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Systematic Review

From oxygen biology to surgical outcomes: translating hyperbaric oxygen therapy mechanisms into tissue salvage

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ABSTRACT

Hyperbaric oxygen therapy (HBOT) has emerged as a valuable adjunct in the management of ischemic and complex surgical wounds; however, its clinical application remains heterogeneous and often empirically driven. Despite growing evidence supporting its efficacy, a critical gap persists between the mechanistic understanding of HBOT and its integration into surgical decision-making. This systematic review aimed to synthesize current evidence on the biological mechanisms underlying HBOT and translate these mechanisms into clinically relevant outcomes. A structured search of PubMed/MEDLINE, Scopus, and Web of Science identified 312 records, of which 30 studies were included in the final qualitative synthesis. The evidence identified enhanced oxygen diffusion, angiogenesis and neovascularization, inflammatory modulation, antimicrobial activity, and cellular regeneration as interconnected mechanisms underlying the therapeutic effects of HBOT. Across surgical contexts, these mechanisms were associated with improved wound healing, enhanced tissue viability, infection control, reduced tissue necrosis, and lower amputation risk in selected clinical settings. Considerable heterogeneity was identified in treatment timing, pressure, session duration, frequency, and total number of sessions, with therapeutic responsiveness appearing to depend on the underlying pathophysiology, stage of tissue injury, and residual tissue viability. Based on these findings, a translational framework linking tissue hypoxia, ischemia, inflammation, infection, and impaired regeneration with specific HBOT-mediated mechanisms and expected clinical outcomes is proposed. Collectively, the findings support conceptualizing HBOT as a targeted adjunctive therapy rather than a universally applicable intervention, emphasizing mechanism-driven patient selection, appropriate treatment timing, and individualized therapeutic strategies to optimize its role in surgical tissue salvage and wound healing.

Keywords: Hyperbaric oxygen therapy, Tissue oxygenation, Wound healing, Tissue salvage, Angiogenesis, Surgical outcomes, Ischemic injury, Translational medicine

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) has emerged as a clinically valuable adjunct in the management of ischemic and complex wounds, particularly within surgical and reconstructive settings. By delivering 100% oxygen under increased atmospheric pressure, HBOT enhances the amount of dissolved oxygen in plasma, thereby improving tissue oxygenation beyond hemoglobin-dependent transport mechanisms. This physiological effect is particularly relevant in hypoxic environments, where impaired oxygen delivery contributes to delayed wound healing, compromised graft viability, and increased susceptibility to infection.[1,2]

At the cellular and molecular level, HBOT has been associated with multiple biological effects, including the promotion of angiogenesis, modulation of inflammatory pathways, enhancement of fibroblast activity, and potentiation of antimicrobial mechanisms.[3-5] These processes are especially relevant in conditions characterized by chronic hypoxia or ischemia-reperfusion injury, such as diabetic foot ulcers, radiation-induced tissue damage, and complex surgical wounds.[6-9] Consequently, HBOT has been increasingly incorporated into treatment protocols across diverse clinical scenarios, including chronic wounds, burns, surgical site infections, and compromised flaps and grafts.[10-13]

Despite its expanding clinical use, the application of HBOT remains heterogeneous across institutions and specialties. Variability in treatment protocols, including pressure settings, duration, and timing relative to surgical interventions, reflects a lack of standardized, mechanism-driven frameworks guiding its use. Current evidence, including systematic reviews and meta-analyses, supports its potential benefit in specific conditions such as diabetic foot ulcers, radiation tissue injury and aesthetic plastic surgery; however, inconsistencies in study design and patient selection continue to limit the generalizability of findings.[6-8,14,15]

Although the therapeutic potential of HBOT has been documented across multiple clinical contexts, a critical gap persists between the mechanistic understanding of its biological effects and their integration into surgical decision-making. Existing literature often presents either mechanistic insights in isolation or clinical outcomes without adequately linking these findings into a cohesive translational framework.[1,2] This fragmentation limits the ability of clinicians to apply HBOT in a rational, targeted manner tailored to specific pathophysiological conditions.

In particular, the relationship between oxygen-mediated molecular pathways and clinically relevant endpoints, such as tissue salvage, wound healing, and graft survival, remains insufficiently synthesized. While several studies demonstrate improved healing outcomes and reduced complication rates with adjunctive HBOT, the underlying mechanisms explaining these benefits are not consistently integrated into clinical protocols.[7,15,16] Additionally, key aspects such as optimal timing of therapy, dose-response relationships, and patient selection criteria are inconsistently addressed, contributing to heterogeneity in reported outcomes.[17,18]

Bridging this gap requires a structured integration of mechanistic evidence with clinical applications, allowing for a more precise understanding of how HBOT exerts its therapeutic effects and under which conditions it is most effective. Such an approach aligns with the principles of translational medicine, aiming to convert biological insights into actionable clinical strategies that improve patient outcomes.

This systematic review aims to bridge the gap between the biological mechanisms of HBOT and their clinical application in surgical care. Specifically, it seeks to synthesize current evidence on the mechanistic pathways through which HBOT influences tissue oxygenation, angiogenesis, inflammation, and infection control, and to translate these insights into clinically relevant outcomes such as tissue salvage and wound healing. Additionally, this review explores the implications of treatment timing and therapeutic strategies, with the goal of providing a conceptual framework to support more rational and effective use of HBOT in surgical practice.

METHODS

This systematic review was conducted and reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) statement. The review aimed to synthesize current evidence regarding the biological mechanisms of hyperbaric oxygen therapy (HBOT) and their translation into clinically relevant outcomes in surgical tissue salvage and wound healing. Given the mechanistic and translational focus of the review and the expected heterogeneity of the available literature, a qualitative evidence synthesis was planned.

A structured literature search was performed in PubMed/MEDLINE, Scopus, and Web of Science. The search included studies published from January 2000 to February 2026 and was restricted to articles published in English. The search strategy incorporated Medical Subject Headings (MeSH) and free-text terms combined with Boolean operators. The core search string was adapted across databases and included the following terms: (“hyperbaric oxygen therapy” OR “HBOT”) AND (“tissue salvage” OR “wound healing” OR “surgical wounds” OR “flap” OR “graft” OR “ischemic injury” OR “radiation injury” OR “burns” OR “chronic wounds”). To ensure broader coverage, reference lists from key reviews and clinically relevant studies were also manually screened.

Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Disagreements regarding study eligibility were resolved through discussion and consensus. Titles

and abstracts identified through the search strategy were screened for relevance, followed by full-text evaluation of potentially eligible articles. Study selection prioritized publications with direct clinical and translational relevance to HBOT in surgical contexts.

Data extraction was performed using a standardized data collection form that included study characteristics, patient population, clinical indication, HBOT treatment parameters, and reported outcomes relevant to tissue salvage and wound healing. Eligible studies included clinical trials, systematic reviews, meta-analyses, cohort studies, case series, and observational studies with clinically relevant outcome reporting evaluating HBOT in surgical wound healing, tissue salvage, or reconstructive settings. Studies were considered relevant when they reported clinically meaningful outcomes such as wound healing, graft or flap survival, infection control, tissue perfusion, angiogenesis, or other regenerative endpoints. The study selection process was documented using a PRISMA 2020 flow diagram to enhance transparency in study identification, screening, and inclusion (Figure 1).

Studies were excluded if they addressed non-surgical indications of HBOT, such as decompression sickness or carbon monoxide poisoning, or if they lacked clear relevance to wound healing, tissue salvage, or surgical care. Purely experimental animal studies were excluded unless they provided clear translational relevance to clinical wound repair mechanisms. Conference abstracts, editorials, opinion articles, and publications without full-text availability were also excluded.

For each eligible publication, relevant information was extracted, including study design, patient population, clinical indication, HBOT treatment parameters, and reported outcomes. Particular emphasis was placed on treatment pressure, session duration, number of sessions, timing of therapy, and the relationship between biological mechanisms and clinical endpoints. Extracted findings were organized into thematic domains, including oxygen physiology, angiogenesis, inflammatory modulation, antimicrobial effects, tissue salvage, and surgical wound outcomes.

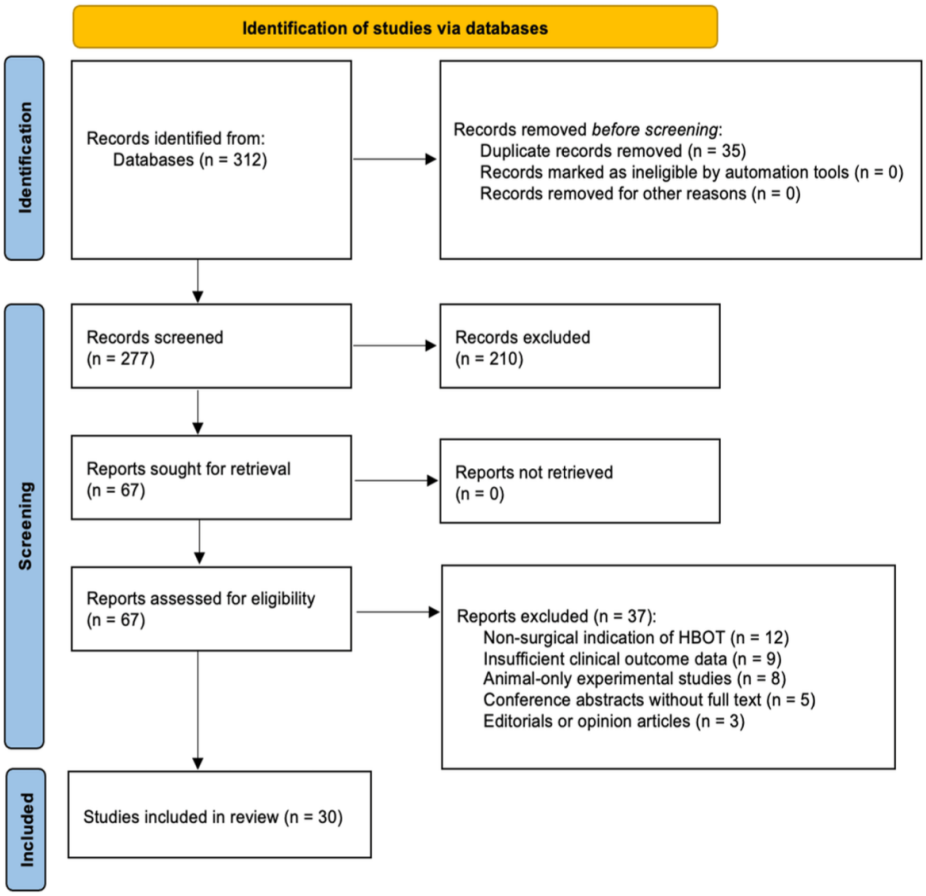

Figure 1: Study selection process for the literature review.

*PRISMA flow diagram illustrating the process of identification, screening, eligibility assessment, and inclusion of studies evaluating the role of hyperbaric oxygen therapy (HBOT) in surgical wound healing and tissue salvage. A total of 312 records were identified through database searches. After the removal of 35 duplicate records, 277 articles underwent title and abstract screening, of which 210 were excluded. Sixty-seven full-text articles were assessed for eligibility, and 37 were excluded based on predefined criteria, including non-surgical indications of HBOT, insufficient clinical outcome data, animal-only experimental studies without clinical correlation, conference abstracts lacking full text, and editorial or opinion articles. Ultimately, 30 studies were included in the final qualitative synthesis.

Given the heterogeneity of study designs, patient populations, HBOT protocols, and outcome reporting, quantitative meta-analysis was not performed. Given the broad translational objective of this review and the substantial methodological heterogeneity of the included evidence (including systematic reviews, clinical trials, cohort studies, observational studies, and case series), a formal risk-of-bias assessment was not performed. Instead, the evidence was synthesized qualitatively to integrate mechanistic and clinical findings across diverse surgical contexts.

This approach was considered more appropriate than quantitative evidence grading because the primary objective was conceptual integration rather than comparative effectiveness assessment. Because no formal risk-of-bias assessment was performed, the findings should be interpreted as a qualitative synthesis intended to provide a translational conceptual framework rather than a comparative assessment of treatment efficacy.

RESULTS

Study selection

A total of 312 records were identified through the database search. After removal of 35 duplicate records, 277 articles underwent title and abstract screening, of which 210 were excluded. Sixty-seven full-text articles were assessed for eligibility, and 37 were excluded because they addressed non-surgical indications of HBOT, provided insufficient clinical outcome data, consisted of animal-only experimental studies without clear clinical correlation, were conference abstracts without available full text, or were editorials or opinion articles. Ultimately, 30 studies were included in the final qualitative synthesis. The study selection process is summarized in Figure 1.

Oxygen physiology and tissue diffusion

The included evidence identified enhanced oxygen delivery as a primary physiological effect of HBOT, particularly in hypoxic and ischemic environments. Under hyperbaric conditions, administration of 100% oxygen at pressures typically ranging from 2.0 to 3.0 atmospheres absolute (ATA) substantially increases the amount of oxygen dissolved in plasma and elevates arterial oxygen tension, facilitating oxygen diffusion into poorly perfused tissues.[1,2]

Increased plasma-dissolved oxygen was associated with greater diffusion gradients between capillaries and hypoxic tissues, supporting oxygen delivery in areas with compromised microcirculation and contributing to the maintenance of cellular metabolism and tissue viability.[1] Improved oxygen availability was also associated with oxygen-dependent processes involved in wound healing, including mitochondrial metabolism, ATP production, collagen synthesis, extracellular matrix formation, and leukocyte-mediated bacterial killing.[3-5]

Repeated hyperoxic exposure was additionally associated with adaptive microvascular responses, including improved capillary perfusion and oxygen utilization, suggesting that some physiological effects may persist beyond the period of immediate hyperoxia.[19,20] Clinically, restoration of tissue oxygenation was associated with tissue salvage and wound healing in ischemic wounds and compromised flaps and grafts.[11,13]

Angiogenesis and neovascularization

The included evidence also demonstrated angiogenic and neovascular responses associated with HBOT. Hyperoxic exposure was associated with increased expression of angiogenic mediators, particularly vascular endothelial growth factor (VEGF), and with endothelial proliferation, migration, and capillary formation.[1,3]

Repeated cycles of hyperoxia followed by relative normoxia were associated with activation of hypoxia-inducible factor (HIF-1α) signaling and downstream angiogenic mediators, including increased VEGF expression and microvascular network formation.[3,19] At the tissue level, these responses were associated with improved long-term perfusion, granulation tissue formation, and epithelialization in ischemic wound environments.[20,21]

Clinical evidence linked improved neovascularization with enhanced wound closure, reduced healing time, and decreased risk of major complications in diabetic foot ulcers, venous leg ulcers, and radiation-induced tissue injury.[7,8,10] Angiogenesis was also identified as an important mechanism supporting graft integration and flap viability in reconstructive surgery.

The magnitude of the angiogenic response varied according to HBOT pressure, number of sessions, and timing of treatment, reflecting substantial protocol heterogeneity across the included evidence.

Inflammatory modulation and immunoregulation

HBOT was associated with modulation of inflammatory and immune pathways relevant to ischemic injury and wound healing. The included evidence demonstrated attenuation of pro-inflammatory responses through effects on molecular and cellular pathways involved in immune regulation.[3-5]

At the molecular level, HBOT was associated with reduced expression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), as well as modulation of NF-κB-related inflammatory signaling.[22] HBOT also enhanced the functional activity of neutrophils and macrophages, supporting oxidative bacterial killing and phagocytic activity.[4,5]

Clinically, these immunomodulatory effects were associated with improved healing trajectories and decreased infection and tissue necrosis in chronic wounds and postop complications.[11,23,24] Variability in treatment timing and frequency observed across studies evaluating these inflammatory and immunological effects.

Antimicrobial and immune effects

The included evidence demonstrated both direct and indirect antimicrobial effects of HBOT through oxygen-dependent inhibition of microbial activity and enhancement of host immune function.[4,5,25]

Increased tissue oxygen tension enhanced neutrophil bactericidal activity through reactive oxygen species generation during the oxidative burst, supporting microbial killing in hypoxic and ischemic environments.[4,5] Hyperoxic conditions were also associated with inhibitory effects on selected microorganisms, particularly anaerobic bacteria, as well as potential effects on bacterial biofilms.[3,5]

HBOT was additionally associated with enhanced antimicrobial therapy through improved tissue oxygenation and potential potentiation of antibiotic activity in poorly perfused tissues.[4] In clinical settings, adjunctive HBOT was associated with improved infection control, reduced need for surgical debridement, and lower amputation rates in diabetic foot infections and necrotizing soft tissue infections.[11,23,24]

Cellular proliferation and tissue regeneration

HBOT was associated with several cellular and regenerative processes involved in wound healing, including fibroblast activation, collagen synthesis, extracellular matrix deposition, and re-epithelialization.

Increased oxygen availability enhanced fibroblast proliferation and supported oxygen-dependent collagen synthesis, including hydroxylation processes involved in collagen stabilization and cross-linking.[11,23,24] HBOT was also associated with extracellular matrix formation, keratinocyte proliferation and migration, mitochondrial activity, and ATP production.[19,20]

At the tissue level, these effects were associated with granulation tissue formation, wound healing, tissue remodeling, and restoration of tissue integrity. Clinical evidence from diabetic foot ulcers, radiation-induced tissue injury, and complex surgical wounds associated these regenerative mechanisms with faster healing and improved functional outcomes.[7,8,10]

Overall, the included evidence demonstrated an interconnected pattern of enhanced oxygen diffusion, angiogenesis, immunomodulation, antimicrobial activity, and tissue regeneration. These findings and their proposed translation into surgical outcomes, including wound healing, graft and flap survival, infection control, and tissue salvage, are summarized in Figure 2.

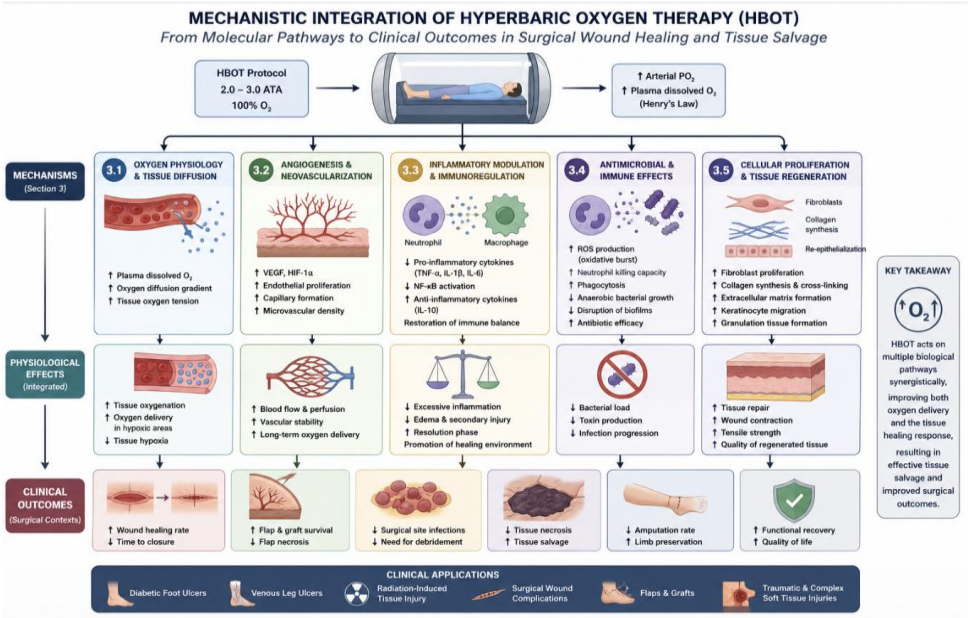

Figure 2: Mechanistic integration of hyperbaric oxygen therapy: from oxygen-mediated biological pathways to clinical outcomes in surgical tissue salvage and wound healing.

*Schematic representation of the mechanistic effects of HBOT and their translation into clinically relevant outcomes. Under hyperbaric conditions (2.0-3.0 atmospheres absolute with 100% oxygen), increased plasma-dissolved oxygen enhances tissue oxygenation and diffusion gradients, particularly in hypoxic environments. This triggers multiple interconnected biological pathways, including angiogenesis (via VEGF and HIF-1α signaling), modulation of inflammatory responses, enhancement of immune cell function and antimicrobial activity, and stimulation of cellular proliferation and extracellular matrix formation. These integrated effects lead to improved microvascular perfusion, reduced infection and inflammation, and enhanced tissue repair. Clinically, these mechanisms translate into improved wound healing, increased graft and flap survival, reduced tissue necrosis, lower amputation rates, and improved functional recovery. The figure highlights the synergistic and multi-level nature of HBOT as a translational therapeutic strategy in surgical and ischemic conditions. Created with BioRender.com.

Clinical applications in surgical contexts

Across the included evidence, HBOT was evaluated across multiple surgical contexts, including chronic and ischemic wounds, postoperative surgical wounds, compromised flaps and grafts, infected soft tissue wounds, radiation-induced tissue injury, and complex traumatic wounds.

The reported clinical benefits varied according to the underlying pathophysiology but generally included improved wound healing, enhanced tissue viability, better infection control, reduced tissue necrosis, and lower amputation risk in selected clinical settings. The principal clinical applications, underlying pathophysiological mechanisms, and reported outcomes are summarized in Table 1.

Table 1: Clinical applications, underlying mechanisms, and reported outcomes of hyperbaric oxygen therapy across surgical contexts.

Clinical context	Dominant pathophysiology	Main HBOT mechanisms	Main reported outcomes	References
Chronic and ischemic wounds	Persistent hypoxia, impaired perfusion, dysregulated inflammation	Enhanced oxygen diffusion, angiogenesis	Improved wound healing, reduced time to closure, lower risk of major amputation	7, 8, 23, 32 and 33
Surgical wound healing and postoperative complications	Hypoxia, inflammation, microbial contamination	Improved tissue oxygenation, collagen synthesis, cellular proliferation, immunomodulation	Reduced complications and improved recovery in high-risk surgical wounds	11 and 24
Flaps and grafts in reconstructive surgery	Ischemia, venous congestion, impaired perfusion	Enhanced oxygen diffusion, neovascularization, edema reduction	Improved flap survival, reduced necrosis, improved graft integration	11 and 34
Infected surgical wounds and soft tissue infections	Infection, poor perfusion, necrotic tissue	Enhanced immune function, anaerobic inhibition, improved antibiotic activity	Improved infection control, fewer repeated debridements, lower amputation rates	7, 8 and 23
Radiation-induced tissue injury	Chronic hypoxia, fibrosis, impaired vascularization	Angiogenesis, improved tissue oxygenation	Improved tissue quality, symptom reduction, facilitation of reconstruction	10 and 13
Complex surgical wounds and traumatic injuries	Ischemia, inflammation, infection risk	Improved oxygen delivery, angiogenesis, immunomodulation	Improved tissue salvage, reduced progression of necrosis, better functional outcomes	11 and 13

Table 2: Treatment parameters and therapeutic considerations of hyperbaric oxygen therapy across included evidence.

Parameters	Main finding	Clinical relevance	References
Timing of intervention	Earlier HBOT was associated with greater potential benefit in acute ischemic or infectious conditions, whereas delayed initiation may be less effective after irreversible necrosis or advanced fibrosis has developed.	Treatment timing should account for the stage of tissue injury and residual tissue viability.	11 and 13
Preoperative and postoperative administration	Preoperative HBOT may improve tissue oxygenation and microvascular function, while postop treatment may support graft integration, reduce edema, and mitigate ischemia-reperfusion injury.	HBOT administration may be aligned with biological phase of tissue repair and the surgical intervention.	11 and 13
Pressure and session duration	HBOT was typically administered at 2.0-3.0 ATA with 100% oxygen for approximately 60-120 minutes per session.	Treatment intensity requires a balance between adequate tissue oxygenation and the potential risk associated with excessive hyperoxic exposure.	40 and 44
Frequency and number of sessions	Acute conditions may benefit from more frequent treatment, whereas chronic wounds and radiation-induced injury often require prolonged treatment courses to support sustained	Treatment frequency and duration vary according to the acuity and underlying pathophysiology of the	11, 13, 25, 29 and 31

Continued.

Parameters	Main finding	Clinical relevance	References
	angiogenesis and tissue remodeling.	condition.	
Therapeutic window and tissue responsiveness	Greater responsiveness was reported during early or intermediate stages of tissue injury when viable cells remained and hypoxia and inflammation predominated. Extensive necrosis or fibrosis was associated with reduced regenerative potential.	Identification of residual tissue viability may help define the therapeutic window in which HBOT is most likely to provide meaningful benefit.	1, 5, 29, 33 and 35

Timing, dosage, and therapeutic windows

Considerable variability was identified across HBOT protocols, particularly regarding the timing of intervention, treatment pressure, session duration, frequency, and total number of sessions. Earlier administration was generally associated with greater therapeutic potential in acute ischemic and infectious conditions, whereas chronic wounds and radiation-induced tissue injury frequently required longer treatment courses. Treatment pressures typically ranged from 2.0 to 3.0 ATA, with session durations of approximately 60 to 120 minutes. Tissue responsiveness also appeared to depend on the stage of injury, with greater potential benefit when viable tissue remained and hypoxia or inflammation predominated. The principal treatment parameters and therapeutic considerations identified across the included evidence are summarized in Table 2.

DISCUSSION

Mechanism-to-outcome translation framework

The findings of the present review demonstrate that the biological effects of HBOT operate through interconnected mechanisms that collectively influence clinically relevant surgical outcomes. While the individual biological effects of HBOT have been extensively described, their clinical application remains limited by the lack of an integrated framework linking mechanistic pathways to specific therapeutic outcomes. Previous literature has similarly highlighted that surgical decision-making frequently relies on the empirical use of HBOT rather than a structured understanding of how its underlying mechanisms influence tissue viability, infection control, and wound healing.[1,2] The present findings therefore support a translational model connecting oxygen-mediated biological processes with clinically actionable endpoints.

As illustrated in Figure 2**,** enhanced tissue oxygenation through increased plasma-dissolved oxygen emerged as the physiological foundation for the downstream effects identified in this review. This finding is consistent with previous evidence demonstrating that increased oxygen availability supports cellular metabolism and critical oxygen-dependent processes, including collagen synthesis, leukocyte function, and energy production.[26-28] These effects provide a biological basis for the relationship between restoration of tissue oxygenation and improved viability in hypoxic and ischemic surgical tissues.

Angiogenesis and neovascularization represented a second major pathway identified in the present synthesis. HBOT was associated with restoration of microvascular networks and improved long-term tissue perfusion, consistent with previous studies describing enhanced vascular remodeling and perfusion following repeated hyperoxic exposure.[19,20,29] These effects are particularly relevant in ischemic and chronically hypoxic tissues, where inadequate blood supply represents a fundamental barrier to healing. Improved perfusion may consequently enhance oxygen delivery, nutrient transport, and waste removal, creating a more favorable microenvironment for tissue repair.

The present findings also demonstrate an interaction between inflammatory modulation and enhancement of immune function. Previous studies have similarly reported reductions in excessive pro-inflammatory signaling together with improved leukocyte-mediated bacterial clearance following HBOT.[30,31] These observations support the potential relevance of HBOT in infected or high-risk surgical wounds, in which persistent inflammation and impaired host defense may coexist and contribute to progressive tissue injury.

At the cellular level, the regenerative findings identified in this review are consistent with previous evidence demonstrating enhanced fibroblast activity, collagen deposition, and extracellular matrix formation following improved tissue oxygenation.[3,5] Importantly, these regenerative processes should not be considered isolated effects; rather, they appear to depend on preceding improvements in oxygen delivery, vascularization, and immune regulation, supporting the concept that HBOT acts through an interconnected biological cascade.

From a clinical standpoint, the integration of these mechanisms provides a plausible explanation for the surgical outcomes identified across the included evidence. Enhanced oxygen diffusion and angiogenesis were associated with improved graft and flap viability, whereas immunomodulatory and antimicrobial effects were associated with reduced infection and tissue necrosis. Similarly, enhanced cellular proliferation and matrix formation supported wound closure and tissue repair. These observations are consistent with previous clinical evidence reporting improved tissue salvage and

surgical outcomes with adjunctive HBOT in selected clinical settings.[11,13,23,24]

Taken together, these findings support a mechanistic-to-clinical continuum in which the therapeutic effects of HBOT depend on the dominant pathophysiological processes present in each clinical scenario. Rather than representing a one-size-fits-all intervention, HBOT may therefore be more appropriately considered within a mechanism-driven framework that accounts for tissue hypoxia, impaired perfusion, inflammation, infection, and regenerative capacity when determining its potential therapeutic role.

Collectively, this translational framework highlights HBOT as a multifaceted intervention operating through synergistic biological pathways to influence clinically relevant outcomes. Integrating mechanistic understanding with clinical application may support a more rational and targeted approach to HBOT in surgical tissue salvage and wound healing. To further translate these findings into clinical practice, a decision-oriented framework is presented in Figure 3**.** This model integrates underlying pathophysiological triggers of tissue injury with dominant biological mechanisms activated by HBOT and links them to specific surgical indications and expected clinical outcomes. By aligning hypoxia, ischemia, infection, inflammation, and impaired tissue regeneration with their corresponding HBOT-mediated effects, proposed framework provides structured approach for interpreting potential role of HBOT in patient selection and therapeutic decision-making.

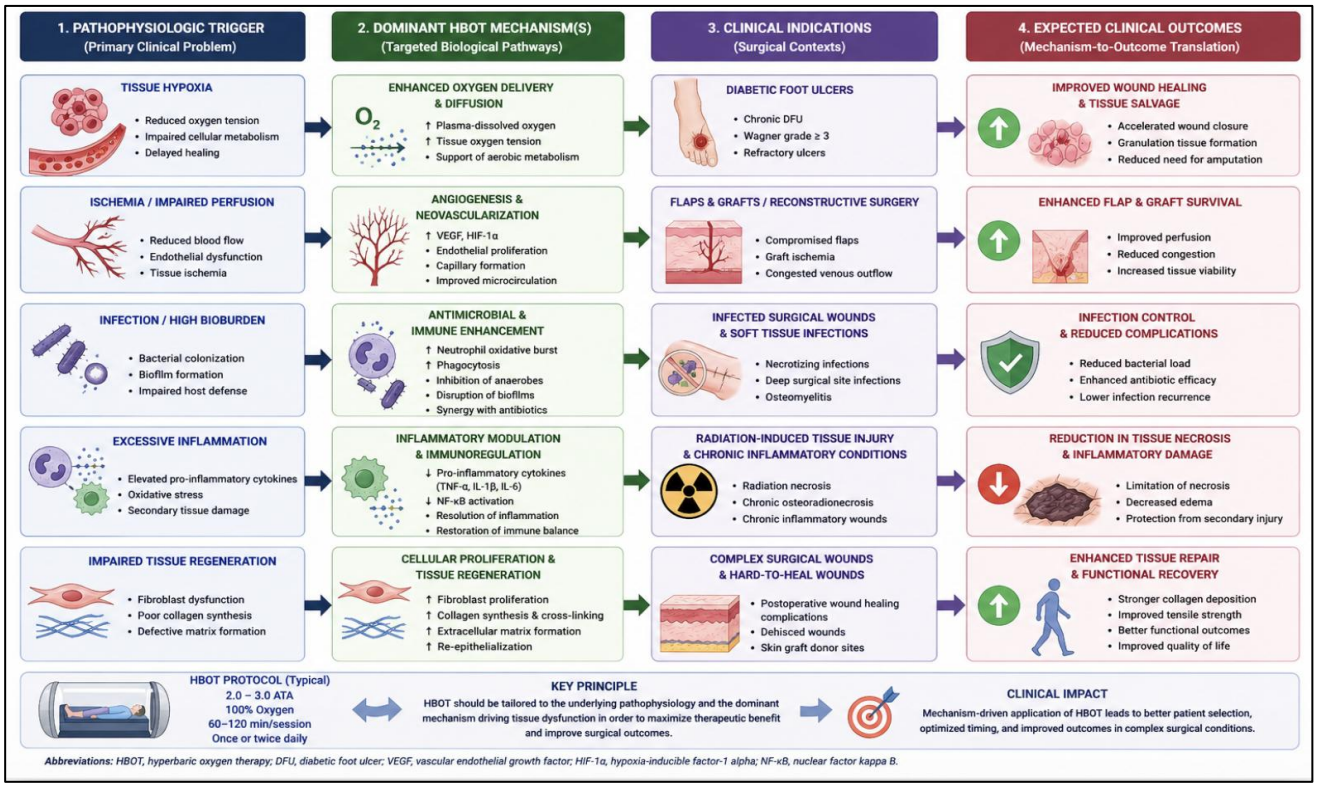

Figure 3: Clinical decision framework for the use of HBOT in surgical contexts: linking pathophysiology, biological mechanisms, and clinical outcomes.

*Schematic representation of a clinical decision-making framework for HBOT based on the integration of pathophysiological conditions, dominant biological mechanisms, and expected clinical outcomes. The model organizes clinical scenarios according to primary triggers, including tissue hypoxia, ischemia, infection, inflammation, and impaired tissue regeneration. Each condition is linked to specific HBOT-mediated mechanisms such as enhanced oxygen diffusion, angiogenesis, immunomodulation, antimicrobial activity, and cellular proliferation. These targeted effects are mapped to common surgical indications, including diabetic foot ulcers, compromised flaps and grafts, infected surgical wounds, radiation-induced tissue injury, and complex postoperative wounds. The resulting clinical outcomes include improved wound healing, enhanced tissue viability, infection control, reduced necrosis, decreased amputation rates, and improved functional recovery. This framework emphasizes a mechanism-driven approach to HBOT application, supporting more precise patient selection and optimized therapeutic strategies in surgical practice. Created with BioRender.com.

Clinical applications and comparison with previous evidence

The clinical findings summarized in Table 1 demonstrate that the potential benefits of HBOT extend across several surgical contexts, although the mechanisms and expected outcomes vary according to the underlying pathophysiology. This variability reinforces the importance of interpreting HBOT efficacy according to the dominant biological processes present in each clinical

scenario rather than considering its effects uniform across indications.

In chronic and ischemic wounds, particularly diabetic foot ulcers, the present synthesis identified improved wound healing, shorter time to closure, and a lower risk of major amputation as the principal reported outcomes. These findings are consistent with previous clinical studies and meta-analyses demonstrating beneficial effects of adjunctive HBOT in selected patients with diabetic foot ulcers.[7,8,23,32,33] The relationship between these outcomes and enhanced oxygen diffusion and angiogenesis supports the biological plausibility of HBOT in wounds characterized by persistent hypoxia and impaired perfusion.

In postoperative surgical wounds, the findings suggest that improved tissue oxygenation, cellular proliferation, and immunomodulation may contribute to reduced complications and improved recovery, particularly in high-risk patients. Previous clinical evidence has similarly supported the use of HBOT as an adjunct in selected surgical wounds characterized by vascular compromise, delayed healing, or increased susceptibility to infection.[11,24] Nevertheless, the heterogeneity of surgical populations and treatment protocols limits the generalization of these findings to all postoperative wounds.

The findings involving compromised flaps and grafts are also consistent with previous evidence describing improved tissue viability, reduced necrosis, and enhanced graft integration following adjunctive HBOT.[11,34] These effects are mechanistically coherent with increased oxygen diffusion, neovascularization, and improved microcirculatory function. Importantly, these observations support HBOT primarily as an adjunct for compromised or high-risk reconstructive tissues rather than as a substitute for correction of surgically reversible causes of flap or graft compromise.

In infected surgical wounds and severe soft tissue infections, the present synthesis identified improved infection control, reduced need for repeated surgical debridement, and lower amputation rates among the reported clinical outcomes. Previous studies have reported similar findings in diabetic foot infections and necrotizing soft tissue infections.[7,8,23] The combination of enhanced leukocyte function, inhibition of anaerobic microorganisms, and improved antimicrobial activity may explain these observations, although HBOT should remain complementary to appropriate antimicrobial therapy and surgical source control.

Radiation-induced tissue injury represents a distinct clinical context in which chronic hypoxia, fibrosis, and impaired vascularization contribute to progressive tissue dysfunction. The findings of this review are consistent with previous evidence supporting improved tissue oxygenation, vascular regeneration, tissue quality, and reconstructive potential following HBOT in selected radiation-induced injuries.[10,13]

These observations further illustrate how the therapeutic relevance of HBOT may depend on its ability to address the dominant pathophysiological mechanism underlying a particular tissue injury.

Finally, in complex surgical wounds and traumatic injuries, HBOT was associated with improved tissue salvage, reduced progression of necrosis, and better functional outcomes. Previous clinical evidence has similarly described potential benefits in selected traumatic and ischemic injuries.[11,13] In these scenarios, the simultaneous presence of ischemia, inflammation, and infection risk may provide a rationale for the multimodal biological effects of HBOT.

Overall, comparison across these clinical contexts suggests that the therapeutic value of HBOT is closely related to the presence of reversible hypoxia, impaired perfusion, infection, inflammation, or compromised regenerative capacity. The findings summarized in Table 1 therefore support a selective, pathophysiology-oriented approach to HBOT rather than its indiscriminate application across surgical conditions.

Treatment parameters and therapeutic windows

Beyond clinical indication, the findings summarized in Table 2 indicate that the therapeutic effects of HBOT may be influenced by treatment timing, pressure, session duration, frequency, and the physiological state of the affected tissue. The considerable variability observed across treatment protocols likely contributes to the heterogeneity of clinical outcomes and limits the definition of a universally optimal HBOT regimen.[26-28]

Timing appears particularly relevant in acute ischemic and infectious conditions. The present synthesis suggests greater therapeutic potential when HBOT is initiated before irreversible tissue necrosis or advanced fibrosis has developed. This observation is consistent with previous evidence emphasizing the potential importance of early intervention in restoring oxygen gradients, limiting inflammatory injury, and supporting tissue viability.[11,13] In reconstructive surgery, previous studies have also described both preoperative and postoperative applications, with preoperative treatment aimed at improving tissue oxygenation and microvascular conditions and postoperative treatment supporting graft integration and limiting ischemia-reperfusion injury.[11,13]

Treatment pressure and session duration represent additional sources of variability. Across the included evidence, HBOT was commonly administered at pressures between 2.0 and 3.0 ATA for approximately 60 to 120 minutes. These ranges are consistent with previously described therapeutic protocols.[40,44] However, the balance between achieving adequate tissue

oxygenation and limiting excessive hyperoxic exposure supports the need to interpret pressure and duration according to clinical indication rather than assuming that greater oxygen exposure necessarily produces superior outcomes.

The number and frequency of sessions also appear to depend on the biological target and chronicity of tissue injury. Acute conditions may require more frequent treatment to rapidly restore oxygenation and support infection control, whereas chronic wounds and radiation-induced injuries often require prolonged courses to promote sustained angiogenesis and tissue remodeling. These findings are consistent with previous literature describing indication-dependent variation in HBOT treatment schedules.[11,13,25,29,31]

Tissue responsiveness further appears to define a clinically relevant therapeutic window. The present findings suggest that HBOT may provide greater benefit during early or intermediate stages of tissue injury, when viable cells remain capable of responding to improved oxygen availability and when hypoxia and inflammation remain potentially reversible. Previous studies have similarly emphasized reduced regenerative potential in tissues characterized by extensive necrosis or advanced fibrosis.[1,5,29,33,35] This distinction may help explain why apparently similar HBOT protocols can produce different outcomes depending on the stage and severity of tissue injury.

From a translational perspective, optimizing timing, dosage, and treatment frequency represents a critical step toward maximizing the therapeutic potential of HBOT. A mechanism-driven approach that aligns treatment parameters with the underlying pathophysiology, tissue viability, and stage of injury may improve clinical outcomes and reduce variability across studies.[11,13,25,29,31] These findings support the interpretation of HBOT as a targeted adjunctive therapy whose protocol should be adapted to the clinical and biological context rather than applied as a standardized, one-size-fits-all intervention.

CONCLUSION

HBOT represents a multifaceted therapeutic strategy that extends beyond simple oxygen supplementation, exerting its effects through a coordinated network of biological mechanisms that collectively support tissue repair and recovery. By enhancing oxygen diffusion, promoting angiogenesis, modulating inflammatory responses, improving antimicrobial activity, and stimulating cellular regeneration, HBOT addresses several of the fundamental pathophysiological processes underlying tissue hypoxia and impaired healing.

The integration of these mechanisms into a unified translational framework provides a more comprehensive understanding of how HBOT may influence clinically relevant outcomes, including wound healing, tissue viability, infection control, and surgical success. Rather than a universally applicable intervention, the findings of this qualitative synthesis support conceptualizing HBOT as a targeted adjunct whose effectiveness may depend on appropriate patient selection, timing of intervention, treatment parameters, and alignment with the dominant biological drivers of tissue injury.

Adopting a mechanism-based approach to HBOT application may help reduce variability in clinical outcomes and support more rational decision-making in surgical practice. Furthermore, emerging advances in biomarker discovery, personalized treatment strategies, and artificial intelligence hold significant potential to refine patient selection and optimize therapeutic protocols, paving the way toward a precision medicine model in HBOT.

Ultimately, the evolution of HBOT from an empirically applied adjunct toward a mechanism-driven, precision-oriented therapy may enhance its clinical utility. Continued efforts to integrate biological insights with standardized clinical pathways and higher-quality comparative evidence will be essential to better define its role in surgical tissue salvage and wound healing.

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