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RESEARCH ARTICLE

EFFECTIVENESS OF HYPERBARIC OXYGEN THERAPY IN RHEUMATOID ARTHRITIS

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ABSTRACT

Background: Rheumatoid arthritis (RA) is characterized as a symmetric, inflammatory, peripheral polyarthritis, arising from an autoimmune response primarily affecting women. Synovial hypoxia is characterized by a reduced oxygen partial pressure (pO2), involved in RA pathophysiology. Hypoxia leads to the induction of angiogenesis, inflammation, apoptosis, cartilage erosion, abnormal energy metabolism, and oxidative damage. ***Objective:*** The objective of the study is to examine the contemporary understanding of hyperbaric oxygen therapy (HBOT) as a treatment modality for rheumatoid arthritis. HBOT is a non-invasive medical procedure wherein patients inhale nearly 100% oxygen within a hyperbaric chamber that is pressurized to levels exceeding those of sea level pressure (1 atmosphere absolute or ATA). ***Results:*** The study indicates that HBOT offers advantages for patients with RA, including alleviation of pain, reduction of inflammatory responses, and enhancement of physical activity. Further research is required to establish the efficacy of HBOT in the context of RA.

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INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases. It primarily involves the joints, but should be considered a syndrome that includes extra-articular manifestation affecting multiple organs (1). If RA is untreated, it will eventually lead to bone erosions and cartilage loss causing a possible loss of function(2). The pathophysiology of Rheumatoid arthritis is complex and multifaceted, involving an interplay between genetic and environmental factors that triggers an abnormal autoimmune response in predisposed individuals resulting in tissue damage and disease manifestation. The development and progression of RA are significantly impacted by synovial hypoxia. (3), which is thought to cause a steady infiltration of immune cells such as monocytes, T cells, and B cells resulting in inflammatory cascade. The mainstay of management is early diagnosis, the best non pharmacological and pharmacological course of treatment, and the regular assessments of the safety and efficacy of the therapy. The target of therapy is to obtain remission and to reduce side effects (4).

The American College of Rheumatology (ACR) has defined a new class of non-biologic disease-modifying anti rheumatic drugs (DMARDs) that can all help maintain joint function. Inadequate symptom control in RA patients requires the use of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) as adjunctive therapy in reducing inflammation (5). Hyperbaric oxygen therapy (HBOT) is thought to be an effective treatment option for patients with RA. A patient receiving pure oxygen while experiencing elevated ambient pressure is the foundation of HBOT.

Pathophysiology of Rheumatoid Arthritis: RA is an autoimmune condition involving inflammation of joints primarily synovial joints and affecting other organs. Inflammation of joints eventually leads to the destruction of the joint with cartilage loss and bone erosions. RA, if not treated, is a progressive disease with morbidity and increased mortality (2). The development of RA involves the interplay of genetic, environmental, and epigenetic factors. Genetic studies have identified susceptibility alleles and the strongest genetic predisposition for RA is from the HLA-DRB1 region (shared epitope) (3).

Environmental triggers, such as tobacco use and exposure to toxins like silica and asbestos, have also been implicated but tobacco has the strongest association in its development(4). The presence of autoantibodies, including RF and ACPA, is a hallmark of RA, with ACPA which is a citrullinated protein and positivity associated with a more severe disease course. The immune response in RA starts at sites distant from the synovial joints, such as the lung, gums, and GI tract(1). Patients are genetically predisposed to develop an immune response to modified proteins, and the immune response is characterized by the activation of both innate and adaptive immunity. Autoantibodies appear before the onset of clinical arthritis. Synovial compartment of the body is triggered by cytokines and chemokines, including tumor necrosis factor (TNF), IL-6, and GM-CSF, which also activate endothelial cells and attract immune cells. Osteoclast generation, which leads to bone erosions in rheumatoid arthritis (hallmark of RA), causes RANKL production by FSC and inflammatory cells. Endothelial cells and other cells are part of the innate immunity, which allows immune and inflammatory cells, such as neutrophils, to migrate to the synovial fluid and produce pro-inflammatory mediators that results in cartilage destruction (6).

Modified citrullinated protiens are the main antigens that trigger the autoimmunity in RA which activates T cells at the mucosal sites eventually producing AMPA and ACPA by B cells(7). These autoantibodies bind to the antigen resulting in activation of the Complement system causing cytokines release leading to bone erosions and cartilage loss (8).

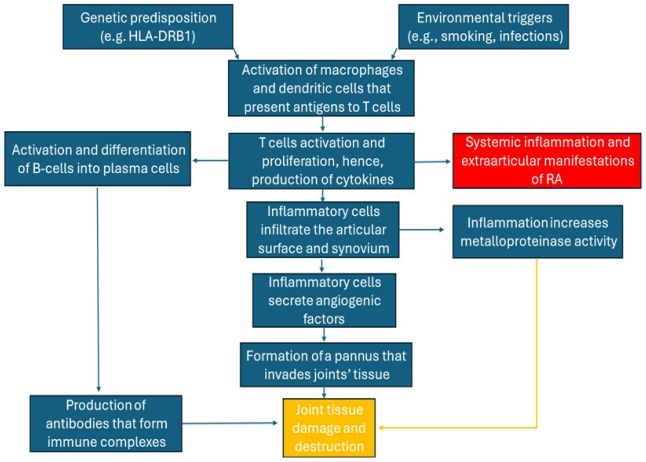

Figure 1. Pathophysiology of rheumatoid arthritis

Hyperbaric Oxygen Therapy: Mechanism and General Uses: HBO Tinvolves breathing 100% oxygen at pressures higher than atmospheric pressure inside a pressurized chamber. Under pressure, oxygen dissolves into plasma and tissues, reaching areas with poor blood flow. This stimulates the release of growth factors and stem cells, reduces inflammation and increases body's ability to fight for infections which is necessary for tissue repair and regeneration. The therapy is based on principle of gas laws, particularly Henry's law. According to Henry's law, the amount of gas dissolved in a liquid is directly proportional to the partial pressure of that gas above the liquid. In HBOT, breathing 100% oxygen at high pressure allows more oxygen to dissolve into plasma and tissues which promotes healing by reaching areas with compromised blood flow (1).

Hyperbaric medical therapy began in 1662 with the "domicilium," an airtight, pressurized chamber created by a British physician, predating Boyle's law and the discovery of oxygen. In 1872, Paul Bert studied the effects of pressurized air, identifying Central Nervous System Oxygen Toxicity, known as the "Paul Bert Effect," followed by J. Lorrain Smith's research on Pulmonary Oxygen Toxicity. In 1877, Fontaine built the first mobile hyperbaric operating theatre, and by 1891, Dr. J.L. Corning introduced North America's first hyperbaric chamber in New York, exploring treatments for syphilis, arthritis, and diabetes. He also established a "hyperbaric hotel" in Cleveland in 1928. Dr. John Scott Haldane's decompression models in 1908 aided Navy divers, leading to detailed dive charts and treatment protocols during World War II. In the 1930s, Behnke and Shaw pioneered the use of pressurized oxygen for decompression sickness. Research progressed in the 1950s, with Dr.

Ite Boerema's 1959 study, "Life Without Blood," demonstrating that swine could survive using hyper oxygenated plasma substitutes, significantly advancing HBOT applications (9,10). Mechanism of HBOT is based on gas laws and hyperoxia's physiological and biochemical effects. At the cellular level, 80% of oxygen is used by mitochondria for ATP production via Electron transport chain, while remaining 20% is used by other organelles. Hypoxia increases oxidative stress, generating harmful reactive oxygen and nitrogen species, leading to cellular damage and apoptosis.

HBOT corrects hypoxia by increasing oxygen delivery, improving antimicrobial activity, and decreasing hypoxia-inducible factor effects. HBOT increases oxygen free radicals, damaging bacterial proteins, lipids and DNA, and increasing leukocyte antibacterial functions. It also helps antibiotic transport and promotes wound healing through angiogenesis. In ischemic tissues, HBO reduces leukocyte adherence, decreases vasoconstriction, and minimizes tissues damage. Despite causing vasoconstriction in normal tissues, HBO increases oxygen delivery in ischemic conditions, reduces edema and supports ATP production while lowering lactate levels. HBO also dissociates carbon monoxide from cytochrome C oxidase, increasing electron transport and cellular energy (10,11).

Diseases	HBOT effects
Necrotizing infections	reduces tissue loss and systemic illness, aiding surgical treatment.
Osteomyelitis	promotes osteogenesis, neovascularization, and collagen production, reducing the need for extensive surgery
Carbon monoxide poisoning	dissociating carbon monoxide from hemoglobin and myoglobin, providing alternative tissue oxygenation
Decompression sickness and arterial gas embolism	relieve symptoms and prevent permanent damage.
Osteoradionecrosis	increases oxygen concentration, aiding tissue regeneration, and preventing tissue death.
Skin grafts, flaps, and wound healing	improves oxygenation, fibroblast function, collagen synthesis, and neovascularization.
Brain stroke and acute cerebral edema treatment	inducing angiogenesis, reducing inflammatory cytokine levels, and promoting cell regeneration

RESULTS

HBOT has been successfully used as adjunctive therapy not just for wound healing but also for treating a variety of inflammatory diseases, ranging from chronic brain injury to exercise-induced muscle soreness. The effect of hyperbaric oxygen treatment is very similar in magnitude to the effect of acetylsalicylic acid treatment. Potentially, hyperbaric oxygen could be used to treat pain and inflammation in patients with arthritis. The studies shows that there was a statistically significant effect of HBOT therapy with lower DAS28–Global Health, the DAS28–C-reactive protein, and the DAS28–erythrocyte sedimentation rate. The limitation of the study includes small data samples and challenge for this therapy to determine the optimal dosing along with the frequency and number of HBOT treatments which should be specially tailored for different RA patients.

DISCUSSION

Preclinical studies investigating HBOT for RA have provided evidence supporting its potential effects on inflammation and pain associated with arthritis. HBOT experimental studies involved inducing arthritis in animal subjects, like mice or rat with two groups divided into sham treatment and standard care. Pain and inflammation are assessed through measures like paw diameter, mechanical withdrawal thresholds, and histological examination of joint tissues (12). Evidence from these studies consistently demonstrated that HBOT reduces joint inflammation and relieves pain in animal models of arthritis compared to controls. Studies also compared HBO treatment with standard medications like aspirin. HBOT showed similar efficacy to aspirin in reducing inflammation and pain, indicating its potential as an alternative or adjunctive therapy for RA. This indicates a positive response to avoid aspirin long term side effects like ulcers common in RA patients. Overall, animal studies in the adjuvant model of arthritis indicated HBOT as an effective treatment at decreasing inflammation; but neither study addresses the effect HBO treatment has on pain thresholds.

Although inflammation and pain thresholds are correlated, distinct mechanisms are involved in each (12). In a pilot study conducted by Sit et al., the effects of HBOT on RA were evaluated. This case series included ten patients with RA who underwent 30 HBOT over a period of 6 to 10 weeks. Various rheumatologic assessments, such as the Disease Activity Scale (DAS28), the Routine Assessment of Patient Index Data 3 (RAPID3), and the Pain and Sleep Quality Questionnaire (PSQ-3), were administered at baseline, during the study, and at a 6-month follow-up. Significant improvements were observed in several clinical measures, particularly the DAS28–Global Health, DAS28–C-reactive protein (CRP), and DAS28–erythrocyte sedimentation rate (ESR), especially when excluding patients who were in clinical remission at baseline. The study suggested that HBOT could effectively reduce joint pain and inflammation in RA patients (13), but emphasized the need for further research with larger sample sizes and control groups to validate these findings (13). There was a notable reduction in RA disease activity as measured by the DAS28 scores. Pain levels assessed through the RAPID3 and PSQ-3, also showed significant decreases by the end of the treatment period. Improvements were seen in physical function and sleep quality (13).

Another study evaluated the impact of HBOT on Th17/Treg polarization and HIF-1α expression in an antigen and collagen-induced arthritis (ACIA) mouse model. Post-treatment, the mice were assessed for HIF-1α, Th17 (CD196), and Treg (IL-2Rβ) expression, as well as oxidative stress markers (SOD), pro-inflammatory cytokines (IL-17a), RF, CRP levels, and clinical signs of arthritis (14). The study revealed significant decreases in HIF-1α, Th17, IL-17a, RF, and arthritis symptoms in the HBOT group compared to controls. Treg expression increased significantly, while SOD levels showed a non-significant rise. CRP levels did not significantly change. Mechanistically, HBOT reduced HIF-1α activity, which in turn decreased Th17 cell numbers and increased Treg cells. The drop in IL-17a levels, a crucial cytokine in RA, led to reduced inflammation. The observed reduction in RF levels suggested decreased autoantibody production, likely due to diminished Th17 cell activity. Clinically, this translated to reduced paw swelling and better arthritis scores, indicating an overall improvement in disease symptoms (14).

CONCLUSION

RA is an autoimmune condition involving inflammation of joints primarily synovial joints and affecting other organs. HBOT is a noninvasive therapy that involves administering 100% oxygen at a pressure greater than atmospheric pressure at sea level. It can be the effective and safe treatment options for RA patients as the treatment can lead to reduced inflammation, improved circulation, and eventually promoting healing of affected joints. HBOT bypasses the side effects associated with immunomodulators and NSAIDS. HBO treatment has a limitation as its benefits are not permanent and no fixed dosage mentioned for the patients. Hence it is vital to conduct large sample size studies and to include a control group with inclusion criteria involving younger patients with RA for prolonged study outcomes with evident results.

REFERENCES

1. Klareskog L, Rönnelid J, Saevarsdottir S, Padyukov L, Alfredsson L. The importance of differences; On environment and its interactions with genes and immunity in the causation of rheumatoid arthritis. J Intern Med. 2020 May;287(5):514-533. doi: 10.1111/joim.13058. PMID: 32176395.514-533.
2. Pincus T, O'Dell JR, Kremer JM. Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. Ann Intern Med. 1999 Nov 16;131(10):768-74.
3. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987 Nov;30(11):1205-13. doi: 10.1002/art.1780301102. PMID: 2446635.
4. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, Kumagai S. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010 Jan;69(1):70-81. doi: 10.1136/ard.2008.096487. PMID: 19174392.
5. van Delft MAM, Huizinga TWJ. An overview of autoantibodies in rheumatoid arthritis. J Autoimmun. 2020

Jun;110:102392. doi: 10.1016/j.jaut.2019.102392. Epub 2020 Jan 3. PMID: 31911013.
6. Fang Q, Zhou C, Nandakumar KS. Molecular and Cellular Pathways Contributing to Joint Damage in Rheumatoid Arthritis. Mediators Inflamm. 2020 Mar 17;2020:3830212. doi: 10.1155/2020/3830212. PMID: 32256192; PMCID: PMC7103059.
7. Volkov M, van Schie KA, van der Woude D. Autoantibodies and B Cells: The ABC of rheumatoid arthritis pathophysiology. Immunol Rev. 2020 Mar;294(1):148-163. doi: 10.1111/imr.12829. Epub 2019 Dec 16. PMID: 31845355; PMCID: PMC7065213.
8. Fang Q, Zhou C, Nandakumar KS. Molecular and Cellular Pathways Contributing to Joint Damage in Rheumatoid Arthritis. Mediators Inflamm. 2020 Mar 17;2020:3830212. doi: 10.1155/2020/3830212. PMID: 32256192; PMCID: PMC7103059.
9. Jones MW, Brett K, Han N, Cooper JS, Wyatt HA. Hyperbaric Physics. 2024 Jan 31. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 28846268.
10. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM. 2004 Jul;97(7):385-95. doi: 10.1093/qjmed/hch074. PMID: 15208426.
11. Sen S, Sen S. Therapeutic effects of hyperbaric oxygen: integrated review. Med Gas Res. 2021 Jan-Mar;11(1):30-33. doi: 10.4103/2045-9912.310057. PMID: 33642335; PMCID: PMC8103971.
12. Wilson HD, Toepfer VE, Senapati AK, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis. J Pain. 2007 Dec;8(12):924-30. doi: 10.1016/j.jpain.2007.06.005. Epub 2007 Aug 9. PMID: 17690013.
13. Sit MT, Schmidt TW, Edmonds LD, Kelly JA, Sky KM, Thornton JA, McNeary-Garvin AM, Thom SR, Slade JB. The Effects of Hyperbaric Oxygen on Rheumatoid Arthritis: A Pilot Study. J Clin Rheumatol. 2021 Dec 1;27(8):e462-e468. doi: 10.1097/RHU.0000000000001540. PMID: 32947434.
14. Harnanik T, Soeroso J, Suryokusumo MG, Juliandhy T. Effects of Hyperbaric Oxygen on T helper 17/regulatory T Polarization in Antigen and Collagen-induced Arthritis: Hypoxia-inducible Factor-1α as a Target. Oman Med J. 2020 Jan 23;35(1):e90. doi: 10.5001/omj.2020.08. PMID: 31993228; PMCID: PMC6982795.

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