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REVIEW ARTICLE

Hyperbaric Oxygen Therapy in Orthopaedics: An Adjunct Therapy with an Emerging Role

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Abstract

Introduction Hyperbaric oxygen therapy (HBOT) has emerged as an adjunct treatment modality in various orthopedic and rheumatological conditions. Undersea and Hyperbaric Medical Society (UHMS) defined the minimum number of HBOT cycles, dose, and frequency for various diseases. UHMS laid the 14 absolute indications for HBOT. This article deals with the mechanism of actions of HBOT and evidence of various musculoskeletal disorders where HBOT was utilized to accelerate the healing process of the diseases.

Materials and methods The review literature search was conducted by using PubMed, SCOPUS, and other database of medical journals for identifying, reviewing, and evaluating the published clinical trial data, research study, and review articles for the use of HBOT in musculoskeletal disorders.

Results Various clinical researchers documented cellular and biochemical advantages of HBOT which possess allodynic effects, anti-inflammatory, and prooxygenatory effects in patients with musculoskeletal conditions. Studies on the usage of HBOT in avascular necrosis and wound healing provide a platform for exploring the plausible uses of HBOT in other musculoskeletal conditions. Literature evidence states the complications associated with HBOT therapy.

Conclusion The existing HBOT protocols have to be optimized for various musculoskeletal disorders. Large scale blinded RCTs have to be performed for demonstrating the level of evidence in the usage of HBOT in various musculoskeletal clinical scenarios.

Keywords Hyperbaric oxygen · Avascular necrosis · Wound healing · Chronic osteomyelitis

Introduction

Hyperbaric oxygen therapy (HBOT) dates back to the 1600 s. The first HBOT chamber was built and operated by a British Clergyman named Henshaw [1]. The Undersea and Hyperbaric Medical Society (UHMS) defines hyperbaric oxygen therapy (HBOT) as "An intervention in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber that is pressurized to greater than sea level pressure" [2]. HBOT can be administered via multiplace chambers, monoplace chambers, topox (diabetic wounds and uncomplicated wounds), and portable mild hyperbaric chamber (altitude illness) [3, 4].

The therapeutic index of HBOT depends on the positive gradient diffusion of hyper-oxygenated lungs to hypoxic tissues, the amount of oxygen concentration in blood (Henry's law), and decreases in the air bubble size in blood (Boyle–Mariotte law and Henry's law) [5]. HBOT creates

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hyperoxaemia and hyperoxia without the contribution of haemoglobin [3, 6]. At the cellular level, HBOT enhances the production of reactive oxygen species and reactive nitrogen species, which lead to the synthesis of various growth factors, cytokines inducing neovasculogenesis, and immunoregulatory effects to exert its clinical actions [7, 8]. HBOT upregulates HIF by the ROS/RNS and ERK1/2 pathways [9, 10]. Excess production of ROS/RNS leads to metabolic dysregulation, DNA damage, oxidative bursts, endothelial cell dysfunction, acute pulmonary injury, and neurotoxicity [9–13].

Presently, UHMS has approved 14 indications for the usage of HBOT at a rate of 100% oxygen in a pressurized chamber to a minimum of 2ATA [14]. For a few critical conditions, various physicians use 100% oxygen at 6 ATA, but subtle benefits are reported from more than 3 ATA [14]. 100% oxygen increases oxygen tension by 270 kPa in arterial blood and 53 kPa in tissues, which improves oxygen supply in the cells and tissues by raising the oxygen diffusion gradient and improves neoangiogenesis [15]. The tissue healing process helps cells and tissues with compromised perfusion, but requires further validation. An orthopaedic surgeon must comprehend the usage of this adjunct therapy when the conventional treatments were ineffective for musculoskeletal disorders, as evidence for its utility in orthopaedics continues to rise as shown in Fig. 1. This article deals with the mechanism of action and evidence of HBOT in various musculoskeletal disorders.

Mechanism of Action of HBOT

Hyperbaric oxygen acts by two primary mechanisms, namely, hyperoxygenation and decreased bubble size [7]. The mechanism of actions of HBOT is as follows.

(a) *Hyperoxygenation* (decompression sickness, osteonecrosis, CO poisoning, central retinal artery occlusion, crush injury/compartment syndrome, compromised grafts and flaps, and severe blood loss anaemia): Henry's law states that "the quantity of a perfect gas dissolved in the solution is directly proportional to its partial pressure". HBOT enhances oxygen absorption at the cellular level with relative hypoxia by developing the oxygen dissolved in circulating plasma. Hyperbaric oxygen alleviates ischaemia–perfusion injury by expressing reactive oxygen species.

(b) *Decreased bubble size* (air embolism) Decreased nitrogen bubbles in the vessels are observed with HBOT. While administering HBOT, the additional oxygen dissolved in the plasma is directly proportional to the partial pressure of the oxygen. A tenfold increased dissolved oxygen in plasma is observed at 2–2.5 ATA oxygen pressure. HBOT generates a good gradient for oxygen diffusion to ischaemic tissues.

The secondary mechanisms by which HBO acts are.

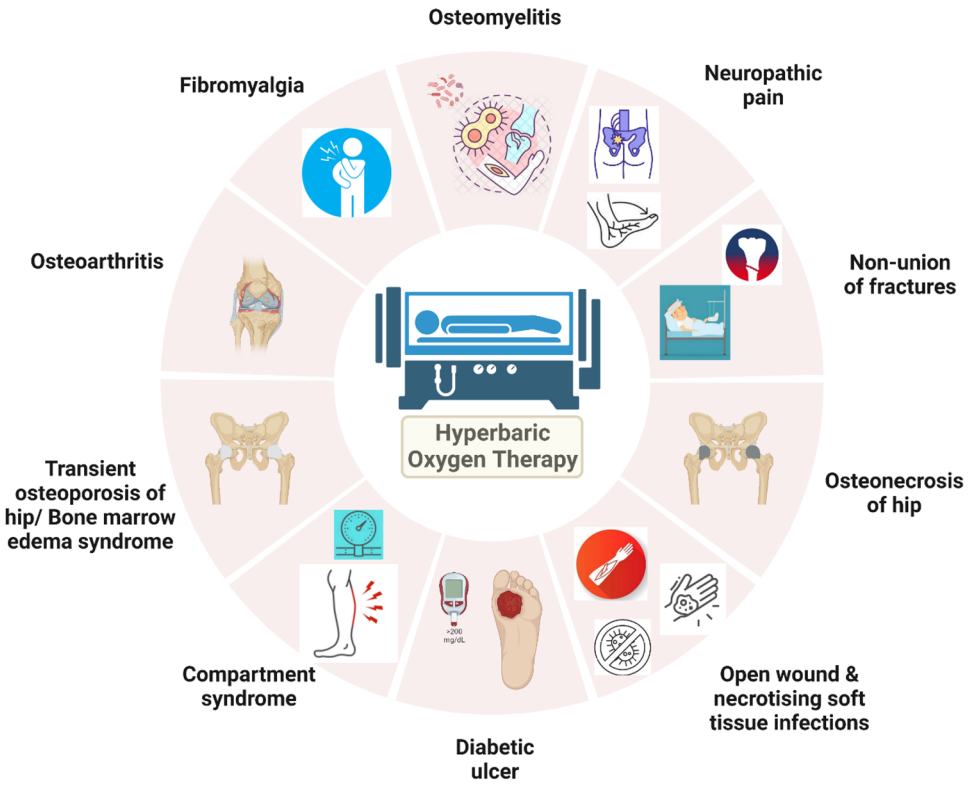


Fig. 1 Evidences of hyperbaric oxygen therapy in musculoskeletal disorders

(a) Vasoconstriction (osteonecrosis, crush injury/compartment syndrome, and thermal burns).
(b) Neovasculogenesis (non-healing ulcers and wounds, compromised grafts and flaps, and radiation-induced injury).
(c) Migration and proliferation of fibroblasts (non-healing ulcers and wounds and radiation-induced injury).
(d) Oxidative killing by leukocytes (refractory osteomyelitis and necrotizing soft tissue infections).
(e) Inhibition of toxins (clostridial myonecrosis).
(f) Antibiotic synergy (refractory osteomyelitis and necrotizing soft tissue infections).
(g) Reduction of intravascular leukocyte adherence (crush injury/compartment syndrome).
(h) Lipid peroxidation (CO poisoning and crush injury/compartment syndrome).

The excessive increase of cellular oxygen level leads to increased production of reactive oxygen species (ROS), and reactive nitrogen species (RNS) in turn leads to a sequence of events that are as follows [16–19]:

(a) Increased growth factor synthesis → elevated tissue SDF-1, angiopoietin, bFGF, and TGF-β1 via HIF-1 leading to neoangiogenesis.
(b) Mobilization of progenitor cells from bone marrow → increased peripheral site progenitor cells and HIF and HIF-related gene products → enhanced angiogenesis.
(c) Activation of neutrophil, β-actin, and S-nitrosylation → impaired β2 integrin function → improved post-ischaemic tissue survival.
(d) Decreased monocyte–chemokine synthesis and ischaemic pre-conditioning changes in HO-1, HSPs, and HIF-1 → downregulated inflammatory responses → enhanced tissue survival and regeneration.

Uses of HBOT in Orthopaedics

Fractures

HBOT has been instituted in the management of acute fractures, and delayed and non-union of fractures. Demirtas et al. reported an insignificant outcome on fracture healing with HBOT in nicotinized rats with femur fractures, both radiologically and histopathologically. [20]. The Cochrane review is unable to find any pertinent clinical evidence to support or dispute HBOT's efficacy in treating bone fractures with delayed union or known non-union [21]. Further, a study has recognized the synergistic role of HBOT along with platelet-rich plasma (PRP) in animal models. The use of both can increase bone regeneration and neovascularization of autologous bone grafts [22]. The role of HBOT for fracture healing as a supplementary therapy has been recognized recently. Atesalp et al. treated two of their patient with reinfection after the treatment of infected non-union was managed successfully with HBOT [23]. Rollo et al. demonstrated the use of HBOT (20 HBOT sessions over approximately 20 days in 4 weeks) in tibia non-union. The HBOT can be used as a callus accelerator and allows more rapid healing of the regenerated bone along with the removal of the external fixator [24].

Osteonecrosis of the Femoral Head (ONFH)

In ONFH, the pathology causes damage to microcirculation [25, 26]. Osteoclastogenic activity is highly oxygen dependent for removing the necrotic area of the osseous tissue. Enhanced oxygen supply to ischaemic osseous tissue facilitates collagen synthesis, fibroblast proliferation, and neovasculogenesis [27, 28]. Deploying HBOT to ONFH leads to the reduction of tissue oedema by vasoconstriction and hence reduces intraosseous pressure, restoring venous drainage and rapidly improving the microcirculation [29]. Administration of HBOT to osteoblasts leads to enhanced proliferation rate and increased alkaline phosphatase (ALP) activity [30]. HBO facilitates differentiation of osteoblasts, suppression of osteoclasts, and directs the environment towards osseous regeneration [30]. HBOT facilitates osteosynthesis and neovasculogenesis and enhances the functioning of osteoblasts and osteoclasts in osseous repair and remodelling [8]. HBOT downregulates TNF-α and IL-6 by providing a favourable osteogenic environment to homeostatic levels by modulating the interaction of IL-1β, IL-6, and/or TNF-α with OPG/RANK/RANKL [31, 32]. HBOT has been successfully used in the management of ONFH, osteonecrosis of the knee, and mandibular osteomyelitis.

The exact dose number of sessions and duration of HBOT for the treatment varies among the published studies as mentioned in Table 1.

Salameh et al. treated 15 patients for pre-collapse AVN (Steinberg I and II) of the femoral head with HBOT. Each patient received 25 to 40 sessions of HBOT with 3 to 4 sessions per week. HBOT specialist delivered 100% oxygen at 2.2 atm in an HBO chamber for 90 min with a satisfactory clinical–radiological outcome and less complication rate at the end of 1-year follow-up [37]. Reis et al. demonstrated normalcy in 81% of patients with stage 1 AVN femoral head treated with 6 sessions per week up to 100 sessions of HBOT for 90 min at the rate of 2–2.5 atm at the end of 24 months follow-up [33]. Moghamis et al. proved HBOT ($n = 11$) as a promising and effective non-invasive treatment modality of choice when compared with core decompression ($n = 12$) in stage 2 AVN femoral head [36]. Koren et al. reported a significant functional outcome was observed in stage 1 and

Table 1 Hyperbaric oxygen therapy in osteonecrosis of the femoral head

Author (year)	Study type	No. of hips/cases	Grade of osteonecrosis	HBO protocol	Outcome
Reis et al. [33] (2003)	Retrospective review of prospective study	12 patients (16 hips)	Steinberg I	Six daily sessions each week up to a total of 100	10 out of 12 patients were symptom free and returned to their occupation; 1 patient with lupus on steroid with 4 years follow-up: same stage as previously, but with persistent pain; 1 patient with chronic renal disease developed collapse of the FH and underwent THR Nine were restored to a normal MRI appearance, while one developed collapse and two remained unchanged at stage II. In a further four femoral heads, the subchondral lesion was 12.5 mm or more long, but not 4 mm or more thick. In each of these, the MR image returned to normal on the T2-weighted scan
Camporesi et al. [34] (2010)	RCT: two groups of ten patients each received 30 sessions of HBA and HBO, respectively	20 patients (20 hips)	FICAT stage II	30 sessions of HBO or HBA for 6 weeks (HBA: hyperbaric air)	VAS: HBO group showed marked significant improvement after 20 treatment sessions ($P=0.002$ vs HBA) and after 30 sessions ($P<0.001$) At the 7-year follow-up, all 17 patients reported minimal pain with no decrease in activities of daily living; none had received hip arthroplasty surgery or developed contralateral disease. Two patients had demonstrable bony defect at 7 years and exhibited minimal symptoms

Table 1 (continued)

Author (year)	Study type	No. of hips/cases	Grade of osteonecrosis	HBO protocol	Outcome
Koren et al. [35] (2015)	68 patients with 78 symptomatic joints with Steinberg stage I and II osteonecrosis of the femoral head	39 hips of each Steinberg type I and II	Steinberg type I and II	Six sessions per week [mean no. of sessions: 78.3 ± 24.2 (range: 25–135)]	Lesions on post-treatment MRI: Stage I showed 95% improvement and stage II showed 81% improvement Only four joints (7%) had undergone hip joint replacement at the time of follow-up, for an overall 93% survival rate Stage I had a survival rate of 97% and stage II had a survival rate of 90% HHS: In stage I, the improvement was from 17 to 79 points ($P < 0.0001$) and in stage II, the improvement was from 21 points to 68 points ($P < 0.0001$)
Vezzani et al. [32] (2017)	Prospective observational study	23 patients (23 hips), only 19 patients completed the study	FICAT I (1 patient), II (7 patients), and III (15 patients)	Patients were exposed to breathing 100% oxygen at 2.4 ATA in a multiplace pressure chamber for 90 min using an over board demand regulator 60 sessions to each patient (5 sessions per week)	All patients of FICAT I (1 patient) and FICAT II (7 patients) returned to normal anatomy and 2 out of 11 patients of FICAT III showed decrease in the size of lesion, whereas 3 patients of FICAT III had deterioration of radiological outcome and 6 were unchanged Improvement in VAS score observed in all patients of FICAT I (1 patient) and FICAT II (7 patients) and only 3 out of 11 patients of FICAT III In almost all patients, there were increased levels of plasmatic OPG above control level in response to HBO therapy

Table 1 (continued)

Author (year)	Study type	No. of hips/cases	Grade of osteonecrosis	HBO protocol	Outcome
Moghamis et al. [36] (2021)	Retrospective cohort study	12 hips were treated with core decompression, while 11 hips received a range of 25–40 HBO sessions	Steinberg II	25–40 HBO sessions (3–4 sessions/week)	No Significant diferences in OHS or SF12 were reported with a *P* value of 0.13 and 0.67, respectively 37.5% of the HBO group had AVN progression on one year radiographs compared to 62.5% in the core decompression group
Salameh et al. [37] (2021)	Retrospective case series	15 patients (17 hips)	Steinberg I and II	Between 25 and 40 sessions of HBO therapy, with three to four sessions per week Mean sessions: 39.5 ± 13	13 (86.7%) patients had satisfactory outcome with average final follow-up OHS score of 37.3 The mean pre-treatment VAS score (13 patients) was 5.1 ± 2.1 compared to 1.5 ± 1.6 at the last follow-up
Bozkurt et al. [38] (2021)	Comparative prospective study (retrospective review of prospectively collected data of two groups at two institutions)	63 patients (80 hips) (i) HBO group: 46 patients [30 (II A); 16 (II B)] (ii) HBO + CD group: 34 patients (22 + 12)	FICAT II: II A: 52; II B: 28	HBOT was solely applied or combined with CD 1 week after the operation The sessions were applied 6 days a week, at 2.4 ATA for 120 min, for a total of 30 sessions in each group	Both VAS and HHS were improved statistically significant in each group On comparison, improvement was more distinct and evident in the CD + HBO combination group than the HBO alone group ($P < 0.001$) HHS in CD + HBO: good or excellent on 30 of 34 hips, HHS in HBO alone in 29 of 46 hips Of the 5 poor results, only one was in the combination group

Table 1 (continued)

Author (year)	Study type	No. of hips/cases	Grade of osteonecrosis	HBO protocol	Outcome
Paderno et al. [39] 2021	Systematic review and meta-analysis	Ten studies involving 353 controls and 368 HBO-treated cases were included			According to the subgroup analysis principle, the population was divided into Asian and non-Asian subpopulations Among the included studies, eight refer to Asian populations and two to non-Asian populations For the Asian subpopulation, random effect model meta-analysis showed that I2 = 57%, $P = 0.02$, and clinical efficacy in the HBO group was 3.53 times higher than in the control group, and the difference was statistically significant (OR = 3.53, 95% CI (1.87, 6.64), $P < 0.00001$) For the non-Asian subpopulation, random effect model meta-analysis showed that I2 = 60%, $P = 0.11$, and the clinical efficacy in the HBO group was 7.41 times higher than in the control group, but the difference was **not** statistically significant (OR = 7.41, 95% CI (0.73, 75.71), $P = 0.09$) This meta-analysis suggests that patients with femoral head necrosis treated by HBO therapy at early stages can achieve a significantly improved clinical treatment effect, in particular the Asian population showed statistically significant results, probably because of a superior numerosity

2 cases of AVN femoral head ($n=58$) when treated with HBOT with a mean follow-up of 11 years [35]. Paderno et al. analysed ten studies with 368 HBO-treated AVN cases and reported clinically significant improvement in the follow-up period [39]. Bozkurt et al. reported that the combination of core decompression with HBOT demonstrates significantly superior results in stage 2 AVN hips than HBOT alone [38]. Vezzani et al. deployed HBOT (100% oxygen at 2.4 atm in a multiplace pressure chamber for 90 min for 5 days a week) for FICAT stage 1 ($n=1$), 2 ($n=7$), and 3 ($n=15$) ONFH and obtained serum osteoprotegerin (OPG) level at the beginning of HBOT (T0), after 15 sessions (T1), 30 sessions (T2), after a 30-day break (T3), and after 60 sessions (T4) along with MRI at T0 session and after 1 year from the end of HBO treatments to measure the lesion size. HBOT decreases lesion size in all cases of stages 1 and 2 and 2 out of 11 cases in case of stage 3 in MRI follow-up. HBOT increases only serum OPG levels and not RANKL levels [32].

Refractory osteomyelitis

Chronic refractory osteomyelitis (CRO) is defined as a persistent infection of bone and bone marrow lasting for more than 6 months despite appropriate medical and surgical interventions [40]. In CRO cases, HBOT acts as an adjuvant treatment modality. The combination of treatment with HBOT and appropriate medical and surgical interventions demonstrates a successful outcome in CRO cases. HBOT provides remission up to 80–85% for 2 to 3 years in CRO patients. The appropriate dose of HBOT in CRO cases deploying 100% oxygen at 2.4 atm for up to 40–60 sessions for 90 min with 5-min air breaks every 30 min for 5 days per week. Patients are monitored with ESR and CRP every 4–6 weeks during treatment [41]. In CRO, HBOT acts by direct killing both aerobic and anaerobic bacteria, improves oxygen-dependent killing of PMN leukocytes, enhances proliferation of fibroblasts and collagen synthesis, facilitates neovasculogenesis, enhances equilibrium in osteoblastic and osteoclastic response, and enhances the activity of aminoglycoside, fluoroquinolone, vancomycin, and sulphonamide antibiotics [42, 43]. High oxygen levels enhance both bacteriostatic and bactericidal effects [43].

Sovvidou et al. analysed 45 studies utilizing HBO for 460 patients with CRO. Adjuvant HBO was effective in 80% of the cohort and 95% of case studies. A total of 73.5% of cases reported successful outcomes without relapse [44]. Ahmed et al. reported the usage of HBOT in bacterial [*S.aureus* ($n=4$), CONS ($n=1$), and MRSA ($n=1$)] spinal osteomyelitis in six adult cases [45]. Bingham et al. instituted 2 atm of HBO for 2 h daily 5 days a week till the evidence of wound healing for 28 cases of CRO (*S. aureus*, *Klebsiella* group, *Pseudomonas*, *Escherichia coli*, and *Enterobacter*) with the follow-up ranging from 6 months to 6 years and reported no relapse or recurrence of CRO among these cases [46]. Yu et al. treated 12 cases of sternal osteomyelitis [MRSA ($n=8$), *Mycobacterium tuberculosis* ($n=1$), *Klebsiella pneumoniae* ($n=1$), and *E. coli* ($n=1$)] after thoracotomy and cardiothoracic surgeries with HBOT at the rate of 100% oxygen under 2.5 ATA for 90 min for 5 days per week till the wound epithelizes [47]. HBOT has been utilized as adjuvant therapy in an immunocompromised 64 years old male with RCO of post-traumatic (left subtrochanteric fracture fixed with long proximal femoral nail) origin despite aggressive management [48]. Complete eradication of CRO was observed in 92% ($n=12$) cases without any recurrence with HBOT (2.5 atm for 120 min for 5 days per week in all cases) [49].

HBOT is efficacious in pyogenic spinal infections [MSSA ($n=3$), MRSA ($n=4$), *S. epidermidis* ($n=2$), *Pseudomonas aeruginosa* ($n=2$), *Klebsiella pneumoniae* ($n=1$), and *Candida albicans* ($n=1$)] ranging from SSI following spinal surgery, spondylitis, spondylodiscitis, vertebral osteomyelitis, and epidural abscess [50]. For refractory pyogenic spinal infections, HBOT is administered in the form of a multiplace HBO chamber at 2.5 atm for 90 min, with 5-min air breaks for every 30 min, once a day for 5 days in a week ranging from 2 to 12 weeks [50]. No relapse or recurrence was reported at the end of 24 months with 22 cases of postoperative discitis treated with IV vancomycin 1 g BD for 4 weeks and HBOT (100% O_2 at 2.4 ATA for 90 min BD for the initial 5 consecutive days, and additional treatment of 100% O_2 at 2.4 ATA for 90 min daily for 25 days) [51]. HBOT remains an alternative treatment of choice for surgical removal of infected flaps or bones in complex situations. HBOT reduces reoperative rates, allows the control of mixed and multidrug-resistant infections, and improves the quality of life of patients complicated with postoperative neurosurgical infections [52]. Onen et al. demonstrated the use of HBOT in iatrogenic spinal osteomyelitis following spinal instrumentation in 19 cases, which prevented re-surgical morbidity in the patients. [53]. The appropriate time duration of HBOT in pyogenic spinal infection remains controversial. However, the published literature states 40–60 sessions of HBOT for wound healing and infection control [45, 51–53]. Goerger et al. demonstrated the successful outcome of multidrug-resistant osteomyelitis by OXA-48 type carbapenemase-producing *K. pneumoniae* with HBO and without concomitant use of antimicrobials [54].

Diabetic Foot Ulcers (DFU)

Diabetic foot ulcers are difficult to treat. HBOT has been used as an adjunct to treat these ulcers. For DFU, HBOT is deployed at a rate of 1.4–3.0 atm of 100% oxygen intermittently for 90 min with 5 min air break intervals every

30 min in a hyperbaric chamber daily. [55–57]. In DFU and chronic non-healing ulcers, HBOT facilities wound and tissue hypoxia, increases perfusion, downregulates oedema and inflammatory cytokines, and upregulates proliferation of fibroblasts, synthesis of collagen, and neovasculogenesis [55, 57]. In DFU, there are contradictory findings in the HBOT treatment modality.

In Wagner grade 2–4 DFU, Fedorko et al. evaluated 54 cases in the control group and 49 cases in the HBOT group. The control group revealed 22 healed cases and 13 amputation cases, whereas the HBOT group revealed 10 healed cases and 11 amputation cases. They found no significant difference in wound healing rates and amputation rates [58]. For diabetic lower limb ischaemic wounds, $DAMO_2$ CLES research instituted standard management along with or without HBOT in 120 cases. HBOT did not improve the healing rates and the risk of limb salvage in these cases [59].

Cochrane review analysed ten RCTs of cases with DFU and revealed that HBOT improved short-term wound healing with a lower rate of amputation [60–65]. Oliveria et al. administered HBOT at a rate of 100% oxygen at 2.4 atm for 5 days a week in a multi-seat hyperbaric chamber for 90 min with 5 min of air break for every 30 min for 26-foot lesions (13-foot ulcers of Wagner grade 2 or more and 13 amputation stump ulcers). 88.4% of cases got healed with complete epithelialization of the wound with HBOT for an average of 16 weeks [56]. Sharma et al. analysed 14 trials (12 RCTs and 2 CCTs) with 768 participants of DFU treated with HBOT and reported complete healing of DFU without any relapse or recurrence [66]. Increased oxygen concentration facilitates better wound healing and declines microbial colonizations. In DFU, HBOT has dropped the amputation rates and re-surgical debridement rates. HBOT facilitates oxygen-dependent wound repair by activating the production of mesenchymal stromal cells in the bone marrow and improving host antimicrobial responses. The reported adverse effects in this meta-analysis are barotrauma and oxygen toxicity [66]. In their meta-analysis (20 RCTs and 1263 trials), Zhang et al. reported that HBOT offers an efficient adjunct treatment modality of choice for DFU with reduced amputation rates [67]. Salama et al. [68] reported that the combination of conventional treatment along with HBOT appears to be more effective than conventional treatment for the healing of chronic non-ischaemic DFU [38].

Fibromyalgia

Fibromyalgia syndrome (FMS) is a chronic debilitating disorder with abnormal brain activity, which is characterized by chronic widespread pain, prolonged muscle spasms, weakness in the limbs, allodynia, fatigue, and sleep disturbances [68]. It is estimated that FMS impairs the quality of life in 2–4% of the population [69]. FMS affects females over males with a ratio of 9:1. FMS complex remains elusive and refractory. In fibromyalgia, HBOT upregulates cellular and tissue metabolism, neurotrophin, and nitric oxide levels by facilitating the functions of mitochondria in neurons and glial cells and downregulates oxidative stress and apoptosis of cells [70]. HBOT promotes the neurogenesis of endogenous neural stem cells [71]. HBOT induces neuroplasticity and repairs impaired brain functions [72]. Zhao et al. demonstrated an anti-nociceptive response in a CCI animal model along with the inhibition of mechanical and thermal hyperalgesia in a single HBOT session, whereas multiple HBOT sessions lead to aggravation of neuropathic pain and inhibition of astrocyte activation [73]. Inamato et al. suggested the immunosuppressive role of HBOT by demonstrating the decreased levels of IL-1 and PGE2 production [74].

Efrati et al. analysed 24 FMS cases of the treated group (evaluated at baseline and after HBOT) and 24 FMS cases of the crossover group (evaluated at baseline, after a control period of no treatment, and after HBOT). A total of 40 sessions of HBOT were delivered at the rate of 100% oxygen at 2 atm for 5 days per week for 90 min. SPECT revealed the rectification of abnormal brain activity in pain-related areas of FMS patients. They concluded that HBOT ameliorates the symptoms of FMS and induces neuroplasticity in the brain [70]. HBOT downregulates pro-inflammatory cytokines such as IL-1β and TNF-α, changes the phosphorylation of proteins involved in neuropathic pain such as NMDA receptors, and decreases the expression of spinal neuronal and inducible nitric oxide synthases [60, 75]. Vargas et al. evaluated 15 cases of FMS with HBOT at the rate of 100% oxygen at 2 atm for 60 min for 5 days per week for 20 sessions. They concluded that HBOT acts as an adjuvant by reducing pain and fatigue in obese patients presenting with fibromyalgia [76]. Atzeni et al. commented that HBOT improves pain and fibromyalgia symptom scores significantly after 10 and 20 sessions without any improvement in sleep disturbances in 87.5% of cases with fibromyalgia [77].

Complications of HBOT

With hyperoxia and a hyperbaric environment in the tissues, the complications of HBOT are reported in the literature [78]. Claustrophobia and middle ear barotrauma (MEB) are the two most common complications which occur during either monoplace or multiplace chamber HBOT compression. Claustrophobia causes a degree of confinement anxiety in multiplace chambers and 8 events per 10,000 treatments in monoplace chambers of HBOT therapy, which can be prevented by patient education, reassurance, and proper counselling and coaching by anticipating episodes of claustrophobia [79]. About 84% of non-intubated and 94% of intubated patients undergoing HBOT

experience MEB [78, 80]. Various studies suggest either a high (4.1 psi/min) or low (1 psi/min) rate of compression increases the risk of MEB [81]. Adequate patient counselling and education mitigate MEB occurrence. MEB resolves in the absence of repetitive HBOT sessions. Short-term injuries of the ear include tympanic membrane rupture and oedema and serous otitis media, which heal spontaneously and with medications. Long-term ear complications (ossicular disruption, perilymphatic fistula, and sensorineural hearing loss) of HBOT are rare [82].

HBOT increases systolic and diastolic blood pressure in both non-hypertensive and hypertensive patients undergoing HBOT [83]. Literature evidence state that no hypertensive urgency or emergency was reported with HBOT treatment [84]. A theoretical risk of an increased occurrence of pulmonary oedema is anticipated in patients with compromised left ventricular function undergoing HBOT, but limited [1 in 1000 (0.1%) and 1 in 4500 (0.02%)] data is available on this complication [85–87]. HBOT induces hypoglycaemia in patients who are prediabetic and diabetic. To prevent HBOT-induced hypoglycaemia, it is mandatory to set serum glucose levels as low as 100 mg/dl and as high as 150 mg/dl and monitor serum glucose on the day of HBOT treatment [84, 88].

The rarely reported complications of HBOT are barosinusitis (1 per 10,000 treatments) [78], barodontalgia/odontocrexis (9.2–21.6% among American and Australian civilian divers) [89], pulmonary barotrauma [90, 91], arterial gas embolism [91, 92], oxygen-dependent rigid tonic–clonic seizures (1 per 2000 to 3000 treatments) [93–96], progressive myopia [97], cataracts [97], and retrolental fibroplasia [98, 99]. The complications with multiple sittings of HBOT were not reported in the literature, but they were rare.

Level of Evidences Available with HBOT in Orthopaedics

As HBOT is an emerging and an adjunct treatment modality in various musculoskeletal disorders, we present the available level of evidence in Table 2.

Though level I and II evidences are available with ONFH, refractory osteomyelitis, and DFUs, randomized control trials (RCTs) on various dosage and frequency of HBOT have to be figured out. Low level of evidences are available on HBOT with fracture management, fibromyalgia, neuropathic pain, osteoarthritis, osteoporosis, and compartment syndrome. Large-scale blinded and multicentric RCTs have to evolve to provide level I and II evidences on HBOT in musculoskeletal disorders.

Table 2 Level of evidences available with HBOT in orthopaedics

Sl. No	Musculoskeletal disorder	Level of evidence
1	Fractures	Pre-clinical
2	Osteonecrosis of the femoral head	I
3	Refractory osteomyelitis	II
4	Diabetic foot ulcers	I
5	Fibromyalgia	IV

Future Directives

The mechanistic and therapeutic aspects of HBOT for musculoskeletal disorders are comprehensively narrated in this review. Still, a few issues remain with HBOT research. HBOT protocols for various musculoskeletal disorders vary which makes it difficult to compare and integrate different results. The available HBOT protocols for various indications have to be scaled up and a large number of randomized control trials have to be performed to validate the available results. Moreover, updates on published clinical protocols are warranted to accommodate the general ageing populations rather than currently approved indications. Therefore, a generally applicable HBOT protocol needs to be defined in the subsequent step. Repeated intermittent HBOT leads to transcriptome changes and telomere elongation in the genomic structure. With the hyperoxic–hypoxic paradox, the activation of SIRT1 by mitochondrial metabolism occurs and improves oxidative metabolism. Although the potentials of HBOT were demonstrated in pre-clinical studies, there is a lack of clinical trials in the cellular oxidative mechanism. The safety, efficacy of existing protocols, dose–response curves, exposure time, frequency of intervals, and the number of sessions need to be optimized for various musculoskeletal disorders.

Conclusions

The available literature provides a bird's eye view of HBOT application in various musculoskeletal disorders. The standardization and optimization need to be performed in terms of dose, frequency, number of sessions, safety, and efficacy of existing protocols of HBOT in musculoskeletal conditions. With the significant implications of HBOT, clinical applications have to be explored in the future.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standard Statement Article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study informed consent is not required.

References

1. Krishnamurti, C., & Krishnamurti, C. (2019). *Historical aspects of hyperbaric physiology and medicine*. London: IntechOpen.
2. Home - Undersea & Hyperbaric Medical Society. Retrieved November 8, 2022. https://www.uhms.org/
3. Hyperbaric Oxygen Therapy: Overview, Hyperbaric Physics and Physiology, Contraindications. Retrieved November 3, 2022. https://emedicine.medscape.com/article/1464149-overview
4. Different types of Hyperbaric Oxygen Chambers. Retrieved November 3, 2022. https://hbot.plus/articles/hyperbaric-oxygen-chambers
5. Ortega, M. A., Fraile-Martinez, O., García-Montero, C., Callejón-Peláez, E., Sáez, M. A., Álvarez-Mon, M. A., et al. (2021). A general overview on the hyperbaric oxygen therapy: Applications. *Mechanisms and Translational Opportunities Medicina, 57*(9), 864.
6. Leach, R. M., Rees, P. J., & Wilmshurst, P. (1998). Hyperbaric oxygen therapy. *BMJ, 317*(7166), 1140–1143.
7. Thom, S. R. (2011). Hyperbaric oxygen: Its mechanisms and efficacy. *Plastic and Reconstructive Surgery, 127*(Suppl 1), 131S-141S.
8. Camporesi, E. M., & Bosco, G. (2014). Mechanisms of action of hyperbaric oxygen therapy. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 41*(3), 247–252.
9. Schottlender, N., Gottfried, I., & Ashery, U. (2021). Hyperbaric oxygen treatment: Effects on mitochondrial function and oxidative stress. *Biomolecules, 11*(12), 1827.
10. De Wolde, S. D., Hulskes, R. H., Weenink, R. P., Hollmann, M. W., & Van Hulst, R. A. (2021). The effects of hyperbaric oxygenation on oxidative stress. *Inflammation and Angiogenesis Biomolecules, 11*(8), 1210.
11. Chen, W., Liang, X., Nong, Z., Li, Y., Pan, X., Chen, C., et al. (2019). The multiple applications and possible mechanisms of the hyperbaric oxygenation therapy. *Medicinal Chemistry, 15*(5), 459–471.
12. Hadanny, A., & Efrati, S. (2020). The hyperoxic-hypoxic paradox. *Biomolecules, 10*(6), 958.
13. Longobardi, P., Hoxha, K., & Perreca, F. (2021). Is hyperbaric oxygen an effective treatment for the prevention of complications in SARS-CoV-2 asymptomatic patients? *Infectious Microbes & Diseases, 3*(2), 109–111.
14. Camporesi, E. M., Mascia, M. F., & Thom, S. R. (1996). Physiological principles of hyperbaric oxygenation. In G. Oriani, A. Marroni, & F. Wattel (Eds.), *Handbook on hyperbaric medicine* (pp. 35–58). Milano: Springer.
15. Weaver, L. K. (1995). Hyperbaric medicine for the hospital-based physician. *Hospital Practice, 40*(3), 88–101.
16. Di Meo, S., Reed, T. T., Venditti, P., & Victor, V. M. (2016). Role of ROS and RNS sources in physiological and pathological conditions. *Oxidative Medicine and Cellular Longevity, 2016*, 1245049.
17. Mandal, M., Sarkar, M., Khan, A., Biswas, M., Masi, A., Rakwal, R., et al. (2022). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) in plants– maintenance of structural individuality and functional blend. *Advances in Redox Research, 5*, 100039.
18. Kilgour, J., & Roberts, R. (2014). Pathophysiological roles of reactive oxygen and nitrogen species. In I. Laher (Ed.), *Systems biology of free radicals and antioxidants* (pp. 171–206). Berlin: Springer.
19. Checa, J., & Aran, J. M. (2020). Reactive oxygen species: Drivers of physiological and pathological processes. *Journal of Inflammation Research, 13*, 1057–1073.
20. Demirtaş, A., Azboy, I., Bulut, M., Uçar, B. Y., Alemdar, C., Alabalık, U., et al. (2014). The effect of hyperbaric oxygen therapy on fracture healing in nicotinized rats. *Ulusal travma ve acil cerrahi dergisi = Turkish Journal of Trauma & Emergency Surgery, 20*(3), 161–166.
21. Bennett, M. H., Stanford, R. E., & Turner, R. (2012). Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union. *The Cochrane Database of Systematic Reviews, 2012*(11), CD004712.
22. Schneppendahl, J., Jungbluth, P., Sager, M., Benga, L., Herten, M., Scholz, A., et al. (2016). Synergistic effects of HBO and PRP improve bone regeneration with autologous bone grafting. *Injury, 47*(12), 2718–2725.
23. Atesalp, A. S., Komurcu, M., Basbozkurt, M., & Kurklu, M. (2002). The treatment of infected tibial nonunion with aggressive debridement and internal bone transport. *Military Medicine, 167*(12), 978–981.
24. Rollo, G., Bonura, E. M., Falzarano, G., Bisaccia, M., Ribes Iborra, J., Grubor, P., et al. (2020). Platet rich plasma or hyperbaric oxygen therapy as callus accellerator in aseptic tibial non union. Evaluate of outcomes. *Acta Bio-Medica: Atenei Parmensis, 91*(4), e2020188.
25. Chen, Y., Miao, Y., Liu, K., Xue, F., Zhu, B., Zhang, C., et al. (2022). Evolutionary course of the femoral head osteonecrosis: Histopathological - radiologic characteristics and clinical staging systems. *Journal of Orthopaedic Translation, 32*, 28–40.
26. Petek, D., Hannouche, D., & Suva, D. (2019). Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment. *EFORT Open Reviews, 4*(3), 85–97.
27. Schmidt-Bleek, K., Kwee, B. J., Mooney, D. J., & Duda, G. N. (2015). Boon and bane of inflammation in bone tissue regeneration and its link with angiogenesis. *Tissue Engineering Part B Reviews, 21*(4), 354–364.
28. Zhu, G., Zhang, T., Chen, M., Yao, K., Huang, X., Zhang, B., et al. (2021). Bone physiological microenvironment and healing mechanism: Basis for future bone-tissue engineering scaffolds. *Bioactive Materials, 6*(11), 4110–4140.
29. Bosco, G., Rizzato, A., Vezzani, G., Zanon, V., & Camporesi, E. (2018). *Therapeutic mechanisms of action for hyperbaric oxygen on femoral head necrosis*. London: IntechOpen.
30. Gardin, C., Bosco, G., Ferroni, L., Quartesan, S., Rizzato, A., Tatullo, M., et al. (2020). Hyperbaric oxygen therapy improves the osteogenic and vasculogenic properties of mesenchymal stem cells in the presence of inflammation in vitro. *International Journal of Molecular Sciences, 21*(4), 1452.
31. Bosco, G., Vezzani, G., Mrakic Sposta, S., Rizzato, A., Enten, G., Abou-samra, A., et al. (2018). Hyperbaric oxygen therapy ameliorates osteonecrosis in patients by modulating inflammation and oxidative stress. *Journal of Enzyme Inhibition and Medicinal Chemistry, 33*(1), 1501–1505.
32. Vezzani, G., Quartesan, S., Cancellara, P., Camporesi, E., Mangar, D., Bernasek, T., et al. (2017). Hyperbaric oxygen therapy modulates serum OPG/RANKL in femoral head necrosis patients. *Journal of Enzyme Inhibition and Medicinal Chemistry, 32*(1), 707–711.
33. Reis, N. D., Schwartz, O., Militianu, D., Ramon, Y., Levin, D., Norman, D., et al. (2003). Hyperbaric oxygen therapy as a treatment for stage-I avascular necrosis of the femoral head. *The Journal of Bone and Joint Surgery British, 85-B*(3), 371–375.

34. Camporesi, E. M., Vezzani, G., Bosco, G., Mangar, D., & Bernasek, T. L. (2010). Hyperbaric oxygen therapy in femoral head necrosis. *The Journal of Arthroplasty, 25*(6 Suppl), 118–123.
35. Koren, L., Ginesin, E., Melamed, Y., Norman, D., Levin, D., & Peled, E. (2015). Hyperbaric oxygen for stage I and II femoral head osteonecrosis. *Orthopedics, 38*(3), e200-205.
36. Moghamis, I., Alhammoud, A. A., Kokash, O., & Alhaneedi, G. A. (2021). The outcome of hyperbaric oxygen therapy versus core decompression in the non-traumatic avascular necrosis of the femoral head: Retrospective Cohort Study. *Annals of Medicine and Surgery, 62*, 450–454.
37. Salameh, M., Moghamis, I. S., Kokash, O., & Ahmed, G. O. (2021). Hyperbaric oxygen therapy for the treatment of Steinberg I and II avascular necrosis of the femoral head: A report of fifteen cases and literature review. *International Orthopaedics, 45*(10), 2519–2523.
38. Bozkurt, I., Yalcin, N., Uluyardimci, E., & Akgul, E. A. (2022). Combination of hyperbaric oxygen and core decompression therapies improve outcomes in the treatment of hip osteonecrosis. *HIP International, 32*(6), 759–765.
39. Paderno, E., Zanon, V., Vezzani, G., Giacon, T. A., Bernasek, T. L., Camporesi, E. M., et al. (2021). Evidence-supported HBO therapy in femoral head necrosis: A systematic review and meta-analysis. *International Journal of Environmental Research and Public Health, 18*(6), 2888.
40. Rose, D. (2012). Hyperbaric oxygen therapy for chronic refractory osteomyelitis. *American Family Physician, 86*(10), 888–889.
41. Hanley, M. E., Hendriksen, S., & Cooper, J. S. (2022). *Hyperbaric treatment of chronic refractory osteomyelitis*. StatPearls Treasure Island (FL): StatPearls Publishing.
42. O'Toole, K. (2002). Hyperbaric oxygen therapy and chronic refractory osteomyelitis. *Operative Techniques in Orthopaedics, 12*(4), 282–285.
43. Memar, M. Y., Yekani, M., Alizadeh, N., & Baghi, H. B. (2019). Hyperbaric oxygen therapy: Antimicrobial mechanisms and clinical application for infections. *Biomedicine & Pharmacotherapy, 109*, 440–447.
44. Savvidou, O. D., Kaspiris, A., Bolia, I. K., Chloros, G. D., Goumenos, S. D., Papagelopoulos, P. J., et al. (2018). Effectiveness of hyperbaric oxygen therapy for the management of chronic osteomyelitis: A systematic review of the literature. *Orthopedics, 41*(4), 193–199.
45. Ahmed, R., Severson, M. A., & Traynelis, V. C. (2009). Role of hyperbaric oxygen therapy in the treatment of bacterial spinal osteomyelitis. *Journal of Neurosurgery Spine, 10*(1), 16–20.
46. Bingham, E. L., & Hart, G. B. (1977). Hyperbaric oxygen treatment of refractory osteomyelitis. *Postgraduate Medicine, 61*(6), 70–76.
47. Yu, W.-K., Chen, Y.-W., Shie, H.-G., Lien, T.-C., Kao, H.-K., & Wang, J.-H. (2011). Hyperbaric oxygen therapy as an adjunctive treatment for sternal infection and osteomyelitis after sternotomy and cardiothoracic surgery. *Journal of Cardiothoracic Surgery, 6*, 141.
48. Delasotta, L. A., Hanflik, A., Bicking, G., & Mannella, W. J. (2013). Hyperbaric oxygen for osteomyelitis in a compromised host. *The Open Orthopaedics Journal, 7*, 114–117.
49. Chen, C.-E., Ko, J.-Y., Fu, T.-H., & Wang, C.-J. (2004). Results of chronic osteomyelitis of the femur treated with hyperbaric oxygen: A preliminary report. *Chang Gung Medical Journal, 27*(2), 91–97.
50. Körpınar, Ş. (2019). Could hyperbaric oxygen be a solution in the treatment of spinal infections? *Medicina, 55*(5), 164.
51. Kutlay, M., Colak, A., Simsek, H., Yildiz, S., Topuz, K., Kaya, S., et al. (2008). Antibiotic and hyperbaric oxygen therapy in the management of post-operative discitis. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 35*(6), 427–440.
52. Larsson, A., Engström, M., Uusijärvi, J., Kihlström, L., Lind, F., & Mathiesen, T. (2008). Hyperbaric oxygen treatment of postoperative neurosurgical infections. *Neurosurgery, 62*(Suppl 2), 652–671.
53. Onen, M. R., Yuvruk, E., Karagoz, G., & Naderi, S. (2015). Efficiency of hyperbaric oxygen therapy in iatrogenic spinal infections. *Spine, 40*(22), 1743–1748.
54. Goerger, E., Honnorat, E., Savini, H., Coulange, M., Bergmann, E., Simon, F., et al. (2016). Anti-infective therapy without antimicrobials: Apparent successful treatment of multidrug resistant osteomyelitis with hyperbaric oxygen therapy. *IDCases, 6*, 60–64.
55. Yazdanpanah, L., Nasiri, M., & Adarvishi, S. (2015). Literature review on the management of diabetic foot ulcer. *World Journal of Diabetes, 6*(1), 37–53.
56. Oliveira, N., Rosa, P., Borges, L., Dias, E., Oliveira, F., & Cássio, I. (2014). Treatment of diabetic foot complications with hyperbaric oxygen therapy: a retrospective experience. *Foot and Ankle Surgery, 20*(2), 140–143.
57. Thackham, J. A., McElwain, D. L. S., & Long, R. J. (2008). The use of hyperbaric oxygen therapy to treat chronic wounds: A review. *Wound Repair and Regeneration, 16*(3), 321–330.
58. Fedorko, L., Bowen, J. M., Jones, W., Oreopoulos, G., Goeree, R., Hopkins, R. B., et al. (2016). Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: A prospective, double-blind, randomized controlled clinical trial. *Diabetes Care, 39*(3), 392–399.
59. Santema, K. T. B., Stoekenbroek, R. M., Koelemay, M. J. W., Reekers, J. A., van Dortmont, L. M. C., Oomen, A., et al. (2018). Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: Results of the DAMO-2CLES multicenter randomized clinical trial. *Diabetes Care, 41*(1), 112–119.
60. Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized, controlled study of hyperbaric oxygen therapy: Effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. *Ostomy/Wound Management, 59*(3), 18–24.
61. Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care, 33*(5), 998–1003.
62. Kessler, L., Bilbault, P., Ortéga, F., Grasso, C., Passemard, R., Stephan, D., et al. (2003). Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: A prospective randomized study. *Diabetes Care, 26*(8), 2378–2382.
63. Khandelwal, S., Chaudhary, P., Poddar, D. D., Saxena, N., Singh, R. A. K., & Biswal, U. C. (2013). Comparative Study of different treatment options of grade III and IV diabetic foot ulcers to reduce the incidence of amputations. *Clinics and Practice, 3*(1), e9.
64. Kranke, P., Bennett, M. H., Martyn-St James, M., Schnabel, A., Debus, S. E., & Weibel, S. (2015). Hyperbaric oxygen therapy for chronic wounds. *The Cochrane Database of Systematic Reviews, 6*, CD004123.
65. Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., et al. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: A double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery, 25*(6), 513–518.
66. Sharma, R., Sharma, S. K., Mudgal, S. K., Jelly, P., & Thakur, K. (2021). Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of controlled clinical trials. *Scientific Reports, 11*(1), 2189.
67. Zhang, Z., Zhang, W., Xu, Y., & Liu, D. (2022). Efficacy of hyperbaric oxygen therapy for diabetic foot ulcers: An updated

systematic review and meta-analysis. *Asian Journal of Surgery, 45*(1), 68–78.
68. Jahan, F., Nanji, K., Qidwai, W., & Qasim, R. (2012). Fibromyalgia syndrome: An overview of pathophysiology, diagnosis and management. *Oman Medical Journal, 27*(3), 192–195.
69. Fibromyalgia | Arthritis | CDC. Retrieved September 11, 2022, https://www.cdc.gov/arthritis/basics/fibromyalgia.htm.
70. Efrati, S., Golan, H., Bechor, Y., Faran, Y., Daphna-Tekoah, S., Sekler, G., et al. (2015). Hyperbaric oxygen therapy can diminish fibromyalgia syndrome – prospective clinical trial. *PLoS ONE, 10*(5), e0127012.
71. Gottfried, I., Schottlender, N., & Ashery, U. (2021). Hyperbaric oxygen treatment—From mechanisms to cognitive improvement. *Biomolecules, 11*(10), 1520.
72. Palzur, E., Zaaroor, M., Vlodavsky, E., Milman, F., & Soustiel, J. F. (2008). Neuroprotective effect of hyperbaric oxygen therapy in brain injury is mediated by preservation of mitochondrial membrane properties. *Brain Research, 1221*, 126–133.
73. Zhao, B.-S., Meng, L.-X., Ding, Y.-Y., & Cao, Y.-Y. (2014). Hyperbaric oxygen treatment produces an antinociceptive response phase and inhibits astrocyte activation and inflammatory response in a rat model of neuropathic pain. *Journal of Molecular Neuroscience: MN, 53*(2), 251–261.
74. Inamoto, Y., Okuno, F., Saito, K., Tanaka, Y., Watanabe, K., Morimoto, I., et al. (1991). Effect of hyperbaric oxygenation on macrophage function in mice. *Biochemical and Biophysical Research Communications, 179*(2), 886–891.
75. Li, F., Fang, L., Huang, S., Yang, Z., Nandi, J., Thomas, S., et al. (2011). Hyperbaric oxygenation therapy alleviates chronic constrictive injury-induced neuropathic pain and reduces tumor necrosis factor-alpha production. *Anesthesia and Analgesia, 113*(3), 626–633.
76. Winfield-Vargas, J.-G., Ramírez-Nava, J. C., Rodríguez-Ayala, V., Cruz-Sánchez, J. A., Solís-Chagoyán, H., Aquino-Gálvez, A., et al. (2021). Hyperbaric oxygen therapy ameliorates pain in overweight or obese patients diagnosed with fibromyalgia. *World Academy of Sciences Journal, 3*(4), 1–6.
77. Atzeni, F., Casale, R., Alciati, A., Masala, I. F., Batticciotto, A., Talotta, R., et al. (2019). Hyperbaric oxygen treatment of fibromyalgia: A prospective observational clinical study. *Clinical and Experimental Rheumatology, 37 Suppl 116*(1), 63–69.
78. Camporesi, E. M. (2014). Side effects of hyperbaric oxygen therapy. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 41*(3), 253–257.
79. Heyboer, M., Sharma, D., Santiago, W., & McCulloch, N. (2017). Hyperbaric oxygen therapy: Side effects defined and quantified. *Advances in Wound Care, 6*(6), 210–224.
80. Heyboer, M., Wojcik, S. M., Grant, W. D., Chambers, P., Jennings, S., & Adcock, P. (2014). Middle ear barotrauma in hyperbaric oxygen therapy. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 41*(5), 393–397.
81. Vahidova, D., Sen, P., Papesch, M., Zein-Sanchez, M. P., & Mueller, P. H. J. (2006). Does the slow compression technique of hyperbaric oxygen therapy decrease the incidence of middle-ear barotrauma? *The Journal of Laryngology and Otology, 120*(6), 446–449.
82. Physiology and Medicine of Hyperbaric Oxygen Therapy - 1st Edition. Retrieved November 5, 2022, https://www.elsevier.com/books/physiology-and-medicine-of-hyperbaric-oxygen-therapy/9781416034063.
83. Heyboer, Rd. M., Wojcik, S. M., Smith, G., & Santiago, W. (2017). Effect of hyperbaric oxygen therapy on blood pressure in patients undergoing treatment. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 44*(2), 93–99.
84. Al-Waili, N. S., Butler, G. J., Beale, J., Abdullah, M. S., Finkelstein, M., Merrow, M., et al. (2006). Influences of hyperbaric oxygen on blood pressure, heart rate and blood glucose levels in patients with diabetes mellitus and hypertension. *Archives of Medical Research, 37*(8), 991–997.
85. Abel, F. L., McNamee, J. E., Cone, D. L., Clarke, D., & Tao, J. (2000). Effects of hyperbaric oxygen on ventricular performance, pulmonary blood volume, and systemic and pulmonary vascular resistance. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 27*(2), 67–73.
86. Weaver, L. K., & Churchill, S. (2001). Pulmonary edema associated with hyperbaric oxygen therapy. *Chest, 120*(4), 1407–1409.
87. Whalen, R. E., Saltzman, H. A., Holloway, D. H., Mcintosh, H. D., Sieker, H. O., & Brown, I. W. (1965). Cardiovascular and blood gas responses to hyperbaric oxygenation. *The American Journal of Cardiology, 15*, 638–646.
88. Stevens, S. L., Narr, A. J., Claus, P. L., Millman, M. P., Steinkraus, L. W., Shields, R. C., et al. (2015). The incidence of hypoglycemia during HBO2 therapy: A retrospective review. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 42*(3), 191–196.
89. Zadik, Y., & Drucker, S. (2011). Diving dentistry: A review of the dental implications of scuba diving. *Australian Dental Journal, 56*(3), 265–271.
90. Cakmak, T., Battal, B., Kara, K., Metin, S., Demirbas, S., Yildiz, S., et al. (2015). A case of tension pneumothorax during hyperbaric oxygen therapy in an earthquake survivor with crush injury complicated by ARDS (adult respiratory distress syndrome). *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 42*(1), 9–13.
91. Rivalland, G., Mitchell, S. J., & van Schalkwyk, J. M. (2010). Pulmonary barotrauma and cerebral arterial gas embolism during hyperbaric oxygen therapy. *Aviation Space, and Environmental Medicine, 81*(9), 888–890.
92. Wolf, H. K., Moon, R. E., Mitchell, P. R., & Burger, P. C. (1990). Barotrauma and air embolism in hyperbaric oxygen therapy. *The American Journal of Forensic Medicine and Pathology, 11*(2), 149–153.
93. Heyboer, M., Jennings, S., Grant, W. D., Ojevwe, C., Byrne, J., & Wojcik, S. M. (2014). Seizure incidence by treatment pressure in patients undergoing hyperbaric oxygen therapy. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc, 41*(5), 379–385.
94. Sanders, R. W., Katz, K. D., Suyama, J., Akhtar, J., O'Toole, K. S., Corll, D., et al. (2012). Seizure during hyperbaric oxygen therapy for carbon monoxide toxicity: A case series and five-year experience. *The Journal of Emergency Medicine, 42*(4), e69-72.
95. Yildiz, S., Aktas, S., Cimsit, M., Ay, H., & Toğrol, E. (2004). Seizure incidence in 80,000 patient treatments with hyperbaric oxygen. *Aviation, Space, and Environmental Medicine, 75*(11), 992–994.
96. Banham, N. D. (2011). Oxygen toxicity seizures: 20 years' experience from a single hyperbaric unit. *Diving and Hyperbaric Medicine, 41*(4), 202–210.
97. Palmquist, B. M., Philipson, B., & Barr, P. O. (1984). Nuclear cataract and myopia during hyperbaric oxygen therapy. *The British Journal of Ophthalmology, 68*(2), 113–117.
98. Teoh, S. L., Boo, N. Y., Ong, L. C., Nyein, M. K., Lye, M. S., & Au, M. K. (1995). Duration of oxygen therapy and exchange transfusion as risk factors associated with retinopathy of

prematurity in very low birthweight infants. *Eye (London, England), 9*(Pt 6), 733–737.
99. Ashton, N., Ward, B., & Serpell, G. (1953). Role of oxygen in the genesis of retrolental fibroplasia. *The British Journal of Ophthalmology, 37*(9), 513–520.

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