

REVIEW

Progress in the mechanism of hyperbaric oxygen therapy for erectile dysfunction: a narrative review

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Abstract

Erectile dysfunction (ED) is a prevalent sexual disorder characterized by the persistent inability to achieve or maintain an adequate penile erection for satisfactory sexual intercourse, primarily affecting middle-aged and elderly men. Current treatment options include oral phosphodiesterase type 5 inhibitors (PDE5-i), intracavernous injections, vacuum erection devices, extracorporeal low-energy shockwave therapy and penile prostheses, each with its limitations. This review article aims to synthesize recent research findings on hyperbaric oxygen therapy (HBOT) as a potential alternative or adjunctive treatment for ED. The review analyzes various mechanisms by which HBOT may improve erectile function, focusing on its effects on vascular function, nerve regeneration, nitric oxide (NO) levels, RhoA protein expression, inflammation, androgen levels and mood disturbances. The review highlights HBOT's impact on erectile function through its effects on vascular health, nerve regeneration, NO levels, RhoA protein expression, inflammation and hormonal balance. HBOT shows promise in enhancing erectile function by improving vascular health, promoting nerve regeneration, increasing NO levels, reducing RhoA protein expression and alleviating inflammation. It may also help preserve androgen levels and address mood disturbances associated with ED. Recent research suggests that HBOT could be a valuable addition to the therapeutic arsenal for ED, offering a multifaceted approach to management. Further studies are needed to elucidate its efficacy and establish optimal treatment protocols.

Keywords

Hyperbaric oxygen therapy; Erectile dysfunction; Research advances

Avances en el mecanismo de la terapia hiperbárica con oxígeno para la disfunción eréctil: una revisión sistemática

Resumen

La disfunción eréctil (DE) es un trastorno sexual prevalente caracterizado por la incapacidad persistente para alcanzar o mantener una erección penil adecuada para una relación sexual satisfactoria, que afecta principalmente a hombres de mediana y avanzada edad. Las opciones de tratamiento actuales incluyen inhibidores orales de la fosfodiesterasa tipo 5 (PDE5-i), inyecciones intracavernosas, dispositivos de erección por vacío, terapia de ondas de choque extracorpóreas de baja energía y prótesis penianas, cada una con sus limitaciones. Este artículo de revisión tiene como objetivo sintetizar los hallazgos de investigaciones recientes sobre la terapia hiperbárica con oxígeno (THO) como un posible tratamiento alternativo o adyuvante para la DE. La revisión analiza los diversos mecanismos por los cuales la THO puede mejorar la función eréctil, centrándose en sus efectos sobre la función vascular, la regeneración nerviosa, los niveles de óxido nítrico (NO), la expresión de la proteína RhoA, la inflamación, los niveles de andrógenos y los trastornos del estado de ánimo. La revisión destaca el impacto de la THO en la función eréctil a través de sus efectos sobre la salud vascular, la regeneración nerviosa, los niveles de NO, la expresión de la proteína RhoA, la inflamación y el equilibrio hormonal. La THO muestra promesas para mejorar la función eréctil al mejorar la salud vascular, promover la regeneración nerviosa, aumentar los niveles de NO, reducir la expresión de la proteína RhoA y aliviar la inflamación. También puede ayudar a preservar los niveles de andrógenos y abordar los trastornos del estado de ánimo asociados con la DE. Investigaciones recientes sugieren que la THO podría ser una adición valiosa al arsenal terapéutico para la DE, ofreciendo un enfoque multifacético para su manejo. Se necesitan más estudios para aclarar su eficacia y establecer protocolos de tratamiento óptimos.

Palabras Clave

Terapia hiperbárica con oxígeno; Disfunción eréctil; Avances en la investigación

1. Introduction

Erectile dysfunction (ED) is a prevalent sexual dysfunction characterized by the inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse [1]. With a global prevalence of more than 50% in men aged 40 to 70 years, ED not only reduces the quality of life and satisfaction of patients and their partners but also imposes a heavy psychological burden on patients [2].

The fundamental nature of penile erection is a neurovascular phenomenon governed by a multitude of regulatory factors. In conditions of penile flaccidity, the persistent stimulation of the autonomic sympathetic nervous system sustains the contraction of vascular smooth muscle [2]. However, during sexual arousal, the release of neurotransmitters from the cavernosal nerve endings induces vasodilation of the arteries and arterioles that supply the erectile tissue, consequently enhancing arterial blood flow. Concurrently, the submembranous venous plexus between the peripheral sinusoidal capillaries and the tunica albus becomes compressed, reducing venous outflow and elevating the pressure within the corporal bodies, thus facilitating erection. The principal neurotransmitters implicated in the erectile process are nitric oxide (NO) and acetylcholine. NO, predominantly secreted by non-adrenergic non-cholinergic (NANC) nerve fibers and endothelial cells, acts as the principal mediator of smooth muscle relaxation. Upon sexual stimulation, NO activates guanylate cyclase, leading to an increase in cyclic guanosine monophosphate (cGMP) levels. The dysfunction of the NO-cGMP pathway is implicated in approximately 80% of ED cases. Acetylcholine, released by parasympathetic cholinergic nerve fibers, stimulates adenylate cyclase, elevating cyclic adenosine monophosphate (cAMP) levels. Both cAMP and cGMP serve as intracellular second messengers, initiating a cascade that activates specific proteases and induces the phosphorylation of proteins, culminating in a reduction of intracellular calcium ion concentration, which results in smooth muscle relaxation. This relaxation allows arterial blood to fill the cavernous, exerting pressure on the submembranous venous plexus, impeding venous return and realizing the transition from flaccidity to full erection [3].

ED can be addressed through a variety of treatment modalities; however, each has its inherent limitations when applied clinically [1]. Hyperbaric oxygen therapy (HBOT) is a medical treatment in which patients are exposed to pure oxygen at pressures greater than one atmosphere. This increased pressure enables higher oxygen levels to dissolve in the blood plasma and reach tissues with limited oxygen supply under normal conditions. HBOT has emerged as a novel therapeutic approach [4]. The efficacy of HBOT in the management of ED has garnered increasing attention in recent years, with a meta-analysis suggesting its effectiveness as a treatment option [5]. This review aims to elucidate the therapeutic mechanisms by which HBOT exerts its beneficial effects on ED.

2. Methods

We searched comprehensive literature in several major databases, including PubMed, Embase and Web of Science. The search was performed using a combination of keywords

such as “hyperbaric oxygen therapy”, “erectile dysfunction”, “vascular function”, “nerve regeneration”, “nitric oxide”, “RhoA protein”, “inflammation”, “androgen”, “mood disturbances” and their synonyms. We limited our search to English-language articles published within the last 10 years to ensure the currency of the information. Only studies with original research data, including clinical trials and basic research studies, were considered for inclusion. Two independent reviewers screened the titles and abstracts of the retrieved articles based on these predefined criteria. In case of disagreement between the two reviewers, a third reviewer was consulted to reach a consensus. This process was designed to ensure the objectivity of the literature selection and minimize potential biases.

3. HBOT can improve ED caused by different etiology

Vascular disease is a major cause of ED, and any disease that results in a decrease in artery diameter may cause the cavernous arteries of the penis to be unable to provide sufficient blood flow to make the cavernous body sufficiently engorged to compress the submembranous venous plexus, leading to ED effectively. When vascular endothelial dysfunction occurs, the obstruction of NO production and other lesions will damage the spongy artery diastolic function, which is an important mechanism of ED. The atrophy of the capillary bed also plays an important role in the occurrence and development of ED. HBOT has a therapeutic effect on arterial diameter contraction, vascular endothelial injury, and capillary bed atrophy under various diseases [6].

3.1 HBOT can improve ED caused by diabetes

Diabetes mellitus is a metabolic disorder distinguished by persistent hyperglycemia, which can precipitate a reduction in arterial caliber and endothelial dysfunction. HBOT, with its potential to augment insulin sensitivity and ameliorate the microvascular complications of diabetes, is thus posited as a promising therapeutic intervention for vascular ED associated with diabetes [7].

Research has delineated that chronic hyperglycemia can lead to endothelial cell proliferation, thickening of the vascular walls and luminal narrowing, which collectively accelerate the progression of atherosclerosis and, in some instances, result in thrombosis [8, 9]. These pathological alterations culminate in luminal stenosis. Additionally, the accumulation of advanced glycation end-products within the diabetic milieu incites inflammatory responses in the vascular walls, thereby inducing endothelial dysfunction [10]. The pathophysiological changes observed within the penile corpora cavernosa in diabetes are akin to those in the lower limb microvasculature [7]. HBOT, as evidenced in its efficacy for diabetic foot ulcers, facilitates vasodilation and enhances the blood and oxygen supply to the ulcerated tissue, suggesting its potential to rectify the hypoxic conditions within the penile corpora cavernosa and thus serve as a therapeutic modality for ED [11]. Recent studies by Cruz-Villanueva *et al.* [12] have demonstrated that HBOT can

enhance insulin sensitivity [12–14], alleviate insulin resistance and improve glycemic control in diabetic patients, potentially exerting a therapeutic effect on diabetes-induced ED.

3.2 HBOT can improve ED caused by hypertension

Hypertension, a prevalent chronic condition, is primarily associated with vascular fibrosis and reduced compliance, leading to arterial constriction and, in advanced stages, apoptosis of corporal smooth muscle cells [15]. HBOT has demonstrated the potential to reverse fibrosis, enhance vascular compliance and delay apoptosis. It exerts vasodilatory and hypotensive effects through multiple mechanisms, suggesting its therapeutic efficacy in treating erectile dysfunction (ED) induced by hypertension [16].

As hypertension progresses, the penile vasculature exhibits structural abnormalities, including a reduction in vascular smooth muscle cells, disarrayed cellular arrangement and an accumulation of collagen fibers within the vessel walls, which diminish vascular compliance and reduce arterial diameter, culminating in ED [17]. Concurrently, hypertensive patients often present with atherosclerosis, where arterial walls are subjected to hypoxic conditions. Hypoxia can trigger the release of intracellular calcium ions and the influx of extracellular calcium, leading to vascular constriction and excessive proliferation of arterial smooth muscle cells, thereby reducing arterial blood flow [18]. This mechanism, although initially described in the pulmonary system, has implications for the penile vasculature as well. In the penile context, this exacerbates the existing vascular problems caused by hypertension and further contributes to the development of ED. Furthermore, hypertension may deplete vascular elastic fibers, increase sinusoidal collagen fibers, attenuate the tunica albuginea of the penis, and induce fibrotic proliferation of vascular smooth muscle and other tissues, ultimately altering the ultrastructure of the penis and contributing to ED [17].

Research by Hassanin *et al.* [2] (2020) indicates that HBOT possesses therapeutic potential against hypertension, particularly in mitigating the effects of angiotensin II, which is closely linked to apoptosis and fibrosis in the corporal tissue, with HBOT capable of inhibiting this process. In the context of apoptosis occurring in ED, HBOT can augment the activity of fibroblasts, facilitating the formation of connective tissue [19, 20]. Additionally, HBOT has been shown to modulate hypertension through various pathways, including the reduction of calcium ion levels, elevation of nitric oxide (NO) concentration and downregulation of endothelin-1 (ET-1) levels, thereby controlling the onset and progression of ED and offering therapeutic benefits [20, 21].

3.3 HBOT can improve ED caused by hypoxia

Individuals subjected to chronic hypoxia, such as patients with sleep apnea syndrome, high-altitude residents and smokers, exhibit an increased incidence and severity of ED [22–24]. This correlation may be attributed to the elevated intracellular calcium ion concentrations from hypoxic conditions, leading to smooth muscle contraction. HBOT has the potential to mitigate this effect by reducing calcium ion concentrations

in tissues and diminishing the number of open calcium ion channels, thereby offering a therapeutic approach to ED [7].

Prolonged hypoxic conditions are known to increase calcium ion concentrations in vascular smooth muscle and endothelial cells, inducing smooth muscle contraction. During ED, the abnormal activation of L-type voltage-dependent calcium ion channels in penile smooth muscle cells results in membrane depolarization, channel opening and calcium ion influx, further elevating intracellular calcium ion levels [25]. Consequently, hypoxia may facilitate the progression of ED by enhancing vascular contraction through increased calcium ion concentrations. HBOT can lower intracellular calcium ion concentrations and reduce the activity of L-type calcium ion channels, potentially improving erectile function in hypoxic patients [25].

Furthermore, a study by Sahin *et al.* [1] indicates that nicotine-induced peripheral vasoconstriction and hypoxia caused by smoking can persist for approximately one hour. HBOT has been shown to enhance the oxygen-carrying capacity in smokers, correcting hypoxic states. Based on this, Sahin and colleagues conclude that HBOT may be a good alternative treatment for ED in this population.

3.4 HBOT can improve ED caused by nerve injury

Neurogenic ED arises from a reduction or absence of neural signals entering the penile corpora cavernosa and is associated with damage to the central or peripheral nervous systems [26]. HBOT has demonstrated therapeutic efficacy in both forms of neurogenic ED [27].

In pathological injury to the central nervous system, an inflammatory immune response mediated by cytokines leads to the expression of inducible nitric oxide synthase (iNOS) RNA by cytokines. The induction of iNOS results in the local generation of high concentrations of NO, causing demyelination changes. These changes can disrupt the parasympathetic and sympathetic nerves originating from those that govern the smooth muscle of the penile corpora cavernosa, leading to aberrations in neural regulation and conduction pathways, culminating in ED [28]. HBOT is capable of activating and upregulating peroxisome proliferator-activated receptor-gamma (PPAR- γ), reducing free radical levels, inhibiting the expression of iNOS, decreasing the production of inflammatory cytokines, and thereby preserving and maintaining erectile function [29].

Diabetic peripheral neuropathy, urethral disruption and radical prostatectomy are common etiologies of ED associated with peripheral nerve damage. Research models support the therapeutic potential of hyperbaric oxygen therapy (HBOT) in improving erectile function in these scenarios. In a rat model subjected to long-term hyperglycemia, pathological structural changes in the distal segment of the cavernous nerve were observed, including nutritional deficits, demyelination and abnormal accumulation of glycogen particles in the pre-synaptic axons, culminating in significantly slowed nerve conduction velocity [30]. Yuan *et al.*'s [31] study demonstrated that HBOT significantly increased axonal diameter, suggesting its potential in promoting the growth and repair of cavernous nerves.

In diabetic peripheral neuropathy, the increased production of vasoconstrictive prostaglandins such as prostaglandin F₂ α (PGF₂ α) and thromboxane A₂ leads to persistent vascular constriction and tissue perfusion disorders; HBOT has been shown to ameliorate these conditions, enhancing peripheral nerve function and its regulatory effect on surrounding blood vessels [32]. Up to 50% of patients experience ED following urethral reconstruction surgery [31], and Yuan *et al.*'s [31] research indicated that HBOT significantly preserves erectile function and improves the International Index of Erectile Function (IIEF) scores. In this study, the treatment group underwent pure oxygen therapy at elevated pressure, while the control group was subjected to the same duration of "treatment" under normal atmospheric conditions, with both groups receiving daily sessions for 14 consecutive days [31]. Post-radical prostatectomy or radiotherapy, ED is often attributed to nerve paralysis, reduced oxygenation and changes in corporal tissue structure, potentially leading to decreased smooth muscle oxygenation, diminished erectile function or even corporal fibrosis and veno-occlusive dysfunction [33]. Müller *et al.*'s [34] research on rats found that HBOT significantly protected erectile function following simulated bilateral thermal injury during radical prostatectomy. However, clinical data summarized by Kelly A. Chiles *et al.* [35] showed no significant improvement in erectile function one year after early postoperative HBOT treatment for patients with ED following radical prostatectomy. This discrepancy may be attributed to the late initiation of HBOT treatment post-discharge, missing the optimal period for nerve and vascular repair, and the short duration of HBOT, which was only 10 days compared to the recommended one month or longer [35]. Additionally, it's important to note the differences between rats and humans. In rat studies like Müller *et al.*'s [34], experimental conditions are highly controlled, allowing for more precise treatment protocols. Rats have a simpler physiological makeup compared to humans. Their metabolism and tissue repair mechanisms might respond more uniformly to HBOT. In contrast, human patients present greater complexity in their physiological and pathological processes. The factors contributing to ED, such as nerve paralysis, reduced oxygenation and changes in corporal tissue structure, may interact more intricately, making it harder to achieve consistent results with HBOT. This could partly explain why the positive effects seen in rats don't always translate directly to humans.

3.5 HBOT can improve ED caused by adverse emotions

The role of adverse emotions in the etiology and progression of ED is significant, and HBOT has been demonstrated to ameliorate these emotional states markedly [36]. The majority of ED cases present a combination of physiological and psychological factors. Pedraza *et al.* [37] have reported that adverse emotional responses such as depression, stress and anxiety are associated with the production of pro-inflammatory cytokines, leading to poorer prognosis and increased incidence of urinary incontinence and erectile dysfunction. There is a positive correlation between the occurrence of ED and psychological distress in Chinese male patients with type 2

diabetes; these patients often experience post-onset emotional issues such as fear, anxiety, pessimism and depression. These adverse emotions may generate inhibitory signals for erection via the cerebral cortex and limbic system, thereby inducing ED [38]. Furthermore, the severity of ED in type 2 diabetic patients is closely linked to emotions such as depression and anxiety [39], which may contribute to the development of ED.

Studies have shown that HBOT effectively alleviates depressive symptoms, with therapeutic effects comparable to, or slightly superior to, those of antidepressant medications [40]. The combination of HBOT with antidepressant treatment such as fluoxetine produced a more pronounced improvement [41]. This may be attributed to HBOT's ability to reduce inflammation in neural tissues and potentially inhibit serotonin reuptake [40]. In animal experiments, HBOT is as effective as fluoxetine in significantly improving depressive symptoms in rats, including promoting appetite, alleviating anhedonia, and enhancing exploratory and grooming behaviors, which may be related to its inhibition of monoamine oxidase and increase in norepinephrine concentrations in various brain regions [42]. Additionally, in research on post-traumatic stress disorder (PTSD), HBOT has been found to restore the extinction of fearful memories effectively and significantly reduce conditional anxiety [43].

Adverse emotions are often associated with chronic pain. Research by Lindsay G. Flegge *et al.* [44] has found that sexual dysfunction is a common comorbidity in patients with chronic musculoskeletal pain. HBOT is considered efficacious in treating chronic neuropathic pain, including conditions such as chronic headaches, fibromyalgia, complex regional pain syndrome, radiculopathy, postherpetic neuralgia and trigeminal neuralgia [45, 46]. Jacob *et al.* [47] conducted a study on patients with fibromyalgia. Participants who received HBOT reported a significant reduction in pain intensity compared to the control group, as measured by a standardized pain scale. Another study by Shai Efrati *et al.* [48] focused on fibromyalgia syndrome patients, which validates that HBOT has been shown to significantly alleviate symptoms of fibromyalgia, leading to improvements in pain threshold, quality of life and neurological function.

4. Possible mechanisms by which HBOT improves ED

4.1 HBOT can improve ED by increasing the concentration of NO

NO, a pivotal mediator within the penile vasculature and sinusoidal spaces, is instrumental in the etiology of erections. It exerts vasodilatory effects, stimulates angiogenesis and shields endothelial cells from undergoing apoptosis [20]. However, pathological states, including diabetes, hypertension and metabolic dysregulation, have been identified to diminish NO levels [2]. Recent findings by Dragic *et al.* [20] indicate that HBOT can markedly elevate NO concentrations. This discovery posits HBOT as a potential therapeutic intervention for ED, with the premise that it may ameliorate the condition by increasing the availability of NO.

4.2 HBOT can improve ED through the Rho-ROCK system

The Rho-associated Kinase (Rho-ROCK) signaling pathway plays a pivotal role in the pathogenesis of ED, with various stimuli capable of activating this pathway [49]. Activation of the Rho-ROCK system leads to smooth muscle contraction, impaired endothelial cell function, hindrance to neoangiogenesis, reduction in NO levels, potentiation of endothelin-1 effects and increased vascular sensitivity to calcium ions, all of which contribute to the development of ED [49–51]. HBOT has demonstrated the potential to treat ED by inhibiting this critical pathway.

The RhoA/Rho kinase pathway enhances the sensitivity of smooth muscles to calcium ions by increasing the phosphorylation of myosin light chains, thereby facilitating smooth muscle contraction and implicating itself in the pathogenesis of ED [52]. Moreover, RhoA influences the permeability of endothelial cells and the process of angiogenesis [49]. The RhoA/Rho kinase pathway, through its downstream kinases ROCK1/2, negatively regulates endothelial nitric oxide synthase (eNOS), reducing NO production and further promoting ED, with ROCK1/2 being widely expressed in the smooth muscle and endothelial cells of vertebrate blood vessels [53]. In severe ED patients, there is a particularly pronounced overexpression of ROCK2 [2].

The RhoA/Rho kinase pathway also amplifies the vasoconstrictive effects mediated by endothelin-1 by reducing and blocking the activity of nitric oxide synthase (NOS) [54]. Studies have indicated that during diabetic conditions, the kinase activity of the RhoA/Rho kinase pathway is elevated, leading to the inhibition of eNOS and the subsequent development of ED [53, 55]. Dysregulation of lipid metabolism, closely associated with ED, may also upregulate the activity of Rho kinase [49]. Increased expression of RhoA has been observed in animal models with bilateral corporal nerve injury [2]. Furthermore, the calcium sensitivity pathway mediated by the RhoA/Rho kinase pathway is implicated in age-induced ED. Not only in the elderly population but also in young adults with vascular issues, an increase in Rho/RhoA kinase activity has been detected [49].

Recent research has shown that HBOT can suppress the expression of RhoA, suggesting that it may also inhibit the expression of RhoA/Rho kinase in the corporal smooth muscle, thereby increasing penile blood flow and treating ED by inhibiting this significant pathway [56].

4.3 HBOT can improve ED by reducing the inflammatory response

ED is closely associated with the augmentation of inflammatory responses, and HBOT has demonstrated the capacity to mitigate these responses through various mechanisms, offering a therapeutic approach to ED. A higher prevalence of ED is observed in obese populations compared to those with normal body weight, potentially due to the substantial expression of inflammatory mediators by adipocytes, which can compromise the integrity of the vascular bed [57]. The inflammatory reaction triggered by cytokines also amplifies oxidative stress, producing a plethora of oxidative metabolites. The exces-

sive accumulation of these metabolites results in endothelial damage and dysfunction of the vasculature. Age-related mild inflammation is also implicated in the pathogenesis of ED, with the condition likely arising from the inflammatory damage caused by the aging process [49].

Research has indicated that HBOT can enhance the function of neutrophils [1], augment the activity of lymphocytes and macrophages [19], modulate the activity of natural killer (NK) cells, regulate leukocyte adhesion [20] and interfere with the signaling pathways of nuclear factor kappa-B (NF- κ B) and its inhibitor I κ B α (inhibitor of nuclear factor κ B alpha) [58]. Moreover, the antibacterial effects of HBOT against anaerobic bacteria also contribute to the reduction of inflammatory responses, which may be beneficial in the amelioration of ED [1].

4.4 HBOT can improve ED by blocking oxidative stress

ED is intimately associated with cellular damage caused by oxidative stress [49]. HBOT mitigates the detrimental effects of oxidative stress on erectile function by enhancing the body's tolerance to such stress [59]. The intake of uric acid and alcohol can activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thereby promoting the generation of reactive oxygen species (ROS), exacerbating oxidative stress and leading to endothelial dysfunction [1, 59]. Hypercholesterolemia also fosters ROS and superoxide anions, intensifying oxidative stress and causing damage to vascular endothelial cells [60]. In a hyperglycemic state, the overproduction of ROS can injure endothelial cells, induce thrombosis and cause vasoconstriction, further contributing to the progression of ED [61]. In diabetic patients with ED, the substantial generation of ROS in the penile corpora cavernosa induces the uncoupling of eNOS, inhibits NO production, impairs the normal function of vascular endothelium and ultimately results in ED [62]. Moreover, the reaction between ROS and NO forms peroxynitrites, which are closely related to vascular aging [49]. HBOT, through repeated sessions, can stimulate the body's adaptive mechanisms to protect tissues and organs from oxidative damage [63].

4.5 HBOT can improve ED by improving the level of testosterone

Androgens play a crucial role in preventing apoptosis and fibrosis of penile tissue, sustaining vascular relaxation functions and maintaining endothelial cell functionality [64]. Empirical evidence has demonstrated that HBOT can enhance erectile function by improving testosterone levels. Observations by Hassanin *et al.* [2] have underscored the pivotal part that androgens play in preserving normal erectile functions, encompassing the integrity of penile innervation, vascular endothelium, vascular smooth muscle and tunica albuginea.

Subsequent studies have indicated that low androgen levels are associated with heightened RhoA/Rho kinase signaling, potentially leading to endothelial dysfunction. Furthermore, testosterone facilitates the migration of vascular smooth muscle cells via the NADPH oxidase pathway. A deficiency in androgens may culminate in apoptosis and fibrosis of the

corporal tissue, precipitating ED [49]. Post-prostatectomy erectile function is largely contingent upon testosterone levels, with substantial evidence highlighting the influence of androgens on libido, nitric oxide synthase (NOS) production, phosphodiesterase 5 (PDE5) regulation and corporal nerve functionality [37]. In ovariectomized rat models, there is a significant decrease in serum testosterone levels, corporal smooth muscle content and eNOS activity [64]. Androgenic deficiency may also elevate oxidative stress in penile tissue, contributing to endothelial cell dysfunction and the subsequent development of ED [65]. Research by Volkan Sen *et al.* [4] has found that HBOT can ameliorate erectile function by elevating testosterone levels in patients with decreased testosterone.

4.6 HBOT can improve ED by stimulating angiogenesis

Many studies have demonstrated the capacity of HBOT to promote angiogenesis and enhance perfusion, potentially elucidating its therapeutic effects on ED. Rahmah *et al.* [66] have posited that HBOT fosters neovascularization following penile injury [66]. Sander *et al.* [31], utilizing a murine ear wound model, discovered that HBOT accelerates epithelialization and neovascularization at the site of injury. The underlying mechanism is likely attributed to the role of oxygen in augmenting cellular proliferation, bacterial defense and facilitating the proliferation of endothelial cells, angiogenesis and collagen synthesis, which are integral to the tissue repair process [19, 66]. It has been documented that HBOT may stimulate angiogenesis through the activation of growth factors such as epidermal growth factor (EGF), keratinocyte growth factor, placental growth factor (PGF) and vascular endothelial growth factor (VEGF) [58]. Pedraza *et al.* [37] have suggested that HBOT may induce stem cell differentiation, leading to subsequent neovascularization. Nunes *et al.* [49] have identified a significant role for angiogenesis in improving erectile function, even in the absence of tissue injury. In a controlled study of non-surgical ED patients by Amir Hadanny *et al.* [7], magnetic resonance imaging (MRI) measurements of blood perfusion using the volume transfer constant (K-trans) value confirmed that HBOT significantly promotes angiogenesis, increases perfusion of the penile vascular bed, and markedly enhances the International Index of Erectile Function (IIEF) scores, addressing the fundamental vascular pathology of ED. Mehmet Oguz Sahin *et al.* [1] have shown that in men around 58 years of age, HBOT improved erectile function, with IIEF scores increasing from 16 to 20 units, even when ED was not attributed to tissue injury. Similarly, studies and follow-ups by Volkan Sen *et al.* [4] have indicated that in men around 59 years of age, the IIEF scores improved from 21 to 25 units following HBOT. In these studies, the patients did not receive other treatments specifically targeting erectile function, such as phosphodiesterase type 5 inhibitors (PDE-5i) or intracavernous injections.

Oral administration of phosphodiesterase-5 inhibitors (PDE-5i) is recognized as the first-line treatment for ED. Recent comparative studies have been conducted to evaluate the efficacy of PDE-5i in conjunction with HBOT. In a study led by Eker *et al.* [67], HBOT was compared with PDE-5i (tadalafil), revealing

that both modalities offer similar therapeutic outcomes for ED without significant statistical differences ($p < 0.05$). The advantage of HBOT lies in its capacity to induce spontaneous erections and accommodate unplanned sexual encounters, unlike PDE-5i, which requires prior administration. Among diabetic patients with ED, HBOT has demonstrated superior efficacy to PDE-5i [7]. Furthermore, Hadanny *et al.* [7] reported that in cases where PDE-5i therapy was ineffective, HBOT was still able to restore sexual function in some patients.

5. Limitations

This study has several limitations to be addressed when interpreting the results. First, the sample size is small, which may limit generalizability. Second, the study was carried out in a controlled experimental setting and may differ based on individual patient factors regarding the effect of hyperbaric oxygen therapy (HBOT) on erectile dysfunction (ED) in clinical practice. Since this study was only concerned with particular mechanisms of HBOT, there was no emphasis on longer-range efficacy or side effects. Additional research is needed, which is larger in sample size, and longitudinal long-term follow-up is required to support the findings and reveal other possible benefits for HBOT in ED.

6. Conclusions

The present review delineates the potential mechanisms through which hyperbaric oxygen therapy (HBOT) may exert its therapeutic effects on erectile dysfunction (ED). Evidence suggests that HBOT could ameliorate ED through a multifaceted approach, including enhancement of vascular function, facilitation of neural recovery, elevation of nitric oxide (NO) levels, reduction of RhoA expression, mitigation of inflammatory responses, maintenance of androgen levels and alleviation of adverse emotional states.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

TFW—contributed significantly to this work by conducting a comprehensive review of recent research advancements on hyperbaric oxygen therapy (HBOT) for the treatment of erectile dysfunction (ED); analyzed HBOT's therapeutic mechanisms, including its impact on vascular function, nerve regeneration, nitric oxide levels and more. This contribution provides valuable insights into HBOT's potential as a therapeutic strategy for ED.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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