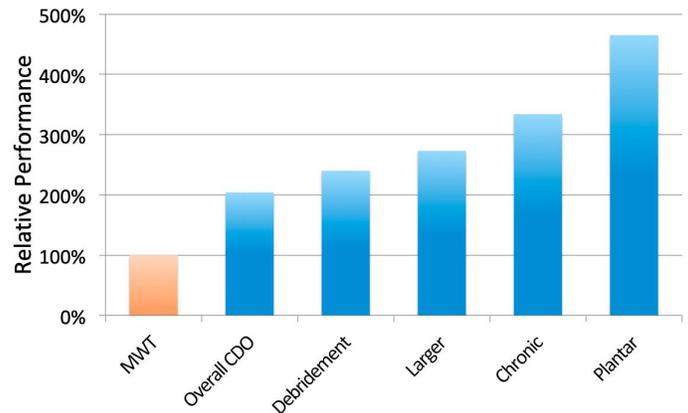


Multicenter DFU Study^{7,8,9}

Results from a Level 1A Diabetic Foot Ulcer clinical trial involving 146 patients across 34 sites show Continuous Diffusion of Oxygen (CDO) therapy to be statistically significant compared to a placebo arm. The rigor of this study is rare in the medical device world: it is a fully-blinded, prospective, randomly-controlled trial with a placebo and an active arm. Both arms received identical treatment (device, dressings, etc.) and the devices were functional in both arms. However, the oxygen did not flow to the wound in the placebo arm. In essence, this is on par with a pharmaceutical trial where the patients and clinicians do not know the treatment arm. CMS cited the study design as the "Gold Standard" for how studies should be designed.

A significantly higher proportion of people, more than twice as many (204%), healed in the active CDO arm compared to sham (46% vs 22%, P = .016). Frequent debridement increased the relative performance to 240% (51% vs 21%, P = 0.006). The relative performance became greater as wounds increased in size (273%), were more chronic (334%) and were weight bearing (plantar, 465%). Patients with CDO experienced significantly faster rates of closure relative to the placebo (P < .001), with the time to 50% wound closure being almost halved with CDO.

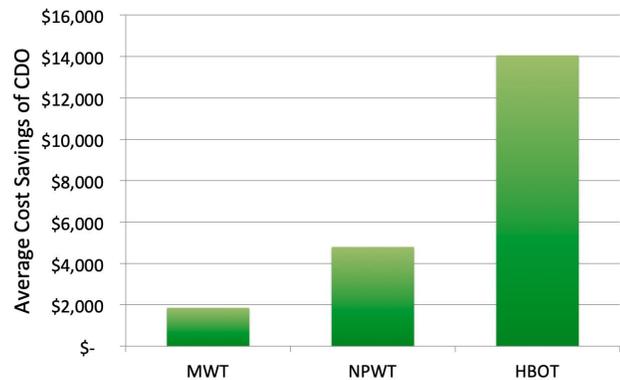
Performance of CDO Relative to MWT



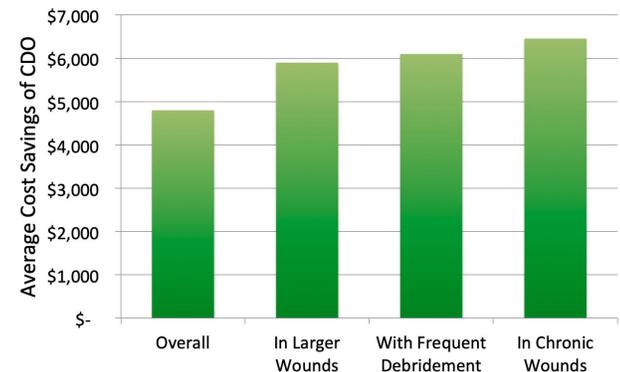
Economic Evaluation Study⁶

This study used published data to compare the outcomes of CDO therapy versus moist wound therapy (MWT), negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy (HBOT), with the focus primarily on NPWT as the primary standard of comparison, and report on cost savings and impact on quality life years. The model predicted that continuous diffusion of oxygen would cost \$4,800 less compared to negative pressure wound therapy with a slight increase in quality-adjusted life (extension of life). Lower cost and improved outcomes were observed in most scenario analyses (87% of cost analyses and 90% of quality-adjusted life analyses). The results of this economic evaluation show that CDO therapy should reduce health care economic burden with a modest increase in quality of life outcomes. Authors state that health care decision-makers should consider the inclusion of CDO for the treatment of DFUs.

Cost Savings of CDO vs. Other Therapies



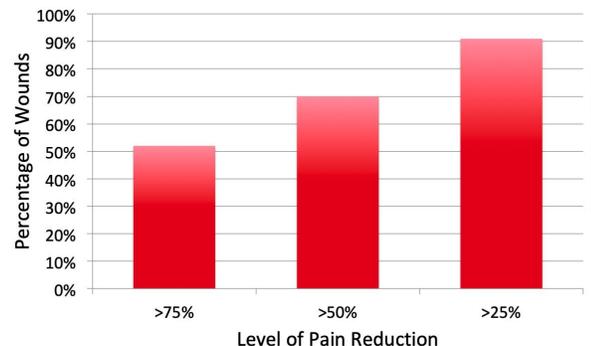
Cost Saving of CDO vs. NPWT



Pain Reduction Study¹¹

Results from a prospective trial of 20 patients to investigate reduction in pain in patients with 23 chronic lower extremity ulcers found that subjects experienced wound associated pain relief quickly after starting CDO: over half the patients experienced at least a 75% reduction in pain relief by the first follow-up visit (median of 4 days) and over 90% had noticeable pain reduction (>25%) by the first follow-up visit. All subjects (100%) experienced complete pain relief regardless of wound closure rate. Multiple subjects reported complete pain relief within hours of application of CDO. Subjects also reported being able to cease using narcotics with CDO.

Pain Relief with CDO at First Visit

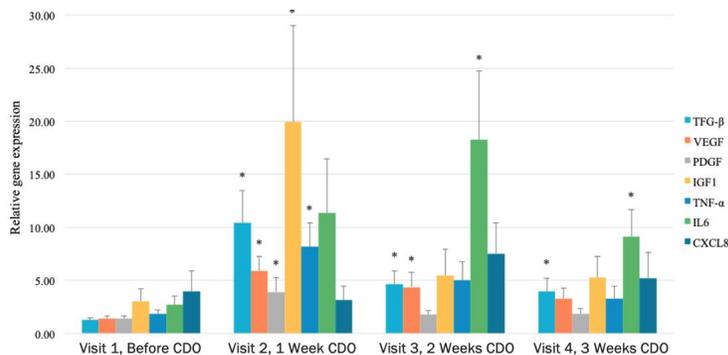


How CDO Works



Growth Factors, Cytokines & Perfusion: 20 Patients¹⁰

A prospective study of 20 patients investigating inflammatory cytokines (IL-6, IL-8, TNF- α), growth factors (VEGF, PDGF, IGF, TGF- β), perfusion changes peripheral the wound bed, changes in, and reduction in bioburden in a 3 week timeframe. Results showed significant increases in cytokines, growth factors and TCOM one week after application of CDO. Growth factors significantly increased between 280% to 820% in the first week. Several cytokines increased over 400% in the first two weeks and then decreased. Significant increases in TCOM indicate increased oxygen perfusion in wound periphery. Over half the wounds healed at least 50% in 3 weeks.



Clinical Registry

These results are bolstered by those from our post-market surveillance registry that demonstrates a success rate of 74% in 59 days in the field for a wide variety of wounds. These wounds range from small, persistent ulcers to large Stage IV ulcers and include dehisced surgical wounds, large venous ulcers, and acute surgical incisions, to name a few. It is important to note that this registry success rate is on very difficult wounds that have already been unresponsive to other advanced therapies such as NPWT and HBO and had been open for an average of 359 days (as a new technology, CDO is typically first tried on challenging, unresponsive wounds). More details of the current registry results can be found on our website (eo2.com).



Toe Ulcer Closure & Patient Compliance: 20 Patients¹²

A retrospective analysis on the impact of CDO in chronic toe ulcer healing for 20 patients showed an overall success rate (full closure) of 74% on wounds that were unresponsive to other therapies. The author highlighted a chief benefit being that of high patient compliance (95%), which he attributed to the device's ease of use, the noticeability of improvement within a short period of time, and the reduction of pain.



Ulcers in Veterans Healthcare with Tissue/Skin Substitutes: 25 Patients¹³

Another retrospective analysis of 25 patients in a Veteran's Healthcare Administration environment showed 68% full closure, both as a stand-alone and adjunctive therapy. The author found that CDO improves wound healing potential, including in wounds receiving advanced tissue/skin substitute applications.



Prospective RCT with MWT Control Group: 9 CDO & 8 MWT Patients¹⁴

A prospective, randomized clinical trial of CDO versus MWT followed 17 patients (9 CDO, 8 MWT) for 4 weeks and found significant differences in wound volume reduction. The CDO group had an average volume reduction of 87%, whereas the MWT group had an average volume reduction of 46% ($P < .05$).



Prospective RCT with MWT Control Group in DFUs: 9 CDO & 9 MWT Patients¹⁵

Significant differences in the healing rate of CDO as compared to MWT were recently demonstrated in a prospective, randomized pilot clinical trial with 9 patients receiving MWT and 9 receiving CDO. The study focused on smaller DFUs (approx. 1.5 cm²), UT Grade I-III, over an 8-week period. CDO was shown to close 90% of the wounds by the end of the study, whereas the MWT group experienced 30% closure. The authors also noted significantly faster wound closure rates in the CDO arm and more noticeable differences from CDO in the more advanced ulcers (Grades II and III).



Pain Reduction and Wound Closure in Venous Ulcer: Case Study¹⁶

For a patient who served as her own control during CDO therapy treatment, her pain levels were reported as high as 8/10 on a visual analogue score (VAS), with pain medications taken as needed, during the 5-month duration of the ulcer prior to CDO therapy. After 20 days of CDO therapy, the patient reported a pain level of 2/10 and was no longer taking pain medications. At this time, CDO therapy was temporarily discontinued since the patient was leaving town for a holiday. Six days later the patient returned to the clinic with a pain level of 10/10 and reported difficulty sleeping. CDO therapy was reapplied and, within three days, the patient's pain level was controlled (VAS 2/10) and she ceased taking narcotics.

How CDO Works



Pain Reduction in Uncontrolled Study of Venous Ulcers: 10 Patients¹⁷

In an uncontrolled, nonrandomized study of 10 patients with venous ulcers, CDO therapy was reported to significantly ($P < .009$) reduce pain in a six-week period. The corresponding mean reduction in wound size was 58.9%.

NOTE: Refer to the Clinical Research Summary for most up-to-date overview of EO2 clinical research.

REFERENCES

- ¹ EO2 White Paper: How Oxygen Works in Wound Healing. p/n 690024 (current revision)
- ² P. W. Atkins, Physical Chemistry, 6th ed., Oxford University Press, 1998. Henry's law constant for oxygen taken from Table 7.1 on page 174.
- ³ Fries, RB, Wallace, WA and Roy, S. Dermal excisional wound healing in pigs following treatment with topically applied pure oxygen. *Mutat Res.* 2005, 579, pp. 172-81.
- ⁴ Howard MA, Asmis R, Evans KK, Mustoe TA. Oxygen and wound care- A review of current therapeutic modalities and future direction. *Wound Rep Reg.* 2013; 21(4):503-511.
- ⁵ Kimmel HM, A Comparison of Continuous Oxygen Therapy to Topical Oxygen, *Foot & Ankle Quarterly*, Winter 2019, 30(4) 203-209.
- ⁶ Chan BCF, Campbell, KE, An economic evaluation examining the cost-effectiveness of continuous diffusion of oxygen therapy for individuals with diabetic foot ulcers. *Int Wound J.* 2020;1-18. <https://doi.org/10.1111/iwj.13468>
- ⁷ Niederauer MQ, Michalek JE, Armstrong DG. A Prospective, Randomized, Double-Blind Multicenter Study Comparing Continuous Diffusion of Oxygen Therapy to Sham Therapy in the Treatment of Diabetic Foot Ulcers. *J Diabetes Science Tech.* 2017, Special Issue, 1-9. <https://dx.doi.org/10.1177%2F1932296817695574>
- ⁸ Niederauer MQ, Michalek JE, Liu Q, Papas, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. *J Wound Care* 27(9):s30-s45 2018.
- ⁹ Lavery LA, Niederauer MQ, Papas KK, Armstrong DG, Does Debridement Improve Clinical Outcomes in People with DFU Ulcers Treated with CDO? *Wounds* 31(10):246-251 2019. Epub 2019 July 31
- ¹⁰ Lavery LA, Killeen AL, Farrar D, Akgul Y, Crisologo PA, Malone M, Davis KE. The effect of continuous diffusion of oxygen treatment on cytokines, perfusion, bacterial load, and healing in patients with diabetic foot ulcers. *Int Wound J.* 2020;1-10. <https://doi.org/10.1111/iwj.13490>
- ¹¹ Bowen J, Ingersoll MS, Carlson R. Effect of CDO on Pain in Treatment of Chronic Wounds. *Wound Central* 2(4);186-195 2018.
- ¹² Urrea-Botero G. Can continuous diffusion of oxygen heal chronic toe ulcers? *Podiatry Today.* 2015;28(10).
- ¹³ Couture M. Does continuous diffusion of oxygen have potential in chronic diabetic foot ulcers? *Podiatry Today.* 2015;28(12).
- ¹⁴ Driver VR, Yao M, Kantarci A, Gu G, Park N, Hasturk H. A prospective, randomized clinical study evaluating the effect of transdermal continuous oxygen therapy on biological processes and foot ulcer healing in persons with diabetes mellitus. *Ostomy Wound Manage.* 2013;59(11):19-26.
- ¹⁵ Yu J, Lu S, McLaren A, Perry JA, Cross KM. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. *Wound Rep Regen.* 2016;24(6):1066-1072.
- ¹⁶ Brannick B, Engelthaler M, Jadzak J, Wu S. A closer look at continuous diffusion of oxygen therapy for a chronic, painful venous leg ulcer. *Podiatry Today.* 2014;27(11).
- ¹⁷ Mani R. Topical oxygen therapy for chronic wounds: a report on the potential of Inotec, a new device for delivering oxygen to chronic wounds. *J Wound Technol.* 2010;9:1-4.
- ¹⁸ Lowell DL, Nicklas B, Weeily W, Johnson F, Lyons MC. Transdermal continuous oxygen therapy as an adjunct for treatment of recalcitrant and painful wounds. *Foot Ankle Online J.* 2009;2(9):4.
- ¹⁹ Hirsh F, Berlin SJ, Holtz A. Transdermal oxygen delivery to wounds: a report of 6 cases. *Adv Skin Wound Care.* 2008;22:20-24.