Hyperbaric Oxygen Therapy for Diabetic Foot Ulcers

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ABSTRACT
Foot ulcers are a common and devastating complication of diabetes. Many patients with diabetic foot ulcers experience significant disability and ultimately require amputation. Despite attentive management with multiple modalities including surgical debridement, relief of pressure, and other standard measures, many diabetic foot ulcers persist as chronic, non-healing wounds. Hyperbaric oxygen (HBO) therapy is an effective adjunct to standard modalities for the treatment of diabetic foot ulcers. HBO therapy increases oxygen tension in tissues, thereby supporting physiologic wound healing while inhibiting the growth of anaerobic organisms. Randomized clinical studies confirm that HBO therapy accelerates wound healing and decreases the need for amputation in patients with diabetic foot ulcers.

INTRODUCTION
Though diabetics are prey to many foot disorders, including infection, neuropathy, Charcot arthropathy, and peripheral arterial disease,1 foot ulcers are the most common and characteristic diabetic foot wound, and they remain a significant source of morbidity and disability. Ulcers are defined as any break in the cutaneous barrier and usually extend through the full thickness of the dermis.

Americans with diabetes numbered 20.8 million in 2005, and the prevalence of diabetes in the United States is expected to increase about 60% over the next 20 years. The annual prevalence of diabetic foot ulcers varies among populations and ranges from 2% to 10%. An estimated 15% of patients with diabetes will develop a foot ulcer during their lifetime.2

Foot ulcers are a leading cause of hospitalization in patients with diabetes and account for billions of dollars in direct and indirect health care expenditures annually in the U.S. As many as 20% of patients with diabetes and foot ulcers will subsequently require an amputation, and foot ulcers precede about 85% of lower extremity amputations in persons with diabetes. About 67,000 diabetes-related amputations are performed each year in the U.S., and the mortality rate within 3 to 5 years of amputation is 50%.

All patients with diabetes are at risk for developing foot ulcers regardless of age, gender, symptoms, or adequacy of glycemic control. Factors associated with an increased risk of foot ulcers in patients with diabetes include neuropathy, foot deformity, limited joint mobility, trauma, ischemia, male sex, and previous history of ulceration.3 Screening tests can help identify patients at increased risk of diabetic foot ulceration and include neuropathy symptoms and disability scoring indexes, use of Semmes-Weinstein monofilaments, and measurement of vibration perception threshold and peak plantar foot pressures.4 Patients with diabetes at increased risk for foot ulceration may benefit from prophylactic interventions including education, prescription footwear, intensive podiatric care, and evaluation for surgical interventions.5

The management of diabetic foot ulcers is multifactorial and is based on a comprehensive clinical examination and an understanding of the underlying etiology.6,7 Common treatment options in patients with diabetic foot ulcers include mechanical and surgical debridement, pressure relief/off-loading, and the use of various dressings and topical agents designed to facilitate wound closure and promote re-epithelialization. Advanced care modalities for the treatment of diabetic foot ulcers include the use of growth factors, bioengineered tissues, electrical stimulation, ultrasound therapy, and negative pressure wound therapy.

Hyperbaric oxygen (HBO) therapy
HBO therapy is defined as breathing 100% oxygen at pressures higher than normal atmospheric pressure at sea level in a hyperbaric chamber. (1 ATM is 14.7 pounds per square inch (PSI), 1 kg per square centimeter, or 760 mm Hg.) Since oxygen has an important role in the physiology of wound healing, HBO therapy is a useful adjunct in the treatment of diabetic foot ulcers8,9 by helping to increase tissue oxygen tensions to levels that
promote wound healing, limit edema, and destroy certain anaerobic bacteria. HBO therapy is currently approved for a variety of tissue healing and other applications (Table 1).

**PATHOPHYSIOLOGY**

Peripheral neuropathy, a key factor in the development of diabetic foot ulcers, is already present in up to 10% of patients at the time their diabetes is diagnosed, and in nearly half of patients who have diabetes for 7 years or more. It is characterized by neuronal demyelination and atrophy, with a combination of sensory, motor, and autonomic deficits.

Diabetic foot ulcers commonly begin as a minor wound, often caused by ill fitting shoes, foreign bodies, improper nail trimming, or burns from hot bath water. The highest incidence of diabetic foot ulcers occurs at sites of previous ulceration. Ulceration may also result from moderate repetitive stress associated with walking or day-to-day activity, and is often preceded by a callus at the site of injury.

Sensory neuropathy diminishes perceptions of pain and pressure and predisposes to worsening of the initial injury and exacerbation of the inflammatory process. Autonomic system deficits contribute to chronic wound formation via inhibition of normal sweat and oil production, leaving the skin dry and nonelastic. Motor neuropathy may cause atrophy of intrinsic muscles and fibrosis resulting in unfavorable weight distribution and gait patterns, and increased risk of pressure-related ulceration.

Diabetes may also compromise healing of chronic wounds by causing abnormal cellular and inflammatory pathways, vascular disease, and tissue hypoxia. Chronic hyperglycemia may be toxic to macrophages and fibroblasts, and the accumulation of advanced glycosylation end products may adversely affect cytokine function, growth factor production, and extracellular matrix formation.

**Oxygen and Wound Healing**

The role of oxygen in wound healing is well established. Molecular oxygen serves as a nutrient to support the increased energy demand of regenerating tissues and is needed for replication of fibroblasts, mobility of macrophages, ingrowth of granulation tissue, and other key elements of wound healing. Oxygen administered under increased ambient pressure enhances in vitro phagocytosis in regions of limited perfusion by increasing local oxygen tension to levels consistent with normal phagocytic function. In addition, derivatives of oxygen commonly referred to as reactive oxygen species (ROS) appear to promote wound repair. Enzymes that convert oxygen to ROS are found in nearly every cell type in the wound microenvironment. At low concentrations, ROS may serve as cellular messengers that regulate a variety of events closely linked to wound repair including cell proliferation, angiogenesis, and synthesis of extracellular matrix.

Since oxygen is so important to wound healing, hypoxemia due to peripheral vascular disease (PVD) may be a contributing factor to the initial formation of diabetic foot ulcers. About 8% of patients with diabetes have PVD at the time of initial diagnosis, and its prevalence increases to 45% after 20 years. Impaired circulation may also inhibit delivery of leukocytes and antibiotics to the wound, and promote the growth of anaerobic organisms. In addition, aminoglycosides and other antibiotics depend on oxygen to function.

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**TABLE I. CURRENT APPROVED INDICATIONS FOR HBO THERAPY.**

- Air or gas embolism
- Carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning
- Clostridial myositis and myonecrosis (gas gangrene)
- Crush injury, compartment syndrome and other acute traumatic ischaeas
- Decompression sickness
- Enhancement of healing in selected problem wounds
- Exceptional blood loss (anemia)
- Intracranial abscess
- Necrotizing soft tissue infections
- Osteomyelitis (refractory)
- Delayed radiation injury (soft tissue and bony necrosis)
- Skin grafts and flaps (compromised)
- Thermal burns

*Source: Undersea and Hyperbaric Medical Society*
OVERVIEW OF HBO THERAPY

Administration of 100% oxygen at ambient pressure causes a 5-fold increase in the amount of dissolved oxygen in blood. HBO therapy – administration of 100% oxygen at 2 to 3 ATM – increases the dissolved oxygen in blood and tissues up to 20-fold, a level that is high enough to sustain life without any contribution from oxygen bound to hemoglobin.16

Hyperbaric chambers are classified by the National Fire Protection Association as Class A (multi-occupant) or Class B (single occupant). Both generally use compressed

Limb salvage in two diabetic patients was accomplished by utilizing multiple modalities including a course of hyperbaric oxygen. Plates A-C display progressive healing of an exposed Achilles tendon, and Plates D & E display healing of an infected foot.
100% oxygen as both the pressurization gas and the hyperbaric treatment gas.

a. Class A chambers are usually hard shelled structures made of steel and aluminum with view ports made of acrylic. Larger Class A chambers that accommodate multiple patients and medical staff operate at absolute pressures up to 6 ATM and patients typically breathe from individual masks which supply pure oxygen and remove the exhaled gas.

b. Class B hyperbaric chambers operate at pressures up to 2 ATM. Since the chamber is flooded with pure oxygen the solitary patient does not wear a mask.

c. Several portable topical “hyperbaric” chambers consisting of sleeves, boots, and pouches have been approved by the FDA as Class III devices for use in a physician’s office or clinic, or for self-administration at home. These systems provide a hermetic seal around a patient’s limb and apply humidified oxygen topically at a pressure slightly greater than 1 ATM. According to the Undersea and Hyperbaric Medical Society (UHMS), topical oxygen treatment should not be considered equivalent or identical to HBO therapy. The UHMS maintains that mechanisms of action or clinical study results for hyperbaric oxygen cannot and should not be co-opted to support topical oxygen since HBO therapy and topical oxygen have different routes and probably efficiencies of entry into the wound and their physiology and biochemistry are necessarily different.

**Inside the Chamber**

After a patient enters the hyperbaric chamber, the door is closed and sealed, and oxygen is circulated. The flow of oxygen leads to a gradual increase in internal chamber pressure, called compression. Some patients may experience a sense of fullness in their ears during the compression phase, which progresses at a variable rate that generally lasts from 10 to 15 minutes depending on the patient’s comfort and tolerance.

When the interior of the chamber reaches the prescribed pressure, the sensation of “fullness” in the ears usually ceases and the patient is free to rest, sleep, watch TV, listen to music, or chat with family members over the intercom. The interior of the chamber remains at room temperature during treatment.

The duration of single HBO treatments varies from 45 minutes for carbon monoxide poisoning to nearly 5 hours for some severe decompression disorders. Most protocols for the treatment of non-healing diabetic foot ulcers average 90 minutes for each of 20 to 30 treatments.

At the end of the treatment, the chamber pressure is gradually decreased. During the decompression phase, which generally lasts from 10 to 15 minutes, patients may experience a slight “popping” sensation in the ears, similar to the sensation associated with driving up a mountain or ascending in an airplane. Equalizing ear pressure is usually easier during decompression than during the compression phase.

**EFFICACY OF HBO THERAPY**

The role of HBO therapy in the treatment of diabetic foot wounds with hypoxia severe enough to interfere with healing was controversial for a long time. Undeniably, most studies of HBO therapy were hampered by small sample size, potential sources of bias, inadequate evaluation of co-morbid conditions relevant to wound healing, and other methodological problems that precluded the establishment of a definitive role for this modality in the routine treatment of diabetic foot ulcers.

Fortunately, the efficacy of adjunctive HBO therapy has been examined in several randomized studies. In one study of 70 diabetic patients hospitalized for severe foot ulcers all patients received aggressive multidisciplinary management, whether or not they received HBO therapy. In addition, patients in the HBO group received a mean of 38.8 sessions of HBO therapy. The rate of major amputation was 8.6% in the HBO therapy group and 33.3% in the control group (P = .016). The relative risk for amputation in the HBO therapy group was 0.26.
A group of 28 patients with diabetes whose foot ulcers did not improve after 3 months of standard treatment were randomized to HBO therapy or a control group. HBO therapy was administered twice daily, 5 days per week for 2 weeks, and each session lasted 90 minutes at 2.5 ATM. After completion of HBO therapy, the mean decrease in ulcer size was 41.8% in the study group and 21.7% in the control group (P = .037). The difference in healing rates between the groups was no longer significant at 4 weeks after the completion of HBO therapy.

HBO therapy enhanced the healing of ischemic, non-healing diabetic leg ulcers in a study of 18 patients randomized to receive 30 sessions of HBO therapy (100% oxygen at 2.4 ATM for 90 minutes daily) or a control group. Healing with complete epithelialization was achieved in 5 of 8 ulcers in the treatment group and 1 of 8 ulcers in the control group. The median decrease of the wound area was 100% in the treatment group and 52% in the control group (P = .027).

Transcutaneous oximetry, performed either during HBO therapy or with the patient breathing 100% oxygen at ambient pressure, can help identify patients who are likely to benefit from HBO therapy. Clinical factors that affect the response to HBO therapy include renal failure, smoking history, number of HBO treatments, and interruption of the HBO treatment regimen.

Adverse Effects
The risks associated with HBO therapy are similar to those of some diving disorders. Pressure changes can cause barotrauma to the tissues surrounding air trapped in the lungs, the paranasal sinuses, and behind the eardrums. Breathing high-pressure oxygen for long periods can cause cerebral oxygen toxicity and seizures; vision changes can be caused by swelling of the lens. These problems are usually temporary and resolve following completion of HBO therapy.

The only absolute contraindication to HBO therapy is untreated pneumothorax. Relative contraindications include fever, grand mal seizures, and inability to clear the ears or sinuses. Some medications are incompatible with HBO therapy, including high doses of aspirin, corticosteroids, and morphine. Alcohol should be discontinued within 8 hours of HBO treatment, and patients should stop the use of tobacco in any form until therapy is complete.

Patients generally experience no negative effects following HBO therapy. Some patients report a “cracking” sensation in their ears between treatments as oxygen behind the eardrums is absorbed into the circulation. This sensation can be relieved in the same manner as clearing the ears during compression and decompression. Other patients report feeling light headed immediately following a HBO therapy session, but this sensation is usually brief and self-limiting.

HBO therapy has historically been the focus of substantial political maneuvering among providers, insurers, and pharmaceutical companies, due in part to the fact that oxygen is not patentable and does not benefit from the political advocacy used to promote other therapies. Systemic HBO therapy is expensive, with a session costing anywhere from $200 to $400 in private clinics to over $2,000 in U.S. hospitals. Even at that, given the high costs of amputation and rehabilitation, HBO therapy may be a cost-effective modality in select patients. In 2003, Medicare and Medicaid extended coverage for HBO therapy to ulcers that had failed standard wound care therapy and were classified as Wagner grade 3 or higher (i.e. a wound that is no longer superficial, but probes to bone and may be ischemic and/or infected.).

CONCLUSIONS
The discovery of the beneficial cellular and biochemical effects of oxygen has strengthened the rationale for its use in patients with chronic wounds and other disorders. In selected patients with diabetic foot ulcers, HBO therapy can be a valuable adjunct to conventional treatments. It appears to accelerate the rate of wound healing, reduces the need for amputation, and increases the number of wounds that heal completely. Unfortunately, most prospective studies that support the beneficial effects of HBO therapy for diabetic foot ulcers suffer from methodological shortcomings. Important questions therefore remain regarding the appropriate time to initiate HBO therapy, the optimal duration of treatment, and the characteristics of patients most likely to benefit. Additional randomized, placebo-controlled, clinical trials in large populations are needed to definitively establish the role of HBO therapy in patients with diabetic foot ulcers.
REFERENCES


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