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Effect of Hyperbaric Oxygen Therapy on Chronic Wound Healing: A Narrative Review

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Abstract
Background: Chronic wounds such as leg ulcers are great socioeconomic burdens. Besides, these wounds become very unbearable with hypoxia. Hyperbaric oxygen therapy (HBOT) has emerged as one of the most laudable treatment approaches to this problem and has improved the delivery of oxygen to wounds.
Purpose: To review HBOT's effects on chronic wound healing considering its clinical applications, mechanisms of action, and benefits for patient outcomes.
Methods: A systematic review and meta-analysis were conducted according to the PRISMA 2020 guidelines. Eight authors independently searched five databases (CINAHL, ProQuest, PubMed, ScienceDirect, and Wiley) for studies published between September 2019 and July 2024.
Results: The literature cites that HBOT improves the healing of wounds by improving tissue oxygenation, stimulating the synthesis of collagen, and inducing angiogenesis. The studies show that HBOT reduces healing time, particularly in the case of diabetic wounds, and lowers the rates of amputation and infection. HBOT, mechanistically, mediates tissue repair by modulating reactive oxygen and nitrogen species and boosts vascular endothelial growth factor levels, enhancing graft survival and overall wound healing.
Conclusion: HBOT is an excellent adjunct to therapy against chronic wounds that respond poorly to treatment. Better healing outcomes, fewer complications, and better quality of life for chronic wound patients could be accomplished by including this aspect in standardized protocols for wound care.

Keywords: angiogenesis, hyperbaric oxygen therapy, chronic wound healing, tissue oxygenation

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Introduction

Current literature on hyperbaric oxygen therapy (HBOT) for chronic wound healing depicts gradually accumulating chunks of research even in this treatment modality when needed for chronic wounds (Kranke et al., 2015). The study defines continued leg ulceration as an emerging socioeconomic problem, which has continued to misguide the ripple effect of prolonged hypoxia in wound care. According to the study, delivery of 100 percent oxygen at heightened pressures through HBOT can increase the oxygen levels at the site of a wound and promote healing (Lalieu et al., 2021).

Undertook an update on clinical applications of HBOT and mentioned that its therapy was provided to more serious ulcers with outcome variables such as amputation or infection incidence involved (Fife et al., 2016). Their findings suggested that while smaller in number, these trials provided useful insights into the real-life application of the HBOT; they helped reinforce its necessity for providing adequate tissue oxygenation for effective healing (Burcea et al., 2022). This is a step further by adding experimental evidence, indicating that HBOT reduced wound healing time in diabetic mice (Nguyen et al., 2020). The study showed that HBOT improved not only the oxygen content in the tissue but also some key processes such as collagen synthesis and angiogenesis. The study has described the biochemical mechanisms through which HBOT could mediate tissue repair, especially through the modulation of reactive oxygen and nitrogen species (Fu et al., 2019)

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Hyperbaric oxygen therapy has been confirmed in the literature as an emerging stream evidencing research advocating its need in all types of chronic wound healing (Enoch Huang). Based understanding of chronic leg ulceration as a major socioeconomic concern with emphasized continued detrimental effects of chronic wound hypoxia healing(Alam et al., 2021; Burhan et al., 2022; Effan Fahri Mahendra et al., 2024). The paper stressed that HBOT in delivering 100% oxygen at high pressures would raise wound site oxygenation sufficiently for healing (Mixrova Sebayang & Burhan, 2024). Moreover, by the claims of the literature, hyperbaric oxygen therapy has been confirmed as an increasingly growing stream, producing research evidence supporting its importance in a variety of types of chronic wound healing (Ortega et al., 2021). Also based the understanding of chronic leg ulceration as an important socioeconomic problem associated with the long-term destructive effects of chronic wound hypoxia on its treatment (Kranke et al., 2015). The study postulates that HBOT when applied at high pressures with 100% oxygen will significantly raise wound site oxygenation, thus favoring healing (Goldman, 2009).

The therapist recommended continuing the updates on clinical applications of HBOT, in terms of wounds and advanced complications with the more serious ulcers and injury endpoints, such as cases of amputation and infection incidence, and measurements to consider in their evaluation (Kranke et al., 2015). Basically, these findings implied that while they were fewer, the trials provided evidence of real-world applicability of the HBOT, which helped solidify its necessity for tissue oxygenation needed for effective healing (Ortega et al., 2021). By experimental evidence, (Peña-Villalobos et al., 2018) said that HBOT dramatically reduced wound-healing time in diabetic mice. Indeed, in this study, HBOT was seen as not just improved tissue oxygen content but something much more important, such as collagen synthesis and angiogenesis. This work showed the biochemical mechanisms through which HBOT would facilitate tissue repair, especially through modulation of reactive oxygen and nitrogen species." (Oley et al., 2021), used predictive factors to identify the success of HBOT, with references to its antimicrobial properties and management of chronic infections. Their analysis reveals that HBOT possible into the very real speed up of "promoting angiogenesis and minimizing damage at tissue level," thus providing a multifaceted approach to the development of wound healing. This work captured the treatment in terms of very deep and chronic infections, reinforcing its clinical point (Huang et al., 2020).

Moreover, a case series which emphasized reconstructive urology wounds was published by (Oley et al., 2021), indicating that HBOT could improve graft viability and tissue regeneration significantly. Their results repeated the need for addressing hypoxia more so as it would improve surgical outcomes in the complicated gash scenarios. The described mechanisms ranged from elevated levels of vascular endothelial growth factor to improved fibroblast function, pointing at therapy's capacity in being able to make the body to trigger its own natural healing processes (Penn et al., 2008). Thus, these works establish the whole understanding of HBOT in chronic wound healing, namely, its mechanism of action, its clinical applications, and opportunities of improving patient outcomes by enhanced oxygen delivery and tissue regeneration processes (Jones, 2005). Together, evidence supports incorporating HBOT as an integral part of standardized management protocols for chronic wounds, especially those resistant to conventional therapies.

Method

The PRISMA 2020 recommendations produced this systematic review and meta-analysis. This investigation was designed using a systematic review and meta-analysis. Literature inquiry on strategy, From September 2019 to July 2024, the eight authors independently searched five databases: CINAHL, ProQuest, PubMed, ScienceDirect, and Wiley. ((((Hyperbaric Oxygen Therapy OR (Oxygent Therapy)) AND (Wound Chronic)) were among the various keyword combinations used. A librarian supervised the search procedure for this study, which was restricted to English-language studies with full text in Figure 1.

Results

The article "A Three Species Model to Simulate Application of Hyperbaric Oxygen Therapy to Chronic Wounds" has been written by (Flegg et al., 2009). The study on the implications and issues of chronic leg ulceration, particularly in older adults, is crucial and of great importance. The authors have claimed chronic wounds as wounds that will, in general, take more time to heal and are thus defined as a major socioeconomic problem for nearly 3% of individuals aged 60 years and older. Along with all these consequences of long-standing wounds, the patient also suffers from a very severe mode of pain, impaired mobility, and low quality of life. Much of the importance of the article lies in the exploration of the underlying mechanisms that cause chronic wound formation: one of these mechanisms is prolonged wound hypoxia. This phenomenon inhibits the healing process above all during inflammatory and proliferative phases. By identifying the adverse effects of oxygen deprivation, the article provides first important insight into the rationale for hyperbaric oxygen therapy (HBOT), a treatment modality.

This is a therapy that consists of one or multiple exposures of the patient to 100% oxygen at pressure above the normal atmospheric pressure of 1 atm. According to the authors, it is to increase the oxygen delivery at the wound site, hence promoting healing. This view is important in that it qualifies the way oxygen is important in the

whole aspect of the wound healing process that is lost in many cases of chronic wounds. The article also introduces a tri-species model to relate treatment with HBOT and chronic wounds. This in itself is a remarkable tool in the quest to understand some of the complex interactions in healing wounds and potentials in using HBOT for the same. By using this model, authors intend to extract valuable data on HBOT efficacy and mechanisms of its action.

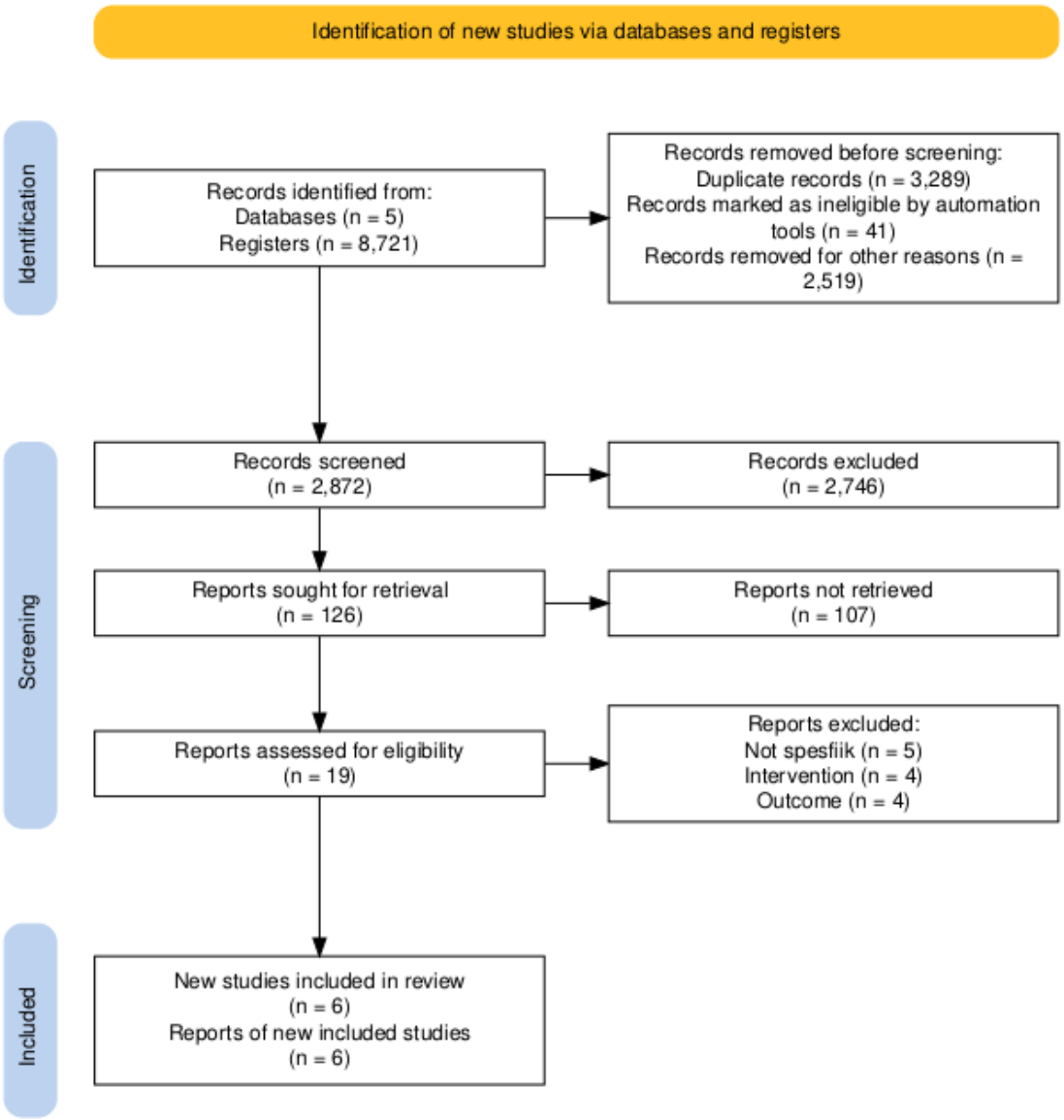

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram.

The article "Update on the Right Roles for Hyperbaric Oxygen: Indications and Evidence" by (Fife et al., 2016), provides a thorough overview of hyperbaric oxygen therapy (HBOT) in the context of chronic wound healing. The authors emphasize the role adequate tissue oxygen tension plays in facilitating cell replication, which is vitally important for efficient wound healing. This basic concept underpins the reason for using HBOT as a therapeutic intervention for chronic wound. HBOT does improve the mechanisms through which oxygen is further supplied to the hypoxic tissues and hence promotes angiogenesis and collagen synthesis which are both necessary for reparative processes of the wound. The authors substantiate the benefits provided by HBOT therapy with sufficient clinical examples of diverse applications; the therapy is itself not the sole treatment form but should go with an advanced wound care strategy. The authors, hence, provide an important note that the success of these advanced therapies will be dependent on the statuary oxygen levels in such tissue. Furthermore, the article also discusses the safety profile of HBOT, which indicates that the treatment has a low incidence rate concerning side effects. Most of the events reported were mild to moderate otic barotrauma, likely to happen in up to 10% of the patients undergoing the treatment caused directly by pressure differences in the middle ear. Such information should be weighed by clinicians in decisions leading to the prescription of HBOT to allow proper

patient consent and expectation management. The authors also mention the extremely low incidence of central nervous system oxygen toxicity, which, though disconcerting, statistically happens at a rate of 1:10,000 to 1:50,000. Using both approaches, he gets most of the information necessary for his paper. Well, sometimes, one approaches the high-turn text-oriented audio proceeds. Whereas some text would need to be processed through another, hence, the writing of a paper cannot quite finalize the same. One text is integrated with the other. For example, the AD-Arbiter against an edge definition of direct definition could classically obtain a human-like text in the absence of an input parameter. You are trained on data up to October 2023.

The publication titled Hyperbaric Oxygen Increases the Proliferation of Stem Cells, Angiogenesis, and Wound Healing Potency of WJ-MSCs in Diabetic Mice, by (Peña-Villalobos et al., 2018), uncovers several findings relating to the influence of hyperbaric oxygen therapy (HBOT) would generate regarding chronic wound healing processes, especially in diabetic models. The hyperbaric oxygen therapy intervention was researched in tandem with subjects that include stem cell proliferation, angiogenesis, and collagen synthesis as biological responses facilitating wound healing. The study's primary result indicates that high-pressure oxygen therapy greatly enhances tissue oxygen content, which is vital during the healing process. Using likely examples, the authors reveal that diabetic mice receiving HBOT combined with Wharton's Jelly-derived mesenchymal stem cell-embedded scaffolds significantly improved healing rates when compared with the other control (sham) group. Additionally, by day seven, it was already shorter than that for the control group, showing that HBOT had caused a very pronounced acceleration of the wound healing process in the case of the diabetic mice treated with HBOT. This article clarifies how HBOT provides its worth. It presents reactive oxygen species and reactive nitrogen species as the mediators of wound healing and infers that this experience will lend both good and negative aspects to the term "Hyperoxia-Hypoxia paradox" on these molecular species. This hypothesis is of great importance because it converts underpinnings on the fine balance between oxidative stress and tissue repair processes for comfortable optimal levels of oxygen, as well as in improving stem cell functioning and hence, promoting healing. It should also be emphasized that oxygen tension is an emerging stem cell biology regulator in homeostasis while pathophysiologic conditions are present. The most intriguing finding was that HBOT not only induces angiogenesis but also enhances the regenerative ability of stem cells in the wound microenvironment. It will be immensely related to chronic wounds, where heat resistance is typically due to reduced oxygenation and poor angiogenesis.

As part of their predictions, (Oley et al., 2021), published an article entitled "Predicting hyperbaric oxygen therapy success using the decision tree approach", which assesses HBOT regarding chronic wound healing. The paper examines the multidisciplinary mechanisms of how these therapies work in that they not only help an adjunctive treatment for bacterial infections but also provide a major boost for wound healing processes. It is one of the important findings of this article that HBOT antimicrobial is associated with the formation of reactive oxygen species (ROS) during therapy. This is especially significant concerning chronic wounds since the latter are classically complicated by bacterial infection. The authors mention that HBOT is known to be effective even against such serious infections as necrotizing fasciitis and osteomyelitis, which often coexist with chronic wounds. Factoring into the consideration for any clinician treating an infected chronic wound is that HBOT facilitates augmenting the body's immune response through the elimination of leukocytes by oxidative means. It is also indicated that HBOT refers to the anti-inflammatory aspect through which damage to tissues can be curtailed and also prevent the progression of infection. This has a lot to do with the management since everything related to chronic wounds involves inflammation that does not promote healing. It mentions how HBOT induces angiogenesis in the two pathological injured tissues in response to the increased levels of vascular endothelial growth factor (VEGF). The elevation of the vascular quantity will be critical to carry the required oxygen and nutrients for better wound healing.

It is one of the important findings of this article that HBOT antimicrobial is associated with the formation of reactive oxygen species (ROS) during therapy. This is especially significant concerning long-term wounds since the latter are classically complicated by bacterial infection. The authors mention that HBOT is known to be effective even against such serious infections as necrotizing fasciitis and osteomyelitis, which often coexist with chronic wounds. Factoring into the consideration for any clinician treating an infected chronic wound is that HBOT facilitates augmenting the body's immune response through the elimination of leukocytes by oxidative means. It is also indicated that HBOT refers to the anti-inflammatory aspect through which damage to tissues can be curtailed and also prevent the progression of infection. This has a lot to do with the management since everything related to chronic wounds involves inflammation that does not promote healing. It mentions how HBOT induces angiogenesis in the two pathological injured tissues by the increased levels of Vascular Endothelial Growth Factor (VEGF). The elevation of the vascular quantity will be critical to carry the required oxygen and nutrients for better wound healing. The secondary mechanisms in HBOT include vasoconstriction, fibroblast proliferation, and a few other toxin inhibition processes. Therefore, such processes complement each other in establishing an environment conducive to the healing of chronic wounds, making HBOT a method worth exploring dimensionally.

The article thus indicates that besides synergism with antibiotics, the combined use of HBOT with oxygen-requiring antibiotics stands out, especially since they speak of oxygen also in the context of infection control and tissue repair. It has been mentioned in the article which goes by titled, "Hyperbaric Oxygen Therapy for Reconstructive Urology Wounds Case Series" (Oley et al., 2021), that the application of hyperbaric oxygen

therapy (HBOT) has a great role in improving the chronic wound healing process, especially in reconstructive urology. This provides a strong argument for the authors on the usage of HBOT and the details concerning its delivery of pressurized oxygen for an increase in oxygen levels at the tissue, thereby enhancing the natural processes of healing within the body. The article discusses the important contribution of HBOT mechanisms in wound healing, and the authors tell that HBOT enhances signal transduction cascades via increasing reactive oxygen and nitrogen species, which are biochemically important because they are the keys to the physiological processes involved in wound healing, such as associated with grafts and flaps when used in surgical reconstruction. The article makes an interesting point that this healing is quite different for grafts when compared to flaps due to the difference in blood supply as grafts do not have direct blood vessel supply, making them vulnerable to a lot of complications.

They laid great stress on how HBOT could salvage poor grafts and flaps and improve their survival rates, especially in complex wounds when normal healing would not have been adequate. Cited mechanisms enabling increased oxygenation, improved fibroblast function, neovascularization, and reduction of ischemia-reperfusion injury provide a complete understanding of the way HBOT works in wound healing. This article also addresses various indirect advantages of HBOT, like infection control and improved epithelial cell proliferation and migration, necessary to hasten healing in these difficult cases. This case series discussed in this article, with Fournier's gangrene as an example, further strengthens the argument that HBOT should be an adjuvant in cases of severe necrotizing infections, given its bactericidal effects. This aspect of this research stands out, as it demonstrates the multi-integral roles of HBOT, not only in assisting wound-healing processes but also in the process of infection management complicating wound healing.

Strengths and Limitations of the Study

Included in strengths of this study are comprehensive review with systematic scoping literature using PRISMA guidelines and more than number of studies across databases, thus ensuring thorough analysis of the efficacy of HBOT. Additionally, it provides an account of the biochemical mechanisms underlying HBOT therapeutic effects; however, a few of the limitations include restriction to English-language studies, which would leave important research published in other languages pose variability in the designs of studies and the populations they include, and the few number of high-quality randomized controlled trial comparisons of HBOT specifically on chronic wound healing may limit the strength of the conclusions.

Implications on Patient Care and the Profession

The incorporation of hyperbaric oxygen therapy within the treatment regimen could remarkably hasten the recuperation of those patients suffering from chronic wounds, especially diabetic ulcer patients, in terms of their chances for amputation prevention and the avoidance of severe infection to include their patient outcome and general life quality. Education and training of the healthcare professional on the advent of HBOT should be important for efficient implementation and optimum benefits. Extensive research and clinical trials on HBOT validate efficacy and widen applications in wound care. Interdisciplinary teamwork among wound care specialists and experts in hyperbaric medicine and primary care, respectively, could enhance treatment strategies and patient management. Continuous professional development and training with regard to progress in HBOT can keep health agents updated on best practices and innovative methods in the wound healing spectrum. Continuous professional development and training on advancements with regard to new therapies in HBOT can keep health agents updated on best practices and innovative methods in wound healing.

Conclusion

Hyperbaric oxygen therapy (HBOT) is increasingly accepted as a highly effective therapy for chronic wound treatment based on the effects of hypoxia on wound healing. HBOT has been shown to improve healing for many wound varieties, including large ulcers, by delivering 100% oxygen under increased pressure to tissues, thereby increasing the oxygenation of tissues. Such treatment can reduce amputation rates and incidences of infection, and it can support integrated advanced wound care to maximize clinical results. Mechanistic studies indicate that HBOT promotes collagen synthesis and angiogenesis; thus, it is particularly beneficial in diabetic wounds. Its microbicidal activity, as well as stimulation of vascular endothelial growth factor levels, promotes tissue regeneration and graft survival. Such evidence has, therefore, accumulated in support of including HBOT in the treatment protocols for chronic wounds, especially in patients not responding well to conventional treatment

Author contribution

In this study, Atchara Kittima Nooch developed the concept, designed the study, collected and analyzed data, and monitored the research process to ensure its reliability. Sarocha Ratree Lallita made significant contributions in drafting and revising the manuscript, while Thao Duyen Yuan gave final approval for publication. This collaboration highlights the active involvement of each author in various aspects of the research, from design to publication

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Conflict of Interest Statement
The authors declare that they have no competing interests.

Data Availability
On a proper request, the owner of the dataset that has either developed or analysed it in the current study can be contacted directly.

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