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Review Article

Inflammation A Core Reason of Erectile Dysfunction: Intermittent Hypoxia Training A Proposed Novel Solution

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Abstract

Objective: Erectile dysfunction (ED) is a sexual disorder where sexual arousal/action fails to cause or maintain an erect penis. Based on ED statistics 2022-23, the ED worldwide incidence will increase from 152 million men in 1995 to 322 million men by the year 2025. ED can be treated with a variety of drugs and supplements available from medication outlets. However, not all are beneficial or available to global populations, and some have negative effects. The fact that vascular, neurological, and hormonal dysfunction are the three main physiological and biochemical factors that contribute to ED may be the cause of its ineffectiveness. It is suggested that the three combinations listed above are all caused by inflammation. Thus, research is needed to address ED in non-pharmacological way that targets inflammation. This review aims to highlight the importance of "Intermittent hypoxia training (IHT)" in targeting inflammation for treating ED. **Methods:** A structured search strategy was conducted in PubMed and Google Scholar to search for publications in English using the search term "Erectile Dysfunction"

with "inflammation", "cytokines", "intermittent hypoxia", "yoga", "vascular dysfunction", "neurological dysfunction", "hormonal dysfunction", "obesity", "hypertension", "insulin resistance", "hyper cholesterol" with no date restrictions. **Results:** This review outlines the evidence indicating that inflammation is a causative target that can be used to treat ED irrespective of its cause. Further, in this review "Intermittent hypoxia training (IHT)" is suggested a proposed intervention that can target inflammation at four important related biochemical interaction points (cytokines: VEGF, BDNF, IGF1 and NGF) via the NO pathway that can be implemented for improving ED, in a cost-effective manner. **Conclusion:** This review proposes that IHT may be investigated as a proposed non-pharmacological solution of erectile dysfunction targeting inflammation.

Keywords: Erectile dysfunction; Intermittent hypoxia training; Inflammation; Cytokines

Introduction

Erectile dysfunction (ED) is a sexual disorder that affects men worldwide and is expected to effect 322 million people by 2025 [1]. Several medications and dietary supplements are available to treat ED. However, some of them have adverse impacts, and not all of them are available for communities around the world. The main reason for this may be related to the fact that any one of the three main causes of ED, which are vascular, neurological, and hormonal, could be involved synergistically, contributing equally or partially to the problem. Additionally, risk factors for ED include old age, alcoholism, obesity, metabolic syndrome, kidney illness, heart disease, high cholesterol, and high blood pressure. Interestingly, the causes and risk factors of ED are often off shoots of a common problem, namely inflammation. The majority of ED drugs function by blocking the phosphodiesterase type 5 (PDE5) enzyme, preventing the breakdown of cyclic guanosine monophosphate (cGMP), which prolongs the activity of vasodilation mediators like nitric oxide (NO) [2]. Worth noting is that NO is a signaling molecule that plays a key role in the pathogenesis of inflammation [3].

Inflammation is the common denominator in nearly all of the risk factors that contribute to ED [4]. Also, chronic low-grade inflammation is a critical component of ED pathogenesis and a probable intermediate stage of endothelial dysfunction, especially in metabolic diseases, with the inclusion of obesity, metabolic syndrome, and diabetes. Pharmacological therapy, modification of lifestyle and risk factors may have a significant role in the recovery of erectile response through reduction of inflammatory marker levels. The inflammatory process of ED includes a shift in the complex interactions of cytokines, chemokines, and adhesion molecules [5]. Therefore, the first part of this review explores how inflammation is linked to the metabolic major risk factors that are the cause of ED in conjunction with NO release.

Furthermore, there are four types of cytokines that have been reported contributing to ED and a very recent review has suggested these four cytokines as the major target for therapeutic and pathogenesis of ED. The first cytokine namely vascular endothelial growth factor (VEGF) can encourage angiogenesis and can enhance the function of vascular endothelial cells, encourage endothelial regeneration, and thus enhance erectile function [6,7]. The second cytokine namely insulin-like growth factor 1 (IGF-1) can safeguard cavernous nerves and can encourage nerve regeneration and enhance erectile performance [8]. The third cytokines namely brain-derived neurotrophic factors (BDNF) are capable of protecting smooth muscle function, and can enhance erectile function by promoting smooth muscle expression and preventing penile fibrosis [9,10]. The fourth cytokines are nerve growth factor (NGF) inflammation-related cytokines that can cause penile erection by acting on the corresponding receptor relaxing smooth muscle [11]. Compared with PDE-5 inhibitors, these cytokines may be more targeted for the treatment of ED. However, current studies have been mostly dependent on rat model information and lack of large sample sizes, which has restricted further clinical application of cytokines. Although VEGF, IGF-1, BDNF and NGF can significantly improve erectile function in rats, experiments with larger samples and larger animals are needed to further confirm their efficacy and safety. Therefore, in the second part of the review, we have discussed how these molecules further help in NO release via inflammation pathways and can potentially help cure all cause ED at from root level (Figure 1).

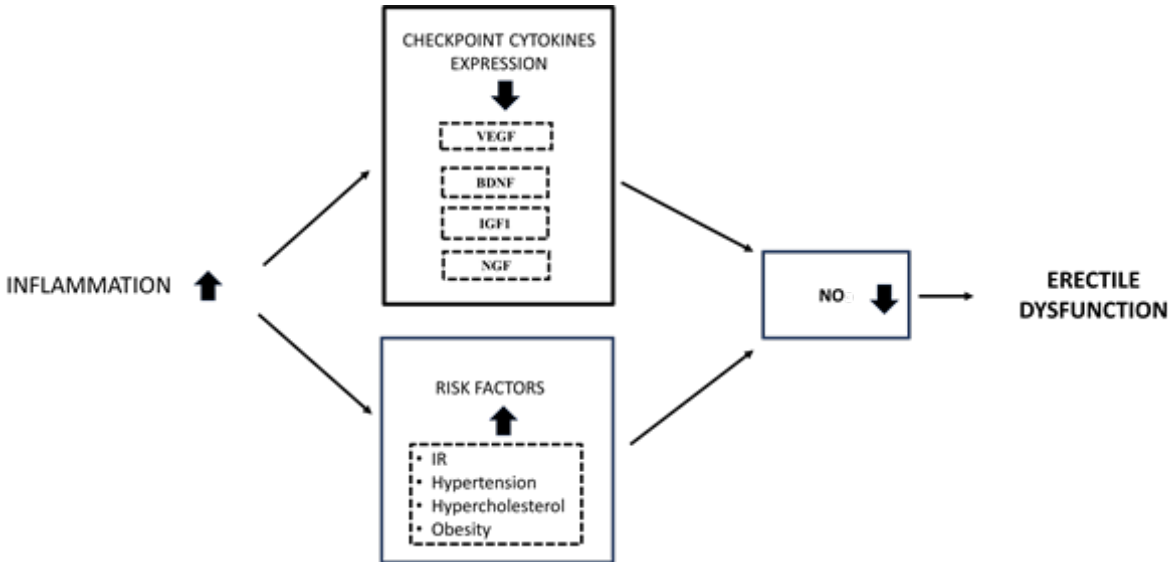

Figure 1: Inflammation proposed as a root cause for erectile dysfunction. Increase in inflammation provides evidence for decreases in the expression of four important cytokines (VEGF, BDNF, IGF1 and NGF) as well as the increases in metabolic risk factors (IR, Hypertension, Hypercholesterol and obesity). Decreased levels of the checkpoint cytokines and increases in the metabolic risk factors leads to the decreases in NO leading to Erectile dysfunction. **Key:** VEGF, vascular endothelial growth factor, BDNF, brain-derived neurotrophic factor, IGF1, insulin-like growth factor 1, NGF, nerve growth factor, NO nitric oxide, IR is insulin resistance.

Due to the potential for harm to cells, tissues, and organs, the word "hypoxia" has been unpopular for medical professionals and students. However, we now understand that transient, intermittent hypoxia triggers a number of adaptive reactions. These reactions generally help the body adapt to hypoxic events and provide positive defenses against a variety of other insults. Indeed, for many years, researchers in the former U.S.S.R. have benefited from short intermittent hypoxia training (IHT) by developing what is known as "hypoxia therapy" over the previous decades [12]. To our surprise and knowledge, no research has been conducted to determine how IHT affects ED. As a result, we have emphasized in the third section that IHT may have therapeutic effects on ED by exerting its effect on the key cytokines responsible for ED. We have also discussed the mechanisms involved.

Investigating these markers in ED subjects after IHT would provide insights into the responses of novel biomarkers as well as solutions for inflammation related ED which may cover all causes of ED.

Methods

A structured search strategy was conducted in PubMed and Google Scholar to search for publications in English using the search term "Erectile Dysfunction" with "inflammation", "cytokines", "intermittent hypoxia", "yoga", "vascular dysfunction", "neurological dysfunction", "hormonal dysfunction", "obesity", "hypertension", "insulin resistance", "hyper cholesterol". We focused on clinical trials, meta-analyses, and review articles. We did not include research related to pharmacological treatment of ED. The search was finished on January 1st, 2024. The most recent articles were picked when there were plenty of similar ones accessible. Random searches and the reference lists of the publications that were retrieved yielded more papers. The search was conducted without a date constraint in order to produce a longitudinal "map" of the study region. These methods produced 115 papers in total that may be included in this review.

Inflammation A Root Cause for Major Metabolic Disturbances Leading to ED

Inflammation-obesity- ED loop

Obesity is a significant public health concern worldwide which is associated with different metabolic alterations, and associated risk factors such as cardiovascular disease, type 2 diabetes mellitus, cancer, metabolic syndrome and many others [13]. Inflammation brought on by oxidative stress, which results in insulin and leptin resistance, is one of the primary pathophysiologic mechanisms of obesity [14,15]. Elevated blood lipid levels, adipokine secretion from hypertrophied adipocytes, and inflammatory reactions brought on by immune cell infiltration into adipose tissues, with subsequent leptin and insulin resistance, are the primary pathological characteristics of obesity [16,17]. The hypothalamus, the brain region responsible for metabolism and reproduction,

experiences inflammation because of elevated free fatty acids (FFA), which also causes lipotoxicity and reactive stress in nearby tissues. The hypothalamic inflammatory reaction interferes with regular regulatory functions such as leptin sensitivity maintenance and neuroendocrine regulation [18]. Among these regulatory functions, leptin resistance-related decreased gonadotropin-releasing hormone (GnRH) secretion lowers testosterone levels, which is one of the major reasons for ED [19].

ED driven by obesity-related disorders such as increased FFA levels, adipokines, inflammation, oxidative stress, and insulin resistance is one of the links between obesity and ED. NO generation is decreased in endothelial dysfunction, which makes it challenging for vessels to smoothly transition between dilation and constriction [20]. Endothelial dysfunction and ED are synonymous with long-term high-fat diets in rodents [21]. Rats fed on a high-fat diet have lower penile endothelial nitric oxide synthase (eNOS) expression [22], and in vitro, reactive oxygen species (ROS) produced by palmitate cause endothelial cell injury [23]. Together, the increased FFA levels brought on by high-fat diets cause ROS to increase and NOS to be suppressed by down regulating the endothelium's 5′-adenosine monophosphate-activated protein kinase (AMPK)-phosphatidylinositol 3-kinase (PI3K)-eNOS pathway, which in turn causes a reduction in NO production [20] which leads to ED. Elevated FFA may cause inflammation by activating Toll-like receptors, an innate immune receptor, triggering intracellular signaling molecules, such as myeloid differentiation primary response gene 88 and nuclear factor κB (NF κB); a transcription factor for pro-inflammatory cytokines, and consequentially produces inflammatory cytokines [24,25], which suppress the eNOS/NO pathway [26]. This ultimately causes endothelial dysfunction and ED. C-reactive protein, a systemic inflammatory marker, is consistently greater in obese men with ED than in obese men without ED, and is correlated with the severity of ED, according to a human study [27]. Some studies suggest that anti-inflammatory drugs protect ED in diabetic rats [28] and enhance erectile function scores in human studies [29]. Adipokines are cytokines produced by fat tissue. They affect several metabolic systems, including vascular function, inflammatory response, and energy metabolism. Adipokines are either over- or under-secreted in an obese condition, and they either promote or inhibit inflammation in the vascular endothelium. ROS are produced because of the dysregulation of adipokine production, which also causes endothelial dysfunction. Adipocytes with hypertrophy primarily generate the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). They induce inflammatory gene transcript in endothelial cells [30] while inhibiting eNOS expression [31]. Mice with TNF-infused corpora cavernosa exhibit reduced eNOS and nNOS gene expression as well as attenuated non-adrenergic noncholinergic nerve-mediated relaxation [32]. Additionally, TNF- depleted animals exhibit elevated eNOS and nNOS expression as well as increased endothelium-dependent relaxation in isolated corpora cavernosa [33]. In human studies, plasma levels of these inflammatory cytokines are correlated with body mass index (BMI) and cause inflammation and insulin resistance [34] and high levels of TNF-α were strongly associated with ED [35]. Hence, inflammation leading to obesity and ED provides a connection via the NO pathway.

Inflammation-hypertension- ED loop

Erection issues are frequently brought on by high blood pressure. According to a study published in the Journal of the American Geriatrics Society, 49% of males with high blood pressure between the ages of 40 and 79 also had ED [36]. Another study of men with high blood pressure showed that 68% of them experienced some form of ED. It was deemed serious for 45% of the men studied [36,37]. The vessels that supply blood to the penis are prevented from dilatation by high blood pressure. Additionally, it impairs the genitalia' smooth muscle's capacity for relaxation leading to erectile dysfunction. It is also likely that men with insufficient testosterone levels also have high blood pressure, the masculine hormone that has a significant impact on sexual arousal. A meta-analysis of cross-sectional data revealed that hypertension was linked to an increased chance of ED after controlling for obesity, unfavorable lipid levels, alcohol abuse, physical inactivity, smoking, level of education, and other lifestyle variables. Their findings confirm that having high blood pressure raises the chance of developing ED [38].

Interestingly, if we consider the metabolic base, we may propose that inflammation correction can cure hypertension and its related ED. Although it is obvious that inflammation plays a crucial role in the onset and maintenance of hypertension, several recent advances in the field and new mechanistic understandings have been achieved in the last ten years. The first mechanism identifies a central role of sodium-induced immune cell activation in the pathogenesis of hypertension by altering the gut microbiome and formation of products of lipid oxidation known as isolevuglandins. The second mechanism is the inflammasomes production of cytokines, which causes immune activation and end-organ failure, contributing to the development of hypertension. The third mechanism proposes that immune cell populations that have not been studied previously might be useful to explore in these processes [39]. Thus, numerous cell types and secreted substances are involved in the complicated process of inflammation, which has been linked to high blood pressure in many instances and nearly all the mechanistic pathways leading to hypertension. In animal models of essential hypertension and in dendritic cells from hypertensive patients, ROS production is increased [40–43]. NO is the main signaling molecule that plays a fundamental role in the pathogenesis of inflammation [3]. It has been demonstrated that cells from the innate and adaptive immune systems are crucial in the development of hypertension [44-46]. A

condition of oxidative stress and low-grade inflammation brought on by high blood pressure may also exacerbate ED [47].

Inflammation-hypercholesterol- ED loop

Hypercholesterolemia primarily causes oxidative stress to increase and endothelial function to be impaired in the penis, which leads to ED. The mechanisms governing the production of ROS in the penis are not well known. Interestingly, mice have already been used to study the molecular processes of ROS production and endothelial dysfunction in hypercholesterolemia-induced ED. An early source of oxidative stress that leads to eNOS uncoupling is activated NADPH oxidase in the penis, which provides a mechanism of eNOS uncoupling and endothelial dysfunction in hypercholesterolemia-induced ED [48]. In a study of 260 subjects with ED, the capacity of blood lipid parameters to distinguish between ED caused by arteriogenic factors was examined. According to the research, lipid-lowering therapy should be considered for patients who have arteriogenic ED as it may be a strong indicator for predicting and diagnosing the condition [49].

When the body is stressed, it produces more cholesterol because the stress hormone cortisol is derived from cholesterol. Emotional worry can also raise cholesterol levels. Additionally, the body's physical strain can cause Low Density Lipoprotein (LDL) to rise. The body creates more cholesterol if there is upsurge of inflammation in the body, as cholesterol helps to repair and heal the body. So, all the variables listed above that can increase inflammation can also cause an increase in cholesterol. Inflammation causes atherosclerosis; without it, cholesterol would not be nearly as hazardous. Atherosclerosis is the stiffening of the arteries that results from an accumulation of LDL cholesterol. When blood cholesterol levels increase, extra LDL cholesterol permeates the interior wall of the artery and results in an inflammatory reaction. This response hastens the build-up of cholesterol in the vessel wall. This cycle continues until the cholesterol deposits solidify into plaque which may be the cause of ED [50]. Blood clots that trigger heart attacks and strokes can form when the plaques rupture [51,52].

Inflammation-insulin resistance- ED loop

Reduced sensitivity and/or reactivity to the metabolic functions of insulin that support glucose disposal is known as Insulin Resistance (IR). NO production is inhibited and endothelin levels are increased when the endothelial function is disrupted by IR [53]. Additionally, a clinical investigation revealed that insulin resistance is a standalone predictor of ED in young adult men [54]. Endothelial dysfunction is brought on by insulin resistance, which increases oxidative stress and inflammatory mediators in endothelial cells. This reduces NO bioavailability and induces endothelial dysfunction [55,56]. Its pathologic characteristics are categorized as biological and psychogenic in nature. The causes of organic ED are endocrinologic, neurogenic, anatomical, and vasculogenic. The most prevalent type of ED, vascular, is primarily caused by endothelial failure. Additionally, compared to other instances of ED, vasculogenic ED has been shown to be more closely linked to obesity and the accompanying hormonal changes [57].

Chronic inflammation caused by obesity plays a significant role in the development of insulin resistance and metabolic syndrome. Adipose tissue, skeletal muscle, and the liver can develop insulin resistance as a result of pro-inflammatory cytokines' inhibition of insulin signal transmission. The insulin target tissue itself, mainly fat and liver, but also to a greater extent the activated tissue resident macrophages, are the sources of cytokines in states of insulin resistance. Chronic inflammation in these tissues may result in localized insulin resistance via autocrine/paracrine cytokine signaling and systemic insulin resistance via endocrine cytokine signaling, both of which contribute to the abnormal metabolic state [58]. It is ambiguous whether inflammation causes IR or the other way around. Additionally, intriguing research by Olefsky and his colleagues using genetically altered mice that were unable to produce macrophages demonstrated that, despite being obese, the mice were "protected from obesity-induced insulin resistance." This disproves the notion that a cure could be developed if the macrophage inflammatory program could be inhibited in people in a less harmful manner. According to Olefsky [59], the key would be to make sure that such a medication did not obstruct vital immune system function. There are numerous cytokines that have been linked to IR. For instance, TNF-α causes insulin resistance by enhancing adipocyte lipolysis stimulating c-Jun N-terminal kinase (JNK) and IKKβ/NF-κB pathway which may increase serine/threonine phosphorylation of IRS1. IL-6 induces IR by reducing the expression of Glucose transporter type 4 and IRS-1 by activating the JAK-STAT signaling pathway and increasing suppressor of cytokine signaling 3(SOCS3) expression, and IL-6 can also lead to IR in skeletal muscle by inducing TLR-4 gene expression through activation of STAT3 [60].

ED related cytokines checkpoints modulation by IHT

A recent review compiled 4 types of cytokines that are related to treatment and pathogenesis of ED [61]. The first type of cytokines can promote angiogenesis and can enhance vascular endothelial function, promote endothelial regeneration, and thus enhance erectile function: VEGF [62]; the second type of cytokines that can promote nerve regeneration can enhance erectile function by safeguarding cavernous nerves: IGF-1 [63]; the third type of cytokines that can protect smooth muscle function and can enhance erectile function by promoting smooth muscle expression and inhibiting penile fibrosis: BDNF [9,10] the fourth type are those inflammation-related cytokines that can induce penile erection by acting on the corresponding receptor relaxing smooth

muscle: NGF [11]. However, since they have all been tested on rats, researchers now have the chance to investigate the actions in humans. The rat genome is comparable to the human genome, making it simple to translate studies using the rat model. Hence, it is suggested that these still need to be explored in human large experimental samples as they have strong potential to treat ED [61]. We hypothesize that targeting inflammation can cure all the cases of ED irrespective of causes (metabolic risk factors) as discussed above.

Below we have discussed the important four cytokine checkpoints in ED which may be investigated for reversal of this pathogenesis by IHT via NO pathways in Subjects with ED. There are nearly nil studies as per our knowledge that directly explore that ED can be treated by IHT. Also, we found that there are very limited studies that demonstrate the effect of IHT on BDNF, NGF, IGF and VEGF in ED.

VEGF-NO pathway target by IHT

By refraining apoptosis in the penile cavernosum, VEGF, a cytokine involved in angiogenesis and closely related to the nitric oxide-cyclic guanosine monophosphate pathway, a target for sildenafil [6] would improve ED caused by diabetes. The change in anti-apoptotic protein expression in the diabetic and VEGF treated groups strongly linked with the decline and recovery of intracavernous pressure. Intracavernous VEGF injections cure ED in diabetic rats by inhibiting apoptosis, according to an intriguing study. A common cause of ED is penile veno-occlusive dysfunction (venogenic ED). In a rat model, venogenic ED can be prevented and reversed by VEGF. Using adult male rats with either venogenic or arteriogenic ED, pharmacological cavernosometry was created and validated. In an experimental model, castrated animals' veno-occlusive dysfunction was reversed by systemic testosterone replacement or intracavernous VEGF (protein and VEGF gene). VEGF therapy corrected the cavernosometric evidence of venous leakage in rats with pre-existing leakage. For patients in whom testosterone therapy is contraindicated, intravenous injection of either the VEGF protein or the VEGF gene may be the recommended treatment to maintain erectile function [7]. NO is produced by eNOS, which is expressed by vascular smooth muscle cells. Increased NO production has recently been found to activate the NO/cyclic guanosine 3',5'-monophosphate (cGMP) pathway, which results in the synthesis and secretion of VEGF. The precursor of NO, L-arginine (L-arg), and specific PDE-5 inhibitors that raise intracellular cGMP levels may complement each other to promote synthesis in corpus cavernosal smooth muscle cells (CCSMCs), which may then restore compromised endothelial function. It has also been documented that the corpus cavernosal smooth muscle expresses eNOS. It is unknown whether CCSMCs can produce NO. CCSMCs produce NO and express eNOS. Through the NO/cGMP pathway, NO production increases VEGF synthesis. Combining L-arg and vardenafil therapy, which can increase the production of VEGF, may offer a cutting-edge therapeutic approach for the management of ED and endothelial dysfunction in general [64].

Both erythropoiesis and angiogenesis are controlled by the proteins erythropoietin (EPO) and VEGF. Elevated VEGF-A and EPO levels may result from altitude/hypoxic training. However, it seems that the selection of the training methodology has a significant impact on the spectrum of adaptive modifications. An insightful study used three distinct altitude/hypoxic training ideas to examine the changes in EPO and VEGF-A levels in athletes. They presented data demonstrating the effectiveness of altitude/hypoxic training in raising VEGF-A and EPO levels. The pattern of adaptations, however, is greatly influenced by the training methodology. EPO levels only rise when a sufficient hypoxic dosage is given, whereas VEGF-A levels rise when exercise, especially vigorous exercise, is paired with hypoxia exposure [65]. Studies have looked into the relationship between VEGF and the neural control of breathing. After chronic prolonged hypoxia, the peripheral, carotid body chemoreceptors undergo remarkable structural plasticity, which is at least partially due to VEGF [66]. In phrenic motoneurons, where they are both expressed, VEGF and VEGFR-2 cause persistent, ERK- and Akt-dependent phrenic motor facilitation (pMF) [67]. Regarding the many functions of VEGF in respiratory plasticity, particularly with chronic IH, significant concerns still need to be answered. The effect of IHT or any breathing exercises on periphery motor neurons, however, has not yet been investigated, revealing a new research area. Also, VEGF and pudenal motor nerves also need to be explored further.

IGF-1-NO pathway target by IHT

IGF-I/IGF-1 Protein, Human (70a.a) is a mitogenic cytokine that mediates neuroprotective mechanisms [8]. We have verified increasing erectile function through IGF-1 gene transfer to the penis is possible. Gene therapies do have certain drawbacks, though, like toxicity or the possibility of insertional mutagenesis. Another option for reducing these hazards is protein therapy to investigate if an intracavernosal injection of the IGF-1 protein can improve erectile function in aging rats [68]. Low serum levels of IGF-1 in ED patients is one of the growth factors with a variety of physiologic effects [63]. IGF-1 has a key role in the development, differentiation, and transformation of cells in various tissues. The pathophysiology of ED is fundamentally influenced by microvascular damage and ED. Serum IGF-1 levels that are standard were discovered to be linked to endothelial dysfunction, which predicts ED. In the male population, serum IGF-1 levels appear to be a useful predictor of ED and may be used for early ED detection [69]. Morphological alterations, erectile responses, and a marker for the nitric oxide-cyclic guanosine monophosphate

(NO-cGMP) signalling pathways were identified. Through the restoration of the corpus cavernosum's smooth muscle's integrity and modification of the NO-cGMP pathways, IGF-1 restored erectile performance in elderly rats. An IGF-1 (Somatmedin-C) or its analogue LR3 IGF1, in a mixture with a pharmaceutically acceptable diluent or carrier is used in a pharmacological composition to improve male erectile function. Such mixtures may also contain substances drawn from the list of androgens, namely testosterone and dihydrotestosterone, a vasodilator, a PDE5 inhibitor, and prostaglandin E1 [70]. To determine if IGF-1 gene transfer to the penis of streptozotocin (STZ)-induced diabetic mice could enhance erectile function. These findings point to the possibility of a novel therapeutic approach for the treatment of ED in STZ diabetic rats, namely the in vivo gene transfer of IGF-1 [71].

As far as we are aware there have been no direct studies which explored effect of IHT on IGF-1 on subjects with ED. However, IHT has be shown by researchers that it stimulates HIF-1α mRNA expression in leukocytes of blood prediabetic as well as healthy subjects, but in prediabetes patients the maximum increase was stunted. It's worth noting that the subjects had no ED which needs investigation. They concluded that IHT may be useful for preventing the development of type 2 diabetes [72] Another study also reported that IHT stimulated glucose disposal and improved post-exercise IR, which was enhanced when exercise was combined with hypoxia [73]. We found a previous study which provided evidence that exhaustive swimming exercises an example of IHT decreased nNOS expression in the gastrocnemius muscles and sildenafil citrate enhanced nNOS expression in exhaustive swimming exercise rats [74].

BDNF-NO pathway target by IHT

A cytokine called BDNF is crucial for the survival, growth, and flexibility of neurons. Additionally, peripheral organs and cells express BDNF [9,10]. In 2005 [75], BDNF mRNA was discovered in the penis. Intracavernosal BDNF injections have been shown to enhance erectile function recovery in CNI rats and improve nNOS-containing nerve regeneration [76]. 30 individuals with diabetes mellitus receiving insulin underwent a double-blind, randomized study investigating BDNF. The researchers discovered that subcutaneous injections of recombinant BDNF in the trunk skin could enhance sexual erectile performance [77,78]. BDNF enhances the restoration of erectile function and the regeneration of nerve fibers that contain neuronal NOS (nNOS) [79-81]. In Schwann cells, BDNF triggers the JAK/STAT pathway to support nerve regeneration. [82]. Through neurite regrowth and stimulation of the JAK/STAT pathway in Schwann cells, BDNF improves the restoration of erectile function. By promoting Schwann cells to make cytokines to regenerate the axonal nerve fibers, BDNF aids in cavernous nerve regeneration [80,83]. The PI3/Akt pathway is the mechanism by which BDNF affects endothelium cell survival [84], and the effects of BDNF on Vascular Endothelial Cells (VECs) [85], endothelial cell survival are mediated via the PI3/Akt pathway [84]. Moreover, it has been found that BDNF can accelerate the occurrence of angiogenesis in vivo and improve the migration and proliferation of VECs. Some authors have demonstrated that BDNF induces endothelial cell migration by upregulating TrkB/ERK/integrin aVb3/FAK signaling [86].

IHT can induce proadaptive modifications of the glucocorticoid system and stimulate the production of neurotrophins, especially BDNF, comparable to hypoxic pre- and postconditioning [87], but to date no studies have investigated these crucial aspects. The effective realization of this method's therapeutic and health-promoting potential for the advantage of human wellbeing and mental health will be made possible by the disclosure of IHT molecular mechanisms [88]. The phenomenon of IHT is important for examining the molecular mechanisms mediating the positive, particularly neuroprotective, effects of hypoxic training at the molecular level. A study highlights the high potential of hypoxic training in preventive and clinical medicine, particularly in the field of neurodegeneration and age-related cognitive decline [88], which is currently far from being realized. IHT has been demonstrated to improve learning and memory deficits, slow the accumulation of beta amyloid (Aβ) in the cerebral cortex and hippocampus, and increase levels of neuroprotective trophic factors like erythropoietin and BDNF in a mouse model of Alzheimer's disease (AD) [89]. The neuroprotective effects of IHT may be related to the production of reactive oxygen species, which in turn triggers a robust defense program, including nuclear factor erythroid 2-related factor 2 (Nrf2), a transcriptional factor that controls expression of many phase II defense enzyme genes and, together with other factors, provides potent antioxidant and anti-inflammatory cytoprotecting [90]. In APP/PS1 rodents, IHT exposure markedly improved cognitive function and reduced anxiety-related behaviors. According to the findings of immunofluorescence and ELISA, IHT pre-treatment significantly decreased A levels in the cortex and hippocampus. The neuroprotective impact of IHT exposure on hippocampal neurogenesis was confirmed by morphological investigations. In the hippocampus of APP/PS1 mice, molecular research found that IHT increased BDNF expression and inhibited the expression of apoptosis-related proteins. However, the effects of IHT on BDNF expression on subjects with ED remains unexplored.

NGF-NO pathway target by IHT

A neurotrophic cytokine known as NGF is known to control the survival and operation of peripheral and central neuronal cells. Recently, non-neuronal cell types like rat mast cells and human

B lymphocytes could be included in the range of activity [11], a novel testosterone shortage treatment involving nerve growth factor [91]. The impact of nerve growth factor intranasal delivery was examined, and the researchers hypothesized that aging male mice in their mouse model have low testosterone because of low NGF signalling in the brain. It is challenging to determine whether a comparable process might be present in humans [92]. In men with type 2 diabetes, hypotestosterone and ED usually develop. The treatment of diabetes-related ED remains clinically challenging. To evaluate the effects of NGF on blood testosterone and ED in diabetic males with sensorimotor polyneuropathy and to determine its underlying processes, a 2-arm randomized clinical trial and in vitro cell line experiments were conducted. As a result, NGF therapy substantially reduced type 2 diabetes-related hypotestosterone and ED outcomes via a mechanism involving the activation of crucial testosterone production enzymes. According to a recent study [93], rats with ED who were injected with a gene therapy vector encoding one of two nerve growth factors were able to regain normal function after four weeks. NGF inhibits the production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, and IL-8) in TLR-activated monocytes while encouraging the release of anti-inflammatory mediators (IL-10 and IL-1 receptor antagonist) [94]. Role of NO in NGF-induced cell differentiation and the distinction between beta and neuronal cells has been already established [94]. Both neuronal cells and pancreatic beta cells (insulin-secreting cells) have functioning NGF receptors. While nerve growth factor has a well-known impact on neuronal differentiation, its impact on pancreatic beta cells is less clear. Another investigation found that patients with ED/Metabolic syndrome had lower plasma concentrations of NGF and thiol as well as lower levels of TrKA expression on WBCs [95].

Yogic breathing (YB, commonly known as Pranayama) is a group of breathing methods for deliberately controlling breathing. Through stimulation of the vagal and parasympathetic nervous systems, YB strongly causes relaxation [96]. Rapid changes in gene expression, particularly those that regulate stress, inflammation, and metabolism, are causally connected to these responses. NGF is known to be present in saliva, which is why yoga and relaxation techniques increase salivation. Saliva includes several biologically active chemicals that could serve as diagnostic markers and therapeutic cues (0.75 to 1.5 litres per day in individuals). The respiratory, neurological, immunological, and digestive systems are all controlled by salivary secretion. To determine if YB can possibly encourage salivary expression of NGF in cognitively healthy volunteers, we undertook a pilot study. Future research on ED subjects may use this as a model [97].

IHT Proposed Novel Solution for Inflammation Reduction

What is IHT?

Repeated hypoxic events separated by normoxic intervals are referred to as intermittent hypoxia. Hypoxia intervals range from 3 to 90 minutes in actual duration, depending on the experimental study.

Several disorders can be treated using the IHT technique. Healthy individuals, on the other hand, can use it to improve their physical performance and stress tolerance, tolerating dangerous exposures, extending their physical and intellectual lives, and preventing dementia and neurodegeneration [98-100]. Clinical human rejuvenation can benefit from the growing preventative, therapeutic, and rehabilitative modality of IHT, according to a comparison of biological and clinical research [101]. IHT has received widespread acclaim outside of professional settings in the fields of sports medicine and is widely used for training athletes [102,103].

IHT as solution if used with caution

IHT has also been successfully used to treat rheumatoid arthritis, anaemia, neurocirculatory dystonia, and bronchial asthma, as well as to prevent postoperative complications [104]. IHT has demonstrated efficacy when employed in the treatment of diseases of the gastrointestinal tract, in dermatology, and in haematology, in addition to disorders directly associated to hypoxia (diseases of the lungs, cardiovascular system) [105]. It has antidiabetic characteristics and has been demonstrated to improve systolic blood pressure, fat and lean mass, weight, and body mass index in adult obese individuals [106]. The usage of IHT can significantly impact the prevention and treatment of diseases brought on by pregnancy-related problems. Application of IHT during pregnancy or to new-borns is advised because many adult disorders have foetal origins and might prevent development of various diseases in later life [107].

IHT has a potent cerebro- and neuroprotective use, as is abundantly obvious from ongoing preclinical research. IHT was also demonstrated to be a highly effective, non-invasive treatment that can offer long-lasting neuroprotection during ethanol withdrawal [108]. It guards against amyloid β accumulation, mitochondrial damage, oxidative stress, and glutamate excitotoxicity in the brain [109]. In older patients with amnestic mild cognitive decline (MCD), moderate IHT via improvement of cerebral oxygenation is able to improve short-term memory and attention [110]. IHT was demonstrated in a pilot trial to enhance cognitive abilities and

the levels of circulating AD biomarkers in blood of individuals with MCI, indicating that it may be able to delay the onset of AD [71]. IHT was touted as an effective therapy for those with depression [111] and Parkinson's disease [104]. When we consider ED and IHT, no study has been conducted previously. Yoga has been solidifying its place as a form of therapy over the past few years. The extraordinary therapeutic benefits of "Nisshesha rechaka" [112] literally, "full exhalation with no residual air," and physiologically, "breath holding at residual volume"—are increasingly being emphasized [113].

It's interesting to note that ED patients frequently report having sleep apnoea, a medical condition marked by breathing pauses or shallow breathing while asleep that disturbs sleep patterns and lowers oxygen levels in the body. IHT, which involves being exposed to low oxygen levels, may make sleep apnoea symptoms worse and be dangerous for those who already have the condition. IHT is a subject of ongoing research and discussion as a sleep apnoea treatment. IHT entails subjecting the body to intervals of lower oxygen levels; this is frequently accomplished by breathing air with lower oxygen content or by using specialized equipment. IHT is intended to potentially lessen the severity of sleep apnoea episodes and help the body become more tolerant of low oxygen levels. IHT may be a promising adjunct treatment for sleep apnoea and it may need to be studied further in ED patients.

The Mechanisms of Intermittent Hypoxic Training

The production of reactive oxygen and nitrogen species, which function as signalling molecules in the tissue injury-repair-regeneration cascade, is increased during intermittent hypoxic exposure (IHE). IHT's precise processes have not been well-researched. We have tried to examine the evidence that either IHT or similar forms like swimming, high altitude hiking, yoga have been investigated to exert their impact on the four major 4 types of cytokines checkpoints including VEGF [65], BDNF [87,88], IGF1 [72,74] and NGF [96,97] that have been linked to therapeutic and prevention of erectile dysfunction in previous studies. Unfortunately, nearly nil studies have investigated these checkpoints by IHT intervention on human subjects with ED and needs further investigation. Daily self-administered brief, intermittent hypoxia may release endogenous EPO (downstream of VEGF, BDNF, IGF1 and NGF) that may increase nitric oxide synthase, and activate p-53, also known as the "guardian of the genome," and have a wide range of positive effects on health and on metabolic regulation [65]. These benefits have been pointed out as the foundation for the benefits of the yogic technique of Pranayama. EPO further modulates, iNOS activity by low-intensity exercise combined with IHT [100]. IHT also causes age-dependent increases in blood superoxide dismutase (SOD) and decreases in catalase (CAT) activities [114] which further increase NO. NO is activated by brief intermittent hypoxia and greatly aids vasodilatation [115]. Vascular endothelium generates NO, which diffuses into the smooth muscle cells of the arteries and triggers the release of cyclic GMP. Drugs like sildenafil work by preventing the breakdown of endogenous cyclic GMP and extending its effects by blocking the metabolizing enzyme PDE5, which enables rapid vasodilation in the penile arteries and prompt and powerful erection. We thus propose that release of GMP by NO will block PDE5 and will prompt powerful erection (Figure 2).

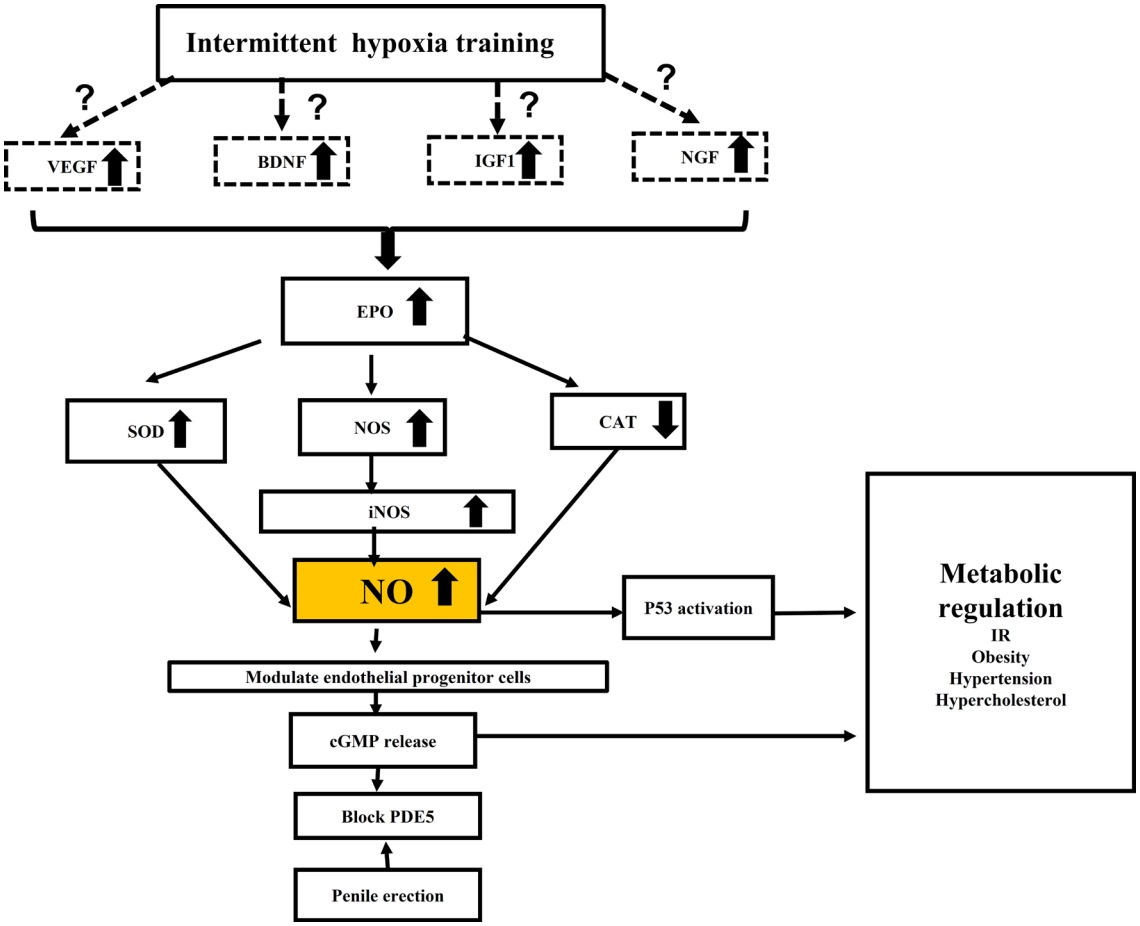

Figure 2: Proposed mechanism of IHT as therapeutic for erectile dysfunction. VEGF is Vascular endothelial growth factor, BDNF is Brain-derived neurotrophic factor, IGF1is Insulin-like growth factor 1, NGF is Nerve growth factor, EPO is erythropoietin, SOD is Superoxide dismutase, NOS is Nitric oxide synthase , CAT is catalase, iNOS is Inducible nitric oxide synthase, NO is Nitric oxide, cGMP is cyclic guanosine 3′,5′-monophosphate, IR is Insulin resistance. ”?” refers to the proposed activation proven in animal studies and needs future research.

Conclusion and Perspectives for Future Research

In summary, this review has demonstrated that inflammation is a major factor in the development of all metabolic abnormalities that contribute to ED. Regardless of the various causes of ED, NO increase brought on by cytokine modulation is the major therapeutic strategy suggested. We also demonstrated that four significant cytokines checkpoints linked to ED share a same NO route and may be responsive to IHT. Since there is evidence that IHT can help treat ED without causing side effects or additional costs, we advise more research should be directed in exploration of IHT effects on ED. Interestingly, there are few safe and effective ways that people can mimic IHT. The suggestions include: specialized yoga, swimming with IHT, hiking, and other activities, examining their potential to treat ED Breath-holding exercises, High-intensity interval training (HIIT), Sprint interval training, Cold exposure. It is important to note that IHT should only be practiced under the guidance of a qualified professional and in a safe and controlled environment. Individuals with certain health conditions, such as heart or lung disease, should not practice IHT without first consulting with their healthcare provider. These suggestions demonstrate the potential therapeutic utility of anti-inflammatory drugs in the management and prevention of ED. For a better understanding of the pathophysiology and effective management of ED, further study is needed on the processes of inflammation that underlie ED as well as the impact of therapeutic interventions designed to reduce inflammation.

Author Contributions

R.S., K.P.S wrote the manuscript; R.S, K.P.S and A.S performed the literature search; Y.G., D.T, Y.Gu and J.S.B. contributed to discussion and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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