Update Article

“Hyperbaric Oxygen Therapy - evidence based role in Diabetic Foot”

Madhur Jain*, Dhiraj Saxena*, Kuldeep Singh*, Arun Prasad*, Ambrish Mittal*, Lee Chin Thang*1, Tarun Sahni+2

Abstract

With the increasing prevalence of diabetes in the community, morbidity and mortality as a result of diabetic feet has been increasing. Foot complications are one of the most serious and yet preventable complications of diabetes mellitus having an economic impact to the individual and adding the burden to the already inadequate healthcare resources.

There are more than 170 million diabetics worldwide of which about 30 million are in India and this number is expected to double by year 2030. Of these about 15% will develop an open foot ulcer. 20% of these ulcers may eventually lead to an amputation. More than 80% of these lesions can be easily prevented or managed with timely and optimum intervention with a combined team approach including Hyperbaric Oxygen (HBO) Therapy.

Recent research in the role of Hyperbaric Oxygen Therapy (HBOT) in diabetic wounds has confirmed its role in promoting oxygenation, enhance immune mechanisms, neovascular formation, fibroblast proliferation and other beneficial actions. It is now accepted as a useful adjunctive treatment in a select group of diabetic patients with severe or limb threatening wounds. This article discusses the physiological basis, role and place of HBOT in the modern multidisciplinary approach to the treatment of diabetic foot wounds.

Key Words: diabetic feet, hyperbaric oxygen therapy

Introduction

There are approximately 30 million people with Diabetes in India today and the number is expected to go to 35 million by 2010 and to 57 million by 2025. Foot ulcers are one of the commonest complications of Diabetes Mellitus resulting in substantial morbidity and mortality accounting for almost 20% hospitalizations. A diabetic is at 15 times higher risk of lower extremity amputation than non-diabetic and 5-15% of people with diabetic foot ulcers require lower extremity amputations, usually because of gangrene.

According to American Podiatric Medical Association 15 percent of all people with diabetes will develop open wounds on their feet at some point during their lifetimes; 20 percent of these ulcerations will result in amputation; 50 percent of those who undergo an amputation of one limb will also lose the other within three to five years.

Hyperbaric oxygen therapy is a form of treatment in which a patient breathes 100% oxygen while inside a special treatment chamber. The pressure in this treatment chamber is increased to higher than normal atmospheric pressure and the patient then breathes oxygen at this higher pressure. Most treatment is carried out at twice the atmospheric pressure and no significant side effects are documented. With continuing growth all over the world Hyperbaric Medicine has found a distinct role in the modern era of evidence-based medicine.

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Physiological basis of HBO therapy

When we normally breathe air at sea level pressure, Hb is 95% saturated with oxygen (O₂) and 100 ml blood carries 19 ml O₂ combined with Hb and 0.32 ml dissolved in plasma. At this same pressure if 100% O₂ is inspired, O₂ combined with Hb increases to a maximum of 20 ml and that dissolved in plasma to 2.09 ml. Most tissue needs of Oxygen are met from the O₂ combined to Hb.

The higher pressure during hyperbaric oxygen treatment pushes more Oxygen into solution and amount of O₂ dissolved in plasma increases to 4.4 ml/dl at a pressure of 2 ATA and to 6.8 ml/dl at 3 ATA. This additional Oxygen in solution is almost sufficient to meet tissue needs without contribution from oxygen bound to hemoglobin and is responsible for most of the beneficial effects of HBO therapy.

![Table 1: Effect of Pressure on Arterial O₂](image)

<table>
<thead>
<tr>
<th>Total Pressure</th>
<th>Content of Oxygen Dissolved in plasma (vol %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATA</td>
<td>Breathing Air</td>
</tr>
<tr>
<td>1</td>
<td>760 0.32</td>
</tr>
<tr>
<td>1.5</td>
<td>1140 0.61</td>
</tr>
<tr>
<td>2</td>
<td>1520 0.81</td>
</tr>
<tr>
<td>2.5</td>
<td>1900 1.06</td>
</tr>
<tr>
<td>3</td>
<td>2280 1.31</td>
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</table>

All values assume arterial pO₂ = alveolar O₂ and that Hb O₂ capacity of blood is 20 vol %

Therapeutic effects of HBO Therapy

- **Hyperoxygenation** causes (i) Immune stimulation by restoring WBC function and enhance their phagocytic capabilities and (ii) Neo-vascularization in hypoxic areas by augmenting fibroblastic activity and capillary growth. This is useful in radiation tissue damage and other problem wounds.
- **Vasoconstriction** reduces edema and tissue swelling while ensuring adequate Oxygen delivery and is thus useful in acute trauma wounds and burns.
- **Bactericidal** for anaerobic organisms & inhibits growth of aerobic bacteria at pressures > 1.3 ATA. It Inhibits production of alpha-toxin by C Welchii and is synergistic with Aminoglycosides and Quinolones. Thus it is life saving in gas gangrene and severe necrotising infections.
- **Reduces half-life of Carboxyhaemoglobin** from 4 to 5 hours to 20 minutes or less and is the treatment of choice for Carbon Monoxide poisoning in fire victims.
- **Mechanical effects**: Direct benefit of Increased pressure helps reduces bubble size in Air Embolism and Decompression Illnesses.
- **Reactivates “sleeping cells” in the penumbra** region around central dead neuronal tissue and is the basis of use in neurological conditions. It also reduces adherence of WBCs to capillary walls and maybe useful in acute brain and spinal cord injury.

Pathophysiology of Diabetic Foot

Diabetic patients are extremely vulnerable to foot problems. Typically there is decreased circulation, decreased or absent sensation, loss of function of the small muscles of the foot and impaired ability to heal. A minor foot problem in a non-diabetic patient can be limb or life threatening in the diabetic patient. The personal and economic costs attached to this problem are staggering.

The triad of peripheral neuropathy, Peripheral vascular disease and mechanical abnormality is the major contributing factor for Diabetic Foot Ulcers– other being infection, trauma and increased plantar pressure leading to ulceration. Approximately 60% of Diabetic Foot ulcers are primarily neuropathic, 20% are primarily ischemic and 20% are both neuropathic and ischemic.

Peripheral neuropathy has a central role and affects 40-60% of diabetic population. In most cases, ulceration is a consequence of unnoticed injuries due to loss of protective sensation.
(sensory neuropathy). Motor neuropathy causes intrinsic muscle atrophy and wasting leading to loss of stabilization force of the toes, resulting in contracture and foot deformities. Autonomic neuropathy leads to A-V shunting (resulting in islands of cutaneous ischemia) and loss of sweating mechanism. All these factors make foot vulnerable to injury and resulting ulcer and infection.

Peripheral Ischemia is another major factor leading to diabetic foot wounds. Peripheral vascular disease has been shown to be a pathogenic factor in 60% of diabetic patients with non-healing ulcers and 46% of those undergoing major amputation. Ischemia weakens local defenses against infection because of reduced blood flow and tissue supply in oxygen, essential nutrients and growth factors and thus plays a major role in delayed wound healing. In diabetics, PVD manifests primarily in the tibial and peroneal blood vessels.

Infection is a frequent complication favored by neuropathy and ischemia. Its severity may range from a mild, localised infection to a limb-threatening necrotizing process with fasciitis. Beside these devastating infections leading often to amputation, bone and joint involvement has been shown to be a factor of delayed healing and subsequent amputation even when ischemia has been relieved by a revascularisation procedure.

Classification of Diabetic Foot Wounds

The well-established widely used Wagner wound classification system and the new University of Texas (UT) diabetic wound classification system both provide descriptions of ulcers to varying degrees. Both wound classification systems are easy to use among health care providers, and both can provide a guide to planning treatment strategies.

The Wagner system assesses ulcer depth and the presence of osteomyelitis or gangrene by using the following grades: grade 0 (pre- or post-ulcerative lesion), grade 1 (partial/full thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep with osteitis), grade 4 (partial foot gangrene), and grade 5 (whole foot gangrene) (Table 2).
Table 2: Wagner Classification System for Dysvascular Foot Lesions

<table>
<thead>
<tr>
<th>Wagner Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Grade 0</td>
<td>No open skin lesions</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Superficial ulcer without penetration to deeper Layers</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Deep ulcer reaching tendon, bone, ligament or joint capsule</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Involvement of deeper tissues with abscess, Osteomyelitis, or tendonitis</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Gangrene of toe, toes, and/or forefoot</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Gangrene of entire foot</td>
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</table>

The UT system assesses ulcer depth, the presence of wound infection, and presence of clinical signs of lower-extremity ischemia. This system uses a matrix of Grade on the horizontal axis and Stage on the vertical axis. The grades of the UT system are as follows: grade 0 (pre- or post-ulcerative site that has healed), grade 1 (superficial wound not involving tendon, capsule, or bone), grade 2 (wound penetrating to tendon or capsule), and grade 3 (wound penetrating bone or joint). Within each wound grade there are four stages: clean wounds (stage A), nonischemic infected wounds (stage B), ischemic noninfected wounds (stage C), and ischemic infected wounds (stage D). (Table 3)

<table>
<thead>
<tr>
<th>STAGE</th>
<th>GRADE</th>
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<tr>
<td>A. No infection or ischaemia</td>
<td>0. Epithelialized wound</td>
</tr>
<tr>
<td>B. Infection present</td>
<td>1. Superficial wound</td>
</tr>
<tr>
<td>C. Ischaemia present</td>
<td>2. Wound reaches tendon/capsule</td>
</tr>
<tr>
<td>D. Infection &amp; Ischaemia present</td>
<td>3. Wound penetrates bone/joint</td>
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The results of the study by Boulton et al revealed that grade and stage affect the outcome of diabetic foot ulcers. The higher the grade, the greater the number of amputations performed. The trend for the UT grade was slightly greater than that for the Wagner grade. The UT system, which combines grade and stage, is more descriptive and shows a greater association with increased risk of amputation and prediction of ulcer healing when compared with the Wagner system. Therefore, for groups rather than individual patients, the UT system, which is simple and easy to use, is a better predictor of clinical outcome.

Recently a new wound score has been developed for improved evaluation of diabetic wounds by Strauss. He has reviewed seven classification systems for foot wounds in patients with diabetes and evaluated them in a table format based on 10 criteria judged to be the most important for assessing their effectiveness. Criteria include such factors as objectivity, versatility, ability to measure progress, validity, and reliability, and five other grading parameters," scientists writing in the journal. This wound score is accomplished by a simple to use five assessment wound score that grades wound base appearance, size, depth, bio-burden and perfusion each from 0 (worse) to 2 (best) using objective criteria. The resultant 0 to 10 score quantifies the severity and provides a guideline for what treatments should be done. The art of surgically treating foot wounds in patients with diabetes is exemplified in doing minimally invasive surgeries in the office or their more complex counterparts in the operating room. The surgeries are classified into five types: debridements, correction of deformities, wound closures,
partial amputations, and miscellaneous procedures including nail care and Charcot arthropathy treatment. (Table 4)

<table>
<thead>
<tr>
<th>(Table 4). Strauss Wound Score</th>
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<tbody>
<tr>
<td>2</td>
</tr>
<tr>
<td>Perfusion</td>
</tr>
<tr>
<td>Size</td>
</tr>
<tr>
<td>Depth</td>
</tr>
<tr>
<td>Colour</td>
</tr>
<tr>
<td>Infection</td>
</tr>
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</table>

TOTAL SCORE

**Rationale for Use of HBO Therapy in the Treatment of Diabetic Foot Wounds**

Revascularization is key in the diabetic patient with an ischemic foot, but even after this, there are some individuals who remain refractory to healing. HBOT may play an important role in improving the outcome in these individuals.

HBOT for diabetic foot wounds is based on sound physiological principles. It greatly increases tissue oxygen levels and acts by:

- Increased oxygen delivery per unit of blood flow and thus enhanced oxygen availability at the tissue level to hypoxic tissues.
- Enhanced oxygen environment lasts up to four hours after exposure and intermittent hypoxia and hyperoxia stimulates the following changes at cellular level
- Enhanced polymorphonuclear cell function to combat local infection
- Restoration of cellular function
- Enhanced fibroblast proliferation
- Collagen deposition
- Neovascularization
- Reduced time to heal, and length of hospitalization and resultant reduced costs.
- Its ability to preserve a limb results in reduced high cost of disability resulting from amputation

**Figure 2 : Increases oxygen delivery to hypoxic tissues with Hyperbaric Oxygen**

![Diagram showing increased oxygen delivery with Hyperbaric Oxygen](image)
Which wounds should be treated with HBO Therapy

Hyperbaric Oxygen Therapy can play a significant role when combined with conventional therapy in carefully selected wounds. Many disease states, such as diabetes, atherosclerotic cardiovascular disease, irradiation, and local trauma, lead to chronic hypoxic wounds. In these patients, most small wounds or minor trauma ultimately heal albeit delayed. It is the larger wounds in the compromised patient where the demand for oxygen exceeds the supply that the non-healing chronic wound develops. It is in these patients that adjunctive HBOT is beneficial. Patients with Class 3, 4, or 5 Wagner lesions are considered for HBOT depending on the assessment of blood flow (Table 2).

Transcutaneous Oximetry for evidence based use of HBO Therapy

Transcutaneous oxygen value (TcPO₂) is recognized as one of the most reliable and useful non-invasive method for evaluation of perfusion and selecting patients for HBOT. This helps by establishing the presence of tissue hypoxia and more importantly to demonstrate the reversal from hypoxic tissue oxygen levels to normoxic or hyperoxic levels with the administration of higher oxygen partial pressures. Patients with Transcutaneous periwound TcPO₂ values greater than 40 mmHg on room air may heal without intervention while those with values less than 20mmHg have poor prognosis. TcPO₂ values less than 10 mmHg indicate amputation will be unavoidable. An increase to 40 mmHg or greater while breathing 100% O₂ at room pressure (1ATA) or >200mmHg inside a Hyperbaric Chamber indicates that HBOT will benefit the patient (Figure 3).

Does HBO Therapy have a role in normal hosts

Hyperbaric oxygen plays no role in enhancing wound healing in the normal host, unless there is evidence of local wound compromise. An example would be a severe crush injury in a previously healthy patient that severely disrupts the capillary blood flow with a resultant chronic non-healing wound. In this situation, adjunctive HBO would be beneficial.

Clinical Experience with HBO Therapy in the Treatment of Diabetic Wounds

At the Hyperbaric Center at Apollo Hospital, New Delhi more than 125 patients with diabetic foot and other non-healing wounds have been treated with approximately 1300 hyperbaric therapies averaging at about 10 treatments per patient. Most patients are referred late in their illness, when their condition has deteriorated.

Case Report 1: SK, a 64 years old male, case of IDDM presented with a toenail infection of the left great toe. The nail was removed and the wound did not heal for over 3 months. He was referred to the hyperbaric unit where he was given 20 HBO therapies and the wound healed completely.
Case Report 1: Diabetic toe healing with Hyperbaric Oxygen

Case Report 2: A 48 years old man, diabetic and smoker was diagnosed as having cellulitis of the feet. He was treated with HBO and other treatment including I/V antibiotics and debridments. Ten days later, he was able to leave the hospital walking on both feet.

Discussion

There is enormous variation in treatment and outcomes in patients with diabetic foot wounds. Although there are limited data to support most treatments for diabetic ulcers, six approaches are supported by clinical trials or well-established principles of wound healing – Offloading, Debridement, Optimum Dressings, Management of Infection by appropriate Antibiotics, Vascular Reconstruction in patients with vascular insufficiency, Amputation and subsequent rehabilitation in long-standing ulcers where all treatments have failed. Besides, Normalization of blood glucose, control of comorbid conditions, treatment of edema, and medical nutrition therapy are important components of prevention and treatment of foot wounds. New technologies where additional randomized controlled trials are warranted include HBOT, growth factors, living skin equivalents, electrical stimulation, cold laser, and heat.

A non-healing diabetic foot ulcer is a result of multiple systemic and local factors, which contribute to inhibition of tissue repair. The basic mechanism is interplay between hypoperfusion and infection leading to decreased fibroblast proliferation, collagen production, and capillary angiogenesis and also impairs bacterial killing by polymorphs. Tissue oxygen tensions (TcPO2) of such wounds usually measure as low as 20 mmHg. Restoration of TcPO2 to normal or higher values enhances epithelialization, fibroplasias, collagen deposition, angiogenesis, and bacterial killing.

Hyperbaric oxygen therapy greatly increases tissue oxygen levels in ischemic and infected wounds. The Consensus Development Conference on Diabetic Foot Wound Care held in 1999 in Boston, Massachusetts stated “It is reasonable to use this modality (HBOT) to treat severe and limb- or life-threatening wounds that have not responded to other treatments, particularly if ischemia that cannot be corrected by vascular procedures is present.”
Fourth European Consensus Conference On Hyperbaric Medicine held a discussion on “Hyperbaric Oxygen In The Management Of Foot Lesions” and the recommendation is as follows “HBOT should be used in the diabetic foot always as a multidisciplinary team and the pre-treatment evaluation should include an assessment of the probability of its success which might include: TcPO2 and O2 challenge at pressure and Assessment of peripheral circulation by invasive and non-invasive methods”

Table 5 is a comparison of the outcome in Diabetic Wounds treated with and without Hyperbaric Oxygen and shows the enhanced wound healing in diabetics as a result of hyperbaric oxygen

<table>
<thead>
<tr>
<th>Table 5: Comparison of Outcome in Diabetic Wounds Treated with and Without HBOT</th>
</tr>
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<tbody>
<tr>
<td>HBO2 Group</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Average wounds per patient</td>
</tr>
<tr>
<td>Average age (yr)</td>
</tr>
<tr>
<td>Average wound base (mm²)</td>
</tr>
<tr>
<td>Average wound duration (months)</td>
</tr>
<tr>
<td>Recommended for amputation</td>
</tr>
<tr>
<td>Rate of limb salvage</td>
</tr>
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</table>

*Undersea and Hyperbaric Medical Society: Hyperbaric Oxygen Therapy Committee Report, 1999:30

In a recent retrospective study of 35 diabetic patients after partial foot amputation and hyperbaric oxygen treatment, Fife CE et al report that seventy percent (n = 28) had a successful outcome, defined as complete healing and absence of ulceration at the amputation site, and lack of further surgical procedures to heal the amputation site; whereas 30% (n = 12) had a failed outcome, defined as lack of healing or the presence of an ulcer at the site of amputation or the need for further surgery to heal the amputation site.

In another study Kalani et al conclude that adjunctive HBO therapy can be valuable for treating selected cases of hypoxic diabetic foot ulcers and additional studies are needed to further define the role of HBOT, as part of a multidisciplinary program, to preserve a functional extremity, and reduce the short- and long-term costs of amputation and disability.

A study of Cochrane Database System Review states that in people with foot ulcers due to diabetes, HBOT significantly reduced the risk of major amputation and may improve the chance of healing at 1 year. Another study by Roeckl-Wiedmann I pooled data from 5 trials including 118 patients, reinforces this view. Kessler et al studied the effect of systemic hyperbaric oxygenation on the healing course of nonischemic chronic diabetic foot ulcers and concluded that HBOT doubles the mean healing rate in select cases.

Most health insurance companies worldwide recognize hyperbaric oxygen as an approved, reimbursable treatment for problematic diabetic wounds. Effective April 1, 2003, a National Coverage Decision by Centers for Medicare & Medicaid Services (CMS) expanded the use of HBO therapy to include coverage for the treatment of diabetic wounds of the lower extremities in patients who meet the following criteria:

1. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes; (ICD-9-CM diagnosis 250.7, 250.8, 707, 707.1, 707.10, 707.12, 707.13, 707.14, and 707.19).
2. Patient has a wound classified as Wagner grade III or higher; and
3. Patient has failed an adequate course of standard wound therapy.
Other wounds where HBOT can be useful

**Problem Wounds:** Wounds that fail to respond to established medical and surgical management like Diabetic dermatopathy and sternal osteomyelitis.

**Vascular insufficiency ulcers:** Selected cases with non-healing wound despite maximum revascularization and for preparation of a granulating bed for skin grafting.

**Clostridial Myositis & Myonecrosis (Gas Gangrene):** Clostridium bacteria are "anaerobic," and their replication, migration, and exotoxin production is inhibited on exposure to high oxygen during Hyperbaric Oxygen Therapy.

**Refractory Osteomyelitis:** Osteomyelitis causes low oxygen tension in infected bones. Studies show that elevating the oxygen tensions in affected bones and the surrounding tissues helps speed healing. The Cierny – Mader classification of osteomyelitis (stage 3B or 4B) can be used as a guide to determine which types of osteomyelitis may be benefited by adjunctive HBOT.

**Necrotizing Soft Tissue Infections:** Crepitant anaerobic cellulitis, progressive bacterial gangrene, necrotizing fasciitis, and nonclostridial myonecrosis. It is well documented that death rates are lower among patients with necrotizing infection who receive HBOT treatments plus standard therapy (debridements and antibiotics), and they require fewer debridements.

**Crush Injury:** The Gustilo Classification is used for evaluating the use of HBOT in Crush Injuries and those in Class III A, B & C (Compromised host, Flaps or grafts required to obtain soft tissue coverage and Major (macro vascular) vessel injury) are recommended HBO treatment for better results at lower costs.

**Acute traumatic ischémias:** The Mess Score is used to evaluate the role of HBOT for Mangled Extremities. Those with Mess Score 7 & 8 (Uncompromised host where age, hypotension, and mild-to-moderate ischemia significantly contribute to the score) Scores 5, 6 (Compromised hosts with diabetes, peripheral vascular disease, collagen vascular disease, etc.) and with score 3, 4 (Severely compromised hosts with advanced levels of the above conditions) are strongly recommended HBO therapy.

**Compartment Syndrome:** Use of HBOT is advised when skeletal-muscle compartment pressure measurements greater than 40 mmHg in the uncompromised host and 20-30 mmHg in hypotensive patients and compromised hosts.

**Skin Grafts And Flaps (Compromised):** HBOT is well recognized for its role in assisting in the preparation and salvage of skin grafts and compromised flaps.

**Thermal Burns:** Adjunctive HBOT in deep second-degree and third-degree burns that involve greater than 20% of the total body surface area or face, hands or groin area, limits the progression of the burn injury, reduces swelling, reduces the need for surgery and diminishes lung damage.

**Conclusion**

Adequate tissue oxygen tension is an essential factor in wound healing. Diabetic foot wounds are ischemic frequently and adequate oxygen levels can be reached only through adjunctive HBOT. This results in more normal fibroblast proliferation, angiogenesis, collagen deposition, epithelialization, and enhancement of bacterial killing. HBOT shortens healing time, and helps in preserving limbs thereby reducing overall costs. As part of a multidisciplinary program of wound care HBOT is cost effective and durable.

**Acknowledgements**

The Dept of Hyperbaric Medicine wants to acknowledge the support given by the referring clinicians especially from Plastic, Vascular and General Surgery and Dept of Endocrinology. The teamwork and the multidisciplinary approach in tackling Diabetic Foot has helped us to understand this problem better resulting in excellent outcomes for the patients. We also want to thank the Diabetic Foot Society of India.
for their support and acknowledging the growing role of HBOT in evidence based management of Diabetic Foot.

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