Canadian Diabetes Association Technical Review: The Diabetic Foot and Hyperbaric Oxygen Therapy

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ABSTRACT

Foot ulcers are a significant source of morbidity, mortality and diminished quality of life for patients with diabetes. Hyperbaric oxygen therapy (HBOT) has been proposed as a possible treatment. In this technical review, the results of clinical trials on the use of HBOT for diabetic foot ulcers are reviewed.

Many of the studies examining the role of HBOT in the treatment of diabetic ulcers have been retrospective, nonrandomized and noncontrolled. In addition, most studies have included small patient populations with heterogeneous classes of ulcers. However, results of these studies suggest that HBOT may accelerate wound healing and reduce amputation in a subset of patients with diabetic ulcers. Most patients with Wagner grade 1 and 2 ulcers will heal with carefully administered conventional care (local wound care and efficacious offloading). Appropriate candidates for HBOT are patients with long-standing nonhealing Wagner grade 3 or higher ulcers with an adequately perfused capillary bed in the wound area (best assessed by the transcutaneous oxygen tension [$TcPO_2$] response to 100% oxygen challenge).

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RÉSUMÉ

Les ulcères du pied sont une importante source de morbidité, de mortalité et de baisse de la qualité de vie chez les personnes diabétiques. On a proposé l'oxygénothérapie hyperbare (OTHB) comme traitement possible. Dans cette analyse technique, on examine les résultats d'essais cliniques sur l'usage de l'OTHB pour les ulcères du pied diabétique.

Un grand nombre d'essais ayant évalué le rôle de l'OTHB pour le traitement des ulcères diabétiques ont été rétrospectifs, non randomisés et non contrôlés. De plus, la plupart des essais ont porté sur de petites populations de patients présentant des ulcères de classes hétérogènes. Les résultats de ces essais laissent cependant entendre que l'OTHB peut accélérer la cicatrisation et réduire le nombre d'amputations dans un sous-groupe de patients présentant des ulcères diabétiques. La plupart des patients qui présentent des ulcères aux stades 1 et 2 selon la classification de Wagner obtiennent une guérison lorsque le traitement classique est administré avec soin (soin local des plaies et redistribution de la pression). Les candidats à qui l'OTHB convient sont ceux qui souffrent d'ulcères de longue date au stade 3 ou plus selon la classification de Wagner et dont le lit capillaire est suffisamment irrigué dans la région de la plaie (la meilleure évaluation est la réponse de la $TcPO_2$ au test à l'oxygène). Néanmoins, il n'existe pas de critères fondés sur des données probantes pour choisir des patients pour recevoir l'OTHB et pour prédire la réponse. Même si l'OTHB est coûteuse, elle est un ajout raisonnable et rentable au traitement classique. Il faudra effectuer des études prospectives pour évaluer le succès à long terme de l'OTHB.

Nonetheless, there are no evidence-based criteria to select patients for HBOT and to predict their response. Although costly, HBOT is a reasonable, cost-effective adjunct to standard therapy. Prospective studies are needed to assess the long-term success of HBOT.

INTRODUCTION

Diabetic foot ulcers are estimated to affect 15% of people with diabetes during their lifetime (1). These lesions are responsible for more hospital days than any other complication of diabetes (2). Epidemiologic data also suggest that foot ulcers precede 85% of amputations (1). People with diabetes have a 15-fold greater risk of lower-extremity amputation than those without diabetes (1). Patients who are >40 years of age and whose diabetes was diagnosed at least 10 years earlier are at highest risk (3). Similarly, more than half of lower-limb amputations in the United States are performed on people with diabetes (1). Within 1 year after an amputation, 9 to 20% of patients with diabetes undergo a second (ipsilateral or contralateral) amputation. Mean perioperative mortality among amputees with diabetes was 5.8% in the 1990s. Five-year mortality following amputation varies between 39 and 68% (1).

There is a tremendous need for treatments that will reduce the human and economic burden and loss associated with diabetic foot ulcers and lower extremity ulcerations. As tissue hypoxia is one of the pathophysiological characteristics of diabetic ulcers, hyperbaric oxygen therapy (HBOT) has been considered as a therapeutic strategy to reduce tissue hypoxia and enhance wound healing. However, there are no uniform and evidence-based guidelines for treatment of the diabetic foot with hyperbaric oxygen. In this technical review, the results of clinical trials on the use of HBOT for diabetic foot ulcers are reviewed.

PATHOGENESIS OF DIABETIC FOOT LESIONS

The pathological changes leading to amputation in people with diabetes result from a combination of events, including peripheral neuropathy, peripheral vascular disease, autonomic neuropathy, foot deformities, trauma, ulceration and infection (4,5). A critical triad of neuropathy, minor foot trauma and foot deformity was found in >63% of people with foot ulcers (6).

Neuropathy

The most common long-term complication of diabetes is neuropathy. It can involve any part of the body and affects 60 to 70% of people with diabetes. The most common type of diabetic neuropathy is peripheral neuropathy, which specifically affects the lower limbs and the hands. It is a distal symmetric sensorimotor polyneuropathy.

The symptoms evolve from pain, burning and tingling to partial and, in a small proportion of patients, a total loss of sensation. The loss of pain sensation leads to various lesions induced by mechanical stress (e.g. foreign body in the shoe, ill-fitting shoe and repetitive stress of walking) or by thermal or chemical injury. The motor nerve damage of the peripheral neuropathy results in interosseous muscle atrophy that induces muscular imbalance with characteristic angled toes and thinning of fat pads over metatarsal heads. The combination of sensory and motor neuropathy is the most significant factor in the pathway leading to lower-extremity ulceration and is found in 80 to 85% of all cases (4,6).

Peripheral vascular disease

Peripheral vascular disease (or atherosclerosis of the peripheral arteries) is 4 times more likely to develop in people with diabetes than in the general population (4). The incidence increases with age and duration of diabetes. Changes in the microcirculation of the diabetic foot contribute to impaired wound healing and constitute a major risk factor for ulceration and amputation. Peripheral vascular disease is involved in 50% of lower extremity amputations (7). Thickening of the basement membrane is 1 of the structural changes that can be observed (8). These modifications do not lead to narrowing of the lumen, but they decrease the elastic properties and therefore impede the dilation capacity of vessels. As a result, the neuropathic diabetic foot should be considered functionally ischemic regardless of the presence or absence of vascular disease (9). As the basement membrane is thicker, it also decreases the ability of the diabetic foot to fight infection (10). Calcification of the media of arteries (Mönckeberg arteriosclerosis) increases the vulnerability of insensitive feet.

Autonomic neuropathy

Diabetes also harms the autonomic or sympathetic nerves that innervate the small blood vessels of the lower extremities. This causes a loss of constrictive tone, resulting in vasodilatation and arteriovenous shunting, increased peripheral perfusion, and accelerated bone resorption and osteopenia (11,12). Autonomic neuropathy also leads to decreased activity of the sweat glands of the feet, which results in skin that is prone to dryness and fissuring—factors that predispose to infection (13).

BIOMECHANICS OF FOOT PROBLEMS

The normal mechanics of the foot and ankle result from the combined effect of muscles, tendons, ligaments and bone function. Muscle wasting and loss of muscle function due to

neuropathy lead to foot deformities in 50% of individuals with diabetes (14). Abnormalities in foot biomechanics result in a dysfunctional gait and lead to more damaging changes in the foot (15). Altered foot biomechanics, limited joint mobility and bone deformities are associated with an increased risk of ulceration and amputation. Diabetic ulcers can occur on any part of the foot, but they are most often observed on the plantar surfaces because of the increased pressure during walking (16). The combination of distal symmetric polyneuropathy and peripheral autonomic neuropathy can lead to neuropathic osteoarthropathy or Charcot deformity. The decreased sensation to trauma caused by neuropathic sensory loss brings about repeated microscopic fractures and intensified osseous response to healing.

FOOT ULCER CLASSIFICATION

Foot ulcers are defined as a break in the cutaneous barrier usually extending through the full thickness of the dermis (17). Various proposals have been set forth to classify diabetic foot ulcers, but generally the wounds are categorized as either ischemic or neurologic. The most frequently used foot ulcer classification system is the Wagner grading scale (18,19) (Table 1). Authors seem to agree that the key issues in wound classification are the depth of the tissue affected and the adequacy of arterial supply to the foot.

PREVENTION AND INTERVENTION STRATEGIES

Prevention is the best approach to diabetic foot ulcers. Tight glycemic control and patient education are the most important components of a prevention program. The approaches most likely to forestall foot ulcers include regular podiatric care with early and aggressive treatment of new lesions, vascular examinations, use of protective shoes, pressure reduction with insoles and ortheses, prophylactic surgery to correct biomechanical foot deformities, and patient and physician preventive education (15,16)

Standard care of diabetic foot ulcers includes good glycemic control, adequate nutrition, off-loading (via bed rest or casts), local care (moist dressings and topical management), lessening of edema, surgical debridement of devitalized wound tissue, antibiotic therapy, granulocytecolony-stimulating factor (G-CSF) and, if needed, vascular surgery, (5,14,20-23). However, wounds that fail to respond to optimal conventional medical and surgical treatment in a reasonable time frame are common. In these situations, HBOT could be considered.

Table 1. Wagner's classification for lesions of the foot (19)

Grade	*Classification*
Grade 0	Cellulitis
Grade 1	Superficial ulcer
Grade 2	Deep ulcer
Grade 3	Deep abscess, osteomyelitis
Grade 4	Forefoot gangrene
Grade 5	Foot gangrene

IMPAIRED WOUND HEALING

Role of oxygen in wound healing

Injuries that damage the microvasculature attract inflammatory cells that consume large amounts of oxygen and concentrate potentially damaging products at the wound site. This creates a low-oxygen environment with low pH, high lactate, increased oxidant production and poor local perfusion. The macrophages respond to this environment by releasing growth factors that induce angiogenesis, multiplication of fibroblasts and collagen synthesis. Therefore, acute wound hypoxia is, to a certain extent, necessary for leukocyte adherence, neovascularization, collagen formation and bone formation (24). However, oxygen availability becomes essential in 2 steps of collagen biosynthesis—proline and lysine are incorporated into growing peptides and hydroxylated when they enter the endoplasmic reticulum. When the PO_2 is 20 mm Hg, this process evolves at half the normal rate; when the PO_2 is 200 mm Hg, this process evolves at 90% of the optimal rate. Moreover, cell multiplication also requires oxygen. An oxygen environment of 40 mm Hg is needed to ensure fibroblast activity (25). Therefore, chronic wound hypoxia weakens the collagen synthesis process (24,26).

Role of oxygen in infection susceptibility

It has been demonstrated that leucocytes kill bacteria most effectively in an environment abundant in oxygen (27). In fact, phagocytosis induces the conversion of oxygen to peroxides, which are lethal to many bacteria. This oxidative reaction demands very high levels of oxygen and is most effective with a high PO_2 (24,26). Therefore, hypoxia impairs the bacteria-killing function of leucocytes.

Role of oxygen in wound angiogenesis

Some regulatory mechanisms involved in the stimulation and regulation of angiogenesis are comparable to those implicated in collagen synthesis and deposition. Oxygen stimulates macrophages to produce angiogenic substances (like vascular endothelial growth factor [VEGF]) that attract and stimulate endothelial cells (26). Therefore, hypoxia weakens the neovascularization process.

HBOT

HBOT has been used since 1943, the year it was adopted by the United States Navy for the treatment of decompression

sickness and air embolism. Over the past 50 years, HBOT has been used for a wide variety of medical conditions, often without acceptable scientific evidence of efficacy or safety. Consequently, a high degree of scepticism has developed regarding its use. However, in the last 20 years, several trials have demonstrated the benefits of HBOT for various conditions. The Undersea and Hyperbaric Medical Society (UHMS), which approves the use of HBOT for a few conditions (20,24) (Table 2), defines HBOT as the "intermittent administration of 100% oxygen inhaled at pressure greater than sea level" (5).

Mechanism of action

The treatment is conducted in a pressure-containment vessel called a hyperbaric, recompression or decompression chamber. It can be administered in either a "monoplace" or "multiplace" setting. In the monoplace setting, the chamber is pressurized with oxygen and the patient breathes the ambient chamber environment, which is 100% oxygen. The multiplace chamber is pressurized with air and patients breathe 100% oxygen through a mask (28). HBOT given in monoplace or multiplace chambers is frequently referred to as systemic hyperbaric oxygen therapy,

The effects of HBOT are 2-fold—those associated with high pressure and those associated with high PaO_2 (29). The increased pressure decreases the volume of gases. This characteristic is used to treat gas embolism or decompression accidents. Increased PaO_2 is the second attribute. Each hemoglobin molecule in a human red blood cell has 4 oxygen-binding sites. At sea level, most people have complete saturation of these red cell-binding sites. Therefore, the levels of oxygen dissolved in the plasma are very low. At sea level, the partial pressure of arterial oxygen (the part of total blood pressure exerted by oxygen gas [PaO_2]) is around 100 mm Hg. When a patient is placed in a hyperbaric chamber, the chamber is pressurized to 2 to 3 atmospheres and the patient is administered 100% oxygen. Once the hemoglobin-binding sites are saturated, dissolved oxygen increases in the plasma. The PaO_2 and the diffusion gradient of the dissolved oxygen increase and reach the compromised tissues. The PaO_2 approaches 1500 mm Hg (30). This pressure is equivalent to diving to approximately 15 m (50 feet) in seawater.

Table 2. Undersea and Hyperbaric Medical Society-approved indications for hyperbaric oxygenation (24)

- Air or gas embolism
- Carbon monoxide/cyanide poisoning
- Gas gangrene
- Crush injury, compartment syndrome and other acute traumatic ischemia
- Decompression sickness
- Enhancement of healing in selected problem wounds
- Exceptional blood loss (anemia)
- Intracranial abscess
- Necrotizing soft-tissue infections
- Refractory osteomyelitis
- Soft tissue/bone radiation necrosis
- Compromised skin grafts and flaps
- Thermal burns

RATIONALE FOR USE OF HBOT

Tissue hypoxia is an important mechanism contributing to the development of diabetic foot infections and impaired wound healing. Human studies have shown that HBOT is effective in radiotherapy-induced hypoxia (31). Therefore, it seems logical that HBOT could be helpful for diabetic foot ulcers. As explained earlier, oxygen is essential in wound healing and wound angiogenesis. Hyperbaric oxygen exposure increases tissue oxygen levels and thereby results in increased cellular proliferation, improved collagen synthesis and increased angiogenesis. Furthermore, anaerobic organisms are found in low oxygen-tension tissues, which are present in one-third of cases of diabetic foot infections (32). HBOT increases the killing ability of leukocytes and is lethal to certain anaerobic bacteria (22,24,26,32). Edema in the periwound area is decreased through the vasoconstrictive action of oxygen and the leukocyte-bacterial-killing ability. HBOT enhances phagocytosis of bacteria and inhibits toxin formation (24,32,33) (Table 3).

TOPICAL HBOT

HBOT given in monoplace or multiplace chambers should not be confused with topical hyperbaric oxygen therapy (THOT) or pure oxygen inhaled at ambient atmospheric pressure. In a double-blind, randomized, controlled trial of 28 patients, THOT applied to the affected extremity applied for 2 weeks was not shown to be beneficial in healing diabetic foot ulcers (34). In 2 more recent non controlled studies by Landau and colleagues, THOT combined with low-energy laser appeared to promote wound healing (35,36). In 1 study, 50 patients with diabetic foot ulcers were treated with THOT alone (n=15) or in combination with low-energy laser (n=35) for a mean duration of 3 months (35). Healing of the ulcer occurred in 86% of the patients, with no clinical difference seen between the patients in the 2 intervention

Table 3. Beneficial effects of hyperbaric oxygenation in wound healing (24)

- Decreased local tissue edema
- Improved cellular energy metabolism
- Improved local tissue oxygenation
- Improved leukocyte-bacterial-killing ability
- Increased effectiveness of antibiotics
- Enhanced uptake of platelet-derived growth factor
- Promotion of collagen deposition
- Promotion of neoangiogenesis

groups. In the other study, 100 consecutive patients with chronic diabetic foot ulcers were treated with THOT in combination with low-energy laser for a mean duration of 3.2±1.7 months. The authors observed a healing rate of 81% in patients who had previously not responded to a comprehensive treatment program. However, this study was open and uncontrolled and the number of required treatments varied greatly amongst patients (25±13 treatments). Heng and colleagues have demonstrated that THOT is effective in stimulating angiogenesis with enhanced healing of necrotic wounds (37). However, in that study of 40 patients, only 54% of patients in the intervention group and 33% of patients in the control group had diabetes. Therefore, these results cannot be indiscriminately applied to the diabetic population. Randomized, controlled trials of well-classified diabetic foot ulcers are needed. Data from existing published studies are currently not sufficient to recommend the use of THOT and low-energy laser for chronic diabetic foot ulcers.

ADVERSE EFFECTS OF HBOT

In general, if pressures do not exceed 300 kPa and if the length of treatment is <120 minutes, HBOT is safe. Potential risks for patients undergoing HBOT include pressure-related traumas (barotraumatic otitis, pneumothorax) and adverse effects due to oxygen toxicity (seizures, pulmonary toxicity). Some patients may experience claustrophobia due to the confined space of the treatment chambers (30). However, pulmonary oxygen toxicity occurs very rarely (32). The 2 most common adverse effects, which occur in <1% of all treated patients, are middle-ear barotraumas and claustrophobia (24). Chang and colleagues concluded that there was no demonstrable pulmonary epithelial permeability change under current clinical HBOT protocols (38). Hypoglycemia is also a complication of HBOT. However, the mechanism underlying this phenomenon is not completely understood. It seems that patients with type 1 diabetes are at higher risk for hypoglycemic episodes during increased barometric pressure and 100% oxygen breathing. Therefore, there must be appropriate monitoring and administration of insulin and nutrients (24). Finally, vitreous hemorrhage has been described after HBOT in a patient with type 1 diabetes with severe diabetic retinopathy (39).

CONTRAINDICATIONS TO HBOT

Absolute contraindications to HBOT include untreated pneumothorax and use of various medications: doxorubicin (toxicity increases under pressure), bleomycin, disulfiram (blocks superoxide dismutase [not available in Canada]) and cisplatin. Untreated pneumothorax can lead to a tension pneumothorax during the decompression phase of the hyperbaric treatment. Other relative contraindications include known malignancies, pregnancy, implanted pacemakers, upper respiratory tract infections, chronic sinusitis, seizure disorders, emphysema, hyperthermia, history of thoracic surgery, optic neuritis or otosclerosis, viral infections and congenital spherocytosis (24).

PATIENT SELECTION FOR HBOT

According to the Centers for Medicare and Medicaid Services guidelines, to qualify for HBOT, a patient must have diabetes and a Wagner grade 2 or higher wound of a lower extremity resulting from diabetes that has not responded to standard wound care treatment (40).

Transcutaneous oximetry can be used for evaluation of tissue perfusion or healing potential, candidate selection for HBOT or for evaluation of amputation level (28,41). Transcutaneous oximetry provides a simple, reliable noninvasive diagnostic technique for an objective assessment of local tissue perfusion and oxygenation. McNeely and colleagues found 3 tests to be significant and independent predictors of foot ulceration: absence of Achilles tendon reflex, a foot insensate to the 5.07 Semmes-Weinstein monofilament and a transcutaneous oxygen tension ($TcPO_2$) <30 mm Hg (42). Of these, impaired cutaneous oxygenation was found to be the strongest predictor of risk for foot ulceration. These characteristics indicate a significant alteration of the wound healing process in the patient with diabetes.

Transcutaneous oximetry is easy to perform. With the patient in the supine position, a skin area in the vicinity of the wound is chosen for assessment. There should be no ischemia, inflammation, bone or superficial vein in the area chosen for assessment. The transcutaneous oxygen pressure monitor, a heated polarographic electrode, is installed on the area to be studied and a control electrode is installed on the chest infraclavicularly. Serial or continuous recordings of $TcPO_2$ are made while the patient breathes room air, 100% oxygen at 1 atmosphere absolute (ATA) and during HBOT.

Patients with baseline dermal hypoxia and the physiologic capacity to respond to a centrally delivered oxygen challenge, as determined by transcutaneous oximetry mapping, may benefit from HBOT. Only a few studies have reported a correlation between $TcPO_2$ and wound healing. Wyss and colleagues demonstrated an increasing probability of wound healing failure with decreasing $TcPO_2$ (43). Wattel and colleagues demonstrated that when the distal $TcPO_2$ value at 2.5 ATA pure oxygen was >100 mm Hg, all patients achieved wound healing (44). Magnant and colleagues state that if the wound PO_2 cannot be raised above 30 mm Hg with normobaric 100% oxygen, HBOT should be tried (45). Brakora and Sheffield advocate the use of $TcPO_2$ for patient selection; patients should be accepted if the $TcPO_2$ is <40 mm Hg and if a 50% rise can be observed with oxygen inhalation. They also suggest that if the room air $TcPO_2$ is <10 mm Hg, the chance of healing with HBOT is minimal (46).

However, these data are controversial and some authors argue that neither the absolute value on room air nor the values obtained with oxygen testing are reliable enough to exclude or include patients (46,47). Fife and colleagues per-

Table 4. HBOT and diabetic foot ulcers: study designs and findings published in the literature

Study	Type of study	N	Inclusion criteria	Atmospheres of pressure	Duration of each HBOT treatment (min)	Mean number of treatments	Study endpoints	Results (HBOT vs. control)	Conclusions
Baroni et al. 1987 (57)	Prospective, nonrandomized, controlled clinical trial	28 18 HBOT 10 conventional	Diabetes and necrotic ulcers	2.5–2.8	90	34	Patients with ulcer healing (%)	89% vs. 10% (p NR)	HBOT superior
							Patients avoiding amputations (%)	89% vs. 60% (p<0.001)	
Oriani et al. 1990 (58)	Prospective, nonrandomized, controlled clinical trial	80 62 HBOT 18 conventional	Diabetes and necrotic ulcers	2.5–2.8	Not reported	72	Patients avoiding amputation (%)	95% vs. 67% (p<0.01)	HBOT superior
Doctor et al. 1992 (60)	Nonblinded, prospective, randomized, controlled clinical trial	30	Diabetes and chronic foot ulcers	3.0	45	4	Mean length of stay (days)	41 vs. 46 days (NS)	HBOT superior
							Wound cultures showing growth (n)	3 vs. 12 (p<0.05)	
							Patients avoiding major amputation (%)	87% vs. 53% (p<0.05)	
Faglia et al. 1996 (61)	Prospective, randomized, controlled clinical trial	68 35 HBOT 33 conventional	Diabetes and severe foot ulcers	2.2–2.5	90	38	Patients avoiding amputation (%)	91% vs. 67% (p=0.02; RR, 0.26)	HBOT superior
Zamboni et al. 1997 (63)	Prospective, nonrandomized, controlled clinical trial	15 10 HBOT 5 conventional	Diabetes and chronic foot ulcers	2.0	120	NR	Change in surface area of ulcer (%)	Wound surface area significantly reduced in HBOT group (p<0.05)	HBOT superior
Kalani et al. 2001 (64)	Prospective, randomized, controlled clinical trial	38 17 HBOT 21 conventional	Diabetes and chronic ischemic foot ulcers	2.5	90	40–60	Patients avoiding amputation (%)	88% vs. 67% (p not reported)	HBOT superior
							Patients healed (%)	76% vs. 48%	
							Healing rate	Accelerated healing rate in HBOT group	
Abidia et al. 2003 (65)	Double-blind, randomized, controlled clinical trial	18 9 HBOT 9 conventional	Diabetes, ischemic foot ulcers	2.4	90	30	Patients healed (%)	At 1 year 5/8 healed in HBOT group (p=0.026). No difference at 6 wk and 6 mo	HBOT increases healing rate
							Major amputations, minor amputation	No significant difference in amputation rate	
							$TcPO_2$	NS	
							Cost	Cost effective	
Kessler et al. 2003 (66)	Prospective, randomized, controlled clinical trial	28 15 HBOT 13 conventional	Nonischemic diabetic foot ulcers Wagner 1–3	2.5	90 BID 5/7 days	20	Size of foot ulcer (mm)	41.8 ± 25.5 mm vs 21.7 ± 16.9 mm p=0.037 at day 15, no difference at day 30	HBOT increases healing rate
							$TcPO_2$	$TcPO_2$ significantly increased in HBOT group	

HBOT = hyperbaric oxygen therapy
NR = not reported
NS = not significant
RR = risk reduction

formed a retrospective analysis of 1144 patients to determine the reliability of $TcPO_2$ measurements in predicting outcome in patients with diabetes who underwent HBOT for lower-extremity wounds. Overall, 75.6% of the patients improved after HBOT. Baseline sea level air $TcPO_2$ identified the degree of tissue hypoxia, but had little statistical relationship with outcome prediction. Breathing oxygen at sea level was unreliable for predicting failure, but 68% reliable for predicting success after HBOT. $TcPO_2$ measured in chamber under hyperbaric conditions provided the single best discriminator between success and failure using a cut-off of 200 mm Hg. This test was 74% reliable (48).

CLINICAL TRIALS

There have been a number of systematic reviews on the role of HBOT in the treatment of diabetic foot ulcers (6,20,22, 24,26,28-30,32,41,46,47,49-56), however, many of the studies are case reports or uncontrolled trials. Furthermore, there seem to be no objective measures to assist clinicians in the choice and follow-up of patients for HBOT. A discussion of the trials conducted to evaluate the role and effectiveness of HBOT in treating diabetic foot ulcers follows.

Baroni and colleagues carried out the earliest prospective, controlled, nonrandomized, nonblinded trial of hyperbaric therapy in the treatment of Wagner class 3 and 4 wounds (57). Patients were under strict metabolic control and received daily debridement with or without daily HBOT. They reported a statistically significant reduction in amputations in the HBOT group. Sixteen of the 18 patients in the HBOT group healed, while only 1 of the 10 controls healed. The amputation rate was 12.5% in the HBOT group vs. 40% in the control group ($p<0.001$), and the length of the hospitalization was reduced in the HBOT group (62.2 vs. 81.9 days), although this was not statistically significant. However, the assignment to the HBOT group or the control group was not random. The control group was composed of those patients who refused HBOT.

In a subsequent study, the same researchers reported a significant reduction in amputation in the HBOT group. The 2 groups were matched for age, severity and duration of diabetes. The recruitment period overlapped with the period of the researchers' first report, and it is unknown whether some subjects were included in both studies. All patients received standard care, with the exception of the patients in the HBOT group, who had the added intervention of HBOT. In the HBOT group, 96% of patients healed and 5% underwent amputation, whereas 66% healed and 33% underwent amputation in the control group (58). The authors have been criticized for not providing data on wound severity or infection status. Details of the HBO treatments were not provided. The control group was small and the authors did not discuss the effects of wound size, depth, infection or peripheral vascular disease on clinical outcome (59).

Wattel and colleagues demonstrated that skin $TcPO_2$ remained above baseline levels for 3 to 4 hours after HBOT, suggesting a beneficial effect that persisted after each treatment session (44). Complete healing occurred in 15 of 20 patients, but the response rate is not provided for the 11 subjects with diabetes.

In another nonblinded, prospective, randomized, controlled trial by Doctor and colleagues, 30 patients with diabetes and a chronic foot lesion were randomized to a treatment group with HBOT ($n=15$) or to the control group ($n=15$). Both groups received standard wound care. The HBOT group was found to have a relative risk reduction (RRR) for major amputation of 72%, an absolute RR of 0.334 and a number needed to treat (NNT) of 3 (60). However, the authors do not indicate what investigations were conducted to rule out peripheral vascular disease. There is no description of the wound size or depth. The HBOT group received 4 sessions at 3 atmospheres of absolute pressure for 45 minutes per session, which is significantly less than what is reported elsewhere in the literature.

The best-designed study to date was performed by Faglia and colleagues (61). The authors showed an 8.6% amputation rate in HBOT patients vs. 33.3% in controls ($p<0.016$) in a prospective, randomized and nonblinded study. A total of 68 patients with Wagner grading 2, 3 or 4 wounds were treated with ($n=35$) or without ($n=33$) hyperbaric oxygen. Among patients with grade 4 lesions, the HBOT group had a major amputation rate of 9.1% vs. 55% in the control group ($p=0.002$). Both groups received a diagnostic and therapeutic protocol that included glycemic control, wound care, debridement, antibiotic therapy, angioplasty or bypass graft and offloading. It is of interest that $TcPO_2$ significantly increased in the HBOT group, but with wide variations (14.0 ± 11.8 vs. 5.0 ± 5.4 mm Hg) compared to the control group ($p<0.002$). The RR for amputation was 0.26 in the HBOT group (95% CI, 0.08–0.84) (61). Unfortunately, the groups were not blinded and the randomization procedure was not described in detail. However, the results of this study suggest that HBO therapy may be helpful in reducing major amputations among patients with diabetes with Wagner grade 4 foot ulcers.

The efficacy of HBOT has been challenged by a retrospective study by Ciaravino and colleagues. HBOT was administered to different groups of patients (17 with diabetic ulcers, 8 with arterial insufficiency ulcers, 13 with dehisced amputation stump, 6 with gangrenous toes and 10 with nonhealing operative wounds). Only 11% showed improvement. However, this case series grouped all wound types together. Therefore, this study is not applicable to diabetic ulcers only (62).

In a small, nonrandomized, prospective trial, Zamboni and colleagues reported that patients in the HBOT group showed significantly greater reductions in wound size than patients in the control group during the 7-week duration of the trial ($p<0.05$). Four of the 5 patients treated with HBOT healed, whereas 4 of 5 patients in the control group continued to

have ulcers. None of the 10 patients had an amputation. Even if this study suggests that HBOT could help in ulcer healing, the sample size was too small to allow these results to be applied to the general population (63).

In a nonblinded prospective study, Kalani and colleagues randomized 38 patients to HBOT and 21 controls to a conventional treatment. They found that the addition of HBOT to the treatment of diabetic foot ulcers decreased amputation risk with an RRR of 64% and an adjusted RR of 0.21, while the NNT was 5 over 3 years. HBOT also improved the healing rate with a RRR of 58%, an adjusted RR of 0.28 and an NNT of 4 over 3 years (64).

Abidia and colleagues reported 1 of the few double-blind, randomized, controlled trials. Eighteen patients with ischemic, nonhealing lower-extremity ulcers were randomly assigned to receive HBOT or placebo. Thirteen of 19 ulcers in the HBOT group healed, compared with only 4 of 14 in the control group ($p=0.024$). The decrease in wound area was 83% in the HBOT group vs. 56% in the control ($p=0.021$). No difference in major amputation rates was found. There was no statistically significant increase in the proportion of ulcers healed following HBOT at 6 weeks or 6 months. However, there was a significant increase in the proportion of ulcers healed following HBOT at 1 year. This relates to an NNT of 2 to avoid 1 failure to heal. The authors concluded that HBOT was a valuable adjunctive therapy in persons when reconstructive surgery was not feasible (65).

In the Cochrane review by Kranke, the pooled data of 3 trials (60,61,65) with 118 patients showed a reduction in the risk of major amputation when adjunctive HBOT was used compared to conventional treatment (RR=0.31, 95% CI, 0.13 to 0.71) with an NNT of 4 in order to prevent 1 amputation in the short term. There was no statistically significant difference in minor amputation rate (60,65). The authors conclude that for people with foot ulcers due to diabetes, HBOT significantly reduces the risk of major amputation and may improve the chance of healing at 1 year. However, they insisted that their results should be interpreted cautiously because of methodological shortcomings and poor reporting.

The actual value of HBOT on diabetic foot healing is, however, still a matter of discussion because of conflicting data on its true therapeutic effect (32,58-60,63). The difficulty in controlling for the different parameters involved in the evolution of the diabetic foot and the lack of prospective, randomized studies on the effect of HBOT make it difficult to establish a clear-cut position on the subject.

Kessler and colleagues have designed a prospective randomized study. Twenty-eight patients with diabetes demonstrating chronic nonischemic Wagner grade 1 to 3 foot ulcers were randomized to standard therapy or standard therapy plus HBOT. Kessler found that $TcPO_2$ during HBOT increased significantly. At day 15, the size of the ulcers decreased significantly in the HBOT group. However, this difference was no longer observed at day 30. One month later, complete healing was observed in 2 patients in the HBOT group and in no patients in the standard therapy group. The authors conclude that HBOT doubles the mean healing rate of nonischemic chronic foot ulcers (66).

The members of the European Committee on Hyperbaric Medicine (ECHM) Consensus Conference on Hyperbaric Oxygen in the Treatment of Foot Lesions in Diabetic Patients stated that there is an urgent need for larger prospective, randomized, controlled trials and collaborative international work (67). Within the framework of the European research network (European Cooperation in the Field of Scientific and Technical Research [COST B14]), such a study has been elaborated. Each COST Action is characterized by a Memorandum of Understanding (MoU), signed by official representatives of the participating countries. The MoU outlines the general background and objectives of the proposed COST Action and defines a tentative timetable. The main objective of COST B14 is to improve the knowledge required for a rational use of HBOT, to a level making it possible to set out specific guidelines for the development and implementation of clinical HBOT centres. The COST B14 Action formed several working groups that have elaborated prospective study protocols in their field of interest. One of these protocols is a prospective randomized controlled trial that will evaluate the efficacy of HBOT in the healing of foot ulceration in patients with diabetes. The major endpoints are failure or success after 6 weeks and the secondary endpoints are major amputation, healing rate, infection, disappearance rate, time for complete healing, disability scale, length of hospital stay, recurrence rate and adverse effects. The study will recruit 200 patients in 8 European centres (68). The authors plan that recruitment will end in 2008.

COST EFFECTIVENESS

The lack of randomized, controlled trials makes it difficult to assess the cost effectiveness of adjunctive HBOT in diabetic ulcers. However, Guo and colleagues reported a study with 1000 hypothetical patients with severe diabetic foot ulcers (Wagner classification 3 or above). The cost-effectiveness model estimated that the incremental cost per additional quality-adjusted life year gained at years 1, 5 and 12 was US $27 310, $5166 and $2255, respectively. This study concluded that HBOT in the treatment of diabetic foot ulcers was cost effective, particularly on a long-term basis (69). The Blue Cross Blue Shield Association reviewed the data and concluded that adequate evidence exists to support the use of adjunctive HBOT in the treatment of adequately perfused nonhealing wounds of the lower extremities (70). The Medical Services Advisory Committee technical assessment completed in Australia also found that people with diabetes with ulcers treated with HBOT had fewer amputations and they concluded that evidence is strong enough to support the use of HBOT to improve healing rates in this population (71).

CONCLUSION

Foot ulcers are a significant source of morbidity, mortality and diminished quality of life for patients with diabetes. Ulcer development is often due to a combination of diabetic neuropathy and peripheral vascular disease, which decreases the supply of oxygen to the affected extremity. Many of the studies examining the role of HBOT in the treatment of diabetic ulcers have been retrospective, nonrandomized and noncontrolled. In addition, most studies included small patient populations with heterogeneous classes of ulcers. However, results of these studies suggest that HBOT may accelerate wound healing and reduce amputation in a subset of patients with diabetic ulcers. Most patients with Wagner grade 1 and 2 ulcers will heal with carefully administered conventional care (local wound care and efficacious off-loading). Appropriate candidates for HBOT are patients with long-standing nonhealing Wagner grade 3 or higher ulcer with an adequately perfused capillary bed in the wound area (best assessed by the $TcPO_2$ response to 100% oxygen challenge). Nonetheless, there are no evidence-based criteria to select patients for HBOT and to predict their response. Although costly, HBOT is a reasonable, cost-effective adjunct to standard therapy. Prospective studies are needed to assess the long-term success of HBOT.

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AUTHOR DISCLOSURES

No duality of interest declared.

STATEMENT OF AUTHORSHIP

All authors contributed substantially to the collection of data from the literature and its analysis. AR drafted the initial draft of the manuscript. CH and J-ME revised it critically for important intellectual content. All authors gave final approval of the version to be published.

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