Efficacy and safety of hyperbaric oxygen therapy in ligament and tendon injuries: a systematic review

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Abstract

Ligament and tendon injuries are one of the major health concerns that affect over 1.71 billion people around the world. They cause functional limitations and affect the quality of life of people. As conventional methods have their limitations, Hyperbaric Oxygen Therapy (HBOT) is becoming a potential solution for the improvement and acceleration of the healing process in ligament and tendon injuries. This systematic review aims to evaluate efficacy and safety of HBOT for ligament and tendon injuries. This systematic review provides a comprehensive analysis by following PRISMA guidelines. We looked for articles published between March 1999 and May 2024 across 6 databases. The articles included investigated the use of hyperbaric oxygen therapy to treat ligament or tendon injuries. Animal studies, as well as human studies, were included in this review. Studies were evaluated for HBOT, and if they were not related or with insufficient data, they were excluded. Risk of bias has been assessed using the ROBINS-I tool. The studies measured outcomes across functional, histological, biomechanical, physicochemical, and even radiological aspects. A total of 13 studies were included in the review, with 693 participants. This study has analyzed the effectiveness of HBOT in two ways, namely, standalone treatment and combined methods like HBOT and other methods like platelet growth factor, steroid injections, intermittent oxygen therapy, or platelet-rich plasma. The pressure observed in this study is between 1.3 to 2.8 atmospheres absolute. The findings suggest that HBOT, whether used alone or as a complementary treatment, enhanced healing compared to controls. The ROBINS-I tool suggested low risk of bias for the majority of studies. Positive impacts in mechanical and histological outcomes were observed in both animal and human studies, such as increased collagen density, fiber alignment, and synthesis. The review highlights the potential of HBOT to especially reduce graft rejection post-ACL reconstruction, enhance functional recovery, and accelerate tendon healing. HBOT seems to be a safe and effective method for speeding up the healing process of tendons and ligaments. But, there is a need for more studies with more number of population for analyzing the effect of HBOT in a long run. It is necessary to make a standard protocol for the HBOT treatment method.

Key Words: efficacy, hyperbaric oxygen therapy, HBOT, ligament and tendon injuries.

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Musculoskeletal problems and Injuries in tendons and ligaments affect the normal functioning and day-to-day life of an individual. Over 1.71 billion people are suffering from musculoskeletal issues globally.[1] More than 50 percent of muscle and skeletal problems are related to injuries to ligaments and tendons.[2] Every year, there are over 17 million people affected by ligament injuries, and they need medical treatment in the United States, and 1.71 billion people in worldwide.[3] The estimated cost for the medical treatment is over 40 billion dollars.[4] Along with the economic cost, these injuries significantly affect the patient's quality of life and their ability in occupation, recreation, and health goals. In most cases, the tendons and ligament injuries are usually sprains and strains, and minor cases can usually heal without any surgical intervention. However, the process is very slow, and inferior scar tissues may be formed. These tissues may take years to change into a functional tissue.[5]

There are several methods used for the treatment of ligament injuries as well as tendon injuries. Some of the methods include surgery or tissue engineering, but other alternative techniques can be applied. However, the latter sometimes fail to provide a full restoration of the function on the injured site, taking more time to heal and not providing an optimal result.[6] Less common methods, like platelet-rich plasma, platelet growth factor-bb, and mesenchymal stromal cells, have shown some promise in enhancing the process of healing, but their clinical efficacy has not yet been identified. This is mainly due to the inconsistency in reporting and the techniques used in preparation.[7] Another adjuvant technique to treat ligament and tendon injuries is Hyperbaric Oxygen Therapy (HBOT). This method has provided an enhanced acceleration in the healing process compared to the controls.[8,9] HBOT proved to be safe, non-invasive, and effective in the treatment of various conditions. It consists of 100% oxygen administration under higher pressure compared to the atmospheric (1ATA), which grants the dissolving of an increased amount of oxygen in plasma. This increases the oxygen delivery and diffusion to the tissue, thus ensuring that necessary oxygen levels reach the injured site. This method has been reported to positively affect cell growth and to accelerate tissue recovery.[10,11]

This systematic review aims to assess the safety and efficacy of HBOT for ligament or tendon injuries. The authors will also provide the study design used, interventions involved in each study, and outcomes obtained for the treatment of tendon and ligament injuries with HBOT. In addition, the risk of bias helped identify any bias in the research and treatment methods used in the study.

Materials and Methods

This systematic review complies to the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to analyse the data collection and the outcome.[12]

Search strategy

A complete search was made using six electronic databases: PubMed, Embase, Science Direct, Google Scholar, clinicaltrials.gov, and Cochrane Library. The search covered the English language between March 1999 and May 2024. The search terms used are ((((Hyperbaric Oxygen Therapy) AND (Ligament)) OR (Tendon Injuries)) AND (Efficacy)) AND (Safety), (Animal Models) OR (Animal Studies)) OR (Alternative therapies)) AND (Hyperbaric Oxygen Therapy) AND (Ligament)) OR (Tendon Injuries)) AND (Efficacy)) AND (Safety) OR ((HBOT) OR (HBOT). Search terms and strategies were refined according to the requirements of each database, and advanced filters were used. Two independent authors have carried out the search process and the discrepancies have been resolved by discussion.

Eligibility criteria were evaluated using the PICO guidelines. That is population (P): Animal models and human subjects with ligament or tendon injuries requiring healing interventions. Intervention (I): Hyperbaric oxygen therapy alone or in combination with other treatments (e.g., platelet-rich plasma, rehabilitation exercises, and growth factors), Comparators (C): No HBOT (i.e., no treatment, standard rehabilitation, or alternative therapies without hyperbaric oxygen therapy) and outcome (O): Evaluation of healing outcomes, including biomechanical, histopathological, radiological, biochemical, functional, and subjective measures specific to the injury type.

Inclusion criteria

Studies that involve animal models or humans having ligament or tendon injuries that require healing interventions, including but not limited to Anterior Cruciate Ligament (ACL) injuries, Achilles tendon ruptures, and atrophic tibial non-union were included. Also, the studies that evaluated the use of HBOT alone or combined with other treatments, such as platelet-rich plasma, rehabilitation exercises, or growth factors, were included. Studies like randomized controlled trials, prospective cohort studies, non-randomized controlled trials, experimental animal studies and retrospective cohort studies have been included. The studies that had reported the outcome measures that were related to healing outcomes such as biomechanical assessments (e.g., tensile strength, stiffness), histopathological evaluations, radiological imaging (e.g., MRI, X-ray), biochemical analyses (e.g., collagen synthesis), functional assessments (e.g., range of motion, joint stability), and subjective measures (e.g., pain scores, patient-reported outcomes) were also included in this systematic review.

Exclusion criteria

Studies that are not relevant to ligament and tendon injuries were excluded. Studies that evaluate HBOT for indications other than ligament or tendon injuries and studies with insufficient data were excluded. Duplicate or overlapping studies were excluded. Studies with a high risk of bias or methodological limitations like inadequate sample size, lack of control group, and studies conducted on healthy subjects without ligament or tendon injuries were screened with ROBINS 1 and eventually removed. Animal studies not relevant to the human condition are also excluded.

Data extraction

Two independent researchers and Excel spreadsheets have carried out the data collection, which has been used for data extraction. The extraction information includes the name of the author, year of study, study design, sample size, study population, control, intervention, and outcomes. Specific variables like Biomechanical outcomes (Maximum force, elastic modulus, etc.), Histological outcomes, Radiological Outcomes, Biochemical Outcomes (Gene expression), Functional Outcomes (functional scores, time to return to play, range of motion, etc.) were also collected for analyzing the efficacy of the HBOT treatment method.

Quality assessment

The quality assessment was carried out by Cochrane's Risk of Bias in Non-randomized Studies (ROBINS-1) tool.[13] The tool's items have been classified into seven domains, such as random sequence generation, allocation concealment, participants and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases. Each domain in the included studies has been assessed as low, moderate, serious, critical, and no information.

Results

Screening literature and results

Figure 1 illustrates the PRISMA flowchart for the process and results in the screening of literature. The screening process was carried out as per the PICO (Population, Intervention, Comparison, Outcome, and Study Design) principle. A total of 2501 articles were identified from 6 databases. After excluding the 495 duplicate articles and the 1105 irrelevant articles, 901 articles were initially screened. Then, 496 articles were removed during the screening of the title and abstract because they were not related to the review and were not available in full-text articles. Then, a total of 405 relevant articles were screened, and 366 articles were excluded after studying full-text articles. In the end, 19 articles were assessed for their eligibility, and 5 articles were removed as they had no expected outcome of interest.

Finally 13 studies[11,14-25] were included as they were eligi-

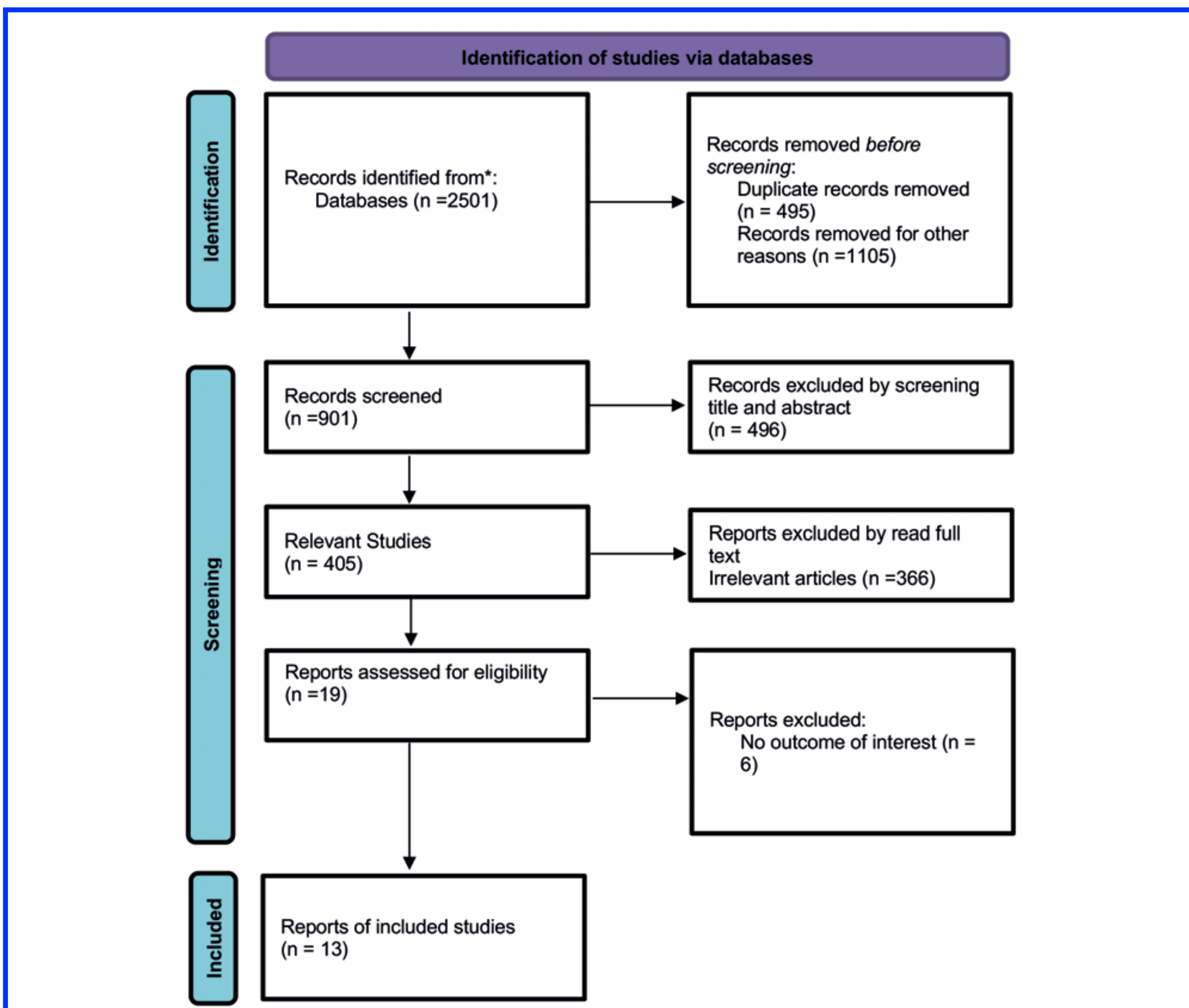

Figure 1. *PRISMA flow diagram.*

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ble and their quality has been assessed. Additionally, the modes of intervention were different among the 14 selected studies, and this may affect the efficacy of HBOT. So, we reported the data on HBOT parameters like study duration, pressure used, number of treatments, and the variables measured during research, which is given in *Supplementary materials, Table 2*.

Basic information about the included studies

The 13 studies included a cumulative number of 693. 12 out of 13 studies were experimental,[11,15-25] and 1 clinical trial[14] have been used in this systematic review. Among the studies, seven have used a 2.5 ATA pressure,[15,16,18,21,22,24,25] one a 1.3 ATA,[17] one a 2.4 ATA,[20] two a 2.8 ATA,[17,23] and one study included four separate groups have been analyzed separately of whose 2 groups used 2 ATA and one group used 1.5 ATA[19] and in the clinical trial study pressure range of 2.0 to 2.5 ATA[11] has been used. In 9 studies HBOT is compared with control,[11,18-25] in one study HBOT was used with platelet growth factor-bb[16] to check its efficacy as support treatment, in one study HBOT was treated alongside intermittent oxygen therapy,[19] 1 study examined HBOT as an adjuvant to enhance graft healing following ACL reconstruction in male rabbits,[11] 1 study, has combined steroid injection and HBOT treatment[20] and 1 study has used HBOT along with platelet-rich plasma[25] for analyzing the feasibility of fastest recovery. The efficacy of the HBOT has been measured by different measurements in different studies, as most of the parameters were different in each study. The comprehensive details regarding the measured variables have been given in *Supplementary materials, Table 2* and the outcomes of each study have been given in *Supplementary materials, Table 1*.

Quality assessment- Risk of Bias (ROBINS-I)

The risk of bias was analyzed for all fourteen research studies using ROBINS I. ROBINS I focuses on analyzing non-randomized control trials with interventions. Hence, this review utilized ROBINS I to determine the risk of bias. There are a total of seven domains and around 95% have a low risk of bias. This means that the intervention, outcome, and information are clear and present. No confounding was seen in all the papers. However, Enokida *et al.*[14] have a certain serious bias as the research is ongoing and the outcome cannot be determined with relevance to the intervention. Two papers[23,25] had the same missing information and were marked as "serious" in the ROBINS-I assessment. However, overall bias remains unchanged as the desired outcome is met despite missing information. Overall, the risk of bias determined using ROBINS-I has satisfactory results on the utilization of the review for further studies in the future. The risk of bias is given in Figures 2 and 3.

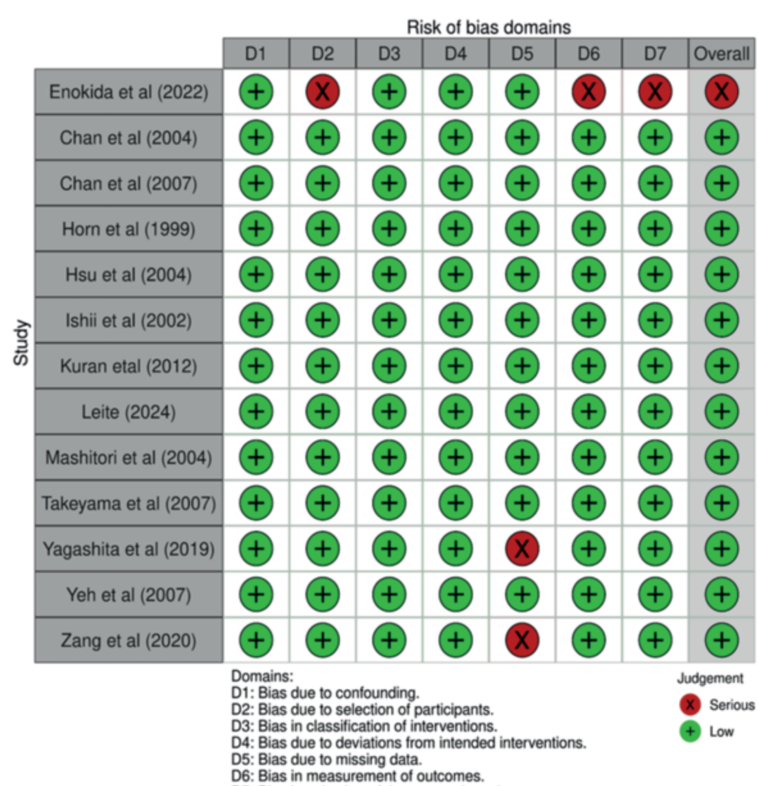

Figure 2. *Traffic light signal on individual studies included in this review.*

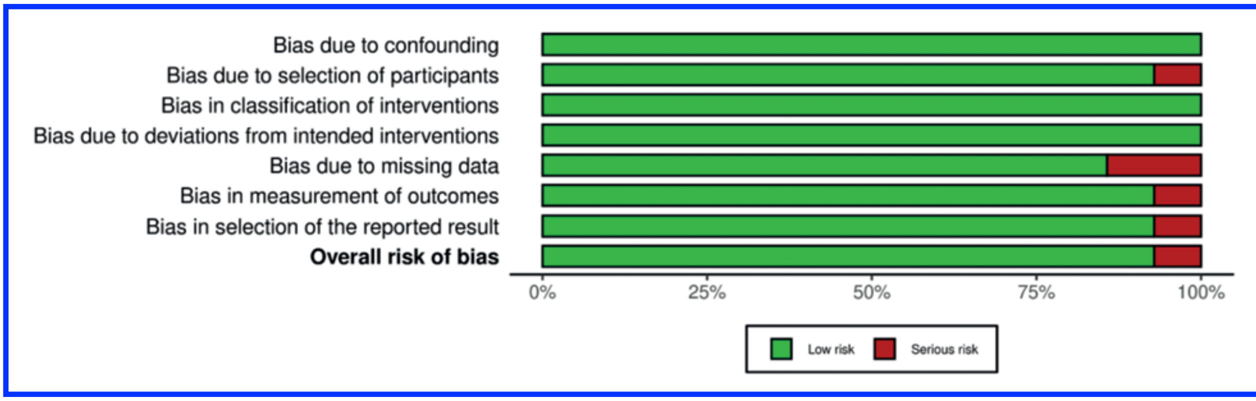

Figure 3. *Overall Summary on risk of bias of HBOT.*

Discussion

The overall study findings in this systematic review are based on the 13 studies that involved 693 subjects, including animals and humans affected by ligament or tendon injuries. They were treated with HBOT either individually or as a complementary therapy, in order to assess whether HBOT improved the healing of the injuries. As reported either as a complementary treatment or individual treatment, HBOT has shown improvement in the healing of injuries compared to control in most of the studies. The pressure used in the hyperbaric chamber varied across studies from 1.3 to 2.8 ATA. A radar chart illustrating the interventions of the first 12 studies (one study was excluded due to the absence of information regarding the treatment pressure (ATA) and duration of HBOT) and comparative outcomes by the Likert Scale is depicted in Figure 4. The Likert-based qualitative ratings of mechanical and histological outcomes are plotted, whereby a rating of '5' is excellent, '3' is good, and '1' is poor. This systematic review identified several experimental studies employing HBOT, most of which assessed functional, histological, biomechanical, biochemical, and radiological outcomes.

Molecular effects

Chan *et al.*[16] have studied the efficacy of HBOT and platelet growth factor-bb, as a combined method as well as individual treatment options. The result showed that the combined method has given an optimal result. This study suggested that HBOT can be a potential treatment method for Medial Collateral Ligament (MCL) healing. In a study by Oyaizu *et al.*,[26,] the rate of skeletal muscle injury model has been used. It has been reported that HBOT therapy can reduce muscle weight, extracellular space, and vascular permeability, which results in the reduction of edema. Regarding the HBOT effects on the healing of ligament injury, various animal studies have been identified. Horn *et al.*[17] have used rat models for surgical MCL laceration and treated with HBOT. This study demonstrates that HBOT can enhance ligament healing, as evidenced by a significantly greater force required to cause failure in surgically divided medial collateral ligaments of rats exposed to HBOT compared to controls, particularly at four weeks post-injury. The findings suggest that HBOT may accelerate early biomechanical recovery in ligamentous tissue. Mashitori *et al.*[21] also treated the MCL in rat models and applied HBOT for 5 days. The maximum failure load and type I collagen gene expression have been examined. This shows that HBOT has helped accelerate the healing process. The clinical reports regarding the MCL injury treatment using HBOT are very scarce. Soolsma[27] reported the effects of HBOT on functional recovery in a double-blind controlled study; however, as it was published only as a university report and not as a peer-reviewed article, it was excluded from this analysis. The results by Yagashita *et al.*,[23] a clinical study, examined the grade 2 MCL injury (a partial tear of the ligament) that happened during sports activities. Here the HBOT has been identified to have short-term effects if used for pain reduction in the acute phase. Also, the long-term effect can be the acceleration of recovery in a reduced period for return to play.

Functional effects

Graft rejection following ACL reconstruction is a relative common complication, and the rates range from 0.7 up to 24 percent; this may arise due to various underlying factors. So the success in the ACL reconstruction is mainly based on the healing of grafts Fu *et al*.[28] In the study by Leite *et al.*,[11] the HBOT treatment method can reduce graft rejection and enhance the healing process, thereby improving the biomechanical properties of the graft.

Best and colleagues[29] conducted a study to analyze any improvement in functional recovery and morphological recovery by using HBOT for muscle stretch in the tibialis anterior muscle. They used a rabbit model, and after 7 days of treatment, they identified that the administration of HBOT increased the recovery pace faster than the control group (functional deficit - percent ankle isometric torque; injured side versus uninjured side – of 14.9% +/- 5.5% (mean +/- SD) for the treated group and 47.5% +/- 5.4% for the untreated group). In the same way, the study by Chan *et al*.[15] used the rabbit model to treat medial collateral ligament healing using HBOT. They have reported that HBOT has a positive effect on treatment.

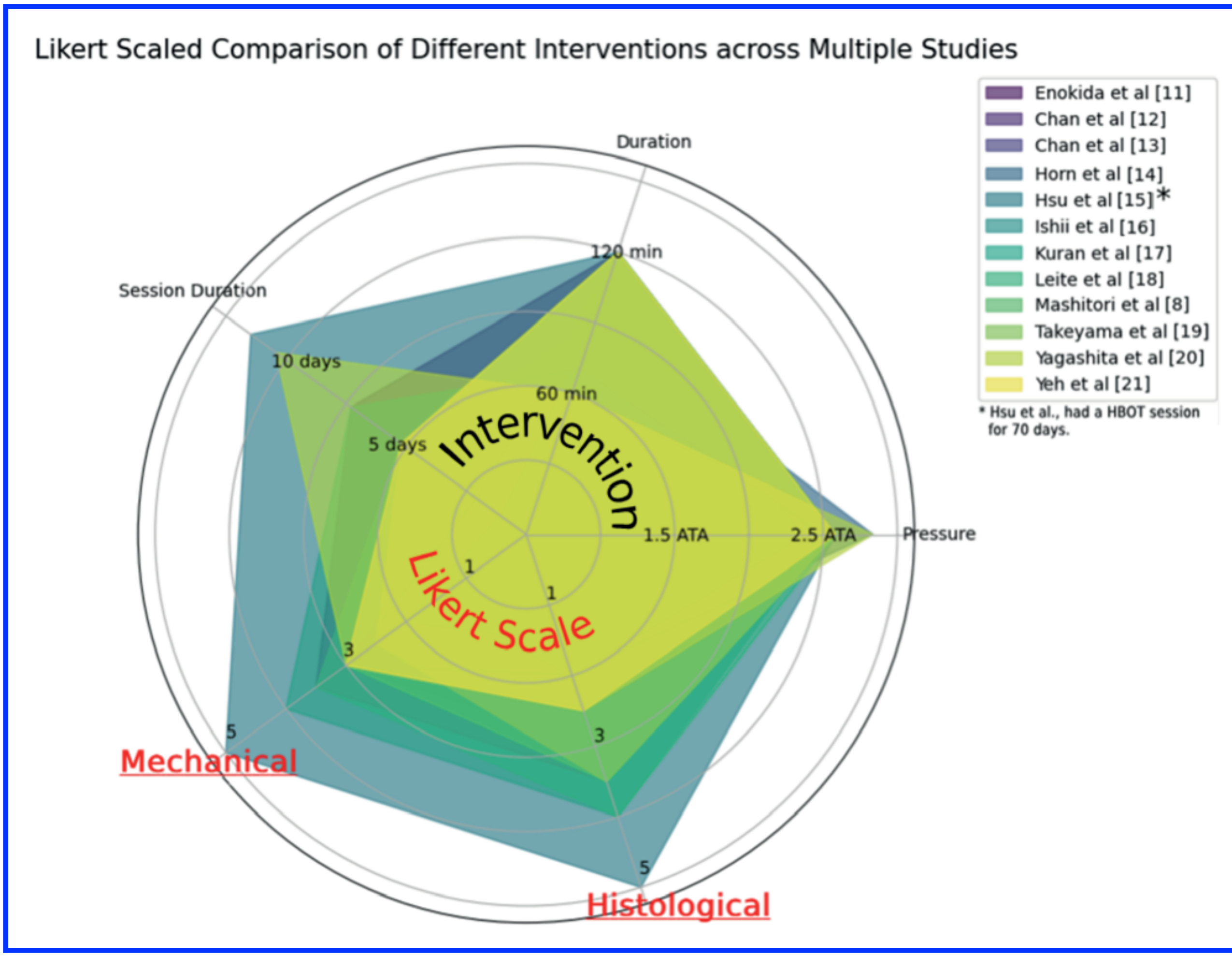

Figure 4. *Likert scale radar chart across studies. The details of the study interventions are plotted (e.g., HBOT session duration, duration, and pressure) and the Likert-based qualitative ratings of mechanical and histological outcomes are plotted. A rating of '5' is excellent, '3' is good, and '1' is poor.*

The use of HBOT has increased, particularly in the treatment of chronic wounds. The fundamentals of wound healing include the synthesis of oxygen-dependent collage, proliferation of fibroblast, and angiogenesis. In the regeneration of the tendon, the fibroblasts can produce collagen, proteoglycan, and protein mediators,[30] which are fundamental for the correct reconstruction of the damaged tissue. In the study by Hsu *et al.*,[18] the histological results showed an increase in the production of mature fibroblast, highlighting that HBOT may enhance early healing by promoting collagen synthesis and cross-link formation. This provides a positive effect of HBOT treatment on the tendon healing process. In the study by Ishii *et al.*,[31] authors suggested that intermittent oxygen exposure may significantly enhance collagen synthesis and support extracellular matrix production in tissue engineering. At the same time, the results of Ishii *et al.*,[19] have reported that HBOT treatment was effective even for the post-injury recovery process, resulting in enhanced extra-cellular matrix deposition as measured by collagen synthesis. Intermittent HBOT treatment has given a positive result. This can be attributed to the fact that HBOT promotes angiogenesis and muscle regeneration by increasing levels of Nitric Oxide (NO), vascular endothelial growth factor, and basic fibroblast growth factor.[31]

After surgery in ligament injuries

As demonstrated, HBOT may have a valuable role in the postoperative management of ligament injuries, particularly in reducing the risk of graft failure and re-injury following ACL reconstruction. Although maintaining a robust rehabilitation schedule is critical to promote graft ligamentization, rates of graft failure and re-injury are still substantial. It is estimated that at least 10 percent of ACL grafts get ruptured, resulting in a significant financial and emotional burden for patient and patient care team.[33] In recent years, there have been various experimental therapies being explored to improve graft healing, such as delivering photopolymerized hydrogels or biologics like stem cells at the graft site.[34] However, the complexity, cost, and variability in their outcomes have limited their application in the current environment. The systematic review reveals how HBOT provides a generalized enhancement of the healing environment, which could potentially lead to a more consistent and widespread benefit in ligamentization.

In the context of complete tendon ruptures and degenerative tendon disease, HBOT can also serve as an adjunct rehabilitative modality. Tendon repair at the molecular level can be understood in three phases: the inflammatory phase, proliferative phase, and consequently, the remodelling phase.[35] The inflammatory phase is triggered by the insult and is orchestrated by pro-inflammatory cytokines such as IL-6. The proliferative phase involves the activation of tenocytes to allow for the synthesis of collagen and other components of the extracellular matrix, and the final remodelling phase is completed by the maturation and alignment of collagen fibers. The enhanced oxygen supply offered by HBOT can help drive the inflammatory and proliferative phases, and its ability to modulate inflammation can simultaneously prevent poor healing outcomes.

This systematic review mainly highlights the benefits of HBOT for ligament and tendon injuries but also has some limitations. This review includes both animal and human studies. The animal studies provide valuable information regarding HBOT in ligament and tendon injury, but it is difficult to generalize them to human treatments. Each study has used different HBOT parameters that include pressure, duration of treatment, and frequency. This inconsistency makes it difficult to compare their effectiveness in HBOT and determine the optimized protocol.

This review has identified a scarcity of high-quality clinical trials investigating HBOT for ligament injuries, such as Medial Collateral Ligament (MCL) tears. Among existing studies, a pilot study[36] investigated the short-term effects of HBOT on athletes with acute ankle sprains. Although there was no control group, the study revealed that HBOT significantly reduced foot and ankle volumes during activity and rest and provided substantial pain relief within 3-4 sessions. There is a need for more clinical trials to confirm the animal studies' findings and assessment of long-term effects on humans.

The limitations analyzed in this systematic review suggest the need for future research to determine the HBOT's role in treating ligament and tendon injuries. There is a need to address a standardized protocol for the HBOT, more high-quality clinical trials with a larger population, and research on the long-term effects of HBOT on the healing of ligament and tendon injuries that includes the functional outcomes and potential side effects.

Conclusions

This systematic review mainly evaluates the efficacy and safety of hyperbaric oxygen therapy in the management of ligament and tendon injuries. The findings of this study have identified the need for more clinical trials and human studies in HBOT. The efficiency of the HBOT method has been observed to accelerate the leaving process compared to control; it can be identified that HBOT can be used as a standalone treatment or as an adjunctive treatment. Collectively, the reviewed studies indicate that HBOT is a safe modality with the potential to facilitate faster recovery in ligament and tendon repair.

List of abbreviations

HBOT, Hyperbaric Oxygen Therapy
ATA, Atmosphere
ACL, Anterior Cruciate Ligament
MCL, Medial Collateral Ligament

Conflict of interest

The authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval and consent to participate

The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Online supplementary material:

Table 1. Study characteristics of included articles in systematic review.

Table 2. The modes of HBOT intervention and variable measured (outcomes) in 14 articles.