Insight on hyperbaric oxygen therapy as an adjunctive treatment in diabetic foot ulcer

ABSTRACT

Diabetic foot ulcers (DFU) are a source of major concern for both patients and health care systems. Diabetic foot ulcers are indeed a major source of concern for patients and healthcare providers worldwide. DFU is the most costly 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 and collagen synthesis. 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, sensori-neural hearing loss and rheumatologically conditions [9-12], even though the exact mechanism of action of HBO and its effect on the individual medical condition treated is still unidentified. 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].

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 [17- 20]. 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) [21]. Aminoglycosides, trimethoprim, nitrofurantoin, and sulfisoxazole have all been demonstrated to have synergistic effects with HBOT [22]. 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 [20, 23].

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 [24].

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 [25, 26].

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 [27].

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 [28]. 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 [29].

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 [30].

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 [31].

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 [32].

In a prospective study of 70 diabetic patients who received HBOT, Faglia et al., [33] 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 [34,35].

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 [36-38].

Kranke et al., [39] 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., [40] discovered low-to-moderate-quality evidence to support the use of HBOT to prevent DFU amputations.

According to a study by Duzgun et al., [41] 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 nonhealing 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., [42] 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 [20].

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 [43].

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 [44].

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 [37] whereas recent evidence on HBOT for DFUs is still ambiguous [38-40, 45]. 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) [46-49].

In a double-blind trial conducted by Abidia et al., in 2003 [50], 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 [51].

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 [52].

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 [53-55]. 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 [56-58].

CONCLUSION

HBOT is a treatment that can be used for both acute and chronic diabetic foot ulcer. HBOT enhances infection recovery by direct bacteriostatic or bactericidal actions, immune system antimicrobial effects, and additive or synergistic effects with specific antibiotics. HBOT is widely regarded as a safe therapeutic option, as evidenced by the low incidence of side effects.

REFERENCES

1. Apelqvist J. Diagnostics and treatment of the diabetic foot. Endocrine. 2012;41:384–97.
2. Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. Ontario health technology assessment series. 2017;17(5):1.
3. Ragnarson Tennvall G, Apelqvist J: Health-economic consequences of diabetic foot lesions. Clin Infect Dis 2004; 39(Suppl. 2): S132– S139 .
4. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, Boulton AJ: The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabet Med 2001; 18: 133– 138.
5. Gershater MA, Löndahl M, Nyberg P, Larsson J, Thörne J, Eneroth M, Apelqvist J: Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia 2009; 52: 398– 407.
6. Nikoloudi M, Eleftheriadou I, Tentolouris A, et al. Diabetic foot infections: update on management. Curr Infect Dis Rep 2018; 20:40.

7. Lipsky BA, Aragón-Sánchez J, Diggle M, et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev 2016; 32Suppl 1:45–74.
8. Ortega MA, Fraile-Martinez O, García-Montero C, Callejón-Peláez E, Sáez MA, Álvarez-Mon MA, García-Honduvilla N, Monserrat J, Álvarez-Mon M, Bujan J, Canals ML. A General Overview on the Hyperbaric Oxygen Therapy: Applications, Mechanisms and Translational Opportunities. Medicina. 2021 Sep; 57(9):864.
9. Buettner MF, Wolkenhauer D. Hyperbaric oxygen therapy in the treatment of open fractures and crush injuries. Emergency medicine clinics of North America. 2007 Feb 1; 25(1):177-88.
10. Fang RC, Galiano RD. Adjunctive therapies in the treatment of osteomyelitis. In Seminars in plastic surgery 2009 May Vol. 23, No. 02, pp. 141-147.
11. Rhee TM, Hwang D, Lee JS, Park J, Lee JM. Addition of hyperbaric oxygen therapy vs medical therapy alone for idiopathic sudden sensorineural hearing loss: a systematic review and meta-analysis. JAMA otolaryngology–head & neck surgery. 2018 Dec 1; 144(12):1153-61.
12. Barilaro G, Francesco Masala I, Parracchini R, Iesu C, Caddia G, Sarzi-Puttini P, Atzeni F. The role of hyperbaric oxygen therapy in orthopedics and rheumatological diseases.
13. Singer AJ, Clarck RAF: Cutaneous wound healing. N Engl J Med 341:738–746, 1999.
14. Meltzer T, Myers B: The effect of hyperbaric oxygen on the bursting strength and the rate of vascularization of skin wounds in the rat. Am Surg 52:659–662, 1986.

15. Roberts GP, Harding KG: Stimulation of glycoaminoglycan synthesis in cultured fibroblasts by hyperbaric oxygen. Br J Derm 131:630–633, 1994.
16. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A: Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. Diabetes Care19:1338– 1343, 1996.
17. Shiratsuch H, Basson MD. Differential regulation of monocyte/macrophage cytokine production by pressure. Am J Surg 2005; 190:757- 62.
18. Sheffield, J.P. Tissue oxygen measurements J.C. Davis, T.K. Hunt (Eds.), Problem Wounds: The Role of Oxygen, Elsevier, New York (1988), pp. 17-51.
19. Cianci P. Salvage of the problem wound and potential amputation with wound care and adjunctive hyperbaric oxygen therapy: an economic analysis. J Hyperbar Med. 1988;3:127-41.
20. Kessler L, Bilbault P, OR Tega FR, Grasso C, Passemard R, Stephan D, Pinget M, Schneider F. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes care. 2003 Aug 1;26(8):2378-82.
21. Jain, K. K. Physical, physiological and biochemical aspects of hyperbaric oxygenation Jain KK, Neubauer R, Correa JG (Eds.), Textbook of Hyperbaric Medicine, Hogrefe & Huber, Toronto (1990), pp. 480-495.
22. Brakora MJ, Sheffield PJ. Hyperbaric oxygen therapy for diabetic wounds. Clinics in podiatric medicine and surgery. 1995 Jan;12(1):105..

23. Strauss MB. Crush injury and other acute traumatic peripheral ischemias. Hyperbaric Medicine Practice. 1994:525-49.
24. Hopf HW, Kelly M, Shapshak D. Oxygen and the basic mechanisms of wound healing. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia: Saunders. 2008 Jan 1:203-28.
25. Shiratsuch H, Basson MD. Differential regulation of monocyte/macrophage cytokine production by pressure. Am J Surg 2005; 190:757‐ 62.
26. Inamoto Y, Okuno F, Saito K, Tanaka Y, Watanabe K, Morimoto I, et al. Effect of hyperbaric oxygenation on macrophage function in mice. Biochem Biophys Res Commun1991; 179:886‐ 91.
27. Huang ET, Mansouri J, Murad MH, Joseph WS, Strauss MB, Tettelbach W, Worth ER. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med. 2015; 42(3):205–47.
28. Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen therapy: Antimicrobial mechanisms and clinical application for infections. Biomedicine & Pharmacotherapy. 2019 Jan 1; 109:440-7.
29. Shah, J. Hyperbaric oxygen therapy J. Am. Col. Certif. Wound Spec., 2 (1) (2010), pp. 9-13.
30. Englisz-Jurgielewicz B, Cholewka A, Firganek E, Knefel G, Kawecki M, Glik J, Nowak M, Sieroń K, Stanek A. Evaluation of hyperbaric oxygen therapy effects in hard-to-heal

wounds using thermal imaging and planimetry. Journal of Thermal Analysis and Calorimetry. 2019 Dec 9:1-1.

31. Santema TB, Stoekenbroek RM, van Steekelenburg KC, van Hulst RA, Koelemay MJ, Ubbink DT. Economic outcomes in clinical studies assessing hyperbaric oxygen in the treatment of acute and chronic wounds. Diving Hyperb Med. 2015 Dec 1;45(4):228-34.
32. Ong M. Hyperbaric oxygen therapy in the management of diabetic lower limb wounds. Singapore medical journal. 2008 Feb 1;49(2):105.
33. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Barbano P, Puttini M, Palmieri B, Brambilla G, Rampoldi A, Mazzola E. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. Journal of Diabetes and its Complications. 1998;12(2):96-102.
34. Kalani M, Jörneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers: Long-term follow-up. J Diabetes Complications. 2002;16(2):153-8.
35. Roeckl-Wiedmann I, Bennett M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. Br J Surg. 2005;92(1):24-32.
36. O'Reilly D, Pasricha A, Campbell K, Burke N, Assasi N, Bowen JM, et al. Hyperbaric oxygen therapy for diabetic ulcers: systematic review and meta-analysis. Int J Technol Assess Health Care 2013;29:269-81.
37. Stoekenbroek RM, Santema TB, Legemate DA, Ubbink DT, Van Den Brink A, Koelemay MJW. Hyperbaric oxygen for the treatment of diabetic foot ulcers: A systematic review. Eur J Vasc Endovasc Surg 2014;47:647-55.

38. Zhao D, Luo S, Xu W, Hu J, Lin S, Wang N. Efficacy and safety of hyperbaric oxygen therapy used in patients with diabetic foot: a meta-analysis of randomized clinical trials. Clin Ther 2017;39:2088-94.
39. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2015:Cd004123.
40. Elraiyah T, Tsapas A, Prutsky G, Domecq JP, Hasan R, Firwana B, et al. A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. J Vasc Surg2016;63(2 Suppl):46S-58S.
41. Duzgun AP, Satır HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. The Journal of foot and ankle surgery. 2008 Nov 1;47(6):515-9.
42. Sharma R, Sharma SK, Mudgal SK, Jelly P, Thakur K. Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of controlled clinical trials. scientific reports. 2021 Jan 26;11(1):1-2.
43. Khandelwal S, Chaudhary P, Poddar DD, Saxena N, Singh RA, Biswal UC. Comparative study of different treatment options of grade III and IV diabetic foot ulcers to reduce the incidence of amputations. Clinics and practice. 2013 Jan;3(1):20-4.
44. Stone JA, Scott R, Brill LR, et al. The role of hyperbaric oxygen in the treatment of diabetic foot wounds. Diabetes 1995; 44(suppl-1): 71A.
45. Golledge J, Singh TP. Systematic review and meta- analysis of clinical trials examining the effect of hyperbaric oxygen therapy in people with diabetes- related lower limb ulcers. Diabetic Medicine. 2019 Jul;36(7):813-26.

46. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. New Engl J Med 1996;334:1642-8.
47. Löndahl M, Katzman P, Hammarlund C, Nilsson A, Landin-Olsson MJD. Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and anklebrachial index in patients with diabetes and chronic foot ulcers. Diabetologia2011;54:65-8.
48. Rollins MD, Gibson JJ, Hunt TK, Hopf HW. Wound oxygen levels during hyperbaric oxygen treatment in healing wounds. Undersea Hyperb Med 2006;33:17-25.
49. Sheffield PJ. Measuring tissue oxygen tension: a review. Undersea Hyperb Med 1998;25:179-88.
50. Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, Masson EA, McCollum PT. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. European journal of vascular and endovascular surgery. 2003 Jun 1;25(6):513-8.
51. Margolis DJ, Gupta J, Hoffstad O, Papdopoulos M, Glick HA, Thom SR, Mitra N. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. Diabetes care. 2013 Jul 1;36(7):1961-6.
52. Fedorko L, Bowen JM, Jones W, Oreopoulos G, Goeree R, Hopkins RB, O'Reilly DJ. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care. 2016 Mar 1; 39(3):392-9.
53. Heyboer M, Sharma D, Santiago W, Mcculloch N. Hyperbaric oxygen therapy: side effects defined and quantified. Adv Wound Care. 2017;6(6):210–24.

54. Davis JC. Hyperbaric oxygen therapy. J Intensive Care Med. 1989; 4:55–7.
55. Camporesi EM. Side effects of hyperbaric oxygen therapy. Undersea Hyperb Med 2014; 41:253-7.
56. Wilkinson D, Chapman IM, Heilbronn LK. Hyperbaric oxygen therapy improves peripheral insulin sensitivity in humans. Diabet Med. 2012; 29:986–9.
57. Fife WP, Fife CE. Hyperbaric oxygen therapy in chronic lyme disease. In: Jain KK, editor. Textbook of hyperbaric Medicine. 5thed.Göttingen: Hogrefe; 2009. Pp.149–55.
58. Fife CE, Eckert KA, Workman WT. Ethical issues, standards and quality control in practice of hyperbaric medicine. In: Jain KK, editor. Textbook of hyperbaric medicine. 6th ed. New York, NY: Springer; 2016.