



## HYPERBARIC OXYGEN THERAPY – AN ADJUVANT IN TREATMENT FOR DIABETIC FOOT

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### ABSTRACT

As Diabetes issues are increasing widely, and because of Diabetic feet, mortality rate is increasing rapidly. Even Foot complications are one of the most serious and Diabetes mellitus is giving more unpredicted and unpreventable complications, hence indirectly burden on healthcare resources are getting increased. The treatment associated with diabetes complications are very costly. Standard treatments to treat diabetic foot ulcers are generally fail, as a result adjunctive therapies must be considered. In these circumstances, use of systemic Hyperbaric Oxygen Therapy (HBOT) as an adjunctive therapy for diabetic foot is safe, reasonable and cost effective modality. HBOT in diabetic ulcers has proven its role in promoting oxygenation, enhancing immune mechanisms, fibroblast proliferation and other benefits. It is now accepted as a useful adjunctive treatment in diabetic patients with severe ulcers. It is confirmed to be an effective treatment when combined with careful attention to diabetic foot wounds.

**KEYWORDS:** Hyperbaric Oxygen Therapy, Diabetes, Wagner-Meggitt's Grade Scale, Diabetic foot ulcer

### INTRODUCTION

In patients with Diabetes, Non-healing ulceration is very common, easily untreated and costly complication. That can cause amputation. Some of the amputation in diabetic patients are due to trauma, some are because of infection, retarded wound healing, impaired cellular function and ischemia. For the healing of ulcers, high amount of oxygen is needed and so adequate blood supply is of great importance. Thus micro and macro circulation disturbances lead to local ischemia and weaken the oxygen supply to the ulcer area. That's why treatment is needed which can improve the microcirculation of the skin so that it can lead to vascular reconstruction.

Hyperbaric oxygen therapy (HBO) has been adopted as a newer and effective approach for not only ulcers or amputation especially in patients with diabetes but also for delayed radiation injury and necrotizing soft tissue infections.

HBOT for diabetic foot ulcers requires patient's involvement, in which the patient has to lay inside the chamber and breathes normally in the exposure of 100% oxygen at 2 to 3 times the normal atmospheric pressure. This therapy is given daily in the session of 90 minutes each, at pressures of 1.5-3.0 atmospheres absolute (ATA) in the chamber. Which leads to increased oxygen

dissolution in blood from 0.32% to 6.8%. Thus by increasing the blood oxygen content oxygen get diffuse easily into the tissues. In tissues with lack of oxygen, the enhanced oxygen supply leads to wound healing. Also Enhancement of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) plays an important role. HBOT may enhance angiogenesis and fibroblast proliferation.

Additionally, the resulting hyperoxia may cause vasoconstriction, thereby decreasing tissue swelling. Thus HBOT reduces inflammation, while simultaneously enhancing the bacterial killing activity of leukocytes.

### WHAT IS HYPERBARIC OXYGEN THERAPY (HBOT)<sup>(1)</sup>?

Hyperbaric Oxygen Therapy (HBO) is the approved treatment by the "Food and Drug administration" and "American Medical association".

Hyperbaric oxygen therapy is an adjacent therapy to cure wounds including treatment of topical area, dead skin and damaged tissues<sup>2</sup>. It also includes some biological applications. When we breathe normally at sea level pressure, oxygen (O<sub>2</sub>) saturates the hemoglobin (Hb) at 95% and makes HbO<sub>2</sub> and rest dissolves in plasma. Now, if 100% oxygen is inspired at

the same pressure level, O<sub>2</sub> combined with Hb increases to a maximum of 20 ml and 2.09 ml dissolves in plasma. Thus HbO<sub>2</sub> can fulfill the needs of oxygen to the tissues. Now the rest of oxygen in solution will help to fulfill tissue needs without contribution from combined HbO<sub>2</sub> and this effect can be shown in HBO therapy which can lead to beneficiary effects.

Now in HBOT, a person breathes 100% medical grade oxygen under special increased pressure which is almost 15 times of normal oxygen inhaled. This treatment is delivered within a multi-place chamber or mono-place chamber. This therapy is very user friendly with both chambers.

- During the healing treatment by HBOT may include the following effects<sup>2</sup>:
- Increased oxygenation at wound tissue
- Reduced dropsy
- Increased ATP production
- Enhanced rate of bacteria killing in presence of oxygen
- Synergism of antibiotics
- Advancement in angiogenesis
- Improved epithelial migration, collagen generation and degradation

#### WHAT IS DIABETIC FOOT ULCERS<sup>4</sup>?

Diabetes mellitus is the most typical and serious metabolic disorder due to deficiency of insulin secretion from B-cells of islet of Langerhans or due to reduced sensitivity of body to insulin.

On the current trend, Diabetes has been found as a global issue as it is growing rapidly at scaring rate. India might have the largest number of diabetic patients during next few years and so it is equally creating trouble for the healthcare system to treat the patients with the complications. Diabetic ulcers are complex, chronic and very painful in patients with Diabetes.

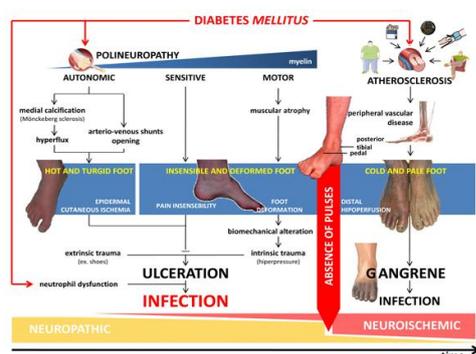


Fig.1-Etiology of Diabetes and Chronic wound

Diabetic ulcers and chronic wounds can be classified under Wagner's Grade Scale, which was established in the 1970s, has become the most widely accepted and universally used grading system for ulcers and abrasion of the diabetic foot.

**Table 1: Wagner-Meggitt's Grading System for Diabetic foot ulcers.**<sup>[2]</sup>

Grade 0	Foot symptoms like pain only
Grade 1	Superficial Diabetic ulcers
Grade 2	Ulcer extension
Grade 3	Osteomyelitis - Deep ulcer to the bone and bone marrow
Grade 4	Gangrene to portion of forefoot
Grade 5	Full foot Gangrene

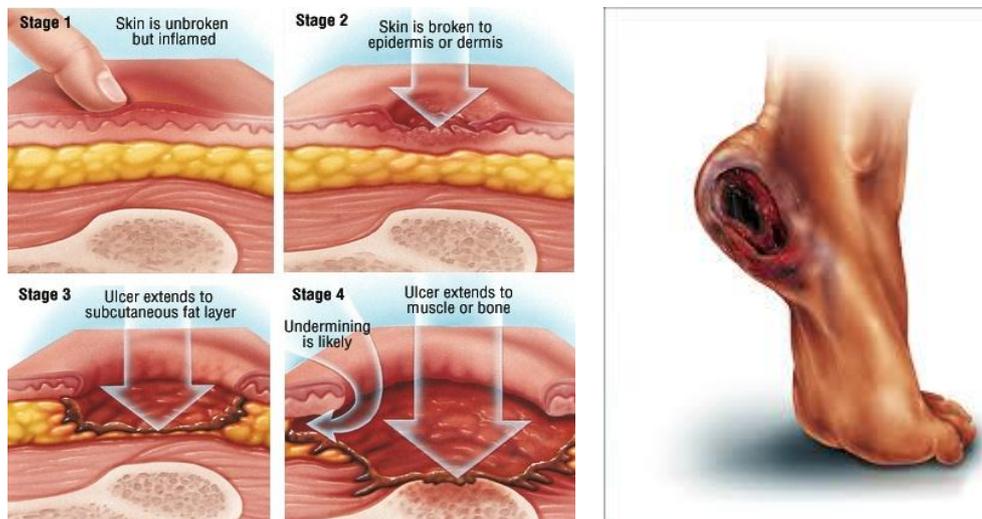
There is a proposed and summarized classification for Diabetic foot ulcer can be suggested which includes 3 types of classes depending upon the foot complication, this classification is simpler and easier to understand. Type 1 is infective class which includes abscess, cellulitis etc. Type 2 is Non-infective, which includes non-healing ulcer, neuropathies, claw toes, peripheral arterial disease, etc. and Type 3 is the mixed class of type 1 and 2, which includes all infective and non-infective lesions complications. This classification could be used for better understanding for the level of ulcer but not for the clinical outcome.

Here, to cure the diabetic ulceration or abrasion, sufficient oxygen must reach to the damaged tissues. This therapy increases the Oxygen saturation in the blood and due to the enhancement of atmospheric pressure and increased oxygen can promote white blood cell activity. This promotes development of tissue and capillary growth. So we can say that this therapy can be proved as a boon for a variety of conditions, including diabetic foot ulcers<sup>4</sup>.

Diabetic foot ulcer treatment also includes improvement of microcirculation of the skin; that can cure dropsy, hypoxia and anemia.

**Table 2: Causes of Diabetic foot Ulcers**

Condition	Wound consequences	Comments
<b>Direct Causes</b>		
Over Injury	Bone and joints deformities	common in Charcot arthropathy
Claw foot	Perforating Ulcers and ulcerations over toe joints	Toes bend into a claw-like position which is caused because of nerve damage in toe muscles.
Repetitive Stresses	Formation of bursae. Breakdown of tissues. Erythroderma	May lead to ulcerations when stresses involve high contact pressures.
<b>Indirect Causes</b>		
Peripheral vascular disease	Insufficient perfusion	Metabolic demands for healing are 20 times more than of a steady state.
Neuropathy	Muscle deformity, Gait abnormalities, pain and numbness	High blood sugar can damage nerve fibers and blood vessels that may lead to sever infection
Skin problems, atrophy	Increased risks to wound	May lead to movement difficulties so it is better to take preventive measures.

**Fig.2-Progression of Decubitus Ulcer****MECHANISM OF HYPERBARIC OXYGEN THERAPY<sup>[5]</sup>**

There are two primary mechanisms on which this therapy is working.

- 1). Increase the pressure on reducing bubble size
- 2). Enhance the partial pressure of oxygen in the blood and affected tissues

The effect of hemoglobin affinity for oxygen may aid wound healing by improving the following activities:

- Improve the immune system activity
- Enhancement of antibiotic effect
- Neovascularization
- Increase fibroblast activity
- Enhance collagen synthesis

Here, when we breathe 100% oxygen from increased atmospheric pressure, the oxygen molecules become condensed and this allows to breathe a higher partial pressure of oxygen. So that oxygen dissolves 10-15 times greater than normal in the plasma.

This leads to oxygen saturation in the body's tissues and enhances:

- Capillary growth
- Blood cell activity
- Tissue regeneration
- Vasoconstriction that may lead to Edema reduction
- Oxygen tension in hypoxic areas
- Gas bubbles size reduction

This effect also blocks cytotoxic effects of carbon monoxide and hypoxia associated with cyanide poisoning, which is the reason HBOT can be useful to treat carbon monoxide poisoning and Cyanide poisoning respectively.

Here is the phenomenon how HBOT works on the basis of Blood flow<sup>5</sup>

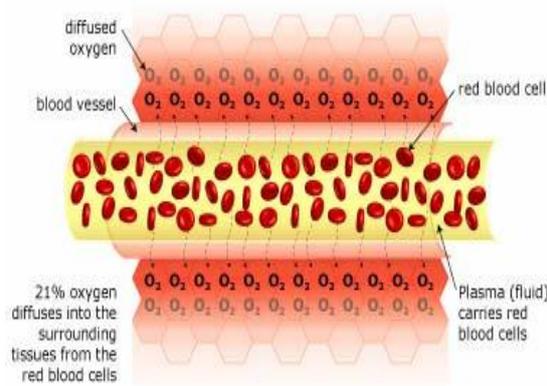


Fig.3-Normal Blood Flow

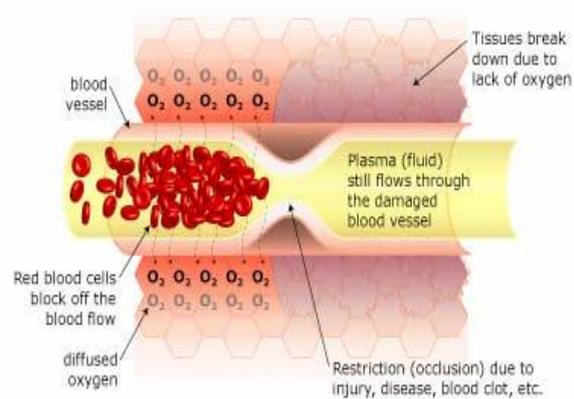


Fig.4-Restricted Blood Flow

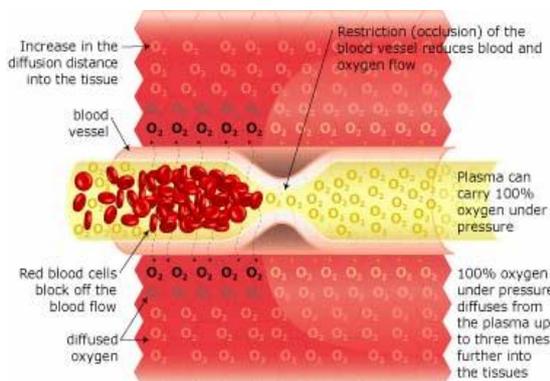


Fig.5-Hyperbaric Oxygenation

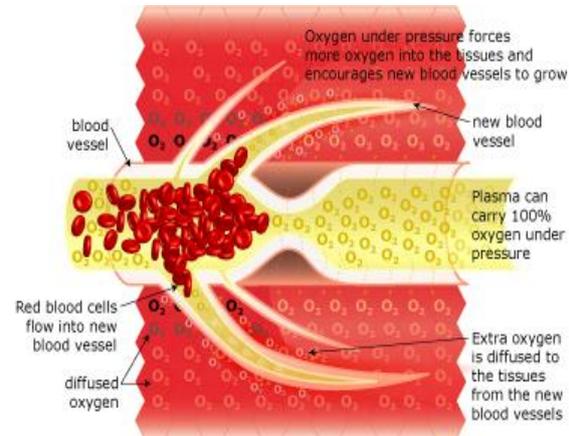


Fig.6-Neurovascular Regeneration

**NORMAL BLOOD FLOW:** We breathe 21% oxygen from the air, which is transported by the lungs to red blood cells with the help of Hemoglobin. And plasma carries these oxygen filled RBCs to blood vessels and oxygen diffuses and delivers into the surrounding needful tissues.

**RESTRICTED BLOOD FLOW:** In case of occlusion in blood flow because of any kind of surgery, blood vessels are blocked by RBCs so oxygen cannot reach to the needed site and which causes swelling, hypoxia and this leads to tissue breakdown.

**HYPERBARIC OXYGENATION:** When we breathe 100% oxygen under atmospheric pressure, oxygen gets diffused into plasma and delivered at the needed site by travelling from the restriction area and again diffuses further more into the tissues, which reduces swelling and discomfort, also can repair damaged or hypoxic tissues.

Hyperbaric Oxygenation directly increases the saturated effects of tissue oxygenation and thus reduces the swelling to hypoxic region.

**NEUROVASCULAR REGENERATION:** HBOT induces the circulation of stem cells, this leads to new blood vessel creation.

#### ADMINISTRATION OF HBOT<sup>[4]</sup>

Hyperbaric Oxygen Therapy is utilized using monoplace or multiplace chambers. Monoplace chambers cost less to build and operate as they can deliver therapy to only one adult at a time. The larger size of the multiplace chambers provides more flexibility and allows additional healthcare personnel to be present inside the chamber. Here patient who may require direct medical intervention can be treated.

### MONOPLACE CHAMBER



Fig.7-Monoplace Chamber

A monoplace chamber can treat only one person at a time, where person can be relaxed. The 100% oxygen is used to pressurize the vessel and also normal breathing air masks are available. Only patient can go within the chamber, equipments are held outside the chamber. Some intravenous lines and ventilation ducts are allowed inside the chamber.

The advantage of this chamber is that patient can have private treatments. He/she can relax, read some book or watch movie. Now a days, Newer Duo place chambers are also available which can hold two persons. This chamber works similar as the monoplace chamber.

### MULTIPLACE CHAMBER

As the name itself suggests, it can treat more than one patients at a time. The advantage of this chamber is that a nurse or doctor can go inside the chamber and can assist patients with equipments and in case of patient

emergency also, the observer will be useful to patient inside.

Here, Patients mask or close-fitting plastic hood, is used to breathe 100% oxygen and the chamber pressure is set at approx. 6 atmospheric pressure.



Fig.8-Multiplace Chamber

The general layout of Large multi-place chamber is with 5ft id and 13<sup>1/2</sup> ft. L (internal). This layout can allow 6 people inside the chamber at a time to have treatment, read, relax, etc.

### EFFICACY OF HBOT<sup>[7-10]</sup>

There are some factors affecting the selection of patients for HBOT as below\*:

- Wagner Grade III and IV
- Failure of response to advanced wound care
- No contraindication for HBOT
- Good arterial supply
- Oxygen saturation  $\geq 92\%$

\*These data are based on some randomized controlled trial in HBOT for diabetic wounds.

### BENEFITS OF HBOT

- As Oxygen is the key element for life and healing, HBOT is proven an effective and intermittent therapy for the whole body. Because normally we breathe 20% O<sub>2</sub> and 80% N<sub>2</sub> at ambient atmosphere, but with HBOT we breathe 100% O<sub>2</sub>.

And this extra oxygen can be helpful in treating so many diseases.

- HBO simulates new blood vessel creation and enhance blood flow at the blockage areas.
- Therapy enhances the white blood cell action and helps in the infection treatment.
- Hyper oxygenation of the tissues stimulates bacteria killing and can cure bactericidal infections too.
- HBOT has gained importance in treatment of chronic degenerative diseases, like stroke, peripheral vascular disease, brain injury, multiple sclerosis, etc.
- By enhancing vasoconstriction of blood vessels at injured tissues can help to reduce edema and tissue injuries.
- HBOT is beneficiary for the patients having gangrenous legs or feet. Because this is the result of blocked or slow blood circulation to the tissues and hyperbaric oxygen can unblock the area and enhance the oxygenated blood circulation which results in reduced edema and pain and keep tissues alive.
- HBO leads angiogenesis and enhance the blood flow through the body tissues.
- HBO creates synergistic effect with Fluoroquinolones, Amikacin, Kanamycin, Neomycin, Gentamycin and amphotericin B which help to transport more oxygen across the cell membrane.
- Sometimes it is useful to restore brain functions while brain is injured by stroke or trauma.

- HBOT reduces edema by blocking the lactate accumulation in the affected tissues and that leads to better blood circulation and cure injury.

#### COMPLICATIONS OF HBOT<sup>[6-7]</sup>

The common and potential side effect during treatment is barotrauma and sinuses which is caused by pressure differences.

Adverse effects associated with HBOT are very rare, but it may include oxygen toxicity which affects only 1 person in 10,000. After a large number of treatments, the changes in vision is noticed in some patient. Any changes usually return to pre-treatment vision levels in a 6 week period.

Some patients may experience claustrophobia which can be resolved with relaxation techniques or mild medications.

Additionally, a few patients report a “popping” or “cracking” sensation in their ears between treatments.

- Reversible myopia
- Symptomatic otic barotrauma
- Seizures & Cataracts
- Decompression sickness
- Pneumothorax
- Hypoglycemia
- Congestive cardiac failure

#### CONTRAINDICATIONS OF HBOT<sup>[11]</sup>

Condition / Antibiotics	Potential Side Effects
Doxorubicin	Cardiotoxicity
High fevers	Seizures / lower seizure threshold
Disulfiram	Increased oxygen toxicity
Bleomycin	Pulmonary fibrosis, Pneumonitis
Pregnancy	Effect on fetus
Respiratory infection	Barotrauma / chronic sinusitis
Cisplatin	Impaired wound healing
Pacemakers	Malfunction of device
Congenital spherocytosis	Severe hemolysis due to RBCs breakdown
Optic neuritis	Worsening vision or Blindness
Viral infections	Worsening of infection and no support to therapy
Asthma	pneumothorax
Sulfamylon	Impaired wound healing

#### FDA-APPROVED USES OF HBOT OTHER THAN DIABETIC FOOT ULCER, IN THE U.S. INCLUDE

- Brain Injury
- Air or gas embolism
- Decompression sickness
- Carbon monoxide poisoning
- Intracranial abscess
- Arterial insufficiency
- Radiation tissue damage
- Thermal burns
- Crush injuries, acute trauma
- Necrotizing soft tissue infections
- Osteomyelitis
- Exceptional blood loss anemia

- Gas gangrene

#### NORMAL TREATMENT FOR DIABETIC FOOT ULCERS.<sup>[13,16]</sup>

- Locally, with the Eusol (1.25% w/v boric acid and 1.25% w/v of chlorinated lime)
- Patients having gangrene or foot infection with some amputation was treated with some antimicrobial agents such as cephalixin, clindamycin, etc. during mild infection. For moderate to severe levofloxacin, amoxicillin, cefepime, aztreonam, etc. were used. In case of chronic infection, antibiotics like cephalosporins, aminoglycosides were given based

upon the severity of the infection and sensitivity of the patient, for weeks and so on.

- In some cases, first we have to control diabetes based on the type of the diabetes or with the help of insulin.

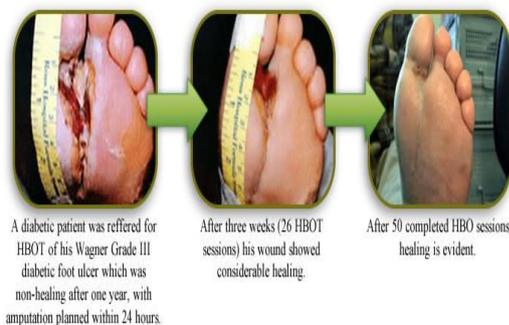
### TREATMENT WITH HBOT.<sup>[17]</sup>

Patients were given treatment at 3 atmospheric pressure everyday for about 45 minutes.

Therapy continued for about 2 weeks.

Based on the following parameters HBOT effect can be evaluated:

1. Wound cultures evaluation before and after each session.
2. Daily analysis of local wound.
3. If amputations are there, assessment of skin and tissue flaps.



**Fig.-9 treatment with HBOT<sup>13</sup>**

### DISCUSSION

On the basis of prospective randomized or comparative studies, it can be concluded that there is positive effects of adjunctive HBO therapy on reduction of amputation and ulcers in patients with diabetic ulcers.

The healing process include inflammation, reproduction and reshaping. But if this process is interrupted, there are chances of non-healing ulceration, generally in the patients with diabetes.

HBO reduced major amputations significantly. Microcirculation and oxygenation improves after a series of HBO treatments. New capillaries are formed in selected ischemic or poorly perfused wounds.

The exact mechanism of HBOT remains poorly understood but some studies have reported that HBOT has important effects on the biology of cytokines and other mediators of inflammation. HBOT causes cytokine down-regulation and growth factor up-regulation.

HBOT transiently suppresses stimulus induced pro-inflammatory cytokine production and affects the deliverance of TNF- $\alpha$  (tumor necrosis factor alpha) and endothelins<sup>18</sup>. VEGF levels are significantly increased with HBOT, whereas the values of PGE<sub>2</sub> (prostaglandin E<sub>2</sub>), COX-2 (cyclooxygenase 2) and mRNA expression are markedly reduced<sup>[19]</sup>. Therefore, cytokines,

prostaglandins (PGs), and nitric oxide (NO) may play a major role in the mechanism of action of HBOT.

### CONCLUSION

In case of wound healing, adequate tissue oxygen tension plays an important role. Diabetic foot wounds are hypoxic and that's why adequate oxygen levels are necessity, which can only be achieved by HBOT. When there is proper oxygen supply to the tissue, it aids in tissue repair process and thus the healing is getting increased and cost of the therapy is relatively decreased. Moreover, advanced wound care technologies in a directed and appropriate way can significantly enhance diabetic wound healing efforts. As part of a multidisciplinary program of wound care, HBOT is cost effective and durable.

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