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## Hyperbaric Oxygen Therapy in Sports Musculoskeletal Injuries

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## **Abstract**

Hyperbaric oxygen therapy (HBOT) is a well-established treatment for a variety of conditions. HBOT is the administration of 100% oxygen breathing in a pressure vessel at higher than atmospheric pressure (1 atmosphere absolute = 101 kPa). Typically, treatment is given daily for between one and two hours at pressures of 2.0 to 2.8 ATA, depending on the indication. Sporting injuries are often treated over 3-10 sessions. HBOT has been documented to be effective and is approved in 14 medical indications by the Undersea and Hyperbaric Medical Society (UHMS), including but not limited to: carbon monoxide poisoning, compromised skin grafts and flaps, crush injuries, necrotizing soft tissue infections, and non-healing ulcers with arterial insufficiencies. Recently, HBOT for sports musculoskeletal injuries is receiving increased attention. HBOT may allow injured athletes to recover faster than normal rehabilitation methods. Any reduction in collegiate and professional athletes' rehabilitation period can be financially significant for top-level sports teams; however, further research is required to confirm HBOT's benefits on sports musculoskeletal injuries. The purpose of this review is to discuss the current understanding of Hyperbaric oxygen therapy as a treatment modality for common musculoskeletal injuries in sport medicine. Moreover, we will highlight the advantages and disadvantages of this modality as well as relevant clinical and research applications.

**Keywords:** Hyperbaric Oxygen Therapy (HBOT), sports musculoskeletal injuries, therapy, rehabilitation

## **Indications and general protocols of Hyperbaric oxygen therapy (HBOT)**

HBOT refers to the administration of pure oxygen intermittently at a pressure higher than 1 atmosphere absolute (ATA) in a hyperbaric chamber. For clinical purposes, the Undersea and Hyperbaric Medical Society indicates that pressurization should be 1.4 ATA (141.86 kPa) or higher to be effective. The common range of pressure used is between 2 and 2.8 ATA. (1) Typically, each session takes between 60 and 120 minutes. Treatment can be carried out in either a monoplace or multiplace chamber. The former accommodates a single patient where the entire chamber is usually pressurized with 100% oxygen, and the patient breathes the ambient chamber oxygen directly. The latter holds two or more people (patients, observers, and/or support personnel) and the chamber is pressurized with compressed air while the patients breathe near 100% oxygen via masks, head hoods, or endotracheal tubes. (1-3) Hyperbaric oxygen therapy (HBOT) has been used in a wide variety of medical settings. (4) In the United States, the Food and Drug Administration (FDA) defers to the Undersea and Hyperbaric Medical Society (UHMS) to establish the list of indications for which HBOT has sufficient evidence to support its use. Currently, 14 medical indications have been approved. However in other countries a larger number of indications are recognized (Table 1). (1) The European Committee for Hyperbaric Medicine (ECHM) has accepted 30 indications for HBOT. These indications are divided in 3 categories, ECHM Type 1- 3: Type 1, where HBOT is strongly indicated as a primary treatment method and its use is supported by sufficiently strong evidence. Type 2, where HBOT is suggested and its use is supported by acceptable levels of evidence. Type 3, where HBOT can be considered as a possible/optional measure, but it is not yet supported by sufficiently strong evidence (5) The branch of Hyperbaric Oxygen Medicine of the Chinese Medical Association (CMA) endorses 12 emergency indications and 48 non-emergency indications. (6)

## Potential mechanisms and physiological effects of HBOT

HBOT in the short-term enhances oxygen delivery with vasoconstriction, which reduces edema; improves neutrophil phagocytic function that mitigates infection; has anti-inflammatory effects, and mitigates ischemia-reperfusion injury. Over longer time periods and with repeat administration, HBOT induces neovascularization and neoangiogenesis as well as stimulation of collagen production by fibroblasts. (7) All of these effects could enhance the rehabilitation of an injured muscle in the inflammatory and proliferative phases of recovery.

The plasma oxygen concentration is normally ~3 ml/L at sea level. (8) Despite the varying need for oxygenation between different tissues, typical resting tissues need about 60 ml of oxygen/L to maintain normal metabolism; dissolved oxygen levels can reach this level (60 ml/l plasma), without considering hemoglobin bound oxygen at a pressure of 3 ATA (304 kPa). (4) During carbon monoxide poisoning or in severe anemia without the possibility of transfusion, this mechanism can help to deliver oxygen without the need for transfer via hemoglobin. Delivering oxygen at 300 kPa leads to achieving 270 kPa (2,025 mmHg) of oxygen in the arterial blood and roughly 53 kPa (~400 mmHg) in the tissues. (4, 9)

The most important effect of HBOT, beyond offering more O<sub>2</sub> to the tissues, is producing free radicals in a therapeutic range for cell signaling. HBOT induces oxidative stress by mean of controlled production of reactive oxygen and nitrogen species, which causes the activation of cellular processes and pathways. (7, 10-12) Some of the most relevant mechanisms are as follow: increased growth factors (e.g. hypoxia-inducible factor 1- $\alpha$  [HIF-1 $\alpha$ ]) (13), vascular endothelial growth factor (VEGF), (14, 15) stromal-derived factor 1,(13) mobilization of bone marrow-derived stem cells (CD34), (7) and the reduction of neutrophil adhesion (modification of integrin  $\beta$ -2) that mitigates ischemia-reperfusion injury. (7, 16)

## Adverse effects of HBOT

HBOT is mostly safe and the adverse effects are mainly mild and reversible. There are two main concerns using hyperbaric oxygen therapy, (A) barotrauma (trauma caused by pressure) and (B) oxygen toxicity (17).

*Barotrauma* is caused by an inability to balance pressure between the pressurized environment and any gas-filled space in the body. The middle ear is the most commonly affected place of barotrauma, which starts with tympanic membrane hyperemia and can lead to a tympanic membrane rupture. Air trapping in sinuses due to obstruction by a polyp or inflammation can also lead to increased susceptibility to barotrauma. Any air pocket in teeth due to dental decay can lead to a large amount of pain. An important but rare consideration is barotrauma to the lungs during depressurization at the end of the HBOT. This represents a risk if the patient holds the breath or has a lung condition with air trapping in the airways, which can lead to pneumomediastinum, pneumothorax or gas embolism.

*Oxygen toxicity* is a condition resulting from the harmful effects of breathing oxygen at increased partial pressures. (18, 19) As noted above, at least some of the beneficial effects of HBOT may be through controlled oxidative stress. Antioxidant defenses are generally adequate during the hyperoxic exposure created by typical clinical hyperbaric oxygen therapy. Nonetheless, there may be negative aspects to high levels of oxygen radicals and oxygen toxicity in the central nervous system can occur. (17) Central nervous system (CNS) oxygen toxicity manifests as symptoms such as visual changes, ringing in the ears, nausea, twitching, anxiety, confusion, and dizziness. The CNS oxygen toxicity during clinical hyperbaric oxygen treatment is an oxygen toxicity seizure. (17) Pulmonary oxygen toxicity (POT) is caused by exposure of the lungs to oxygen. While described after prolonged normobaric exposures to concentrations above 50%,

the development of POT manifestations is much more rapid with hyperbaric exposure. POT is characterized by acute exudative manifestations including edema, hemorrhage and cell destruction, and subacute proliferative manifestations including fibrosis and hyperplasia. Clinically important POT is highly unusual in association with routine doses of HBOT, but can occur with prolonged exposures. (17)

### **HBOT for sports musculoskeletal injuries**

HBOT has become popular among injured athletes because of its hypothetical benefits on accelerated recovery, especially among professional athletes or those with substantial financial resources. However, despite the widespread popular appeal, the evidence supporting this practice is meager. Previous reviews have investigated the possible role of HBOT in specific injuries or sports injuries in general (2, 3, 20-22) but there has not been any new review since 2005.

### **Muscle injury and HBOT**

Muscle injuries encompass a broad range of pathologies, including muscle cramps, delayed onset muscle soreness (DOMS), muscle contusion and muscle tears (23). Muscle tears (often referred to as muscle strains) are one of the most common musculoskeletal injuries and can account for prolonged time missed from sport. In a recent study of injuries among national collegiate athletes from 2009- 2015, muscle strains were found to be the second most common diagnosis that resulted in missed participation for more than 21 days (24). While historically classified into 3 grades based on severity of symptoms and degree of tear, ranging from small partial tear to complete rupture, a number of new classification systems have been proposed. Currently, there is little consensus on a comprehensive and evidenced based system to classify

muscle injuries (25). DOMS is characterized by discomfort in skeletal muscles after more than usual intensity exercise; it peaks in 24-48 hours after the exercise and is typically resolved in 5-7 days. This muscle damage can lead to a transient decline in physical performance (26) and/or increased risk of injury (27). The ability for sports physicians to reduce the recovery period after muscle injuries is extremely significant, especially in the realm of financial incentives in professional sports where slightly faster return to play is of most importance in the light of economy of professional sports. The team has to continue paying the salary of injured athlete despite the fact that he or she is not playing; as an example, the cost of salaries for injured players on the disabled list of Major League Baseball was over \$1.6 billion dollars in 2013 to 2015.(28) this demand for faster return to service is also the case in military settings. (29)

Few clinical studies have suggested an advantage of HBOT for sports injuries over routine care, especially DOMS. (see TABLE 2)

### ***Potential Mechanism of HBOT for muscle injury in acute and proliferative phases***

***Acute phase:*** inflammation after muscle injury includes the production and release of inflammatory cytokines, increased vascular permeability, migration of neutrophils, and edema. (30) Edema increases the diffusion distance for oxygen while at the same time, increases in extracellular pressure can reduce perfusion, a combination that can result in significant hypoxia and necrosis (31) Delivering oxygen by HBOT without an increase in vascular dilation and permeability can hypothetically simultaneously reduce edema and hypoxia. Under the effect of HBOTs, the transition from an inflammatory state to a proliferative state is accelerated. This accelerated transition has been evidenced through the increase in the number of anti-inflammatory M2 macrophages (M2) in compare to pro-inflammatory M1 Macrophages (M1) in



Oyaizu et al study. (32) It has been shown that HBOT accelerates the differentiation of migrated M1 macrophages to M2 macrophages in the initial phase of healing period (32, 33).

***Proliferative phase:*** Satellite cells play a vital role in the proliferative phase of muscle rehabilitation after the injury. (34) Satellite cells can undergo transformation to myoblast lineage to initiate muscle regeneration. (35) Previous studies have shown that HBOT promotes a higher number of proliferating, differentiating and quiescent satellite cells which will be reserved for the next injury (32, 35). One of the important conclusions of Oyaizu and colleagues's study (32) is that HBOT accelerated regeneration processes including satellite cell proliferation (resident stem cells) with improved muscle fiber regeneration and strength. Chaillou et al. showed that the myogenic activity of satellite cells can be compromised in the hypoxic environment (34). Macrophages, neutrophils, and satellite cells in injured muscles release interleukin-6 (IL-6); IL-6 is involved in the IL-6/STAT3 pathway that increases the expression of the genes needed for the proliferation of satellite cells and differentiation to myoblast lineages. (32) A study of HBOT in animal models showed earlier activation of the IL-6/STAT3 pathway compared to their cohorts in the control group (32). In conclusion, the in vitro studies suggest that HBOT can accelerate the needed proliferation and differentiation of proliferative phase.

### ***Delayed onset muscle soreness***

Staples et al. demonstrated the effects of HBO on the faster recovery of DOMS in athletes for the first time (36), but several subsequent studies have shown inconsistent results. (21, 37-39) (see TABLE 2). In their systematic review, Bennett et al demonstrated higher pain scores at 48 and 72 hours in the HBOT group and no differences in longer-term pain, or swelling or muscle strength at any time.(2) There have been no further published randomized studies since that review.

Webster et al. showed that HBOT led to decreased pain, and increased torque and recovery in DOMS subjects (40) with a sample size of 12 patients (six HBOT and six control groups). Mekjavic et al has been the only study which has incorporated completely similar controls with the intervention group in terms of pressure (2.5 ATA normoxic,  $PIO_2 = 0.2$  ATA) (41); the placebo in other studies was pressurized ambient air with lower pressure than the intervention group. Using lower fraction oxygen controls to achieve an  $FiO_2$  of 0.2 as in Webster et al can be controversial due to the increased risk of decompression illness and other concerns about possible (untested) therapeutic effects of pressure itself or the increased pressure of  $N_2$ (42), We have discussed the concerns about the placebo pressure later in the *Performance bias* section.

### ***Muscle strain and/or contusion***

We couldn't find any human clinical studies about using HBOT for athletes with muscle strain and/or contusion.

Cervantes et al. showed that HBOT exposed rats had lower creatinine kinase level, a marker of muscle damage (43) compared to a control group in a rat model of muscle contusion. They also measured the weight of the injured muscle 72 hours after injury and showed that the HBOT group had higher muscle weight in comparison to the control group. This finding should be interpreted with caution however since other studies that have used muscle weight as a marker of inflammation and have shown lower muscle weight in HBOT groups (32). Best et al. used a rabbit animal model of tibialis anterior injury in 1998. They showed a significant difference in isometric torque deficit of injured muscle between the HBOT and control groups. Best et al. suggested that 5 sessions of HBOT 24 hours after the muscle-tendon unit injury can lead to better morphologic healing in the HBOT group as well as better isometric torque results. (44) The number of new in vitro and animal studies and the need for guidance in future studies required us

to reevaluate the current literature, search for gaps in the current literature, and offer suggestions for future studies (45).

### ***Ligament and Tendon injuries***

Horn et al. have reported that higher destructive force is needed before reaching failure in the medial collateral ligament (MCL) of rats treated with HBOT compared with a control group after induction of ligament tear and surgery; however, this difference was only apparent 4 weeks after the injury and they couldn't find any difference after 6 weeks. (46) Ishii et al. showed a dose-response relationship between the concentration and pressure of oxygen in HBOT and its effect on the healing process of ligament healing in rats. They reported that HBOT at 2 ATA was the most effective at enhancing collagen synthesis in the extracellular matrix. (47)

The expression of matrix metalloproteinases (MMPs) and type I procollagen are indicators of the beginning of the proliferation phase in the process of ligament healing (48). Takeyama et al. studied using HBOT in the healing of MCLs and anterior cruciate ligaments (ACL) in rats after laceration. Both ACLs and MCLs in the HBOT group showed significantly greater gene expression of type I procollagen and no change in type III procollagen gene expression compared to the control group. While MCLs in the HBOT group showed macroscopic healing by scar tissue formation, none of the severed ACLs united physically despite the administration of HBOT. This finding can be attributed to the intra-articular location of the ACL (avascularity) in contrast to extra-articular of the MCL. MMP gene expression was higher in MCLs in the HBOT group compared to the MCLs in the control group. The expression of tissue inhibitors of metalloproteinases (TIMPs) was higher in ACLs in the HBOT group compared to ACLs in the control group (48). While Takeyama studied the effectiveness of HBOT on ACL lacerations

without any other intervention, Yeh et al. used HBOT as an adjunct therapy to ACL tendon graft. They reported increased neovascularization and enhanced incorporation between tendon grafts and bone in the HBOT group. They also showed that tendon grafts have higher maximal pullout strength in the HBOT group. (49) Chan et al. designed a 4-arm study to test HBOT and platelet-derived growth factor-BB's (PDGF-BB) effect on cultured cells in rabbit MCLs; HBOT and HBOT plus PDGF-BB groups showed a decrease in Type III collagen/Type I collagen content ratio, which can lead to mechanically stronger collagen fibrils. Hsu et al. used HBOT in rabbits suffering from patellar tendinopathy, which was induced by collagenase; tendons in the HBOT group showed 34.8% greater ultimate tensile load compared to the control group. Finally, and perhaps more concerning, Mashitori et al. reported a higher amount of scar tissue and Type I procollagen gene expression in the injured MCL of the rats in a HBOT, compared to the control group. (50) Only two randomized, controlled, human trials using HBOT in ligament injuries (MCL and ankle sprain) have been reported to date. Both were small, had methodological problems and were inconclusive. (51, 52) Basic and animal studies have justified moving on and designing human studies to investigate the clinical effectiveness of using HBOT in ligament and tendon injured athletes.

### **Limitations of current human studies:**

#### ***Selection Bias***

We cannot reject the possibility of baseline differences between groups, especially when the subjects are recruited after injury and the investigator has no prior data. Soolsma et al. (HBOT for MCL injury) did not report the baseline data after the outcome measures in the groups. (51) Borromeo et al. (HBOT for ankle sprain) did report baseline measurement and

there were significant differences between the groups regarding initial pain and edema (worse in HBOT group); however, the time from injury to first HBOT, and the range of motion and ankle function (main outcome) were uniform. (52) Among DOMS studies, Staples et al. did not report any statistical test for investigating baseline differences between groups, they just have shown the baseline data in the raw data manner in figures; it should be mentioned that HBOT groups had higher baseline eccentric torque forces than other groups according to the reported figures in their study. (36) Mekjavic et al. also did not conduct baseline measurements in HBOT and control groups. (41) Harrison et al. reported no difference between HBOT and control groups in isometric strength but did not report any test for evaluation of baseline cross-sectional area, T2 relaxation time and serum creatinine kinase. (39) Webster et al. did not report baseline values and only reported outcomes as percentage change from non-disclosed baselines, except for the cross-sectional area, which they did report baselines for and emphasized no significant differences between groups. It is important to mention that Webster et al. is the only study that could reproduce the findings of Staples et al. about HBOT's effectiveness in treating DOMS. (40) Babul et al. reported a 95% confidence interval of zero mean difference between control and HBOT groups and included all baseline measurements. (38) Germain et al. reported baseline values in figures and tables without mentioning any statistical test for checking baseline difference between groups. (37) We have to emphasize the importance of reporting baseline characteristics of intervention and control groups in future studies. We can use less intimidating tests like isometric muscle strength testing, which can be conducted even with injured athletes.

## *Performance bias*

The only human trial which used the same pressure in the chamber for both HBOT and control groups was Mekjavic et al. (41); Soolsma (51), Borromeo et al. (52), Staples et al. (36), Webster et al. (40) and Babul et al. (38) used 1.1, 1.2 or 1.3 ATA of pressure as sham. There are some concerns that this last type of sham is less effective in blinding than a controls intervention with the same pressure with HBOT but with hypoxic mixture to mimic normoxic conditions ( $\text{PIO}_2 = 0.2$  ATA). However Weaver et al ran a prospective study to test if the divers or other people familiar with hyperbaric situation can discern chamber pressure (1.5 ATA 100% oxygen vs. 1.2 ATA ambient air). They showed that experienced divers could not discriminate chamber pressures of 1.5 ATA and 1.2 ATA. (53) but they did not reach 2.0 or 2.5 ATA which are the most common protocols. Clarke reported that recreational SCUBA divers could not differentiate between 2.0 ATA 100% Oxygen and 1.1-1.3 ATA ambient air protocols. (54) However, it did not report in detail how they evaluated the effect of learning on repeated exposures. A narrative review by Lansdrop and van Hulst in 2018 concluded that the best placebo is using air with a lower pressure than the hyperbaric oxygen therapy group. (55) In the authors' opinion however, there are still two theoretical concerns with this approach:

1. It is not possible to simultaneously treat subjects of the study group with subjects of the control group, nor is possible to have patients under treatment pressure and study subjects of the control group at the same time; (which means they cannot be treated exactly the same). With the placebo approach using the same treatment pressure (2 ATA, for example) breathing a hypoxic mixture (10.5% oxygen and 89.5% nitrogen), patients and study subjects of both groups (control and study) can be treated in the chamber at the same time, completely blinded.

2. In the vast majority of multiplace hyperbaric chambers, it is not possible to obtain an appropriate door seal until the internal pressure reaches at least 1.2 ATA. Without enough pressure to obtain the proper seal, a characteristic noise is produced that would inform the study subjects, and the personnel inside and outside the chamber, that there is little pressure inside the chamber. .

We should also mention that control groups did not receive any treatment in Harrison et al. (39) and Germain et al. (37) studies.

### ***Detection bias***

Half of the eight human trials have used blinded assessor for the outcome measurements (TABLE), three of eight studies did not mention if the assessors of the outcomes measure were blinded and Webster et al. specified that their study was single blinded. (40)

### **Future strategies to bridge the knowledge gap**

We suggest that future studies use larger sample sizes or matching to avoid differences in the baseline of HBOT and control groups. They could report baseline data if there is no difference in the baseline measures of outcome measures. Blindness strategy is another concern in future study designs, and the aforementioned concerns about the blindness should be addressed. The blindness of the investigator who is responsible for the assessment of outcome measures can attenuate substantial bias.

All the current human trials have mentioned randomization in their design, but considering the limited number of participants, randomization might not be enough for

attenuating allocation bias. We suggest that future studies use large pools of injured athletes with different injuries but with stratification and matching. They can use relative outcomes (healing time of any specific injury in HBOT group/healing time of the same injury in control group) as an outcome measure, which enables them to use a pool of injured athletes with different injuries.

Despite the number of basic and animal studies using HBOT in conditions other than muscle soreness, human trial studies are scarce. Designing new human studies for evaluation of the effectiveness of HBOT on muscle strains, contusion, tendon and ligament injuries should be the next step in the light of recent in vitro and animal studies.

## **Conclusion**

Hyperbaric Oxygen Therapy (HBOT) has the special capacity to enhance oxygen delivery, reduce edema and pathologic inflammation, mitigate ischemia/reperfusion injury, improve collagen synthesis and deposition, and induce neovascularization and neoangiogenesis. These underlying mechanisms have the potential to help the process of healing among injured athletes. The last meta-analysis and systematic review still stands which had suggested that HBOT is ineffective for Delayed muscle soreness. The human studies are scarce despite widespread use of HBOT among athletes and require rigorous scientific studies before concluding if HBOT can facilitate the return to play of athletes.



**Conflict of interest**

None.

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ACCEPTED



**Table 1. Therapeutic uses of hyperbaric oxygen according to Undersea and Hyperbaric Medical Society (UHMS)**

1. Air or gas embolism
2. Carbon monoxide poisoning / Carbon monoxide poisoning complicated by cyanide poisoning
3. Clostridial myositis and myonecrosis (gas gangrene)
4. Crush injuries, compartment syndrome and other traumatic ischemias
5. Decompression sickness
6. Arterial Insufficiencies
  - a. Central retinal artery occlusions
  - b. Selected problem wounds - diabetic ulcers (microvascular insufficiency)
7. Severe anemia
8. Intracranial abscesses
9. Necrotizing infections
10. Osteomyelitis (refractory)
11. Delayed radiation injury (soft tissue and bony necrosis)
12. Compromised grafts and flaps
13. Acute thermal burn injury
14. Idiopathic sudden sensorineural hearing loss

The Undersea and Hyperbaric Medical Society approves use of hyperbaric oxygen for a few conditions for which there is thought to be reasonable scientific evidence or well validated clinical experience.(2)

Table 2. Summary of human clinical trials for HBOT in sports related injuries				
Reference	Injury type	groups	Intervention	Summary of Results (effect of HBOT in compare to the control)
Soolsma, 1996 (48)	grade II medial collateral ligament injury	HBOT group N=7	10 sessions of 2.5 ATA 100% O <sub>2</sub>	↓volume of edema ↓muscle wasting ↑range of motion ↑Maximum flexion
		Control Group N=7	10 sessions of 1.2 ATA air	↔ Severity of pain ↔ One legged jump test
Borromeo et al., 1997 (49)	Ankle sprain within 72 hr	HBOT group N=16	3 sessions 2 ATA 100% O <sub>2</sub>	↑functional index improvement * ↔ reduced swelling
		control group N=16	3 sessions 1.1 ATA air	↔ pain ↔ range of motion ↔ time to recovery
Staples et al., 1999(33)	Induced DOMS of quadriceps	Phase 1		Phase 1 ↔ Pain score ↑Recovery of torque (HBO vs. Delayed HBO, Sham, and control) *
		HBO group N=9	3 sessions 2.5 ATA 100% O <sub>2</sub> and 2 sessions 1.2 ATA 21% O <sub>2</sub> after that	
		Delayed HBO group N=9	2 sessions 1.2 ATA 21% O <sub>2</sub> and 3 sessions 2.5 ATA 100% O <sub>2</sub> after that	
		Sham group N=9	5 sessions 1.2 ATA	Phase 2 ↔ Pain score

			21% O <sub>2</sub>	↑Mean eccentric quadriceps torque (5 days HBO vs. Sham and 3 days HBO) *
		Control group N=9	No treatment	
		Phase 2		
		3 days HBO group N=10	3 sessions 2.5 ATA 100% O <sub>2</sub>	
		5 days HBO group N=10	5 sessions 2.5 ATA 100% O <sub>2</sub>	
		Sham group N=10	5 sessions 1.2 ATA 21% O <sub>2</sub>	
Mekjavic et al., 2000 (38)	Induced DOMS of elbow flexors	HBOT groups N=12	7 sessions 2.5 ATA 100% O <sub>2</sub> (PIO <sub>2</sub> = 2.5 ATA)	↔ the rate of recovery ↔ muscle strength ↔ peaked Perceived soreness ↔ increases in arm circumference
		control groups N=12	7 sessions 2.5 ATA normoxic (PIO <sub>2</sub> = 0.2 ATA)	
Harrison et al., 2001 (36)	exercise-induced muscle injury with Preacher Curl	Immediate HBOT N= 6	5 sessions 2.5 ATA 100% O <sub>2</sub> (starting day 0)	↔ cross-sectional area ↔ T2 relaxation time in MRI ↔ isometric strength serum CK level ↔ perceived soreness
		Delayed HBOT N=7	4 sessions 2.5 ATA 100% O <sub>2</sub> (starting day 1)	

		control group N=7	no treatment	
Webster et al., 2002 (37)	exercise-induced muscle injury in gastrocnemius	HBOT group N=6	3 sessions of 2.5ATA 100% O <sub>2</sub>	↑isometric peak torque recovery * ↓pain perception *  ↔ isokinetic peak torque ↔ muscular endurance ↔ T2 relaxation time in MRI ↔ cross-sectional area
		control group N=6	3 sessions of 1.3 ATA air	
Babul et al., 2003 (35)	Induced DOMS of knee flexors	HBOT group N=8	5 sessions of 2.0ATA 100% O <sub>2</sub>	↔ Pain ↔ Strength ↔ quadriceps circumference ↔ creatine kinase ↔ malondialdehyde ↔ MRI images (T2 and STIR)
		control group N=8	5 sessions of 1.2 ATA air	
Germain et al., 2003 (34)	Induced DOMS of quadriceps femoris	HBOT group N=8	5 sessions of 2.5ATA 95% O <sub>2</sub>	↔ creatine kinase ↔ muscle soreness ↔ leg circumference ↔ isokinetic peak torque
		control group N=8	no treatment	
<p>* statistically significant (&lt;0.05 P-value) difference between HBOT and control group in that outcome</p> <p>Abbreviations: HBOT, Hyperbaric Oxygen Therapy. DOMS, Delayed onset muscle soreness. ATA, atmospheres absolute</p> <p>↑ shows the outcome variable is higher in HBOT group in compare to control group</p> <p>↓ shows the outcome variable is lower in HBOT group in compare to control group</p> <p>↔ shows the outcome variable is similar in HBOT and control group</p>				