# Insight on hyperbaric oxygen therapy as an adjunctive treatmentin diabetic foot ulcer: A Narrative Review


## ABSTRACT

Diabetic foot ulcers (DFU) are a source of major concern for both patients and health care systems. DFU is the most expensive and devastating complication of diabetes mellitus, which affect 15% of diabetic patients during their lifetime. That can lead to infection, gangrene, amputation, and even death if necessary care is not provided. On the other hand, once DFU has developed, there is an increased risk of ulcer progression that may ultimately lead to amputation. Overall, the rate of lower limb amputation in patients with diabetes mellitus is 15 times higher than patients without diabetes. Hyperbaric oxygen therapy (HBOT) can be defined as a mode of medical treatment in which the patient is entirely enclosed in a pressure chamber and breathes 100% oxygen at a pressure greater than 1 atmosphere absolute (ATA). HBOT can be used as an adjunct to standard wound care in the treatment of diabetic patients with foot ulcers. HBOT has been demonstrated to have an antimicrobial effect and to increase oxygenation of hypoxic wound tissues. This enhances neutrophil killing ability, stimulates angiogenesis, and enhances fibroblast activity, collagen synthesis and alter vascular activity. Thus, theoretically, HBOT could improve the healing of ischemic foot ulcers in patients with diabetes. This review focuses on providing an up-to-date summary of the currently available evidence-based data on HBOT in DFU, as well as elaborating its use in the management of diabetic injuries both ischemic and non-ischemic ulcers.



***Keywords:*** *Hyperbaric oxygen therapy, Diabetic foot ulcer, Amputation, Ischemic and Non-Ischemic Diabetic Foot Ulcer.*

## INTRODUCTION

Foot ulcer affects about 15% to 25% of diabetics. Because these wounds are relatively difficult to healing, people with diabetes have their lower limbs amputated at a rate that is almost 20 times higher than those who do not have diabetes. Other therapeutic approaches, like hyperbaric oxygen therapy (HBOT), are available if a wound does not heal with routine wound care [1, 2].

Sensory, motor, and autonomic neuropathies characterize the diabetic foot, resulting in pressure distribution changes, foot deformities, and ulcerations. Controlling the progression of the diabetic foot requires a focus on metabolic control and infection therapies. Long-term hospitalizations and frequent outpatient visits are common in treatment. Moreover, loss of mobility is a significant financial burden for both the patient and the health-care system [3].No healing ulcers account for 19–35 % of ulcers at centers of excellence [4–5]. Despite advancements in the healing of DFU, novel therapeutic techniques and procedures are still required.

Following the establishment of infection, the ulceration can be subjected to microorganism invasion accompanied with inflammation, resulting in abscess formation, cellulitis, myositis, paronychia, necrotizing fasciitis, septic arthritis, tendonitis, and osteomyelitis [6, 7]. HBOT involves administering pure oxygen at a high pressure (often 2–3 atmospheres), resulting in elevated oxygen levels in the blood and tissues (hyperoxemia) (Hyperoxia) [8].

HBOT is now used to treat a wide range of medical problems, which include open fractures and crush injuries, osteomyelitis, sensorineural hearing loss and rheumatologically conditions [9-12],HBOT has been suggested as a diabetic foot complementary treatment because it promotes the complicated processes behind healing in vitro[13-15]. HBO has also been shown to lower the risk of major amputation in diabetic individuals with gangrenous feet [16]. Patients with microvascular disorders, such as diabetes, has a reduction in the number of capillaries that supply oxygen to the tissues.

[17].HBOT overcomes hypoxia by raising both the dissolved oxygen contained in plasma and the partial oxygen pressure in the tissue fluid. [18].This raises the total amount of oxygen available to tissues, allowing poorly perfused tissues to fulfill their higher oxygen demands, Modeling and clinical observation have shown that HBOT increases oxygen delivery to hypoxic tissues by about 16-fold.[19]

HBOT has really been found to reduce inflammation by reducing the synthesis of prostaglandins, interferons, IL-1, and IL-6. 25 By reducing immunosuppressive substances, this anti-inflammatory action may boost overall immune system performance (prostaglandins, IL-1, IL10). HBOT enhances the immune system response by assisting leukocytes in the formation of reactive oxygen species (ROS) **[20].**HBOT seems to have an influence on antioxidants synthesis in addition to suppressing cytokines, anti-inflammatory action, and immunological response **[21]**.

**Mechanism of HBOT**

HBOT helps people heal in a multitude of ways. First, HBOT enhances the development of new vasculature needed for wound healing, as well as fibroblast activation and collagen formation [22- 25]. HBOT also exerts bactericidal and bacteriostatic effects on both aerobic and anaerobic bacteria due to the super oxide enzyme's action, which is faster at greater oxygen tensions (30 to 40 mm Hg) [26]. Aminoglycosides, trimethoprim, nitrofurantoin, and sulfisoxazole have all been demonstrated to have synergistic effects with HBOT [27].Additionally, HBOT causes hyperoxic vasoconstriction, which reduces capillary pressure and improves vascular permeability. Extravascular fluid resorption rises as a result of the reduction in trans capillary fluid transfer, reducing lower extremity edema [25, 28].

The development of new vessels through neovascularization allows HBOT to have a long-term influence on tissue oxygenation. The oxygen tension can only stay above baseline for hours after a hyperbaric treatment session. The intermittent interval of hypoxia and hyperoxia in wounds, on the other hand, is thought to start a cascade reaction that eventually induces neovascularization via, an increase in vascular endothelial growth factor [29].

In addition to improving mitochondrial function and neurotransmitter abnormalities, HBO treatment reduced inflammation and pain. The levels of tumor necrosis factor alpha were reduced in one animal research using hyperbaric pressure without extra oxygen, inflammation, discomfort, and edema were all reduced with HBO treatment [30, 31].

## Application of HBOT

During HBOT patient is given an increased oxygen pressure of 1.5 to 3 [ATA] throughout treatment. The therapy starts in a specially equipped single or multi-person hyperbaric chamber. The most usually utilized gas is 100% oxygen; however, it can potentially employ higher pressures, in which case the patients breathe pure oxygen through masks. Patients in a monoplace chamber are kept in pure oxygen and breathe directly from the outside air. In the multi-person chambers, on the other hand, each patient gets his own seat, where he breathes pure oxygen through a special mask or helmet and is in a normal atmosphere, albeit at higher pressure [32].

A single patient breathes directly pressured 100 % $O_2$ in a monoplace chamber. More than one patient breathes pressured 100 % $O_2$ through a head hood, mask, or endotracheal tube in the multiplace chambers [33].The terms HBOT and tropical O2 treatment should not be confused. The supply of O2 under pressure to a specific region of the body is called tropical $O_2$therapy [34].

### *1. Role of HBOT on Diabetic Wounds*

In a study conducted in 2019 to investigate the efficacy of HBOT on difficult-to-heal wounds utilizing thermal imaging and plainmetry its results indicated reduced wound surface area and improved microcirculation, as well as a drop in temperature on the thermal maps as a response to HBOT therapy [35].

HBOT strategy for wound treatment typically entails 60 to 120 sessions in a compression chamber with a pressure between 203 and 204 KPa. The patient inhales 100% oxygen through a mask during the session [36].

Diabetic foot wounds continue to be the leading cause of non-traumatic lower limb amputation. The success rate of HBOT in correctly selected individuals has been demonstrated to be as high as 70–80 %. HBOT, in conjunction with a multidisciplinary team of vascular surgeons, orthopedic surgeons, podiatrists, infectious disease physicians, and endocrinologists, can help reduce the number and severity of amputations, as well as downtime caused by delayed wound healing and its complications, such as prolonged immobilization and repeated infections. When compared to outcomes such as the cost of amputations, repeated debridement, hospital stay, after-care, social and psychological disability, it may also be cost-effective [37].

In a prospective study of 70 diabetic patients who received HBOT, Faglia et al.,[38] found that as compared to normal care, the rate of major amputations (transtibial or more proximal) was lower. Similarly, HBOT was found to reduce the incidence of major amputation in diabetic patients with foot ulcers in multiple other investigations [ 39, 40].

Several studies published literature reviews on HBOT as an adjuvant therapy in diabetic foot ulcers with and without peripheral arterial occlusive disease (PAOD) and concluded that there was

insufficient evidence at the time to support the routine use of HBOT as a standard adjunct to local and systemic wound care in diabetic patients with foot ulcers with and without PAOD [41-43].

Krankeet al., [44] revised their Cochrane review and meta-analysis on the treatment of chronic wounds in 2015, concluding that HBOT improves Diabetic Foot Ulcer (DFU) outcomes at 6 weeks but not at 1 year. Elraiyahet al., [45] discovered low-to-moderate-quality evidence to support the use of HBOT to prevent DFU amputations.

According to a study by Duzgun et al., [46] the use of HBOT in the treatment of diabetic foot ulcers enhanced the prevalence of healing and decreased the incidence of amputations, and none of the amputations were located proximal to the metatarsophalangeal joints. Furthermore, HBOT seems to lessen the need for more expensive and technically challenging surgical procedures such as skin flaps and grafts, as well as amputations and debridement. The results of this study concluded that HBOT is a helpful addition in the treatment of no healing diabetic foot ulcers, and also that the cost of HBOT will decrease and will become more widely available in the clinical setting and as more awareness of its other benefits, such as limited side effects and relative safety, expands.

In a meta-analysis of the efficacy of HBOT on diabetic foot ulcers, Sharma et al.,[47] found that HBOT was related with higher rates of completely healed DFUs and lower rates of major amputation. However, it had no effect on the rate of minor amputations, all-group amputations, death, or mean percent of ulcer size reduction. When compared to HBOT, the usual treatment group had fewer side effects.

### *2. Role of HBOT on Non-Ischemic DFU*

In prospective randomized research conducted by Kessler, he found that HBO doubles the mean healing rate of nonischemic chronic foot ulcers in diabetic patients. It also suggests that the hospitalization period could be shortened [25].

Khandelwal et al. studied 60 patients with non-ischemic diabetic foot ulcers in grades III and IV. Patients were randomly assigned to one of three groups: antiseptics, hyperbaric oxygen therapy, or recombinant platelet derived growth factor, with 20 patients in each group. The writers came to the conclusion that HBO is a good alternative, however it has some drawbacks and adverse effects[48].

HBOT patients were given once daily treatments for 5 days a week, with 2 days off, for a total of 20 to 40 sessions, depending on the ulcer response, in a trial to explore the effect of HBOT on non-ischemic diabetic foot. In a % oxygen atmosphere, the program started with a steady increase in pressure to the authorized treatment pressure of around 2.5 ATA over 10 to 15 minutes. One hour was spent "at pressure" during the procedure. Then, over the course of 10 to 15 minutes, progressive decompression was performed, along with standard treatment, which included initial surgical debridement, antibiotics, and a topical moist saline bandage on a daily basis.Incertain cases, debridement was repeated and proper plantar decompression was performed. The researchers noted that HBOT combined with standard therapy for the healing of chronic diabetic nonischemic foot wounds seems to be as safe as, if not more effective than, standard therapy alone. To verify its role and long-term effect, more trials with longer periods of follow-up are necessary. [49].

Additional research found that 2 weeks of HBO treatment triggers a healing response in chronic DFUs. The Percentage decline in ulceration size after 2 weeks of HBO therapy

was considerably higher than the control group, implying that HBO had a beneficial effect on ulcer healing. At the same time, the findings revealed that HBO therapy can cause oxidative stress in local ulcer tissue, which can build up and obstruct long-term healing. More research is needed to confirm the effectiveness of HBOT in the treatment of DFUs, according to the authors[50].

Diabetics and lower-extremity ulcers treated with growth factor therapy and HBO had higher healing rates than those treated with routine wound care, according to a descriptive, retrospective study. According to the authors, those who received HBO as part of their wound care regimen healed faster than those who got traditional treatment or growth factor therapy[51].

HBOT, on the other hand, does not increase wound healing or eliminate major or minor amputations in patients with DFU who do not have peripheral artery occlusive disease, according to a systematic review and meta analysis. They suggested that more study be done, with a particular focus on patient selection criteria for HBOT[ 52].

### *3. Role of HBOT on ischemic DFU*

Stone et al. compared HBOT (n = 119) against conventional therapy alone (n = 382) in a large retrospective case control study of 501 patients with diabetes mellitus and ischemic wounds. Patients who received HBOT were sicker than those who received normal care, with larger and more wounds per patient. Despite this, the HBOT group had a much higher percentage of limb salvage (72 percent vs. 53 percent; p 0.002) than the control group [53].

Because of the presence of local arterial insufficiency in diabetic foot ulcers (DFUs) with peripheral arterial occlusive disease (PAOD), hyperbaric oxygen therapy (HBOT) has been proposed as a useful adjunct in the complex treatment of DFUs with PAOD [47] whereas recent evidence on HBOT for DFUs is still ambiguous [48-50, 54].HBOT is a treatment that involves inhaling 100%

oxygen at two to three times the normal atmospheric pressure in a hyperbaric chamber, resulting in increased oxygen tension in arteries and tissue it improves transcutaneous oxygen pressure measurement and local tissue oxygenation (TcpO2) [55-58].

In a double-blind trial conducted by Abidia et al., in 2003[59], eighteen diabetic patients with ischemic, non-healing lower-extremity ulcers were enrolled. For 90 minutes daily, patients were randomly randomized to either 100% oxygen (treatment group) or air (control group) at 2.4 atmospheres absolute pressure (total of 30 treatments). Five out of every eight ulcers in the treatment group healed completely epithelialized, compared to one out of every eight ulcers in the control group. The treatment group had a 100 % reduction in wound areas, while the control group had a 52 % reduction ($p = 0.027$). Despite the additional cost of employing hyperbaric oxygen, a cost-effectiveness analysis revealed that the overall cost of treatment for each patient during the research might be reduced. Hyperbaric oxygen improved the healing of ischemic, non-healing diabetic leg ulcers, according to the authors, and could be utilized as a helpful addition to standard therapy when reconstructive surgery is not possible

Margolis et al., (2013), on the other hand, did a cohort trial to evaluate the efficacy of HBO with other conventional therapies provided in a wound care network for the treatment of a diabetic foot ulcer and the prevention of lower-extremity amputation. In a study of 6.259 diabetic patients, the authors discovered that HBO did not appear to be effective in preventing amputation or improving the likelihood of a wound healing in a group of patients [60].

In addition, Fedeorko et al., (2016) found that HBOT does not provide an additional benefit to comprehensive wound management in terms of minimizing the need for amputation or facilitating wound healing in patients with chronic diabetic foot ulcers [61].

HBOT has very few side effects, and they are usually mild. The most prevalent adverse effects are significant otic barotrauma, which can impact up to 10% of patients, or other pressure-related abnormalities affecting air-filled organs including the lungs, ear drums, or sinuses, which is why lower partial pressures are preferable. Central nervous system oxygen poisoning, which appears as a self-limiting grand mal seizure, is a very seldom documented adverse event with a reported incidence of 1:10,000–50,000 patients. Individuals undertaking lengthy treatment courses have also reported myopia, which is usually reversible, as well as a drop in blood glucose in diabetic patients [62-64]. Chronic obstructive pulmonary disease (COPD) is a relative contraindication for HBOT, as air trapping and pulmonary over pressurization can cause pneumothorax and arterial gas embolism [65-67].

## 4. HBOT in the treatment of DFU in animals:

HBOT uses 100% oxygen in most veterinary clinical conditions. The frequency of treatment and the amount of pressure (ATA) used are both decisions made at the discretion of the physician Common treatment pressures are usually within a range of 1.3 to 2.8 ATA [68].

The hypothesis that hyperbaric oxygen therapy would alleviate the effect of stress on wound repair in an animal model of stress-impaired healing was evaluated using a mouse model of stress-impaired healing. Early wound healing using hyperbaric oxygen therapy (HBO) twice a day reduced the impact of stress and brought healing to near-control levels. The wounds of control animals were not significantly affected by HBO.Real-time PCR was used to investigate the gene expression of wound inducible nitric oxide synthase (iNOS), which is controlled by psychological stress and oxygen balance. After injury, iNOS expression increased in stressed mice on days 1 (205 %; p.0001), 3 (96 %; p.03), and 5 (249 %; p.03). Day 1 post-wounding, HBO therapy reduced

iNOS expression by 62.6 % (p.02). There was no significant effect of HBO on wound healing and iNOS expression in the control animals[69].

Monoplace chambers are most typically employed in veterinary medicine, which poses difficulties for better accessibility and monitoring of vital signs, electrocardiograms, and oxygenation parameters if problems emerge. Despite the fact that HBOT chambers may be rapidly decompressed, depending on where the patient is in their treatment cycle, this could take several minutes, raising worries about barotrauma and decompression sickness. Some chambers have built-in monitors or pass-through ports that allow for monitoring, intravenous therapy, or mechanical breathing during HBOT, alleviating some of these problems,person should also receive sufficient training in patient monitoring, chamber safety, and operations [70].

In a diabetic rat model, Prabowoet al assessed the efficiency of HBOT in wound healing and organ viability. Streptozotocin (20 mg/kg sc) was used to induce diabetes in male Wistar rats (n = 10) for three days. The rats were treated HBOT (2.3 ATA for 1 h/day) or were not treated after a wound was induced on the skin over their backs. Blood glucose levels, pancreatic-cell destruction, diabetic nephropathy, and wound healing were all measured. When compared to controls, diabetic rats who were not given HBOT had significantly higher blood glucose levels (26.7 3.3 mmol/L vs. 5.8 0.4 mmol/L; P 0.05). This was linked to a considerable increase in the percentage of -cell destruction (72 percent 9 percent vs. 10% 2 percent; P 0.05) as well as diabetic nephropathy. In diabetic rats, HBOT for three days or longer lowered hyperglycemia to normal levels.. Pancreatic-cell destruction was minimal in rats given HBOT for five days or longer, but nephropathy was reduced in those given HBOT for ten days. From 5 days of HBOT, healing and epithelial closure were both accelerated [71].

Açiksari et al. 2019 conducted another investigation in 32 rats after 60 minutes of acute mesenteric ischemia followed by reperfusion. The goal of this research was to see if HBOT could help the rats' intestinal mucosa repair. The HBOT therapy resulted in a reduction in pre- and post-ischemia-induced lesion size, as well as enhanced cell viability via caspase-3 reduction, enhanced CD34 stem cells, and elevated VEGF [72].

Numerous studies in mammals have shown that multiple HBOT therapies increase vascularization and blood flow in complex laser Doppler flowmetry (LDF) was used to quantify blood circulation in regenerating soft tissue in rats in a study. Vasculature increased not just during the treatments, but also weeks after the therapies ended, showing that the treatment options had a long-term impact on tissue oxygenation [73].

**CONCLUSION**

The current review investigated at how HBOT affected diabetic wounds, ischemic and nonischemic ulcers, and animal trials. Most of the research that were gathered suggested that it can be utilized for both acute and chronic diabetic foot ulcers because it enhances oxygen delivery to the tissues, promotes angiogenesis, wound healing, and immune response via cell signaling. Direct bacteriostatic or bactericidal activity, immune system antimicrobial effects, and additive or synergistic effects with certain antibiotics all help with illness recovery. Because of the low prevalence of adverse effects, HBOT is usually recognized as a safe therapeutic choice. More narrative reviews are needed to assess the effect of HBOT on the various forms of diabetic foot ulcers.

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