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Hyperbaric Oxygen Therapy in Diabetic Retinopathy: Mechanistic Rationale, Clinical Evidence, and Safety Considerations

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Abstract

Hyperbaric oxygen therapy (HBOT) increases dissolved oxygen delivery to tissues and has been proposed as an adjunctive approach for diabetic retinopathy (DR) and diabetic macular edema (DME). Its role in the diabetic retina is biologically complex because tissue hyperoxia may reduce hypoxia-inducible factor 1-alpha (HIF-1α) signaling and retinal vascular endothelial growth factor (VEGF) expression, while HBOT can promote reparative angiogenic signaling in wounds and other ischemic tissues. This structured narrative review evaluates these opposing mechanisms and the direct clinical evidence in DR. PubMed/MEDLINE and Google Scholar were searched from database inception to 4 October 2026 using combinations of terms for HBOT, DR, DME, retinal hypoxia, VEGF, angiogenesis, inflammation, nitric oxide, oxidative stress, and adverse effects. Direct human DR studies were prioritized, while animal and non-retinal studies were used only for mechanistic context. Five clinical studies form the main direct evidence base summarized in a 2025 systematic review and meta-analysis. The only randomized, double-blind, placebo-controlled study included 50 patients and found no significant long-term difference in visual acuity or DR progression. Smaller prospective and open-label studies reported stabilization of DR, changes in retinal or choroidal thickness, or benefit when HBOT was combined with aflibercept. The 2025 meta-analysis of 463 eyes reported a small pooled improvement in best-corrected visual acuity of -0.05 logMAR (95% CI: -0.09 to -0.01) and a reduction in central macular thickness of -75.21 micrometers (95% CI: -90.04 to -60.38), but the visual acuity result was sensitive to removal of the largest study, and heterogeneity for macular thickness was substantial (I2 = 62%). HBOT therefore remains investigational for DR. Current evidence does not support replacing anti-VEGF therapy, laser photocoagulation, corticosteroid therapy when indicated, or vitreoretinal surgery with HBOT. Adequately powered retinal trials with standardized HBOT protocols and stage-specific outcomes are required before routine use can be recommended.

Categories: Ophthalmology
Keywords: diabetes mellitus, diabetic angiopathies, diabetic retinopathy, diabetic retinopathy management, hyperbaric oxygen therapy (hbot), narrative review, vegf angiogenesis

Introduction And Background

Hyperbaric oxygen therapy (HBOT) is a medical intervention in which a patient breathes near-100% oxygen at an ambient pressure above normal sea-level pressure. Modern clinical protocols commonly use pressures near 2.0-2.5 atmospheres absolute for defined treatment periods [1,2]. The idea of pressurized medical environments predates the discovery of oxygen. Nathaniel Henshaw's 17th-century chamber used compressed air and should therefore be viewed as part of the history of hyperbaric medicine, not as modern HBOT [3]. This distinction is important because the physiological effects discussed in this review depend on exposure to hyperbaric oxygen rather than pressure alone.

The ophthalmic relevance of HBOT is narrower than its broader use in hyperbaric medicine. HBOT has been studied in selected acute ocular ischemic disorders and other eye conditions, but the strength of evidence varies markedly across indications [4]. Diabetic retinopathy (DR) is a different problem. It is a chronic neurovascular complication of diabetes in which capillary injury, blood-retinal barrier failure, inflammation, retinal nonperfusion, and hypoxia develop over time. Pathological neovascularization in proliferative diabetic retinopathy (PDR) is driven in part by hypoxia-responsive signaling, including hypoxia-inducible factor 1-alpha (HIF-1α) and vascular endothelial growth factor (VEGF). For this reason, any proposal to use HBOT in DR must distinguish beneficial oxygen delivery from the possibility of harmful vascular, angiogenic, or oxidative effects.

The global burden of DR is large and increasing. A 2021 systematic review and meta-analysis estimated that approximately 103 million adults had DR in 2020, with projected increases to about 130 million by 2030 and 161 million by 2045 [5]. DR remains an important cause of preventable visual impairment among working-age adults [6]. Current evidence-based treatments reduce vision loss and can improve vision in selected patients, but they do not directly restore lost retinal capillary beds. This has sustained interest in approaches that may modify retinal oxygenation or downstream responses to hypoxia.

The published HBOT literature in DR is limited and heterogeneous. Some mechanistic reports suggest reduced blood-retinal barrier leakage or suppression of hypoxia-responsive pathways. Other HBOT literature shows proangiogenic signaling in non-retinal tissues. Direct human studies are few, often involve patients receiving HBOT for diabetic foot ulcers rather than for a retinal indication, and use different retinal outcomes. The objective of this review is therefore to provide a focused and evidence-graded narrative synthesis of HBOT in DR. We examine retinal pathophysiology, current standard care, mechanisms that may be relevant to the diabetic retina, direct human clinical findings, safety concerns, and the research needed before HBOT can be considered a routine retinal therapy.

Review

Methods

Review Design and Literature Search

This review was conducted as a structured narrative review rather than a systematic review or meta-analysis. The purpose was to critically synthesize mechanistic and clinical evidence while making the search approach transparent. The searches covered database inception through 4 October 2026 and used PubMed/MEDLINE and Google Scholar. The core search combined ("hyperbaric oxygen" OR "hyperbaric oxygen therapy" OR HBOT) with ("diabetic retinopathy" OR "diabetic macular edema" OR retina OR retinal). Supplementary searches combined HBOT with VEGF, HIF-1α, angiogenesis, inflammation, nitric oxide, inducible nitric oxide synthase, oxidative stress, blood-retinal barrier, retinal perfusion, choroidal thickness, adverse effects, barotrauma, and oxygen toxicity. Separate searches for current DR management combined diabetic retinopathy or diabetic macular edema with anti-VEGF, corticosteroid, laser photocoagulation, vitrectomy, guideline, or preferred practice pattern. Reference lists of directly relevant reviews and primary studies were also checked to identify additional clinical reports.

Eligibility, Evidence Classification, and Synthesis

Peer-reviewed English-language human studies were prioritized when they directly evaluated retinal outcomes in people with diabetes exposed to HBOT. Prospective cohorts, randomized trials, controlled studies, and case reports were considered because the direct clinical literature is small. Animal retinal studies were retained only when they addressed a mechanism that could not be established from human studies. Studies from wounds, peripheral vascular disease, cardiovascular disease, cerebral ischemia, or unrelated ophthalmic conditions were not used as evidence of clinical efficacy in DR. They were cited only when needed to explain a general HBOT mechanism, and their indirect nature is stated. Current clinical guidance from the American Diabetes Association and the American Academy of Ophthalmology was used to define standard DR care [7,8].

The direct human evidence set was checked against the five studies included in the 2025 systematic review and meta-analysis of HBOT for DR and diabetic macular edema (DME) [9]. Reports meeting these criteria were reviewed for design, sample size, HBOT exposure, comparator, retinal outcomes, and major limitations. One published case report describing proliferative retinopathy during HBOT was included as a safety signal rather than efficacy evidence [10]. No new DR-specific randomized HBOT trial was identified in the update through 4 October 2026. Because this is a narrative review, we did not perform a new meta-analysis, duplicate screening, or formal study-level risk-of-bias scoring. Instead, evidence was weighted qualitatively by directness and study design, and important limitations are presented. This approach avoids presenting mechanistic, animal, observational, and randomized evidence as if they were equivalent.

Diabetic retinopathy: Clinical and pathophysiological context

Disease Progression and Retinal Microvascular Injury

DR develops from chronic metabolic and vascular stress rather than from a single early constriction of large retinal arteries. Early histopathological changes include pericyte loss, endothelial dysfunction, basement-membrane alteration, microaneurysm formation, and capillary closure [11-13]. Hyperglycemia, oxidative stress, inflammatory signaling, protein kinase C activation, and other metabolic pathways contribute to blood-retinal barrier dysfunction. Leakage arises mainly from damaged retinal capillaries and microaneurysms, not from the retinal vein itself. Fluid and lipid accumulation near the macula can produce DME at any stage of DR.

Non-proliferative diabetic retinopathy (NPDR) is characterized by microaneurysms, intraretinal hemorrhages, hard exudates, cotton-wool spots, venous beading, and intraretinal microvascular abnormalities. As capillary nonperfusion increases, local retinal hypoxia becomes more important. Hypoxia stabilizes HIF-1α and promotes VEGF and other mediators that increase vascular permeability and angiogenic drive [12,14]. PDR is defined by pathological neovascularization. Fragile new vessels can cause vitreous hemorrhage, and fibrovascular contraction can cause tractional retinal detachment. In parallel, neural and glial changes contribute to the disease, supporting the current view of DR as a neurovascular and inflammatory disorder [15,16].

Current Evidence-Based Management

Management depends on disease stage, DME status, visual acuity, and systemic control. Glycemic, blood-pressure, and lipid management remain fundamental. For most eyes with center-involved DME that impairs visual acuity, intravitreal anti-VEGF therapy is first-line treatment. Anti-VEGF agents reduce VEGF signaling, vascular permeability, and neovascular activity. They do not directly reverse established retinal ischemia. For PDR, panretinal photocoagulation (PRP) remains an established treatment that reduces the risk of severe vision loss by ablating peripheral ischemic retina and lowering angiogenic drive. Anti-VEGF therapy is a reasonable alternative for selected patients with PDR, provided that reliable follow-up can be maintained [7,8].

Laser treatment should not be described as a routine treatment for uncomplicated NPDR. The 2026 American Diabetes Association guidance recommends PRP for high-risk PDR and in selected cases of severe NPDR, while anti-VEGF therapy for NPDR without DME may reduce progression to PDR or DME but has not shown a corresponding two-year visual benefit sufficient for routine use solely for that indication [7]. Focal or grid laser and intravitreal corticosteroids are reasonable options for persistent DME after anti-VEGF therapy or when anti-VEGF treatment is unsuitable [7]. Corticosteroid exposure can increase intraocular pressure and accelerate cataract. These adverse effects should not be attributed to anti-VEGF drugs. Intravitreal injections instead carry procedure-related risks such as endophthalmitis and retinal tears or detachment, with systemic thromboembolic risk considered in clinical decision-making [8,17,18].

Vitreoretinal surgery is not the routine next step after medical therapy. Vitrectomy is reserved for advanced complications such as non-clearing vitreous hemorrhage, macula-threatening tractional retinal detachment, combined tractional-rhegmatogenous detachment, or selected cases with a significant vitreomacular component [8,18]. This treatment framework is important when considering HBOT. A new adjunct should be evaluated against the specific goal and disease stage for which it is proposed, and it should not be framed as correcting a failure of standard therapies to "halt ischemia," because that is not its primary mechanism.

Rationale for exploring HBOT in the diabetic retina

The retina has a high metabolic demand and depends on tightly regulated oxygen delivery [19,20]. Hyperoxia raises arterial and plasma oxygen tension and can increase the oxygen gradient from the choroid toward hypoxic retinal tissue. At the same time, retinal and choroidal vessels constrict in response to increased oxygen tension. These responses can reduce blood flow while tissue oxygen availability remains high. The net effect in chronic diabetic microvascular disease cannot therefore be inferred from oxygen tension alone.

The older phrase "retinal oxygen poisoning" is imprecise in this context. Oxygen-induced retinopathy in neonatal animals demonstrates that immature retinal vessels are particularly vulnerable to hyperoxia, but this model reflects developing retinal vasculature and is not a direct model of adult DR. Mature adult retinal vessels respond differently to hyperoxia. The neonatal literature is therefore most useful as a reminder that oxygen has stage- and tissue-specific vascular effects, not as evidence that HBOT is either safe or effective in adults with DR.

Evidence from acute central retinal artery occlusion and from ischemia-reperfusion models also should not be transferred directly to DR. Acute arterial occlusion is a sudden near-complete interruption of retinal blood flow, whereas DR is a chronic, spatially heterogeneous microvascular disease. For this reason, specific ischemic time windows reported in experimental occlusion studies are not used here to define a therapeutic window for DR, and wound-debridement analogies are not applied to the retina.

Mechanistic evidence relevant to the diabetic retina

Retinal Oxygenation and Blood-Retinal Barrier Effects

The most direct preclinical evidence comes from a streptozotocin-induced diabetic rat model. Chang et al. exposed diabetic rats to 100% oxygen at 2.5 atmospheres absolute for 90 minutes three times per week for three months [14]. Retinal Evans blue leakage was 18.5 ± 4.2 microliters plasma/g retinal dry weight/h in untreated diabetic animals and 10.2 ± 3.1 in HBOT-treated diabetic animals, compared with 7.6 ± 2.9 in non-diabetic controls ($n = 8$ per group, $p < 0.05$ for relevant comparisons). The study supports a possible effect on blood-retinal barrier permeability, but it remains an animal study and does not establish improved vision or clinical benefit in people with DR.

Changes in retinal and choroidal thickness during HBOT have also been reported in humans, but these anatomical responses are inconsistent and are not equivalent to treatment efficacy. Some studies show choroidal thinning, some show little acute change, and one prospective study reported region-specific macular thickening in mild-to-moderate NPDR [21,22]. These findings are relevant because they show that ocular tissue responds to HBOT, but they do not demonstrate reversal of retinal ischemia.

HIF-1α, VEGF, and the Angiogenesis Paradox

A central problem in interpreting HBOT is that angiogenesis can be either reparative or pathological depending on tissue and context. In the hypoxic diabetic retina, HIF-1α is stabilized and activates hypoxia-responsive genes, including VEGF. Increased VEGF contributes to vascular leakage and pathological neovascularization in PDR [12,23]. When oxygen availability rises, HIF-1α is more readily hydroxylated and targeted for degradation. Experimental hyperoxia can therefore reduce HIF-1α-dependent signaling and retinal VEGF expression. It is inaccurate to state that VEGF is unaffected by oxygen tension or that HBOT necessarily increases HIF-1α in the retina.

HBOT can nevertheless promote reparative angiogenic signaling in chronic wounds and peripheral ischemic tissues through mechanisms that include oxygen-dependent collagen formation, growth-factor signaling, endothelial progenitor responses, and transient reactive oxygen species signaling [24,25]. These observations do not mean that HBOT should promote angiogenesis in the diabetic retina. The desired retinal effect would be improved oxygen availability without stimulation of pathological neovascularization. Direct evidence that HBOT suppresses or increases vitreous VEGF in human DR is lacking. Thus, the wound-healing literature and retinal VEGF biology should be treated as context-dependent processes rather than merged into a single proangiogenic claim.

This distinction also explains why the present review does not describe HBOT as an angiogenesis-promoting treatment for DR. Human clinical reports have not demonstrated a consistent increase in DR stage, and the randomized placebo-controlled study was ophthalmologically neutral over two years [26]. However, an isolated case report described progression of previously treated PDR during a course of HBOT for diabetic foot ulcers [10]. A case report cannot establish causality, but it supports caution in patients with active or unstable proliferative disease and reinforces the need for retinal outcomes in future trials.

Inflammation, Nitric Oxide, and Nuclear Factor Kappa B Signaling

Inflammation contributes to endothelial injury, neuroglial dysfunction, vascular permeability, and progression of DR [12,15,16]. HBOT can modify inflammatory signaling, but the direction and clinical importance depend on the pathway and tissue studied. Nitric oxide is a good example. Physiological endothelial nitric oxide synthase (eNOS)-derived nitric oxide supports vascular homeostasis. In contrast, sustained high-output nitric oxide generated by inducible nitric oxide synthase (iNOS) during inflammatory and hyperglycemic stress can contribute to nitrosative injury. A pilot study in people with type 1 diabetes reported early changes in lymphocyte iNOS activity and expression after HBOT [27], while human physiology studies show that HBOT can alter nitric oxide generation more broadly [28]. Neither study is a clinical DR trial.

The iNOS pathway has direct pathogenic relevance to diabetic retinal inflammation in experimental and translational literature [29]. This makes downregulation of excessive iNOS activity a plausible hypothesis, but it should not be described as a proven retinal mechanism of HBOT. The same caution applies to nuclear factor kappa B (NF-κB). IκBα is a predominantly cytoplasmic inhibitory protein that restrains NF-κB signaling by retaining NF-κB outside the nucleus [30]. It is not a nuclear protein. Hyperoxia-related modulation of NF-κB and IκBα has been reported in broader, non-retinal HBOT literature [24], but a clinically meaningful anti-inflammatory effect in human DR has not been established.

Oxidative Stress and Unresolved Retinal Risk

HBOT transiently increases reactive oxygen and nitrogen species. In several non-retinal settings, these species act as signals that trigger antioxidant and repair responses. In diabetes, however, baseline oxidative stress is already increased and contributes to microvascular injury. This creates another context-dependent balance [24]. A short, controlled hyperoxic exposure may activate adaptive signaling, while excessive dose, repeated exposure, or susceptible tissue could increase oxidative injury. The retinal consequences may also vary with DR stage, prior PRP, macular edema, glycemic control, and coexisting vascular disease. This uncertainty is a specific limitation of applying general HBOT mechanisms to DR.

Clinical evidence for HBOT in diabetic retinopathy and macular edema

Direct human evidence remains limited. The studies differ in design, retinal stage, HBOT dose, treatment indication, concomitant therapy, and follow-up. Importantly, most participants received HBOT for diabetic foot ulcers rather than as a primary retinal treatment. Table *1* summarizes the principal human studies and the 2025 quantitative synthesis.

Study	Design and population	HBOT exposure/comparator	Main retinal findings	Key limitations
Sellman et al., 2020 [26]	Randomized, single-center, double-blind, placebo-controlled trial; 50 patients with diabetes and chronic foot ulcers; ophthalmic follow-up to 24 months.	HBOT vs. placebo air; up to 40 treatments.	No significant between-group difference in visual acuity or DR findings. New clinically significant macular edema occurred in 4 eyes in the HBOT group and 3 eyes in the placebo group.	Retinal outcomes were secondary to a foot-ulcer trial; sample was small for stage-specific retinal effects.
Maalej et al., 2020 [31]	Prospective controlled study; 25 patients with NPDR receiving HBOT for foot ulcers and 25 controls with DR.	30 sessions, 90 min at 2.5 ATA, about 5 sessions/week; no-HBOT control.	Regression or stabilization of DR lesions and lower central macular thickness after HBOT; final BCVA favored HBOT.	Non-randomized; short follow-up; HBOT indication was diabetic foot ulcer.
Kaldırım et al., 2019 [21]	Prospective non-randomized cohort; 30 patients, 60 eyes: mild-moderate NPDR, severe NPDR, or inactive laser-treated PDR.	30 HBOT sessions for diabetic foot ulcer; repeated OCT measurements.	No progression or regression of DR stage. Choroidal thickness decreased over time. Region-specific macular thickening occurred in mild-to-moderate NPDR.	No non-HBOT comparator; small stage subgroups; anatomical rather than vision-centered primary outcomes.
Gün et al., 2022 [22]	Cross-sectional acute OCT study; 26 patients, 49 eyes with type 2 diabetes, including eyes with and without NPDR.	Measurements before and about 45 min after a single HBOT exposure at 2.4 ATA.	No consistent acute change in central macular or overall choroidal thickness; a regional nasal choroidal change was reported in DR eyes.	Single-session physiology study; not designed to assess treatment efficacy or long-term DR progression.
Drozdov and Sakovych, 2022 [32]	Open-label case-control study; 91 patients with type 2 diabetes, NPDR, and DME.	Aflibercept alone vs. aflibercept plus 10 HBOT sessions.	The adjunctive HBOT group reported greater improvements in visual acuity and retinal light sensitivity and a larger reduction in DME frequency at follow-up.	Open-label, non-randomized design; treatment schedules differed between groups; single-center evidence.
Moccia et al., 2025 [9]	Systematic review and meta-analysis of 5 eligible studies, 463 eyes.	Pooled HBOT-containing regimens vs. available comparators.	BCVA mean difference of -0.05 logMAR (95% CI: -0.09 to -0.01; I2=0%). CMT pooled difference of -75.21 micrometers (95% CI: -90.04 to -60.38; I2=62%).	BCVA significance was lost when the largest study was removed. CMT heterogeneity was substantial. Included primary studies were clinically heterogeneous.

TABLE 1: Direct human evidence for HBOT in diabetic retinopathy and diabetic macular edema.

ATA: atmospheres absolute; BCVA: best-corrected visual acuity; CMT: central macular thickness; DME: diabetic macular edema; DR: diabetic retinopathy; HBOT: hyperbaric oxygen therapy; NPDR: non-proliferative diabetic retinopathy; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy.

Interpretation of the Clinical Evidence

The randomized study by Sellman et al. is important because it directly addresses the concern that repeated HBOT might worsen diabetic retinal microvascular disease [26]. Over two years, the study found no significant difference in visual acuity or retinopathy between HBOT and placebo groups. This result supports ophthalmic neutrality in the studied population rather than efficacy. It also does not exclude smaller benefits or harms in specific DR stages because the trial was not powered as a dedicated retinal efficacy trial.

Maalej et al. reported more favorable short-term anatomical and clinical findings in NPDR [31], while Kaldırım et al. found no DR stage change and mixed structural effects [21]. Gün et al. examined only the acute response to a single session and therefore informs physiology more than treatment efficacy [22]. Drozdov and Sakovych reported better outcomes when HBOT was added to aflibercept in DME, but the open-label case-control design and differing treatment schedules make causal attribution uncertain [32]. These studies therefore point in different directions and should not be described collectively as proof of benefit.

An earlier prospective, non-comparative case series by Said et al. used HBOT as the primary treatment for

clinically significant macular edema in 19 eyes of 12 patients with diabetes (2.4 atmospheres absolute, 90-minute sessions, five per week, 40 sessions in total) [33]. Mean central macular thickness (CMT) decreased by 149.0 ± 87.7 micrometers during 32 weeks of follow-up, and fluorescein leakage resolved in 10 eyes (52.6%). However, macular thickness increased again in four eyes (21.0%) by the end of follow-up. Figure *1* shows a representative eye from this series. Because the study had no control group, these images illustrate the anatomical response that motivates further trials rather than evidence of efficacy (Figure *1*).

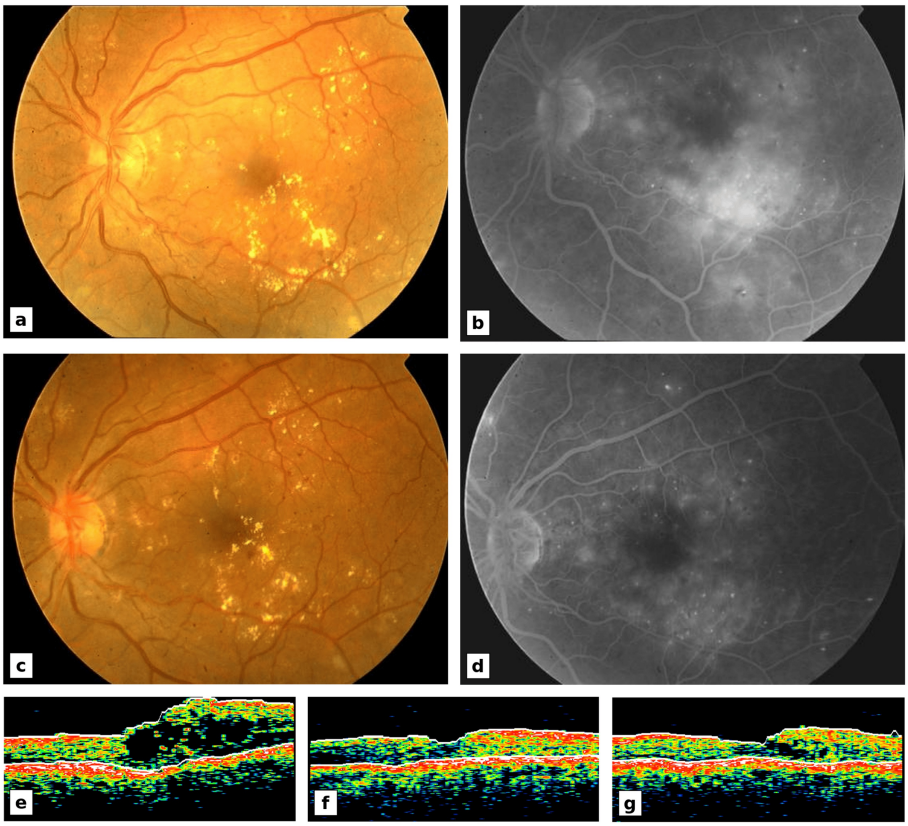


FIGURE 1: Clinically significant macular edema in a patient with diabetes before and after primary treatment with hyperbaric oxygen therapy.

(a) Fundus photograph of the left eye before HBOT showing macular hard exudates. (b) Fluorescein angiography before HBOT showing leakage. (c) Fundus photograph 32 weeks after starting HBOT, with persistent hard exudates. (d) Fluorescein angiography at 32 weeks showing reduced leakage. (e-g) OCT showing a CMT of 497 µm before treatment (e), 470 µm at 12 weeks (f), and 251 µm at 32 weeks (g).

CMT: central macular thickness; HBOT: hyperbaric oxygen therapy; OCT: optical coherence tomography.

Reproduced from Said et al. [33] with permission from the authors.

The 2025 systematic review and meta-analysis provides the strongest quantitative summary currently available [9]. Across five studies and 463 eyes, pooled best-corrected visual acuity improved by 0.05 logMAR and CMT decreased. The magnitude of the visual acuity effect was small, and the authors reported that it lost statistical significance when the largest study was removed. Heterogeneity for CMT was substantial. These findings are best interpreted as an efficacy signal that justifies better trials, not as evidence sufficient for routine clinical adoption.

Position of HBOT relative to standard DR therapy

HBOT is not included as standard treatment for DR or DME in the 2026 American Diabetes Association recommendations or the 2025 American Academy of Ophthalmology Preferred Practice Pattern [7,8]. Anti-VEGF therapy remains the first-line treatment for most center-involved DME with impaired vision and is an accepted option for selected PDR. PRP remains a durable treatment for high-risk PDR and selected severe NPDR. Corticosteroid or focal/grid laser treatment can be used in selected persistent DME, and vitrectomy is reserved for defined advanced complications. Any future role for HBOT would therefore be adjunctive and stage-specific unless comparative trials demonstrate otherwise.

This positioning also resolves a mechanistic misconception. Standard therapies are not unsuccessful attempts to restore normal retinal perfusion. Anti-VEGF treatment reduces permeability and neovascular signaling. PRP reduces the metabolic and angiogenic load of ischemic peripheral retina. Vitrectomy addresses mechanical or hemorrhagic complications and can alter intraocular oxygen distribution. HBOT, by contrast, transiently changes systemic and ocular oxygen availability. These mechanisms are different and should be compared through clinical outcomes rather than through a common claim of "reversing ischemia."

Safety considerations

HBOT is generally well tolerated when delivered in appropriately selected patients under established hyperbaric protocols, but it is not free of adverse effects. The most common pressure-related complication is middle-ear barotrauma. Its reported frequency varies widely because definitions, patient populations, chamber protocols, and surveillance differ [34]. Sinus barotrauma is a separate pressure-related event. Pulmonary barotrauma is uncommon but potentially serious, particularly in patients with an unvented pneumothorax or relevant pulmonary risk. These entities should not be combined under a single incidence figure.

Oxygen-related adverse effects also vary by exposure. Central nervous system oxygen toxicity with a generalized seizure is rare at clinical treatment pressures, while reversible myopic shift can occur during a course of repeated HBOT, and cataract progression has been reported with prolonged exposure [34]. Tympanic membrane rupture is an uncommon severe form of middle-ear barotrauma rather than a routine event. Claustrophobia or confinement anxiety can limit treatment. Small transient increases in blood pressure have been reported in some patients. The effect of concomitant antihypertensive medication should be assessed individually. It is inaccurate to state that calcium-channel blockers or beta blockers generally worsen HBOT through vasoconstriction and increased vascular resistance.

A 2023 systematic review and meta-analysis of randomized trials across HBOT indications found adverse events more often with HBOT than control treatment, with ear discomfort the most frequent event and higher rates in protocols using more sessions or pressures above 2.0 atmospheres absolute [35]. A large retrospective analysis of 2,334 patients also supports the overall feasibility of HBOT in clinical practice while documenting treatment-related events [36]. These data concern HBOT generally and should not be presented as DR-specific safety evidence.

For DR, additional retinal concerns deserve explicit attention. Hyperoxia can cause retinal and choroidal vasoconstriction. HBOT also alters redox signaling in a disease already characterized by oxidative stress. Finally, reparative angiogenic signaling observed in wounds cannot be assumed to be harmless in active PDR. The randomized diabetic foot-ulcer trial did not show worsening of retinopathy [26], but an isolated case report described proliferative progression during HBOT [10]. The overall signal is insufficient to establish a DR-specific retinal hazard, but it supports careful ophthalmic assessment in research protocols, particularly for eyes with active PDR or untreated sight-threatening disease.

Limitations and research priorities

The main limitation is the small direct human evidence base. Only a few studies report retinal outcomes in people with diabetes exposed to HBOT, and most enrolled patients because of diabetic foot ulcers rather than because HBOT was prescribed for DR. Sample sizes are small, DR stages differ, follow-up ranges from minutes to two years, and HBOT protocols vary in pressure, session number, and treatment duration. Concomitant retinal therapy also differs. Only one identified study used a randomized, double-blind, placebo-controlled design, and its retinal findings were neutral [26]. No adequately powered randomized trial has compared an HBOT strategy with contemporary stage-matched standard retinal care as a primary ophthalmic intervention.

The mechanistic evidence also has important directness problems. Animal oxygen-induced retinopathy models address immature retinal vasculature. Acute retinal artery occlusion addresses sudden complete or near-complete ischemia. Wound studies address tissues in which new vessel formation is often desirable. None is equivalent to chronic diabetic retinal microangiopathy. These distinctions are especially important for VEGF, HIF-1α, nitric oxide, and angiogenesis. Retinal hypoxia tends to stabilize HIF-1α and increase VEGF, whereas hyperoxia can reduce this signaling. In contrast, HBOT can promote reparative angiogenic responses in wounds and peripheral ischemic tissue. The net effect in a diabetic retina may depend on local oxygen tension, DR stage, and pre-existing neovascular activity. This uncertainty cannot be resolved by combining findings from different tissues.

DR-specific safety questions also remain. Transient retinal vasoconstriction may be adaptive, but its relevance in eyes with extensive capillary nonperfusion is uncertain. Repeated hyperoxia changes reactive oxygen species signaling in a population already exposed to chronic oxidative stress. The available studies are too small to detect uncommon retinal adverse outcomes or to establish safety in active PDR. Future trials should therefore include standardized DR grading, optical coherence tomography-defined DME outcomes, best-corrected visual acuity, retinal or wide-field nonperfusion measures when feasible, proliferative events, adverse ocular outcomes, and sufficient post-treatment follow-up.

This review also has methodological limitations. It is a structured narrative review, not a systematic review. We did not conduct duplicate independent screening, a formal risk-of-bias assessment, or a new meta-analysis. The quantitative estimates reported here are taken from the 2025 published systematic review and meta-analysis [9]. Our aim was to correct mechanistic overstatements, separate direct from indirect evidence, and update the clinical context rather than to reproduce that meta-analysis. Future evidence syntheses should prespecify a protocol, use duplicate screening and formal risk-of-bias tools, and separate trials in which HBOT is the retinal intervention from studies in which retinal outcomes are secondary observations during HBOT for another condition.

The most informative next study would be an adequately powered, multicenter, randomized trial in a clearly defined DR phenotype. HBOT pressure, oxygen exposure, air breaks, number of sessions, and concomitant retinal therapy should be standardized. Stratification by NPDR, active or treated PDR, and center-involved DME would reduce clinical mixing. A sham or pressure-matched comparator should be considered where feasible. Such trials are necessary before treatment guidelines for HBOT in DR can be developed.

Conclusions

Evidence for HBOT in DR is emerging but remains insufficient for routine clinical use. Although preliminary studies suggest potential benefits, the available clinical evidence is heterogeneous and does not establish definitive efficacy or retinal safety. HBOT should therefore be considered investigational for DR and should not replace anti-VEGF therapy, PRP, selected corticosteroid or focal laser therapy, or indicated vitreoretinal surgery. Standardized, adequately powered trials specifically evaluating efficacy and retinal safety in defined DR stages are required before evidence-based HBOT treatment guidelines can be justified.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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