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Review

Exploring the molecular mechanism to safety of hyperbaric oxygen therapy in diabetic foot ulcer – A narrative review

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Abstract

Diabetic foot ulcers (DFU) are a challenge that requires special management due to the high rate of amputation and death. Hyperbaric oxygen therapy is growing in popularity in diabetic feet with ulceration (DFU). In this review, the authors compile the available evidence regarding the mechanisms and safety of hyperbaric oxygen therapy in DFU patients. We reviewed current knowledge regarding the pathophysiology of DFU and molecular mechanisms, practice guidelines, and safety of hyperbaric oxygen therapy in diabetes with foot ulcers. The pathophysiology of diabetes mellitus wounds reveals persistent inflammation and reduced angiogenesis in hyperglycaemic circumstances, disrupting the diabetic wound healing cascade. Accelerating angiogenesis has been associated with improved wound healing. At the molecular level, hyperbaric oxygen therapy-induced oxidative stress reduces pro-inflammation while increasing growth factors and other pro-angiogenic cytokines. Clinical trials with DFU patients reveal that hyperbaric oxygen therapy outperforms standard therapy in terms of efficacy outcomes, particularly wound and amputation healing rates. Barotrauma and short-term vision impairment are two potential side effects of hyperbaric therapy. Current knowledge advances our understanding of hyperbaric oxygen therapy and its use in diabetic patients with foot wounds. This may inform the development of new DFU therapy.

Keywords: endocrinology, diabetes, chronic ulcer, oxygen, overview

Introduction

Hospitalized diabetes mellitus patients generally experience diabetic ulcers. Ulceration in the lower extremities causes infection in the deep tissue, followed by neurological abnormalities [1]. This condition can cause the skin's protective layer to become contaminated with germs, later damaging the epidermis layer. Based on Diabetic Federation Control data, 20–30% of diabetes patients are hospitalized due to diabetic ulcers. Every year, there is a 5% increase in the number of new cases of diabetes, and 1% of those populations have to undergo leg amputation. Foot ulcers occur in diabetes patients every 1.2 seconds, and diabetes patients undergo an amputation every 20 seconds [2–5]. About 50% of diabetic ulcer patients experience infection, which increases the risk of visits to the ER, hospitalization, and amputation [6]. The 5-year mortality rate for ulcer patients is comparable to that of most cancers [7]. The costs incurred by patients with diabetic foot ulcers exceed the costs of treating most cancer patients [8, 9]. This narrative review explores hyperbaric oxygen therapy in controlling diabetes with foot wounds, from mechanisms to safety.

Etiology

Diabetic foot ulcers are linked to predisposing factors, including a history of foot contact and pressure, increased inflammation, dry, cracked skin, hyperglycemia, callus formation, foot deformity, inappropriate footwear, trauma, and tissue necrosis [10–12]. Initially, patients cannot identify foot ulcers due to neuropathy and arterial disease.

Diabetic peripheral neuropathy is one of the DM complications that is characterized by peripheral nerve disorders. Autonomic, sensory, and motor nerve disorders in this condition inhibit the production of sweat, pain, temperature, touch, and pressure sensations so that patients experience inflammation, dry skin, tissue necrosis, cracked skin, and bone deformities. When a person loses sensation in the foot, the patient will experience thermal trauma and feel the position of the legs disappear. This occurs together with motor neuropathy, which causes abnormal bone protrusions, thereby altering the normal structure of the foot bones and leading to foot deformities including hammer toe and hallux rigidus [13].

Peripheral arterial disease associated with hyperglycemia is characterized by enhanced atherosclerosis and oxidative stress (Figure 1). In diabetes, elevated blood sugar leads to obstructions and narrowing of the arteries. Elevated oxidative stress extends inflammation in the small blood vessels, reducing capillary flexibility and causing ischaemia. The femoral arteries are impacted by atherosclerosis, so diabetic ulcers occur twice as often in non-DM patients. Atherosclerosis prevalence in lower extremities is 20 times higher in type 2 DM patients than in normal patients. Some literature shows that 90% of diabetic ulcer patients are related to neuropathy, and 10% are related to ischemia and other factors [14].

Other factors might cause diabetic ulcers, including hyperglycemia (more than 10 years), gender (male), age (65 years), obesity, retinopathy, peripheral neuropathy, high HbA1c, history of smoking, history of ulcers, history of amputation, increased plantar pressure, infection, and improper foot care. The wound-healing process in DM patients is interrupted by disorders of collagen, the immune system, inflammation, and neovascular disease. The acute inflammatory response is

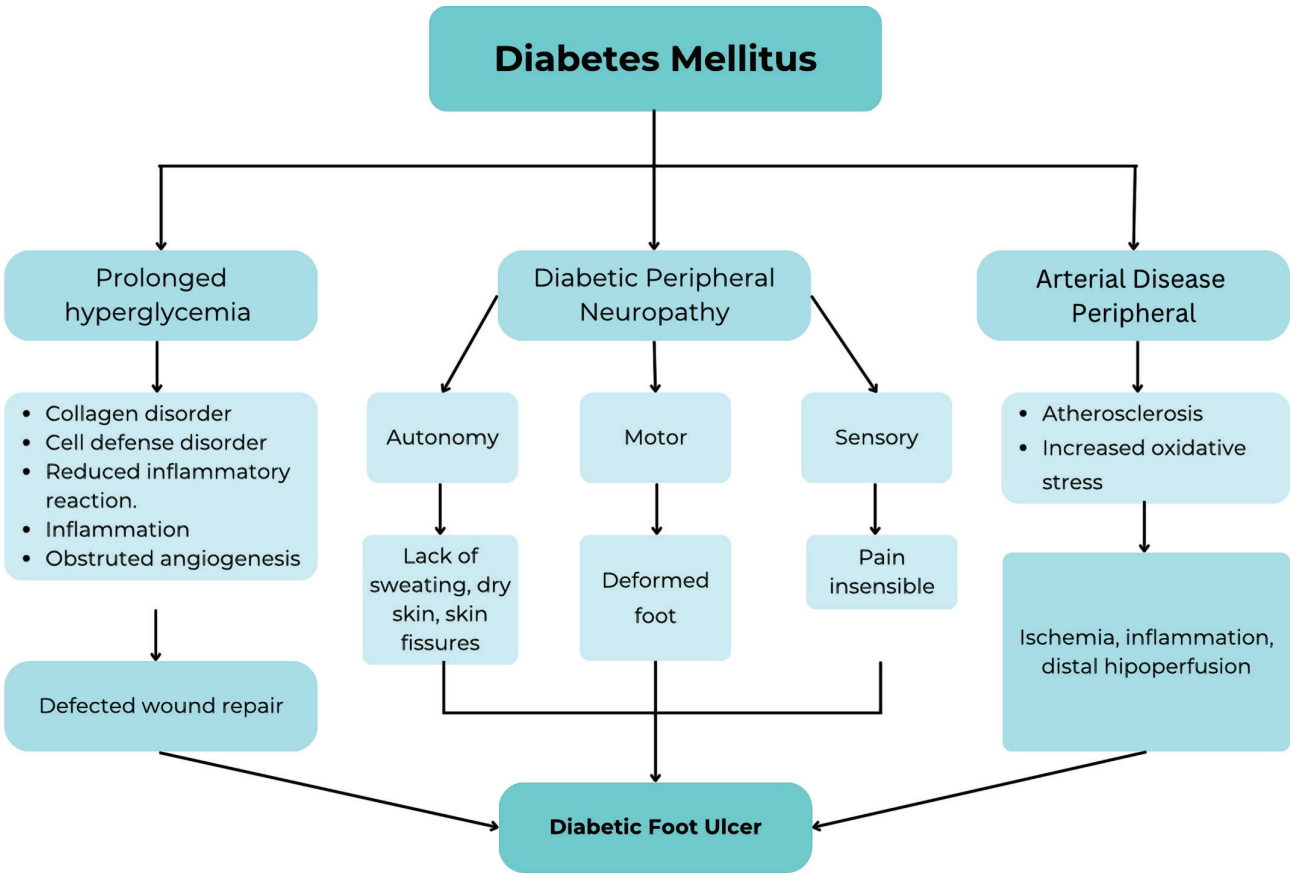

Figure 1: Pathophysiology of diabetic foot ulcer.

slowed by hyperglycemia, and it impacts angiogenesis, thereby inhibiting the process of wound healing.

Pathophysiology

The wound healing process generally goes through several stages, including hemostasis, inflammation, proliferation, contraction, and remodeling. However, the healing process for diabetic ulcers does not completely follow the wound healing stages. The healing stages of diabetic ulcers stop at a certain stage, causing ulcers to appear and slowing the wound healing process. According to previous research, diabetic wound healing can be influenced by many factors, mainly oxidative stress. Prolonged hyperglycemia status, redox conditions, and product overload can inhibit wound healing. The production and release of reactive oxygen species (ROS) are essential for promoting the healing of wounds. However, diabetic ulcers have elevated levels of reactive oxygen species. Elevated glucose levels can lead to an upsurge in substances for energy processing, leading to excessive production of superoxide and heightened oxidative stress and related products [15]. These products then stimulate the formation of AGEs. Separation of NOS causes a reduction in NO production, which is troublesome for wound healing [16].

Monocyte/macrophage infiltration is important in inflammatory circumstances to change the wound's milieu from proinflammatory to anti-inflammatory [17]. However, because of compromised macrophage activity, patients with diabetic ulcers continue to have proinflammatory macrophages [18]. Diabetic ulcers reduce the phagocytic capacity of macrophages and render them ineffective in eliminating necrotic tissue from wounds [19]. Phagocytosis, neutrophil degranulation, and ROS's anti-infective properties are all compromised in diabetic ulcers [20] by releasing cytokines and proteases and controlling the adaptive immune response, infiltration, and excessive activation at the site of tissue injury cause tissue damage [21, 22]. Furthermore, the expression of the neutrophil protein arginine deiminase (PAD)-4 might be regulated by hyperglycemia. Wound healing is slowed when neutrophils assault a wound because this inhibits their ability to release neutrophil-entering macrophages (NETs) [23]. ECM proteins (interstitial collagen and elastin) are broken down by proteases secreted by macrophages and neutrophils in the form of zymogens, activated externally to the cell. MMP, for instance, breaks down fibronectin into pieces and then activates MMP. These fibronectin fragments bring leukocyte infiltration, tissue injury, and chronic inflammation [24].

Insufficient angiogenesis in diabetic ulcers affects the stage of wound proliferation. Compared to normal skin, normal patients have a much higher number of wound blood vessels during the proliferative phase of wound healing. Vascular endothelial growth factor (VEGF) and other pro-angiogenic factors are mostly produced by macrophages [25]. Nevertheless, in diabetic ulcers, the proliferative stage of angiogenesis is impacted by the failure of macrophages to transition to a repair phenotype during the inflammatory stage. Patients with diabetic ulcers and db/db mice were shown to have elevated levels of plasma pigment epithelium-derived factor (PEDF). In diabetic mice, high PEDF inhibits wound skin angiogenesis, diminishes the quantity and function of endothelial progenitor cells (EPCs), and impairs the healing of wounds. Ang2 is still markedly elevated in diabetic wounds, and the Ang2/Ang1 ratio is dysregulated, which hinders wound angiogenesis. In contrast, angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2) are significant routes for angiogenesis and maintenance [26].

Numerous variables, including oxidative stress, hypoxia, AGEs, T lymphocyte activation, and nerve growth factor (NGF) deficiency, can lead to diabetic peripheral neuropathy. Neuropeptides are neuromodulators that play a role in wound healing in diabetics, among other processes. Reduced neuropeptide expression is a hallmark of neuropathy of the autonomic nerves and tiny sensory nerve fibers caused by diabetes mellitus [27]. In the skin of diabetes mice and people, neuropeptide Y expression dropped. Diabetic neuropathy is a multifaceted condition exhibiting a range of clinical presentations. Since silent diabetic peripheral neuropathy (DPN) accounts for about 50% of cases, physicians must diagnose and treat patients with DPN as soon as possible.

Extracellular matrix (ECM) remodeling is impacted by the breakdown of collagen, fibronectin, and other protein components by matrix metalloproteinases throughout the remodeling stage. In patients with diabetic ulcers, MMPs have aberrant activity that is out of balance with their metalloproteinase inhibitors (TIMPs). Prior research revealed that, whereas TIMP-2 levels were much lower in diabetic ulcer patients' wounds than in normal wounds from non-diabetic patients, activated MMP-1, MMP-8, MMP-9, and MMP-2 levels were significantly greater in patients with diabetic ulcers. Individuals with diabetes. High MMP-1 expression in DFU is necessary for wound healing.

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However, excess MMP-8 and MMP-9 may prevent wound healing, and the MMP-1/TIMP-1 ratio may indicate the wound's proteolytic environment [28].

Diabetic ulcers are characterized by reduced angiogenesis, ischemia, chronic inflammation, and low antioxidant levels, which prevent the wound from starting the remodeling phase [29, 30]. Numerous cell types, including fibroblasts, immunological cells, keratinocytes, and endothelial cells, are involved in wound healing. Several substances with chemoattractant qualities are released into the bloodstream as a result of skin injury, which leads to neutrophil and macrophage migration and recruitment. Leukocytes that have been recruited phagocytize necrotic tissue and release growth factors, like insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and tumor necrosis factor-α (TNF-α), as well as cytokines that mediate and facilitate healing [31, 32]. Owing to the intricacy of the wound healing process, various treatment approaches are required, including the following: lowering inflammation, providing intensive local wound care, revascularizing ischaemic extremities, decreasing infection, and enhancing peripheral circulation [33, 34].

Management of diabetic ulcers

Management of diabetic ulcers should be done immediately and consists of several important components, including:

1. Metabolic control: Control metabolic conditions as best as possible, such as blood glucose levels, lipids, albumin, and hemoglobin;
2. Vascular control: Vascular repair through surgery or angioplasty is usually needed in the setting of ischaemic ulcers;
3. Infection Control: Treatment of infection should be given aggressively if clinical signs of infection are seen. Colonization of organism growth on the swab, but not accompanied by clinical signs, does not constitute infection;
4. Wound control: Regular removal of infected and necrotic tissue. Local treatment of wounds, including infection control with the TIME concept, namely tissue debridement (cleaning the wound from dead tissue), inflammation and infection control, moisture balance, and epithelial edge advancement;
5. Pressure control: Reducing pressure, as repeated pressure can cause ulcers, should be avoided. This is very important to do in neuropathic ulcers. Callus removal and wearing shoes of the appropriate size are necessary to reduce pressure;
6. Education: Counseling regarding independent foot care.

In addition to standard management strategies in treating diabetic ulcers, various adjunctive therapies can enhance healing and improve outcomes. Some of these additional therapies include non-surgical debridement, topical dressings and products, oxygen therapy, negative pressure wound therapy, acellular bioproducts, growth factors, skin grafts, energy-based therapies, and systemic therapies.

Mechanism and safety of hyperbaric oxygen therapy in wound healing

Hyperbaric oxygen therapy (HBOT) involves administering oxygen at pressures greater than atmospheric pressure, typically within the range of 2 to 3 atmospheres, while using 100% oxygen [35, 36]. This elevated pressure enhances the pharmacodynamic effects of oxygen, leading to several notable benefits for wound healing and tissue repair. One primary advantage of HBOT is its ability to increase the blood oxygen transport capacity, promoting greater oxygen availability to body tissues, including the plasma [37]. As a result, the therapy significantly enhances the amount of dissolved oxygen in the plasma, which is crucial for tissues that may be hypoxic or have compromised blood flow. According to Henry's law, the solubility of gases in liquids increases with pressure. Consequently, the higher pressures used in HBOT facilitate a greater amount of oxygen to dissolve in blood plasma, allowing for improved oxygen delivery to tissues [38]. This is particularly important in healing processes, as enhanced oxygen levels support cellular functions, promote angiogenesis, and aid in the resolution of inflammation, ultimately improving clinical outcomes for patients undergoing treatment (Figure 2).

Oxygen plays a vital role in the wound healing process, as it is essential for cellular respiration and the production of reactive oxygen species (ROS). These ROS are important for various physiological functions, including cell communication, bactericidal activity, and the promotion of angiogenesis [39]. Insufficient oxygen levels, especially subcutaneous oxygen pressure, are linked to an increased risk of infection, underscoring the importance of oxygen in healing wounds.

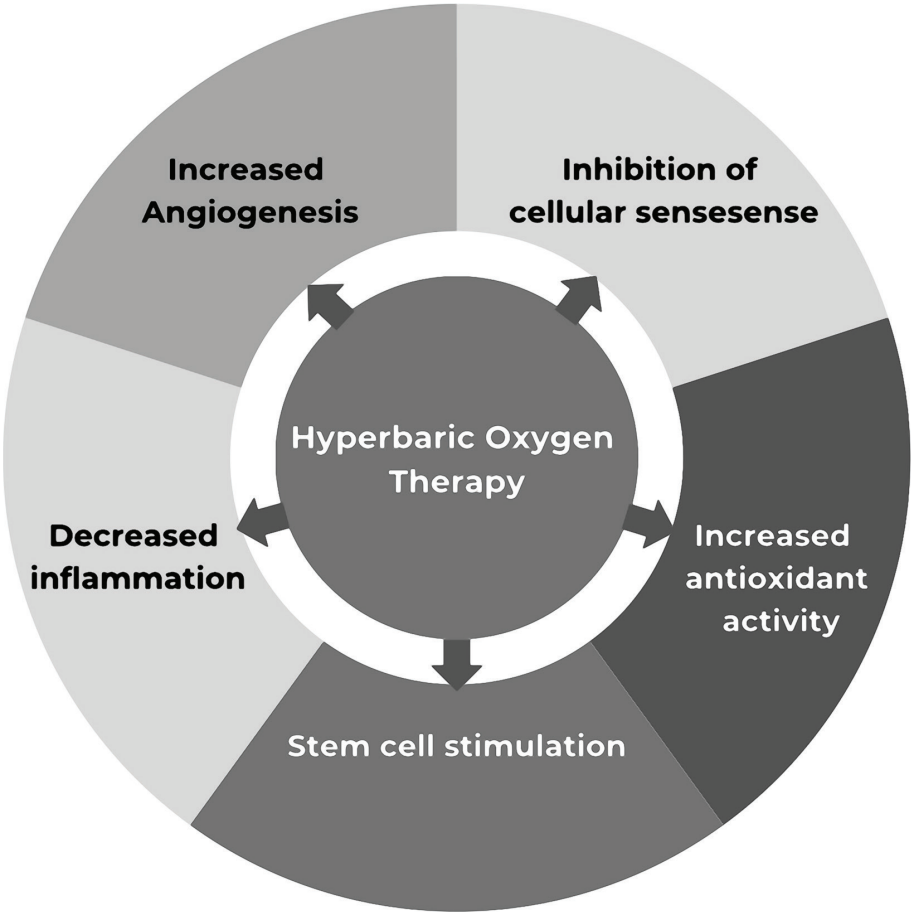

Figure 2: Effect of Hyperbaric oxygen therapy.

Hyperbaric oxygen therapy (HBOT) enhances the availability of oxygen and triggers the formation of ROS, which are thought to help eliminate pathogenic microorganisms and protect the wound from infection [40]. Additionally, studies indicate that HBOT can reduce oxidative stress, inflammation, and tissue edema, creating a more conducive environment for healing [41, 42]. HBOT also stimulates angiogenesis and cell proliferation by upregulating several growth factors, notably Hypoxia-inducible Factor 1 (HIF-1) [43]. Furthermore, research has shown that HBOT enhances plasma antioxidant levels, helps regulate vascular tone, promotes the resolution of inflammation, and stimulates angiogenesis [44]. Other studies have found that HBOT can also facilitate osteoclast formation, increase fibroblast proliferation, and upregulate key growth factors such as PDGF and VEGF, all contributing to improving wound healing outcomes [45].

The initial stage of wound healing is characterized by inflammation, during which proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 are released by leukocytes [46]. In chronic wounds, there is typically an elevation in levels of TNF-α and IL-1β, indicating a prolonged inflammatory response [47]. Research has shown that the highest plasma levels of TNF-α and IL-1β are observed at the onset of treatment, with these levels gradually decreasing following sessions of Hyperbaric Oxygen Therapy (HBOT). Previous studies have indicated that proinflammatory cytokines, notably TNF-α, IL-6, IL-8, and IL-1β, remain elevated during the non-healing stage of wounds and tend to decrease as healing progresses [48]. There is evidence suggesting that HBOT exerts anti-inflammatory effects by inhibiting the proinflammatory Nuclear Factor κB (NF-κB) pathway [49]. Normally, the IκBα protein binds to NF-κB, rendering it inactive in the cytoplasm. However, under conditions of hypoxia, IκBα is degraded [50]. The hyperoxic environment created during HBOT may help maintain levels of IκBα, thereby preventing the activation of the NF-κB signaling pathway and fostering a more favorable healing environment.

Growth factors are bioactive peptides that play a critical role in wound healing by interacting with various cell types, including inflammatory cells, matrix

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metalloproteinases (MMPs), and cells such as fibroblasts and keratinocytes. However, it has been observed that certain growth factors are altered in chronic diseases, particularly with decreased production, which can impede the wound healing process. Platelet-derived growth factor (PDGF) is particularly important for healing as it promotes fibroblast proliferation and extracellular matrix formation, thereby aiding in connective tissue regeneration. Similarly, transforming growth factor beta (TGFβ) stimulates fibroblasts, keratinocytes, and inflammatory cells, thus promoting angiogenesis, vascularization, and extracellular matrix formation [51]. In diabetic wounds, reduced expression of TGFβ, PDGF, and their receptors have been demonstrated [52]. Additionally, it is known that growth factors such as PDGF, TGFβ, and Vascular Endothelial Growth Factor (VEGF) increase plasma levels during the wound healing process. A study showed that after 20 sessions of hyperbaric oxygen therapy (HBOT), there was a significant increase in levels of TGFβ and PDGF, indicative of enhanced wound healing [53].

Collagen constitutes 70–80% of the skin, acting as its primary structural component and serving as the angiogenesis matrix, which relies on adequate oxygen for its formation and regulation. The arrangement of collagen into fibers allows it to stretch in multiple directions without breaking. At the biomolecular level, the proline and lysine residues in procollagen must undergo hydroxylation, a process that requires oxygen. The synthesis of collagen involves several post-translational steps that are dependent on oxygen. Key enzymes such as prolyl hydroxylase, lysyl hydroxylase, and lysyl oxidase all require oxygen for their activity [54, 55]. Prolyl hydroxylase facilitates the formation of triple helical cross-links in collagen fibers, while lysyl hydroxylase connects these fibers to create linear fibrils. Subsequently, lysyl oxidase links the linear fibrils, a crucial step in developing the tensile strength necessary for effective wound healing [56].

Angiogenesis refers to the formation of new blood vessels, a critical process for the development and maintenance of tissue repair. The rate and quality of this vascular formation are directly influenced by oxygen availability. Adequate levels of oxygen are essential for proper collagen synthesis, specifically during the post-translational hydroxylation process. Research has demonstrated that increased oxygen availability can accelerate angiogenesis processes. In particular, hyperoxic conditions have been shown to enhance new blood vessel formation in wounds [57]. Furthermore, the rate of angiogenesis has been found to be directly correlated with oxygen levels and reactive oxygen species (ROS) activity in injured tissues [58].

Vascular endothelial growth factor (VEGF) is regarded as the predominant and most efficacious signaling molecule for angiogenesis, having demonstrated substantial long-term angiogenic stimulation at the wound site. Exposure to oxygen significantly elevates VEGF mRNA levels in both endothelial cells and macrophages [59]. Additionally, existing literature has established that oxygen facilitates the release of VEGF165 from cell-associated storage pools [60].

Topical oxygen therapy and hyperbaric oxygen therapy have been shown to enhance angiogenesis and promote the expression of vascular endothelial growth factor (VEGF) in wound healing [61]. Recent clinical investigations indicate that continuous administration of oxygen significantly elevates the gene expression of several factors associated with angiogenesis, including VEGF, transforming growth factor beta (TGF-β), interleukin-6 (IL-6), and C-X-C motif chemokine ligand 8 (CXCL8) [62].

The majority of published studies indicate that hyperbaric oxygen therapy (HBOT) is associated with only a few adverse effects, suggesting that this treatment modality is relatively safe for managing diabetic ulcers. One study described the occurrence of barotrauma and visual impairment; however, it found no statistically significant differences in the frequency of adverse events between the HBOT group and the control. The most commonly reported side effect of HBOT is middle ear barotrauma, which arises due to pressure fluctuations experienced during treatment sessions [63].

Conclusion

Hyperbaric oxygen therapy has benefits in diabetic foot wounds by accelerating the healing process of foot wounds, preventing reamputation and rehospitalization. Hyperbaric oxygen therapy is an additional therapy while still paying attention to controlling blood sugar, treating infections, routine wound care and vascularization. Larger clinical studies will further elucidate the clinical effectiveness and cost-effectiveness of hyperbaric therapy for diabetic foot wounds.

Conflict of interest

The authors declare no conflict of interest.

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