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PHARMACOLOGY

Using Hyperbaric Oxygen to Treat Diabetic Foot Ulcers: Safety and Effectiveness

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Hyperbaric oxygen therapy is no longer considered a "fringe" treatment. A quick Internet search shows that hyperbaric oxygen therapy is an increasingly popular treatment option for a variety of injuries and disorders. Hyperbaric treatment centers are appearing even in relatively small communities throughout the United States, Canada, and Europe. The primary mechanism of action of hyperbaric oxygen—enhancement of tissue oxygenation—makes this therapy particularly useful for the resolution of hypoxic conditions such as traumatic crush injuries, necrotizing fasciitis, gas gangrene, carbon monoxide poisoning, and anemia due to extensive blood loss. It has also been used with various degrees of success to treat many other disorders, including migraine headaches, morbidity due to radiation damage, multiple sclerosis, cerebral palsy, ulcerative colitis, and anorexia nervosa.

Approximately 17 million persons in the United States (6.2% of the population) have diabetes, and an additional 1 million cases are diagnosed annually.[1,2] The prevalence of diabetes among adults is expected to increase to 9% by 2025.[3] Among patients with diabetes, 60% to 70% have some degree of nerve damage, termed diabetic neuropathy.[4] Poor glycemic control, diabetic neuropathy, and peripheral vascular disease, in conjunction with comorbid foot trauma, can result in the formation of a diabetic foot ulcer. Diabetic foot ulcers develop at some point in approximately 15% of patients with diabetes.[5] Sequelae of the ulcers may include infection, gangrene, osteomyelitis, and ultimately amputation.[6,7] More than half the patients undergoing lower limb amputation in the United States have diabetes.[8] More than 80% of amputations in patients with diabetes are preceded by nonhealing foot ulcers.[9]

Diabetic foot wounds are defined as any break in the cutaneous barrier, usually extending through the full thickness of the dermis.[10] Diabetic foot ulcers can be generally classified as either neuropathic or ischemic[11] (Table 1). A diabetic foot wound that remains unhealed for 1 month is associated with poor outcomes, including osteomyelitis, gangrene, and amputation.[10]

Diabetic foot ulcers are associated with significant morbidity and mortality. The risk of death is 2.4 times greater for patients with

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Table 1 Distinguishing characteristics of neuropathic and ischemic foot ulcers[12]

Characteristic	Neuropathic ulcers	Ischemic ulcers
Patient's age	Younger (fifth to sixth decades)	Older (seventh to eighth decades)
Pedal deformities	Hammer or claw toes, Charcot deformity	None
Skin	Warm with good color	Cool, often red
Ulcer features	Wet with drainage, often located on pressure points of plantar surface	Dry black eschar, often located on dorsal surface of feet and toes
Pulses	Intact	Diminished to absent
Pain	Often absent	Often painful

diabetes who have foot ulcers than for patients with diabetes who do not.[12] Further, diabetic foot complications are the most frequent cause of hospitalization in patients with diabetes, accounting for up to 25% of all admissions among patients with diabetes.[13] The goals of therapy include improvement in function, infection control, and avoidance of amputation.

Table 2 Established risk factors for the development of diabetic foot ulcers[8,12-15]

Risk factor	Proposed rationale
Severe diabetes, longer duration of diabetes	Disease length and severity associated with greater likelihood for peripheral vascular disease and neuropathy
History of foot ulcer and amputation*	Related to disease severity
Greater height and weight*	Increased pressure on feet Decreased oxygen delivery
Sensory neuropathy* (inability to perceive 5.07 monofilament at 1 or more sites on the feet and absence of Achilles tendon reflex)	Decreased sensation, thereby increasing the chances of foot injury
Poor pedal perfusion*	Decreased oxygen delivery to the feet
Reduced skin oxygenation in the lower limbs*	Decreased oxygen delivery to the feet
Poor vision*	Associated with diabetic retinopathy, related to length of disease and poor glycemic control
Foot deformity (specifically hammer/claw toe and Charcot deformities)*	Increased pressure on feet Decreased oxygen delivery
Insulin use	Related to disease severity
Diminished vibratory sensation	Indicative of sensory neuropathy

*Independent risk factors for foot ulcers in patients with diabetes.

PATHOPHYSIOLOGY

Diabetic foot ulcers are thought to result from multiple pathophysiological mechanisms.[11] Risk factors for diabetic foot ulcers are delineated in Table 2.[8,12-15] The occurrence of diabetic neuropathy is the factor most consistently associated with foot ulcers.[7] The decrease in sensory input from the lower limbs due to neuropathy increases the likelihood of foot injury and reinjury, with little awareness on the part of the patient. Pedal injury can come from sources of heat or cold as well as poorly fitting shoes. Once the foot is injured, the ulcer often becomes chronic because of reinjury and hypoxia. Microvascular and macrovascular complications of diabetes diminish the blood flow to the extremities, limiting the gradient of oxygen pressure in the tissue (Figure 1). Wound healing involves a complex series of events initiated by chemoattraction of macrophages, production of growth factors, fibroblast hyperplasia, and production of collagen. Oxygen is an essential controlling factor for bacterial killing, fibroblast growth, angiogenesis, collagen synthesis, epithelialization, and other biochemical processes essential for wound healing (Table 3).[16-19] Ischemia may contribute to 30% to 40% of foot ulcers.[7]

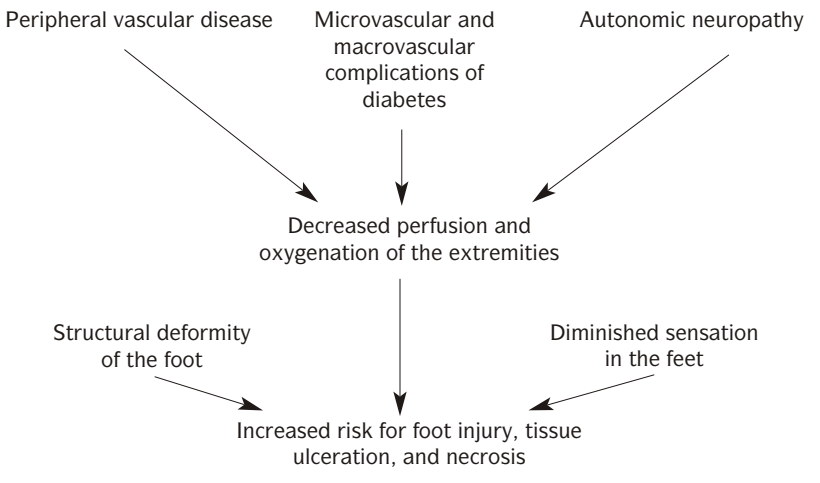


Figure 1 Pathophysiological processes involved in the development of diabetic foot ulcers.

Table 3 Role of oxygen in wound healing[16-19]

Angiogenesis (neovascularization) occurs most rapidly when it proceeds from areas of high oxygen tension to low oxygen tension
The rate of hydroxylation processes required for polymerization and cross-linkage of collagen depends on the local partial pressure of oxygen
Modification of collagen by fibroblasts requires a high partial pressure of oxygen
Decreased oxygen tension increases the likelihood of infection and necrosis
The beneficial effects of increasing oxygen tension and antibiotic therapy are additive in skin lesions
Increasing oxygen increases the synthesis of hyaluronic acid and proteoglycans by fibroblasts
Hypoxia favors the growth of anaerobic bacteria and suppresses killing of aerobic bacteria
Oxygen tension is a major controlling factor in epithelialization
Oxygen is required for the oxidative killing mechanism of leukocytes

Standard care of diabetic foot ulcers includes pressure reduction (via bed rest, casts), debridement of devitalized wound tissue, moist dressings, and management of infection with topical or systemic antibiotics.[7,10,20,21] Unfortunately, none of these therapies effectively increases oxygen delivery to the affected tissue. Hyperbaric oxygen therapy may be a noninvasive alternative to surgical revascularlization for the treatment of diabetic foot ulcers.

PRINCIPLES OF HYPERBARIC OXYGEN THERAPY

In hyperbaric oxygen therapy, patients breathing 100% oxygen are placed in a chamber pressurized to 2 to 3 times atmospheric pressure. This pressure is equivalent to diving to approximately 15 m (50 ft) in seawater. In use since 1943, hyperbaric oxygen therapy is considered the treatment of choice for decompression sickness and severe carbon monoxide poisoning. The Undersea and Hyperbaric Medical Society has identified 13 diseases as approved indications for hyperbaric oxygen therapy, including gas gangrene, crush injuries, and enhancement of healing in selected problem wounds.[22]

Two systems for hyperbaric oxygen therapy are currently available: monoplace and multiplace chambers. In each instance, patients breathe pure oxygen while exposed to barometric pressures greater than normal atmospheric pressure. Monoplace chambers are hollow cylinders compressed with pure oxygen that allow 1 patient to lie supine during hyperbaric therapy. Multiplace chambers accommodate up to 6 patients at once; each patient is given an individual breathing source of 100% oxygen via a hood or mask[19] (Figure 2). Hyperbaric oxygen given in this manner, often referred to as systemic hyperbaric oxygen therapy, should not be confused with topical oxygen therapy or pure oxygen inhaled at ambient atmospheric pressure.

In hyperbaric oxygen therapy, the physical properties of gases under pressure are taken advantage of to expose tissues to greater concentrations of oxygen than would otherwise be possible.[23]

Figure 2 Multiplace chamber at the Bannock Hyperbaric Oxygen Therapy Center in Pocatello, Idaho.

Boyle's Law

At constant temperature, the volume of a gas is inversely proportional to the pressure.

$$V = 1/P$$

Henry's Law

The partial pressure of a gas dissolved in a liquid is equal to the partial pressure of that gas exerted on the surface of the liquid, so

Po_2 in blood = Po_2 in the hyperbaric chamber

P indicates pressure; Po_2, partial pressure of oxygen; V, volume.

Figure 3 Laws of physics relevant to hyperbaric oxygen therapy.

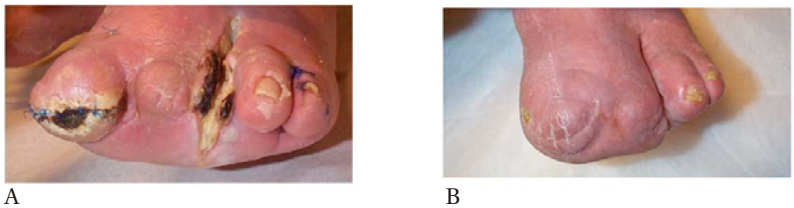
Boyle's law asserts that the volume of a quantity of gas is inversely proportional to the ambient pressure surrounding it. Henry's law states that the amount of gas that can dissolve in a liquid at a given temperature is proportional to the partial pressure of that gas (Figure 3). Exposure to 2 to 3 times normal atmospheric pressure in a hyperbaric chamber concentrates gases the patient is exposed to by a factor of 2 to 3 (Boyle's law) and increases the amount of dissolved gases in the patient's bloodstream by a factor of 2 to 3 (Henry's law).[24] Increasing the partial pressure of oxygen has essentially no effect on the amount of oxygen bound to hemoglobin because hemoglobin is already approximately 97% saturated at sea level in room air. However, exposure to 3 atm of pressure increases the amount of oxygen dissolved in the plasma from 0.32% to 6.8% by volume, a quantity great enough to sustain life even in the total absence of hemoglobin.[25] Therefore, treatment with 100% oxygen during hyperbaric therapy essentially hypersaturates the bloodstream with oxygen, allowing tissues to achieve levels of oxygenation that would otherwise be impossible. Under hyperbaric conditions, the diffusion distance of oxygen from the vasculature to wound tissue increases by a factor of 2 to 3.[19] The partial pressure of oxygen in normal tissue is approximately 40 mm Hg. The partial pressure of oxygen in hypoxic wounds increases from 10 to 20 mm Hg under normobaric conditions to 200 mm Hg after hyperbaric oxygen therapy.[26,27] Figures 4A and 4B depict typical results of hyperbaric oxygen therapy.

CLINICAL TRIALS

Ten studies[16,28-36] have been done to date to assess the effectiveness of hyperbaric oxygen therapy in the treatment of 989 patients with diabetic foot ulcers (Table 4). In all cases, hyperbaric oxygen therapy was used as an adjunct to standard wound care.

When all the trials that used foot amputation as a primary outcome variable are considered, amputation was prevented in from 82% to 95% of patients in the groups receiving hyperbaric treatment. When data from all controlled trials (both retrospective and prospective) are combined and averaged, hyperbaric oxygen therapy resulted in a mean limb salvage rate of 89%, compared with prevention of amputation in 61% of patients who received conventional therapy alone. This difference translates to a relative risk reduction of 0.74 attributable to hyperbaric oxygen therapy. In other words, the patients with diabetes in these studies who underwent adjunctive hyperbaric treatment had approximately one fourth the risk of limb amputation compared with the patients who received conventional therapy only. On average, the calculated number of patients who must receive hyperbaric oxygen therapy in order to prevent 1 amputation (ie, the number needed to treat) is 3.6.

Despite limitations in the power of the studies because of the relatively small sample sizes in most instances, hyperbaric



A B

Figure 4 Right foot of a 72-year-old man before hyperbaric oxygen therapy (A) and 6 months later after 100 hyperbaric oxygen treatments (B).

Table 4 Clinical trials assessing the usefulness of hyperbaric oxygen therapy (HBOT) for the treatment of diabetic foot ulcers

Study	Type of study	No. of subjects	Inclusion criteria	Atmospheres of pressure
Baroni et al, 1987[28]	Prospective, nonrandomized, controlled clinical trial	28 (18 HBOT, 10 conventional therapy)	Diabetics with necrotic foot ulcers	2.5-2.8 (2.5-2.8 × 10^5 Pa)
Cianci et al, 1988[29]	Retrospective, nonrandomized, uncontrolled	19	Patients with diabetes and serious ulcers of the lower extremity refractory to standard therapy for at least 2 months	2.0 (2.0 × 10^5 Pa)
Oriani et al, 1990[30]	Prospective, nonrandomized, controlled clinical trial	80 (62 HBOT, 18 conventional therapy)	Patients with diabetes and necrotic foot ulcers	2.5-2.8 (2.5-2.8 × 10^5 Pa)
Wattel et al, 1991[31]	Retrospective, nonrandomized, uncontrolled	59	Patients with diabetes and foot ulcers	2.5 (2.5 × 10^5 Pa)
Doctor et al, 1992[32]	Prospective, randomized, controlled clinical trial	30	Patients with diabetes and chronic foot ulcers	3.0 (3.0 × 10^5 Pa)
Oriani et al, 1992[33]	Retrospective, nonrandomized, uncontrolled	151	Patients with diabetes and gangrenous foot ulcers	2.5-2.8 (2.5-2.8 × 10^5 Pa)
Faglia et al, 1996[34]	Prospective randomized controlled clinical trial	68 (35 HBOT, 33 conventional therapy)	Patients with diabetes and severe foot ulcers	2.2-2.5 (2.2-2.5 × 10^5 Pa)
Zamboni et al, 1997[35]	Prospective, nonrandomized, controlled clinical trial	15 (10 HBOT, 5 conventional therapy)	Patients with diabetes and chronic foot ulcers	2.0 (2.0 × 10^5 Pa)
Stone et al, 1997[37]	Retrospective, controlled, chart review	501 (119 HBOT, 382 conventional therapy)	Patients with diabetes and ischemic foot ulcers	NR
Kalani et al, 2001[36]	Prospective, randomized, controlled clinical trial	38 (17 HBOT, 21 conventional therapy)	Patients with diabetes and chronic ischemic foot ulcers	2.5 (2.5 × 10^5 Pa)

Table 4 *Continued*

Duration of each HBOT treatment, minutes	Mean No. of HBOT treatments	Study end point(s)	Results (HBOT vs control)	Conclusions
90	34	Percentage of patients with ulcer healing Percentage of patients avoiding amputation	89% vs 10% (statistics not reported) 89% vs 60% ($P < .001$)	HBOT superior
90 to 120	38	Percentage of patients avoiding amputation	89%	
Not reported	72	Percentage of patients avoiding amputation	95% vs 67% ($P < .01$)	HBOT superior
90	29	Percentage of patients avoiding amputation	88%	
45	4	Mean length of stay (days) No. of wound cultures showing growth Percentage of patients avoiding major amputation	41 vs 46, not significant 3 vs 12 ($P < .05$) 87% vs 53% ($P < .05$)	HBOT superior
90	40	Complete wound healing	86%	
90	38	Percentage of patients avoiding amputation	91% vs 67% ($P = .02$; relative risk, 0.26)	HBOT superior
120	NR	Percentage change in surface area of ulcer	Wound surface area significantly reduced in the HBOT group ($P < .05$)	HBOT superior
NR	NR	Percentage of patients avoiding foot amputation	82% vs 53% ($P < .002$)	HBOT superior
90	40 to 60	Percentage of patients avoiding foot amputation	88% vs 67% (statistics not reported)	HBOT superior

oxygen treatment resulted in a significant reduction in amputation rates in all comparative trials. Thus, adjunctive hyperbaric oxygen therapy is superior to conventional ulcer therapy. However, most of the patients studied in these trials had necrotic foot ulcers that were refractory to standard therapy. Also, most of the subjects had ulcers that were primarily ischemic. These facts limit the applicability of these results to those patients with diabetes who have ischemic ulcers complicated by profound peripheral vascular disease. Whether hyperbaric oxygen therapy will be as effective in patients with diabetes who have foot lesions that are predominantly neuropathic remains to be determined.

SAFETY

Absolute contraindications to hyperbaric oxygen therapy include untreated pneumothorax and treatment with certain chemotherapeutic agents (doxorubicin, bleomycin, and cisplatin) or disulfiram.[37] Relative contraindications include seizure disorders, emphysema, upper respiratory tract infections, and a history of thoracic surgery, spontaneous pneumothorax, or surgery for otosclerosis.[37]

In general, if pressures do not exceed 3 atm (3.04×10^5 Pa) and the length of therapy is less than 2 hours, hyperbaric oxygen therapy is considered safe.[38] Other than pressure on the ears (easily managed by decongestants, yawning, or the Valsalva maneuver), the most common adverse effect is a reversible nearsightedness. Myopia associated with hyperbaric therapy usually resolves completely approximately 6 weeks after discontinuation of the therapy. The remaining adverse effects are rare; these may include ear, sinus, or tooth pain from changing pressures of gases in the chamber, an occasional dry cough, a temporary burning sensation under the sternum, and feelings of claustrophobia related to being in a restricted space. A very slight increase in seizure risk has been noted, particularly in patients with a high fever or history of epilepsy.[37]

COST

Hyperbaric oxygen therapy is expensive, but the costs are reimbursable under Medicare and many insurance plans. A 30-session protocol typically costs more than $9000. However, this expense should be viewed in light of the total costs associated with therapeutic failure: the costs for osteomyelitis, amputation, and subsequent rehabilitation.

As our population ages, the prevalence of lower extremity amputations in patients with diabetes continues to increase, accounting for nearly $2 billion and an estimated 2600 patient-years of hospital stay annually in the United States alone.[39] In a recent analysis, Ramsey et al[6] determined that the overall economic impact attributable to a newly diagnosed diabetic foot ulcer was $27 987 for a 40- to 65-year-old man the first 2 years after diagnosis. The cost for pedal amputation ranges from $18 760 to more than $40 000.[29,40,41] These figures do not include rehabilitation expenses, which range from $40 000 to $50 000.[42]

Management of diabetic ulcers of the lower extremity in inpatients cost Medicare an average of $14 400 per episode in 1996.[43] Improving the healing rate would obviously save healthcare dollars. It remains to be seen if the rather substantial costs of hyperbaric oxygen therapy will ultimately result in overall cost savings by avoiding the expenses of amputation and rehabilitation. However, the relatively low number needed to treat of 3.6 suggests that spending $32 400 on hyperbaric oxygen therapy would prevent 1 amputation and the resultant rehabilitation, which would cost approximately $90 000. These dollar figures do not take into account the significant psychological impact of amputation. Thus, it seems that hyperbaric treatment of ischemic foot wounds in patients with diabetes would be cost-effective.

CONCLUSION

Foot ulcers are a significant source of morbidity, mortality, and diminished quality of life for patients with diabetes. Ulcer development is often due to a combination of diabetic neuropathy and peripheral vascular disease, which decreases the supply of oxygen to the affected extremity. Hypoxia can cause otherwise trivial lesions to progress rapidly to infection, gangrene, and limb

amputation. Hyperbaric oxygen therapy increases the amount of oxygen dissolved in the plasma, allowing tissues to achieve levels of oxygenation that would otherwise be impossible.

Hyperbaric oxygen therapy is adjunctive treatment and will never replace good wound care.[19] The American Diabetes Association recommends hyperbaric oxygen therapy as adjunctive treatment for severe and limb- or life-threatening wounds unresponsive to other treatments, particularly if ischemia is present that cannot be corrected by vascular surgery.[10] A review of the available literature reveals that the mean limb salvage rate is 89% after hyperbaric oxygen therapy, compared with 61% after conventional treatment. The importance of oxygen in wound healing was highlighted in the study by Kalani et al,[36] in which the mean trans cutaneous oxygen tension in the wound was significantly higher in patients who healed than in those patients in whom hyperbaric therapy was unsuccessful and who ultimately lost a limb. Albeit costly, hyperbaric oxygen therapy is a reasonable, cost-effective adjunct to standard wound care for patients with ischemic diabetic foot ulcers that have not healed after 1 month, especially for patients with significant vascular disease affecting the lower extremity. ✠

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