Biomedicine & Pharmacotherapy 109 (2019) 629–638

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Hyperbaric oxygen and aerobic exercise in the long-term treatment of fibromyalgia: A narrative review

Kholoud M. El-Shewy[a], Ahmad Kunbaz[b], Mohamed M. Gad[a,c], Muneer J. Al-Husseini[a], Anas M. Saad[a,*], Yasser M. Sammour[c], Mohamed M. Abdel-Daim[d,e,**]

[a] Faculty of Medicine, Ain Shams University, Cairo, Egypt
[b] Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey
[c] Cleveland Clinic Foundation, Cleveland, OH, USA
[d] Laboratory of Veterinary Pharmacology, Department of Veterinary Medicine, Faculty of Agriculture, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Fuchu, Tokyo, 183-8509, Japan
[e] Pharmacology Department, Suez Canal University, Ismailia, Egypt

ARTICLE INFO

Keywords:
Fibromyalgia
Hyperbaric oxygen therapy
Exercise
Multidisciplinary treatment

ABSTRACT

Chronic pain is one of the most common clinical presentations in the primary care settings. In the US, Fibromyalgia (FM) affects about 1–3% of adults and commonly occurs in adults between the ages of 40–50 years. FM causes widespread muscular pain and tenderness with hyperalgesia and allodynia and may be associated with other somatic complaints.

Hyperbaric oxygen therapy (HBOT) has been utilized and has recently shown promising effects in the management of FM and other chronic pain disorders. In HBOT, the intermittent breathing of 100% oxygen in a pressurized chamber where the pressure is higher than 1 atmosphere absolute (ATA) has been utilized. HBOT exhibits a significant anti-inflammatory effect through reducing production of glial cells and inflammatory mediators which results in pain alleviation in different chronic pain conditions. HBOT can also influence neuroplasticity and affects the mitochondrial mechanisms resulting in functional brain changes. In addition to that, HBOT stimulates nitric oxide (NO) synthesis which helps in alleviating hyperalgesia and NO-dependent release of endogenous opioids which seemed to be the primary HBOT mechanism of antinociception.

Moreover, aerobic exercise and meditative movement therapies (MMT) have gained attention for their role in pain alleviation through different anti-inflammatory and antioxidant mechanisms.

In this review, we aim to elucidate the different mechanisms of HBOT and aerobic exercise in attenuating pain as adjuvant therapy in the multidisciplinary treatment strategy of chronic pain, and more particularly fibromyalgia.

1. Introduction

Chronic pain is one of the most common complains in clinical practice [1]. Pain complaints are defined as chronic when the complains continue for more than three months which is the time that the normal tissue needs to heal [2]. A broad spectrum of conditions including neuropathic pain, complex regional pain syndrome, migraine, and fibromyalgia have been implicated as causes of chronic pain condition [3].

Fibromyalgia (FM) is a chronic musculoskeletal disease that affects up to 1–3% of adults in the United States. It commonly occurs in adults between the ages of 40–50 years [4]. FM causes widespread muscular pain and soft tissue tenderness with hyperalgesia and allodynia. Allodynia is defined as an increased nervous system responsiveness to non-painful stimuli which can occur three different forms: a tactile form, which is caused by touch, a mechanical form, which is caused by

Abbreviations: ATA, atmosphere absolute; CCI, chronic constriction injury; CREB, cAMP response element-binding protein; CRP, C- reactive protein; CSF, cerebrospinal fluid; eNOS, endothelial nitrate oxide synthase; FM, fibromyalgia; GR, glucocorticoid receptor; HBOT, hyperbaric oxygen therapy; iNOS, inducible nitrate oxidase synthase; MMT, meditative movement therapies; NMDA, N-methyl-D-aspartic acid; NO, nitric oxide; ROS, reactive oxygen species; TCA, tricarboxylic acid; TNF, tumor necrosis factor

* Corresponding author at: Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Lofty Elsayed Street, Cairo, 11566, Egypt.
** Corresponding author at: Pharmacology Department, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, 41522, Egypt.
E-mail addresses: Anassaad256@gmail.com, anassaad@med.asu.edu.eg (A.M. Saad), abdeldaim.m@vet.suez.edu.eg (M.M. Abdel-Daim).

https://doi.org/10.1016/j.biopha.2018.10.157
Received 6 August 2018; Received in revised form 13 October 2018; Accepted 25 October 2018

movement over the skin and, and a thermal form, which is caused by heat or cold which would not normally cause damage to your tissues [5]. FM is usually associated with other somatic complaints, sleep disturbances, anxiety, cognitive dysfunction, and depressive symptoms [6].

The symptoms significantly impact the quality of life, employment, as well as cause an economic burden on the affected individuals [5,7]. Therefore, a better understanding of the underlying disease process and possible treatment mechanisms can help these patients with a multidisciplinary treatment approach that includes medications, aerobic exercises, meditative movement therapies, as well as cognitive behavioral therapies [1,4,8,9].

Recently, Hyperbaric oxygen therapy (HBOT) has shown beneficial effects in managing chronic pain conditions such as cluster headaches [10,11]. In addition to that, HBOT has been found helpful in patients with complex regional pain syndrome, idiopathic trigeminal neuralgia, fibromyalgia and migraines [12–15]. It is done by intermittently breathing 100% oxygen in a pressure chamber where the pressure is higher than 1 atmosphere absolute (ATA). It is usually administered at 1 to 3 ATA and lasts from 30 to 120 min 15. The anti-inflammatory effects exhibited may lead to glial function changes and rectification of the abnormal FM-associated brain activity [16–18].

In this review, we aim to illustrate the mechanisms of HBOT and aerobic exercise, and the consequent beneficial roles in attenuating pain as adjunct therapies in the treatment strategy of chronic pain, and specifically fibromyalgia.

2. Hyperbaric oxygen treatment for fibromyalgia, the role of action and possible mechanisms

FM can occur after long-lasting mental or physical stress, viral, bacterial or parasitic infection [19,20]. Evidence showed that reactive oxygen species (ROS) and oxidative stress play a significant role in mitochondrial dysfunction in FM patients [21]. These patients have degenerative muscular changes, abnormal oxygen pressure, and lower blood flow in the muscles from local hypoxia [14,22–24]. Approximately, mitochondria use up to 80% of inhaled oxygen to produce ATP [25,26] with local ischemia causing higher levels of free radicals that induce apoptosis, reduce ATP synthesis and increase lactate concentrations in muscle cells which results in muscle weakness and pain [27,28].

HBOT causes hyperoxia that amplifies the tissue-cellular diffusion gradient of oxygen, which as a result raises plasma dissolved oxygen to a level that exceeds the physiological needs of many tissues at rest [29]. HBOT also accelerates wound healing by promoting epithelialization and oxygen-dependent collagen matrix formations needed for angiogenesis. Furthermore, HBOT prevents leukocyte adhesion that contributes to the release of free radicals and proteases, thus protecting cells from pathologic vasoconstriction and cellular damage during reperfusion. HBOT also enhances neutrophil oxygen-dependent microbial killing, reduces edema and inhibits lipid peroxidation in hypoxic tissues [29–31]

It is well accepted that HBOT results in increased reactive oxygen species (ROS) [32–35]. Some studies suggested a correlation between ROS levels and higher HBOT exposure time [33,34]. However, some studies have indicated that HBOT could reduce oxidative stress when used in pathologic conditions by decreasing the activation of caspase 3 and 9 [35,36]. Furthermore, it has been shown that some ROS produced by HBOT such as superoxide could contribute to the HBOT's beneficial properties [31]. These controversial findings manifest the need for a clear understanding of the therapeutic mechanisms of HBOT.

One of the potential mechanisms regarding HBOT is related to its ability to preserve mitochondrial activities as one study showed that HBOT is associated with increased expression of the anti-apoptotic protein (Bcl-2) at the injury site and thus inhibiting apoptosis [37]. Palzur et al. studied HBOT ability to maintain mitochondrial function and decrease the activation of apoptosis in models of traumatic brain injury. They found that mitochondrial trans-membrane defects were restored with HBOT compared to the control group, and assumed that this was due to the effects of HBOT in increasing Bcl-2 expression and intracellular oxygen availability [35]. Another mitochondrial mechanism regarding mitochondrial respiratory chain dysfunction at the levels of complex IV, which induces motor neuron disease in Wobbler mouse; a mouse model of human motor neuron disease [38]. Dave et al. investigated the possible effect of HBOT on mitochondrial integrity in the Wobbler mice, monitored the progression of the disease in both groups HBOT and controls of the Wobbler mice, and noticed a significant delay in the disease onset within HBOT group, suggesting the role of HBOT in protecting motor cortex and spinal cord mitochondria from complex IV dysfunction in Wobbler mouse [39,40].

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by a lesion or disease of the somatosensory system; and due to the lack of evidence regarding any structural abnormalities in FM patients, there has been an ongoing debate about FM possible classification as neuropathic pain [41]. It is plausible that FM results mainly from a functional abnormality of pain processing pathways causing hyperalgesia (hyperexcitability of the CNS neurons) as the patients show increased sensitivity to a wide range of stimuli [42,43]. Another theory was hypothesized by Sörensen et al. who argued that the up-regulation of central nocicoreceptors following inflammation may cause chronic hyperalgesia in FM patients [44]. In addition to that, Inflammation and immune mechanisms may play an important role in the development of neuropathic pain and hyperalgesia [45,46]. Chronic hyperalgesia and neuropathic pain might be the result of inflammatory mediators, including cytokines such as, interleukins 1 and 6 (IL-1, IL6) and tumor necrosis factor (TNF), which activate/accelerate sensitization of afferent fibers without actual sensory damage [47–49]. When central sensitization occurs, only minimal stimulus with nociceptive input is enough to maintain the sensitized state and clinical pain [50]. To investigate neuropathic pain, researchers usually use a model of chronic constriction injury (CCI) of the sciatic nerve [51]. The CCI model was shown to have higher astrocyte activation supplemented by a higher expression of nerve injury-induced molecules such as c-Fos in the spinal dorsal horn [52]. Similarly, Thompson et al. proved the efficacy of HBOT to achieve lower pain behavior and mechanical hypersensitivity in CCI rats [53]. Gu et al. looked into HBOT potential role in neural protection; repetitive HBOT led to a significant, transient inhibition of thermal hyperalgesia, while long-term HBOT induced long-term inhibition of both thermal and mechanical hypersensitivity [14]. Furthermore, Zhao et al. investigated the possible association between HBOT and antinociceptive response in CCI animal model and found that a single HBOT session induced a short-term antinociceptive response and inhibited mechanical and thermal hyperalgesia, while multiple HBOT sessions induced a long-term response, inhibit astrocytes activation and aggravated neuropathic pain [54]. In addition to that, a study by Inamoto et al. indicated the immunosuppressive role of HBOT, significantly reduced both IL-1 and prostaglandin E2 production [55]. In contrast to that, Li et al. found that HBOT alleviated neuropathic pain by inhibiting TNF-α production, but not IL-1β [56], similarly to thalidomide administration in the CCI model [57]. These differences may be explained due to the independent mechanisms of TNF-α and IL-1 in inducing neuropathic pain in the CCI model [58,59].

Nitric oxide (NO) has an important role in the vasoconstriction response to hypoxia and is considered a potent anti-inflammatory molecule through endothelial nitrate oxide synthase (eNOS) activation in the brain [60,61]. Pain sensitivity in FM patients increased significantly with NO synthesis by enhancing positive modulation of N-methyl-D-aspartic acid (NMDA) receptors and increased levels of excitatory amino acids (e.g. glutamate) within the cerebrospinal fluid (CSF) [62]. NMDA receptors along with downstream signaling molecules have a well-documented role in neural plasticity and neuropathic pain [63]. In

addition, low levels of NO facilitated cAMP-dependent PGE2 led to hyperalgesia, whereas higher levels of NO produced a cGMP-dependent hyperalgesia in the primary afferents [64]. Another controversial study by Sackner et al. concluded that 'whole body periodic acceleration', which is a passive exercise technology that leads to NO release from eNOS through increased pulsatile shear stress, alleviates pain and causes NO release into the blood circulation of FM patients [65]. Furthermore, it might also play a role in the central mechanisms of analgesia and nociception as it increases opioid analgesia in patients with chronic pain [66]. Ohagmi and collogues investigated the antinociceptive HBOT mechanism dependence on neuronal NO and found that the short-term antinociceptive result of HBOT was completely abolished following selective inhibition of NO secretion. They concluded that HBOT stimulation of NO synthesis is critical for its mechanism in alleviating hyperalgesia [67]. A subsequent study by Zelinski et al. found that HBOT led to NO-dependent release of endogenous opioids by activation κ and μ opioid receptors in the spinal cord, which seemed to be the primary HBOT mechanism of antinociception [68,69]. Furthermore, Han et al. investigated whether HBOT analgesia mechanism could affect NO expression in CCI model, they found higher number of inducible nitrate oxidase synthase (iNOS) neurons, which has a regulatory consequence on neuropathic pain, within the spinal cord of both pre-HBOT and post-HBOT groups, but no significant increase was found regarding eNOS [70,71]. This provides a possible explanation for the assumption that NO is ubiquitous in the nervous tissue and can exert both excitatory and inhibitory effects, based on its modulation of different neurotransmitter systems [72,73].

Beside animal and lab studies, there has been new clinical evidence supporting the effectiveness of HBOT as a treatment for FM. Yildiz et al. started a randomized controlled study to investigate whether HBOT has a positive role in managing FM patients [12]. They randomly divided patients either to receive HBOT or normal air, and they then examined patients before and after the first and fifteenth sessions of treatment. They found statistically significant improvement in the HBOT group for pre-defined clinical indicators after the first and fifteenth session. There were significant differences between the HBOT group and the controls as well, suggesting an important role of HBOT in relieving FM pain [12]. In addition to that, following the induction of inflammatory pain by carrageenan (Sigma) subcutaneous injection in rats, HBOT showed evidence to decrease mechanical hyperalgesia and inflammation. However, it did not consistently improve anti-inflammatory activity following diclofenac injections [74,75].

Despite some safety concerns, HBOT is a potential treatment approach for FM patients through its efficacy to increase oxygen delivery, inhibit pain and produce an anti-inflammatory response and the mechanisms of this role are illustrated in Fig. 1.

3. Role of aerobic exercise in fibromyalgia treatment

Over the last two decades, the effects of aerobic exercise have been studied as a part of the multimodal treatment strategies for conditions associated with chronic pain [6]. Besides the anti-inflammatory role of aerobic exercise, it has been found to exert a beneficial effect on the mitochondrial pathways and biogenesis, as well as the psychiatric element of FM symptoms [6]. These effects are illustrated in Fig. 2. Aerobic exercise consists of activities like jogging, walking, cycling, and dancing as well as aquatic exercises. Doing aerobic exercise is thought to help control blood sugar, lower blood pressure and improve the circulation [76,77]. A well-established effect of aerobic exercise is mitochondrial biogenesis which includes increased number and volume of muscle mitochondria, along with changes in the organelle composition [78]. Such mitochondrial changes cause a relatively small increase in maximal oxygen uptake (VO2 max) which reflects the whole body aerobic condition. This effect occurs as a result of an increase in proteins that are involved in mitochondrial ATP production, and an improvement of the tricarboxylic acid (TCA) cycle, fatty acids metabolism, glucose transport, glycolytic metabolism, antioxidant effect, oxygen delivery, and oxygen extraction from skeletal muscle [79–81].

FM pathogenesis is hypothesized to include muscle abnormalities such as reduction of type II muscle fibers, low levels of adenosine triphosphate, and damage of nerve fibers [82]. These abnormalities result in abnormal muscle metabolism and clinically cause weakness, fatigue, and muscle pain [83]. Aerobic exercise increases the activity of metabolic enzymes and mitochondrial density enhancing respiratory control sensitivity. Therefore, lower concentrations of [ADP] are utilized when using the same amount of oxygen per gram of muscle, thus a lower oxidative phosphorylation rate per mitochondrion [84].

In addition to that, one of the popular hypotheses regarding FM etiology is the inflammatory and neuroendocrine theory supported by the findings of high circulating concentrations of IL-8, IFN gamma, and C- reactive protein (CRP) along with cortisol in FM patients. Exercise programs could exert an anti-inflammatory effect and achieve a significant decrease in IL-8, IFN gamma, CRP and circulating concentrations of cortisol [85].

Also, FM has been associated with mood and psychiatric disorders that may result from hypothalamic-pituitary axis abnormalities, and interactions between biological, psychological, and behavioral mechanisms [82,83]. Aerobic exercise stimulates the hypothalamus causing increased levels of neurotransmitters such as endorphins, and this effect helps to decrease pain sensation and to improve mood state and sleep [86,87]. Doing physical exercise enhances sleep and reciprocally having a higher quality of sleep improves the physical activity of patients with chronic pain conditions [88].

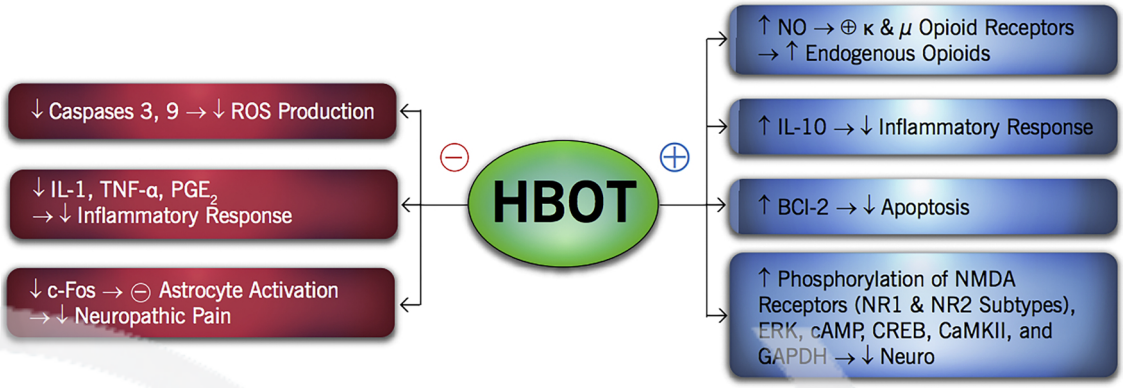
In 2008, a systematic review involving 2276 subjects across 34 studies assessed the efficacy of aerobic exercise for fibromyalgia and reported improvement in the following domains: pain, global well-being, and physical function [89]. In 2017, the update of that systematic review provided moderate-quality evidence about the effectiveness of aerobic exercise to improve the health-related quality of life, and low-quality evidence about the role of aerobic exercise in decreasing pain and improving physical function [90]. This is consistent with the 2017 revised European League Against Rheumatism (EULAR) report [91].

Meditative movement therapies (MMT), including Qigong, Tai Chi or Yoga, represent one of the non-pharmacological therapies that have been engaged in the multidisciplinary treatment approach to chronic pain conditions [92,93]. Qigong and Tai Chi are traditional Chinese exercises that involve body movement and breathe training to improve health. Yoga is an ancient Indian, mind-body approach with a focus on meditation, breathing, and activity or postures [93].

A yoga program that involves breathing and meditative techniques, S Kriya and its associated practices (SK&P), was found to increase glutathione S-transferase mRNA expression along with the levels of glutathione peroxidase, superoxide dismutase activities and glutathione [94]. Also, this program increased the antioxidant genes Cu-Zn and Mn-SOD, and catalase [95]. These findings may elucidate the antioxidant role of yoga practice through its impact on relevant genes expression.

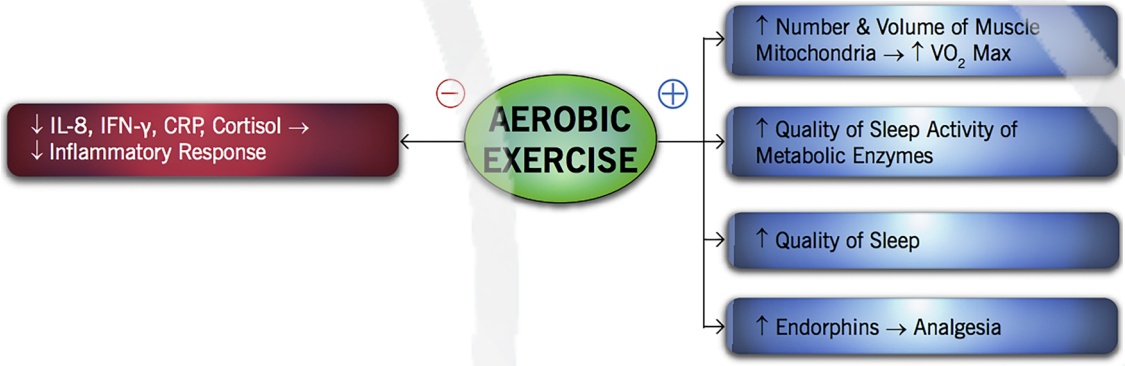
MMT exert an anti-inflammatory effect through decreasing the sympathetic activity and increasing the parasympathetic activity [96,97]. Morgan et al. have found that MMT for eight to twelve weeks caused a reduction of C-reactive protein (CRP) concentrations [98]. Vijayaraghava et al. showed that yoga could reduce the inflammatory response by lowering TNF-α and IL-6 levels [99].

It has also been suggested that tai chi and yoga reduce cAMP response element-binding protein (CREB) family transcription factors activity. This altered response will consequently lead to a reduction in the sympathetic nervous system signaling through β-adrenergic receptors, as well as a reduction in the nuclear factor NF-kB activity [100,101]. In addition to that, Tai Chi, and yoga have been shown to modulate the glucocorticoid receptor sensitivity and increase the anti-inflammatory glucocorticoid receptor (GR) signaling [101,102]. All these mechanisms are illustrated in Fig. 3.



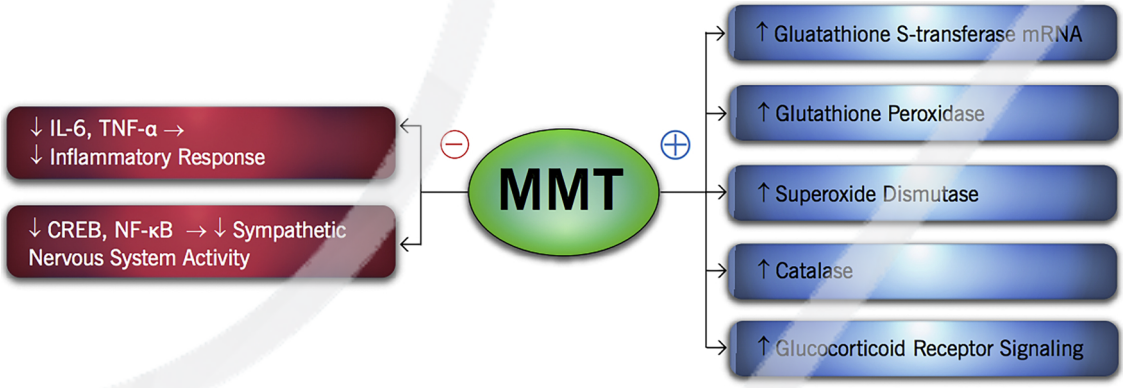
Abbreviations:
HBOT: Hyperbaric Oxygen Therapy | ROS: Reactive Oxygen Species | IL-1: Interleukin-1 | TNF-α: Tumor Necrosis Factor alpha
PGE2: Prostaglandin E2 | NO: Nitric Oxide | IL-10: Interleukin-10 | BCl-2: B-cell lymphoma 2 | NMDA: N-Methyl-D-Aspartate
NR1: NMDA Receptor 1 | NR2: NMDA Receptor 2 | ERK: Extracellular signal-Regulated Kinases
cAMP: Cyclic Adenosine MonoPhosphate | CREB: cAMP Response Element-Binding protein
CAMKII: Ca2+/calModulin-dependent protein Kinase II | GAPDH: GlycerAldehyde 3-Phosphate DeHydrogenase

Fig. 1. Effects of using hyperbaric oxygen therapy in the management of fibromyalgia.



Abbreviations:
IL-8: Interleukin-8 | IFN-γ: Interferon gamma | CRP: C-Reactive Protein

Fig. 2. Effects of using aerobic exercise in the management of fibromyalgia.



Abbreviations:
MMT: Meditative Movement Therapies | IL-6: Interleukin-6 | TNF-α: Tumor Necrosis Factor alpha
CREB: cAMP Response Element-Binding protein | NF-κB: Nuclear Factor Kappa-light-chain-enhancer of activated B cells

Fig. 3. Effects of using meditate movement therapies in the management of fibromyalgia.

Table 1
Clinical uses of hyperbaric oxygen therapy in fibromyalgia.

Reference	Title	Dose of oxygen	Main method	Outcomes	Main results
Yildiz 2004	A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy	HBOT at 2.4 ATA for 90 min a day, 5 days each week for 3 weeks (15 sessions). Control group: breathed air at 1 ATA for the same period.	Randomized control study included patients with FMS who had persistent symptoms despite medical or physical therapy were divided randomly into 2 groups: 26 patients in the HBOT group and 24 patients in the control group. Patients were examined before and after the first and fifteenth therapy sessions. At each examination, the number of tender points, visual analog scale (VAS) and the pressure pain threshold were measured.	After the first and fifteenth therapy sessions, there was a significant reduction in tender points and VAS scores and a significant increase in pain threshold of the HBOT group. There was also a significant difference between the HBO and control groups for all parameters except the VAS scores after the first session.	HBOT successfully break pain-hypoxia vicious cycle since it decreased the tender points and VAS pain scores by increasing the pain threshold.
Efrati 2015	Hyperbaric oxygen therapy can diminish fibromyalgia syndrome - Prospective clinical trial	HBOT at 2.0 ATA for 90 min a day, 5 days each week for 8 weeks (40 sessions).	A prospective active control, clinical trial on 60 female FMS patients who were diagnosed at least 2 years prior to the inclusion. Randomly divided into 2 groups: treated group and crossover group. Patients in the treated group were evaluated twice – at baseline and after 2 months of HBOT. Patients in the crossover group were evaluated three times: baseline, after 2 months control period (no treatment), and after subsequent 2 months of HBOT. Measurements: Tender point count, pain threshold, FIQ, SCL-90, SF-36 scores and brain activity according to SPECT imaging.	- The FIQ, SCL-90 and SF-36 scores significantly improved following HBOT in the treated and in the crossover group after HBOT - Analysis of SPECT Imaging following HBOT revealed rectification of the abnormal brain activity: decrease of the hyperactivity mainly in the posterior region and elevation of the reduced activity mainly in frontal areas.	- HBOT led to a significant decrease in the intake of pain medications by the patients - HBOT in both groups led to significant amelioration of all FMS symptoms, with significant improvement in life quality.
Akarsu 2013	The efficacy of hyperbaric oxygen therapy in the management of chronic fatigue syndrome.	HBOT at 2.4 ATA for 90 min a day, 5 days each week for 3 weeks (15 sessions).	15 patients with CFS. The assessment was made before the treatment and after the completion of 15 sessions. Measurements: VAS, FSS, FQLS.	After HBOT; VAS, FSS, and FQLS scores improved significantly with no complications.	HBOT decreased the severity of symptoms and increased the life quality of CFS patients.
Gu 2012	Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients	HBOT at 2 ATA for 70 min a day with 5 min intervals after 35 min period, for 10 days	Clinical trials on patients with idiopathic trigeminal neuralgia. These patients were taking sufficient doses of CBZ for keeping patient pain at a minimum. They were divided into 2 groups, HBOT (n = 20) and HBOT sham control group (n = 22) Assessment was made at day 1,30,60,90,120,150 and 180 after HBOT. Measurements: VAS and mean dose of CBZ	VAS evaluation indicated that HBOT reduced pain in most patients (60–75%) with no side effects. HBOT group showed a decreased doses of carbamazepine required for keeping patient pain at a minimum	HBOT showed to decrease the severity of symptoms.

Abbreviations: ATA = atmospheres absolute, CBZ = carbamazepine, CFS = chronic fatigue syndrome, FIQ = Fibromyalgia Impact Questionnaire, FSS = fatigue severity scale, FMS = Fibromyalgia Syndrome, FQLS = fatigue quality of life score, HBOT= Hyperbaric oxygen therapy, SCL-90= symptom questionnaire, SF-36= Quality of life questionnaire, SPECT = single photon emission computed tomography, VAS = visual analogue scale.

Table 2
Clinical uses of aerobic exercise in fibromyalgia.

Reference	Model used	Exercise details	Main methods	Main results
Henriksson 1977	13 volunteered, healthy men (age 20–23 years). A muscle biopsy (2040 mg) was taken from the lateral vastus of the quadriceps femoris muscle.	The participants were divided into 2 groups. group (A) was formed of eight subjects who were followed during a 10-week period of training followed by at least 6 weeks of normal physical activity at the pre-training level. In group A the subjects trained by pedaling a bicycle ergometer 20 min a day an average of 4 times a week. Group (B) was formed of 5 subjects who were followed during an 8 week training period, with weekly tests within the first 3 weeks. These subjects trained on the bicycle 40 min a day 4 times per week.	- A muscle biopsy (2040 mg) was taken from the lateral vastus of the quadriceps femoris muscle by the needle biopsy technique. The samples were immediately frozen in liquid nitrogen and stored at 80 °C and the enzyme analyses were performed within 2-3 months. -Vo2 max determination was performed on a bicycle ergometer at 60 rpm. Expired air was collected, subsequently analyzed, and verified with the Scholander micro-technique.	- There was a gradual increase in both Vo, max and muscle oxidative enzyme activities after 3 weeks of training. - After 8 weeks of training, Vo2 max was 19%, vastus lateralis SDH 32%, and cytochrome oxidase activity 35% above the pre-training levels respectively. −6 weeks post-training Vo2 max was still 16% above the pre-training level while vastus lateralis SDH and Cytochrome oxidase activity returned to the pre-training level indicating a high turnover rate of enzymes in the TCA cycle as well as the respiratory chain.
Egan 2011	Eight healthy, sedentary, males volunteered to participate in the study. Skeletal muscle specimens were taken from the vastus lateralis muscle.	Participants were cycling for 60 min per session at the target exercise intensity of 80% VO 2peak on 14 consecutive days. Each training session was supervised and performed in the Human Performance Laboratory at Dublin City University	- A resting muscle biopsy (baseline, day 0), the 7th (day 7) and14th (day 14) Skeletal muscle specimens (approximately 200 mg of tissue) were taken from the vastus lateralis muscle under local anesthesia using the percutaneous muscle biopsy technique. -Mitochondria-enriched protein fractions from skeletal muscle biopsies were subjected to 2-D DIGE analysis.	-Thirty-one protein spots, including subunits of the electron transport chain, enzymes of the tricarboxylic acid cycle were differentially expressed after either 7 or 14 days of training. - Several proteins demonstrated a time course-dependent induction during training.
Talanian 2010	Ten healthy females volunteered to participate in the study.	Subjects performed a 60-min cycling trial at 65% pretraining Vo2 max prior to (PRE) and following 2 and 6 weeks of high-intensity interval training (HIIT). -Approximately 48 h following the pretraining muscle biopsies, subjects began training 3 days/week, completing 18 training sessions in 6 weeks. Each session consisted of ten 4-min cycling bouts at 90% Vo2 max separated by 2 min of rest.	- Vo2 max was measured by collecting respiratory gases and analyzed by using a metabolic cart after 2 and 6 weeks of high-intensity interval training (HIIT). - Approximately 48 h following the PRE, 2-wk, and 6-wk 60-min cycling trials a resting biopsy from the vastus lateralis muscle was taken under local anesthesia. - Intact mitochondria containing both intermyofibrillar (IMF) and subsarcolemmal (SS) fractions were obtained to assess carnitine palmitoyltransferase complex (CPT) and citrate synthase (CS) activities	Training significantly increased maximal oxygen uptake at 2 and 6 weeks. Training for 6 weeks increased FAT/CD36 at the whole muscle (10%) and mitochondrial levels (51%), whole muscle plasma membrane fatty acid binding protein (48%) without alterations in sarcolemmal content. sarcolemmal FABPpm increased (23%), whereas mitochondrial FABPpm was unaltered.
Gavin 2007	Six sedentary young (range 19–30 years) and eight sedentary aged (range 56–74 years) volunteered men.	Subjects were enrolled in an 8-week aerobic exercise training program. Heart rate was monitored and was routinely increased during the training program to maintain an exercise heart rate equivalent to 65% of VO2 max. During the first week, subjects trained every day for 1 h per session. During weeks 2–8, subjects exercised 4 days per week for 1 h per session.	-VO2 max was measured on an electronically braked cycle ergometer by open circuit spirometry prior to (Pre) and after the 8- week (8 weeks) exercise training program. - Pre, 1 week and 8 -week muscle biopsies were obtained from the vastus lateralis and the following indexes were measured: capillary contacts (CC), the capillary-to-fiber ratio on an individual-fiber basis (C/F i), and the number of fibers sharing each capillary (sharing factor(SF).	Exercise training increased capillary contacts (CC) and capillary-to-fiber perimeter exchange index (CFPE) of type I and IIA fibers similarly in young and aged. The CC of type IIA and IIB fibers was lower in aged compared with young independent of training status. Exercise-induced interstitial VEGF protein was lower in aged compared with young independent of training status. In untrained, greater exercise-induced interstitial VEGF protein during exercise was associated with greater type I, IIA and IIB CC. Exercise training increased VEGF mRNA similarly in young and aged.
Ortega 2009	14 women (age range 30–60 years) and 13 healthy women (age range 28–55 years) served as the matched-control group.	FM patients were involved in an aquatic fitness program over a period of four months (October-January). The training program consisted of three weekly 60-minute sessions that were carried out in an indoor swimming pool with stretching exercises out of the water (5 min), aerobic warm-up in the water (5 min), passive stretching of the main muscle groups in the water (5 min), aerobic aquatic choreography (25 min), strength exercises involving the main muscle	- Noradrenaline, CRP, IL-1β, IL-2, IFN-γ, TNF-α, IL8, IL-6, and IL-10 and IL-4 concentration was determined by ELISA. serum cortisol was measured by electrochemiluminescence immunoassay using an automatic analyzer (Roche Elecsys). -Aerobic fitness was assessed by the 6-min walk test. - Perceived Health-related quality of life (HRQoL) was assessed by self-administration of the SF-36 Health Survey questionnaire and Fibromyalgia Impact Questionnaire.	-Circulating IL-1β, IL-2, IFNγ,TNFα, IL-8, IL-6, IL-4, IL-10 and CRP and neuroendocrine (Noradrenaline (NA) and cortisol) markers were higher among FM patients than age-matched healthy control women. -After the exercise program, a significant decrease in IL-8, IFNγ, CRP, and cortisol were found, and increased levels of NA.

(*continued on next page*)

Table 2 (*continued*)

Reference	Model used	Exercise details	Main methods	Main results
		groups of the upper limbs (15 min), cool down: breathing and passive stretching exercises (10 min).		
Scheef 2012	Twenty right-handed healthy male athletes	Each subject participated in 2 different treatment conditions, walking (Walk, control condition) and running (Run, endurance exercise as an experimental condition), in a randomized, counterbalanced within-subject design (group I: Walk/Run, N = 10; group II Run/Walk, N = 10). The experimental and control conditions were conducted on separate days, with a mean interval between examination days of 55 ± 49 days.	On each examination day, participants underwent mood ratings, functional magnetic resonance imaging (fMRI) pain experiment, the rating of the perceived pain immediately after the pain fMRI Experiment, 2-hours outdoor Walk or Run and rating of exertion levels after 1 and 2 hours. The time delay between the end of the exercise challenge/ control condition and the pain fMRI experiment was approximately 45 minutes. The duration of the entire procedure per subject and day was approximately 6 hours.	Imaging revealed a reproducible pattern of distributed pain-related activation in the medial and lateral pain systems, and the periaqueductal gray (PAG) as a key region of the descending antinociceptive pathway. At the behavioral level, running as compared with walking decreased affective pain ratings. where pain-induced activation levels were elevated after walking, but decreased or unchanged after running. Running, but not walking, reproducibly elevated b-endorphin levels in plasma.
Vijayaraghava 2015	Two hundred and eighteen subjects participated in the study.	One hundred and nine volunteers (51 males and 58 females) in the age group of 20 to 60 years, who practiced yoga regularly for over five years for a period of one hour daily, performed a bout of moderate exercise and a bout of strenuous exercise as per Standardized Shuttle Walk test protocol. Anthropometrically matched, age-matched and gender-matched subjects, who did not practice yoga (non-yoga group) were chosen as controls (non-yoga, n = 109). The non-yoga group also performed similar exercises.	The blood samples of both the groups were collected before and after the exercises to measure TNF-αand IL-6 before and after the exercise by Sandwich ELISA (Enzyme-Linked Immunosorbent Assay).	Resting plasma TNF-αconcentration was significantly higher in the non-yoga group when compared to yoga accumulation ($p < 0.05$). There was an increase in TNF-αlevels in both the groups in response to strenuous exercise. There was no gender difference in TNF-αand IL-6 levels before and after exercise in yoga and non-yoga groups.
Bower 2014	31 stage 0-II breast cancer survivors who had completed local and/ or adjuvant therapy at least 6 months.	women were randomized to either a 12-week Iyengar yoga intervention (n = 16) or to a health education control condition (n = 15)	blood samples were collected at baseline, post-intervention, and at a 3-month follow-up for genome-wide transcriptional profiling and bioinformatic analyses. Plasma inflammatory markers and salivary cortisol were also assessed.	The yoga group showed reduced activity of the pro-inflammatory transcription factor nuclear factor kappa B (NF-kB), increased activity of the anti-inflammatory glucocorticoid receptor, and reduced activity of cAMP response element-binding protein (CREB) family transcription factors relative to controls (all ps $< .05$). There was also a significant intervention effect on the soluble tumor necrosis factor receptor type II (sTNF-RII), a marker of TNF activity; plasma levels of sTNF-RII remained stable in the yoga group, whereas levels of this marker increased in the health education group ($p = .028$). A similar, non-significant trend was observed for the interleukin 1 receptor antagonist ($p = .16$). No significant changes in C reactive protein (CRP), interleukin 6 (IL-6), or diurnal cortisol measures were observed.
Irwin 2015	123 older adults with insomnia	Each group participated in 120 minutes of class time weekly for 4 months with 7- and 16-month follow-up. cognitive-behavioral therapy for insomnia (CBT-I) was modified to teach behavioral strategies for management of daytime activity levels and enhancement of mood. Tai chi (TCC) a movement meditation emphasized control over arousal mechanisms, which are thought to contribute to insomnia. Sleep seminar provided sleep hygiene information and education about physical, medical, and psychosocial factors in relation to aging and insomnia.	The author measured C-reactive protein (CRP) at baseline and months 4 and 16; toll-like receptor-4 activated monocyte production of proinflammatory cytokines at baseline and months 2, 4, 7, and 16; and genome-wide transcriptional profiling at baseline and month 4.	As compared with the sleep seminar education active control condition, CBT-I reduced levels of CRP (months 4 and 16, ps $< .05$), monocyte production of proinflammatory cytokines (month 2 only, $p < .05$), and proinflammatory gene expression (month 4, $p < .01$). TCC marginally reduced CRP (month 4, $p = .06$) and significantly reduced monocyte production of proinflammatory cytokines (months 2, 4, 7, and 16; all ps $< .05$) and proinflammatory gene expression (month 4, $p < .001$). In CBT-I and TCC, TELiS promoter-based bioinformatics analyses indicated reduced activity of nuclear factor-κB and AP-1.

A randomized controlled trial included 53 patients with FM with the aim of evaluation of the effectiveness of a specific form of yoga in the treatment of FM. The results revealed more significant improvements in pain, fatigue, and mood among the group of patients who practiced yoga [103].

Interestingly, a recent randomized trial involving more than 200 patients with fibromyalgia was conducted to compare the effectiveness of tai chi with aerobic exercise. The results highlighted that tai chi was at least or more effective than aerobic exercise, a standard therapy for this disorder. After 24 weeks, tai chi caused more significant improvements than aerobic exercise regarding symptom impact. Also, a longer duration of tai chi (24 weeks) was more effective than a shorter period (12 weeks) [104].

4. Clinical use of hyperbaric oxygen in the therapy of fibromyalgia

Hyperbaric oxygen therapy has been utilized in medicine since the early 19th century. For many years it has been used mainly as a therapy for decompression thickness for divers. However, it has been gaining more ground as a clinically utilized modality for the treatment of multiple medical conditions [105]. The prospect of using hyperbaric oxygen therapy for fibromyalgia is promising yet controversial due to lack of large-scale clinical trials to support it and due to the contradicting current evidence on whether it should be used as adjuvant therapy or as stand-alone primary therapy [106] (Tables 1 and 2).

Clinical trials are investigating the use of hyperbaric oxygen for fibromyalgia with promising results [18]. A positive correlation between hyperbaric oxygen use and the improvement of the fibromyalgia symptoms has been illustrated with an association between brain changes and the response to therapy [18]. The theory that fibromyalgia is associated with altered brain activity has been further supported with reported with an increased incidence of fibromyalgia in the setting of traumatic brain injury [107]. However, a conflict between the origin of the neurologic dysfunction exists among researchers with some reports considering the etiology to be more peripheral rather than central and caused by an inflammation of small peripheral nerve fibers [108]. Conversely, other complex pain syndromes have been reported to respond to this therapy, including; trigeminal neuralgia, cluster headaches, and migraines, this further rectifies the theory that the neurologic dysfunction is altered brain activity rather than inflammation of peripheral nerves [13].

The use of hyperbaric oxygen therapy is debated to be used as a sole therapeutic agent versus as an adjuvant therapy used in addition to the traditional agents used routinely in patients with fibromyalgia [12]. Patients with a diagnosis of fibromyalgia are treated by education regarding the disease prognosis, importance of good sleep hygiene, association with other psychiatric comorbidities [109]. In addition to patient education, patients are usually started on an exercise regimen and sometimes on a low dose pharmacological treatment [109]. Hyperbaric therapy has been associated with decreased activity in the posterior brain lobes as well as increased activity in the frontal, parietal, temporal lobes, and the cerebellum [110]. In addition to its function in changing brain activity, HBOT decreases the use of medications for pain control as it has anti-inflammatory effects as well as reducing sensitivity to painful stimuli [111]. Those effects are anticipated considering that fibromyalgia has been associated with increased sensitivity to pain stimuli as well as altered brain function.

5. Conclusion

It has been known that HOBT and aerobic exercise have a promising role in chronic pain management. This role is mediated through different mechanisms that target the reduction of inflammation, mitochondrial dysfunction, and pain which represent the backbone of the pathogenesis of chronic pain disorders especially fibromyalgia. Despite such beneficial effects, there are safety concerns regarding the oxidative damage that may follow HBOT. Further studies and clinical trials are recommended to evaluate the efficacy, the risk/benefit, and the safety of HBOT and aerobic exercise in the management of FM and other chronic pain disorders to reach an optimal treatment protocol.

Competing interests

All authors have no competing interests to declare.

Funding

None.

Acknowledgement

None.

References

[1] A.M. Elliott, B.H. Smith, K.I. Penny, W.C. Smith, W.A. Chambers, The epidemiology of chronic pain in the community, Lancet (London, England) 354 (9186) (1999) 1248–1252, https://doi.org/10.1016/S0140-6736(99)03057-3.
[2] H. Merskey, N. Bogduk (Eds.), Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, IASP Press, 1994, , https://doi.org/10.1002/ana.20394 i-xvi.
[3] A. Tsang, M. Von Korff, S. Lee, et al., Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders, J. Pain 9 (10) (2008) 883–891, https://doi.org/10.1016/j.jpain.2008.05.005.
[4] P. Mease, Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment, J. Rheumatol. 32 (2005) 6–21 http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2009041318&site=ehost-live.
[5] A. Eken, D. Gökçay, C. Yılmaz, B. Baskak, A. Baltacı, M. Kara, Association of fine motor loss and Allodynia in fibromyalgia: an fNIRS study, J. Mot. Behav. (2017) 1–13.
[6] E.N. Thomas, F. Blotman, Aerobic exercise in fibromyalgia: a practical review, Rheumatol. Int. 30 (9) (2010) 1143–1150, https://doi.org/10.1007/s00296-010-1369-6.
[7] G.A. Kelley, K.S. Kelley, D.L. Jones, Efficacy and effectiveness of exercise on tender points in adults with fibromyalgia: a meta-analysis of randomized controlled trials, Arthritis 2011 (2011) 1–10, https://doi.org/10.1155/2011/125485.
[8] C. Gouvinhas, D. Veiga, L. Mendonça, R. Sampaio, L.F. Azevedo, J.M. Castro-Lopes, Interventional pain management in multidisciplinary chronic pain clinics: a prospective multicenter cohort study with one-year follow-up, Pain Res. Treat. 2017 (2017) 1–11, https://doi.org/10.1155/2017/8402413.
[9] B.H. Smith, A.M. Elliott, W.A. Chambers, W.C. Smith, P.C. Hannaford, K. Penny, The impact of chronic pain in the community, Fam. Pract. 18 (3) (2001) 292–299, https://doi.org/10.1093/FAMPRA/18.3.292.
[10] F. Di Sabato, M. Rocco, P. Martelletti, M. Giacovazzo, Hyperbaric oxygen in chronic cluster headaches: influence on serotonergic pathways, Undersea Hyperb. Med. 24 (2) (1997) 117–122 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9171470.
[11] M.H. Bennett, C. French, A. Schnabel, J. Wasiak, P. Kranke, Normobaric and hyperbaric oxygen therapy for migraine and cluster headache, Cochrane Database Syst. Rev. (3) (2008), https://doi.org/10.1002/14651858.CD005219.pub2.
[12] S. Yildiz, M.Z. Kiralp, A. Akin, et al., A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy, J. Int. Med. Res. 32 (3) (2004) 263–267, https://doi.org/10.1177/147323000403200305.
[13] M.Z. Kiralp, Ş Yildiz, D. Vural, I. Keskin, H. Ay, H. Dursun, Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome, J. Int. Med. Res. 32 (3) (2004) 258–262, https://doi.org/10.1177/147323000403200304.
[14] N. Gu, J.Y. Niu, W.T. Liu, et al., Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients, Eur. J. Pain (United Kingdom) 16 (8) (2012) 1094–1105, https://doi.org/10.1002/j.1532-2149.2012.00113.x.
[15] S. Yildiz, G. Uzun, M.Z. Kiralp, Hyperbaric oxygen therapy in chronic pain management, Curr. Pain Headache Rep. 10 (2) (2006) 95–100, https://doi.org/10.1007/s11916-006-0019-x.
[16] J. Hui, Z.J. Zhang, X. Zhang, Y. Shen, Y.J. Gao, Repetitive hyperbaric oxygen treatment attenuates complete Freund's adjuvant-induced pain and reduces glia-mediated neuroinflammation in the spinal cord, J. Pain 14 (7) (2013) 747–758, https://doi.org/10.1016/j.jpain.2013.02.003.
[17] S. Efrati, G. Fishlev, Y. Bechor, et al., Hyperbaric oxygen induces late neuroplasticity in post stroke patients–randomized, prospective trial, PLoS One 8 (1) (2013), https://doi.org/10.1371/journal.pone.0053716 e53716.
[18] S. Efrati, H. Golan, Y. Bechor, et al., Hyperbaric oxygen therapy can diminish fibromyalgia syndrome – prospective clinical trial, PLoS One 10 (5) (2015),

https://doi.org/10.1371/journal.pone.0127012.
[19] T. Theorell, V. Blomkvist, G. Lindh, B. Evengård, Critical life events, infections, and symptoms during the year preceding chronic fatigue syndrome (CFS): an examination of CFS patients and subjects with a nonspecific life crisis, Psychosom. Med. 61 (3) (2018) 304–310.
[20] B. Van Houdenhove, E. Neerinckx, P. Onghena, R. Lysens, H. Vertommen, Premorbid "overactive" lifestyle in chronic fatigue syndrome and fibromyalgia: an etiological factor or proof of good citizenship? J. Psychosom. Res. 51 (4) (2001) 571–576, https://doi.org/10.1016/S0022-3999(01)00247-1.
[21] M. Meeus, J. Nijs, L. Hermans, D. Goubert, P. Calders, The role of mitochondrial dysfunctions due to oxidative and nitrosative stress in the chronic pain or chronic fatigue syndromes and fibromyalgia patients: peripheral and central mechanisms as therapeutic targets? Expert Opin. Ther. Targets 17 (9) (2013) 1081–1089, https://doi.org/10.1517/14728222.2013.818657.
[22] J.H. Park, P. Phothimat, C.T. Oates, M. Hernanz-Schulman, N.J. Olsen, Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia, Arthritis Rheum. 41 (3) (1998) 406–413, https://doi.org/10.1002/1529-0131(199803)41:3<406::AID-ART5>3.0.CO;2-L.
[23] P. Klemp, B. Staberg, J. Korsgård, H.V. Nielsen, P. Crone, Reduced blood flow in fibromyotic muscles during ultrasound therapy, Scand. J. Rehabil. Med. 15 (1) (1983) 21–23.
[24] N. Lund, A. Bengtsson, P. Thorborg, Muscle tissue oxygen pressure in primary fibromyalgia, Scand. J. Rheumatol. 15 (2) (1986) 165–173, https://doi.org/10.3109/03009748609102084.
[25] G. Yu, T. Durduran, G. Lech, et al., Time-dependent blood flow and oxygenation in human skeletal muscles measured with noninvasive near-infrared diffuse optical spectroscopies, J. Biomed. Opt. 10 (2) (2005) 24027, https://doi.org/10.1117/1.1884603.
[26] S.A. Detmer, D.C. Chan, Functions and dysfunctions of mitochondrial dynamics, Nat. Rev. Mol. Cell Biol. 8 (11) (2007) 870–879, https://doi.org/10.1038/nrm2275.
[27] W.M. Behan, I.A. More, P.O. Behan, Mitochondrial abnormalities in the postviral fatigue syndrome, Acta Neuropathol. 83 (1) (1991) 61–65.
[28] S. Myhill, N.E. Booth, J. McLaren-Howard, Chronic fatigue syndrome and mitochondrial dysfunction, Int. J. Clin. Exp. Med. 2 (1) (2009) 1–16.
[29] R.M. Leach, P.J. Rees, P. Wilmshurst, Hyperbaric oxygen therapy, BMJ 317 (7166) (1998) 1140–1143.
[30] E.P. Kindwall, L.J. Gottlieb, D.L. Larson, Hyperbaric oxygen therapy in plastic surgery: a review article, Plast. Reconstr. Surg. 88 (5) (1991) 898–908.
[31] J. Hink, E. Jansen, Are superoxide and/or hydrogen peroxide responsible for some of the beneficial effects of hyperbaric oxygen therapy? Med. Hypotheses 57 (6) (2001) 764–769, https://doi.org/10.1054/mehy.2001.1488.
[32] S. Oter, A. Korkmaz, T. Topal, et al., Correlation between hyperbaric oxygen exposure pressures and oxidative parameters in rat lung, brain, and erythrocytes, Clin. Biochem. 38 (8) (2005) 706–711, https://doi.org/10.1016/j.clinbiochem.2005.04.005.
[33] A. Korkmaz, S. Öter, S. Sadir, et al., Exposure time related oxidative action of hyperbaric oxygen in rat brain, Neurochem. Res. 33 (1) (2008) 160–166, https://doi.org/10.1007/s11064-007-9428-4.
[34] H. Ay, T. Topal, M. Özler, et al., Persistence of hyperbaric oxygen-induced oxidative effects after exposure in rat brain cortex tissue, Life Sci. 80 (22) (2007) 2025–2029, https://doi.org/10.1016/J.LFS.2007.03.002.
[35] E. Palzur, M. Zaaroor, E. Vlodavsky, F. Milman, J.F. Soustiel, Neuroprotective effect of hyperbaric oxygen therapy in brain injury is mediated by preservation of mitochondrial membrane properties, Brain Res. 1221 (2008) 126–133, https://doi.org/10.1016/j.brainres.2008.04.078.
[36] M. Brentnall, L. Rodriguez-Menocal, R.L. De Guevara, E. Cepero, L.H. Boise, Caspase-9, caspase-3 and caspase-7 have distinct roles during intrinsic apoptosis, BMC Cell Biol. 14 (2013) 32, https://doi.org/10.1186/1471-2121-14-32.
[37] E. Vlodavsky, E. Palzur, M. Feinsod, J.F. Soustiel, Evaluation of the apoptosis-related proteins of the BCL-2 family in the traumatic penumbra area of the rat model of cerebral contusion, treated by hyperbaric oxygen therapy: a quantitative immunohistochemical study, Acta Neuropathol. 110 (2) (2005) 120–126, https://doi.org/10.1007/s00401-004-0946-8.
[38] G.P. Xu, K.R. Dave, C.T. Moraes, et al., Dysfunctional mitochondrial respiration in the wobbler mouse brain, Neurosci. Lett. 300 (3) (2001) 141–144.
[39] T. Letellier, M. Malgat, J.P. Mazat, Control of oxidative phosphorylation in rat muscle mitochondria: implications for mitochondrial myopathies, Biochim. Biophys. Acta 1141 (1) (1993) 58–64.
[40] K.R. Dave, R. Prado, R. Busto, et al., Hyperbaric oxygen therapy protects against mitochondrial dysfunction and delays onset of motor neuron disease in Wobbler mice, Neuroscience 120 (1) (2003) 113–120.
[41] T.S. Jensen, R. Baron, M. Haanpää, et al., A new definition of neuropathic pain, Pain 152 (10) (2011) 2204–2205, https://doi.org/10.1016/j.pain.2011.06.017.
[42] R. Staud, M. Spaeth, Psychophysical and neurochemical abnormalities of pain processing in fibromyalgia, CNS Spectr. 13 (3 Suppl 5) (2008) 12–17.
[43] G. Carli, A.L. Suman, G. Biasi, R. Marcolongo, Reactivity to superficial and deep stimuli in patients with chronic musculoskeletal pain, Pain 100 (3) (2002) 259–269.
[44] J. Sörensen, T. Graven-Nielsen, K.G. Henriksson, M. Bengtsson, L. Arendt-Nielsen, Hyperexcitability in fibromyalgia, J. Rheumatol. 25 (1) (1998) 152–155.
[45] D.J. Tracey, J.S. Walker, Pain due to nerve damage: are inflammatory mediators involved? Inflamm. Res. 44 (10) (1995) 407–411.
[46] G. Moalem, D.J. Tracey, Immune and inflammatory mechanisms in neuropathic pain, Brain Res. Rev. 51 (2) (2006) 240–264, https://doi.org/10.1016/j.brainresrev.2005.11.004.
[47] J.-M. Zhang, J. An, Cytokines, inflammation, and pain, Int. Anesthesiol. Clin. 45 (2) (2007) 27–37, https://doi.org/10.1097/AIA.0b013e318034194e.
[48] Y.-Q. Zhou, Z. Liu, Z.-H. Liu, et al., Interleukin-6: an emerging regulator of pathological pain, J. Neuroinflammation 13 (1) (2016) 141, https://doi.org/10.1186/s12974-016-0607-6.
[49] K. Ren, R. Torres, Role of interleukin-1beta during pain and inflammation, Brain Res. Rev. 60 (1) (2009) 57–64, https://doi.org/10.1016/j.brainresrev.2008.12.020.
[50] A. Latremoliere, C.J. Woolf, Central sensitization: a generator of pain hypersensitivity by central neural plasticity, J. Pain 10 (9) (2009) 895–926, https://doi.org/10.1016/j.jpain.2009.06.012.
[51] G.J. Bennett, Y.K. Xie, A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man, Pain 33 (1) (1988) 87–107.
[52] N. Liu, K.-K. Zang, Y.-Q. Zhang, [Activation of microglia and astrocytes in different spinal segments after peripheral nerve injury in mice], Sheng Li Xue Bao 67 (6) (2015) 571–582.
[53] C.D. Thompson, M.L. Uhelski, J.R. Wilson, P.N. Fuchs, Hyperbaric oxygen treatment decreases pain in two nerve injury models, Neurosci. Res. 66 (3) (2010) 279–283, https://doi.org/10.1016/j.neures.2009.11.010.
[54] B.S. Zhao, L.X. Meng, Y.Y. Ding, Y.Y. Cao, Hyperbaric oxygen treatment produces an antinociceptive response phase and inhibits astrocyte activation and inflammatory response in a rat model of neuropathic pain, J. Mol. Neurosci. 53 (2) (2014) 251–261, https://doi.org/10.1007/s12031-013-0213-3.
[55] Y. Inamoto, F. Okuno, K. Saito, et al., Effect of hyperbaric oxigenation on macrophage function in mice, Biochem. Biophys. Res. Commun. 31 (2) (1991) 1–19, https://doi.org/10.1016/0006-291X(91)91901-N.
[56] F. Li, L. Fang, S. Huang, et al., Hyperbaric oxygenation therapy alleviates chronic constrictive injury-induced neuropathic pain and reduces tumor necrosis factor-alpha production, Anesth. Analg. 113 (3) (2011) 626–633, https://doi.org/10.1213/ANE.0b013e31821f9544.
[57] A. George, M. Marziniak, M. Schäfers, K.V. Toyka, C. Sommer, Thalidomide treatment in chronic constrictive neuropathy decreases endoneurial tumor necrosis factor-alpha, increases interleukin-10 and has long-term effects on spinal cord dorsal horn met-enkephalin, Pain 88 (3) (2000) 267–275.
[58] W.-S. Gui, X. Wei, C.-L. Mai, et al., Interleukin-1β overproduction is a common cause for neuropathic pain, memory deficit, and depression following peripheral nerve injury in rodents, Mol. Pain 12 (2016), https://doi.org/10.1177/1744806916646784 174480691664678.
[59] L. Leung, C.M. Cahill, TNF-alpha and neuropathic pain–a review, J. Neuroinflammation 7 (2010) 27, https://doi.org/10.1186/1742-2094-7-27.
[60] N. Kobayashi, S.-i. Mita, K. Yoshida, et al., Celiprolol activates eNOS through the PI3K-Akt pathway and inhibits VCAM-1 via NF- B induced by oxidative stress, Hypertension 42 (5) (2003) 1004–1013, https://doi.org/10.1161/01.HYP.0000097547.35570.70.
[61] S.Y. Zhilyaev, A.N. Moskvin, T.F. Platonova, D.R. Gutsaeva, I.V. Churilina, I.T. Demchenko, Hyperoxic vasoconstriction in the brain is mediated by inactivation of nitric oxide by superoxide anions, Neurosci. Behav. Physiol. 33 (8) (2003) 783–787.
[62] A.A. Larson, S.L. Giovengo, I.J. Russell, J.E. Michalek, Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways, Pain 87 (2) (2000) 201–211, https://doi.org/10.1016/S0304-3959(00)00284-0.
[63] G. Laumet, S.-R. Chen, H.-L. Pan, NMDA receptors and signaling in chronic neuropathic pain, The NMDA Receptors, Springer International Publishing, Cham, 2017, pp. 103–119, https://doi.org/10.1007/978-3-319-49795-2_6.
[64] K.O. Aley, G. McCarter, J.D. Levine, Nitric oxide signaling in pain and nociceptor sensitization in the rat, J. Neurosci. 18 (17) (1998) 7008–7014.
[65] M.A. Sackner, E.M. Gummels, J.A. Adams, Say NO to fibromyalgia and chronic fatigue syndrome: an alternative and complementary therapy to aerobic exercise, Med. Hypotheses 63 (1) (2004) 118–123, https://doi.org/10.1016/j.mehy.2004.01.025.
[66] G.R. Lauretti, M.V. Perez, M.P. Reis, N.L. Pereira, Double-blind evaluation of transdermal nitroglycerine as adjuvant to oral morphine for cancer pain management, J. Clin. Anesth. 14 (2) (2002) 83–86.
[67] Y. Ohgami, C.C. Zylstra, L.P. Quock, E. Chung, D.Y. Shirachi, R.M. Quock, Nitric oxide in hyperbaric oxygen-induced acute antinociception in mice, Neuroreport 20 (15) (2009) 1325–1329, https://doi.org/10.1097/WNR.0b013e3283305a49.
[68] J.H. Heeman, Y. Zhang, D.Y. Shirachi, R.M. Quock, Involvement of spinal cord opioid mechanisms in the acute antinociceptive effect of hyperbaric oxygen in mice, Brain Res. 1540 (2013) 42–47, https://doi.org/10.1016/j.brainres.2013.09.050.
[69] L.M. Zelinski, Y. Ohgami, E. Chung, D.Y. Shirachi, R.M. Quock, A prolonged nitric oxide-dependent, opioid-mediated antinociceptive effect of hyperbaric oxygen in mice, J. Pain 10 (2) (2009) 167–172, https://doi.org/10.1016/j.jpain.2008.08.003.
[70] M. Tanabe, Y. Nagatani, K. Saitoh, K. Takasu, H. Ono, Pharmacological assessments of nitric oxide synthase isoforms and downstream diversity of NO signaling in the maintenance of thermal and mechanical hypersensitivity after peripheral nerve injury in mice, Neuropharmacology 56 (3) (2009) 702–708, https://doi.org/10.1016/j.neuropharm.2008.12.003.
[71] G. Han, L. Li, Meng L-XX, Effects of hyperbaric oxygen on pain-related behaviors and nitric oxide synthase in a rat model of neuropathic pain, Pain Res. Manag. 18 (3) (2013) 137–141, https://doi.org/10.1155/2013/147043.
[72] V.A. Straub, J. Grant, M. O'Shea, P.R. Benjamin, Modulation of serotonergic neurotransmission by nitric oxide, J. Neurophysiol. 97 (2) (2007) 1088–1099, https://doi.org/10.1152/jn.01048.2006.

[73] N.T. Sandor, A. Brassai, A. Pliskas, B. Lendvai, Role of nitric oxide in modulating neurotransmitter release from rat striatum, Brain Res. Bull. 36 (5) (1995) 483–486, https://doi.org/10.1016/0361-9230(94)00229-T.
[74] H.D. Wilson, J.R. Wilson, P.N. Fuchs, Hyperbaric oxygen treatment decreases inflammation and mechanical hypersensitivity in an animal model of inflammatory pain, Brain Res. 1098 (1) (2006) 126–128, https://doi.org/10.1016/j.brainres.2006.04.088.
[75] G. Sumen, M. Cimsit, L. Eroglu, Hyperbaric oxygen treatment reduces carrageenan-induced acute inflammation in rats, Eur. J. Pharmacol. 431 (2) (2001) 265–268, https://doi.org/10.1016/S0014-2999(01)01446-7.
[76] Medicine AC of S. ACSM's Guidelines for Exercise Testing and Prescription, Lippincott Williams & Wilkins, 2013 books.google.com VN - readcube.com.
[77] J. Bidonde, A.J. Busch, C.L. Schachter, et al., Aerobic exercise training for adults with fibromyalgia, Cochrane Database Syst. Rev. 2017 (6) (2017), https://doi.org/10.1002/14651858.CD012700.
[78] J. Henriksson, J.S. Reitman, Time course of changes in human skeletal muscle succinate dehydrogenase and cytochrome oxidase activities and maximal oxygen uptake with physical activity and inactivity, Acta Physiol. Scand. 99 (1) (1977) 91–97, https://doi.org/10.1111/j.1748-1716.1977.tb10356.x.
[79] B. Egan, P. Dowling, P.L. O'Connor, et al., 2-D DIGE analysis of the mitochondrial proteome from human skeletal muscle reveals time course-dependent remodelling in response to 14 consecutive days of endurance exercise training, Proteomics 11 (8) (2011) 1413–1428, https://doi.org/10.1002/pmic.201000597.
[80] J.L. Talanian, G.P. Holloway, L.A. Snook, G.J. Heigenhauser, A. Bonen, L.L. Spriet, Exercise Training Increases Sarcolemmal and Mitochondrial Fatty Acid Transport Proteins in Human Skeletal Muscle, Am. J. Physiol. Endocrinol. Metab. 299 (2010) E180–E188 doi:ajpendo.00073.2010 [pii]r10.1152/ajpendo.00073.2010.
[81] T.P. Gavin, R.S. Ruster, J.A. Carrithers, et al., No difference in the skeletal muscle angiogenic response to aerobic exercise training between young and aged men, J. Physiol. (Paris) 585 (1) (2007) 231–239, https://doi.org/10.1113/jphysiol.2007.143198.
[82] T. Schmidt-Wilcke, D.J. Clauw, Fibromyalgia: from pathophysiology to therapy, Nat. Rev. Rheumatol. 7 (9) (2011) 518–527, https://doi.org/10.1038/nrrheum.2011.98.
[83] J.H. Park, K.J. Niermann, N. Olsen, Evidence for metabolic abnormalities in the muscles of patients with fibromyalgia, Curr. Rheumatol. Rep. 2 (2) (2000) 131–140.
[84] G.A. Dudley, P.C. Tullson, R.L. Terjung, Influence of mitochondrial content on the sensitivity of respiratory control, J. Biol. Chem. 262 (19) (1987) 9109–9114.
[85] E. Ortega, J.J. García, M.E. Bote, et al., Exercise in fibromyalgia and related inflammatory disorders: known effects and unknown chances, Exerc. Immunol. Rev. 15 (2009) 42–65.
[86] L. Scheef, J. Jankowski, M. Daamen, et al., An fMRI study on the acute effects of exercise on pain processing in trained athletes, Pain 153 (8) (2012) 1702–1714, https://doi.org/10.1016/j.pain.2012.05.008.
[87] A.L. Lopresti, S.D. Hood, P.D. Drummond, A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise, J. Affect. Disord. 148 (1) (2013) 12–27, https://doi.org/10.1016/j.jad.2013.01.014.
[88] N.K.Y. Tang, A.N. Sanborn, Better quality sleep promotes daytime physical activity in patients with chronic pain? A multilevel analysis of the within-person relationship, PLoS One 9 (3) (2014), https://doi.org/10.1371/journal.pone.0092158.
[89] A.J. Busch, C.L. Schachter, T.J. Overend, P.M. Peloso, K.A. Barber, Exercise for fibromyalgia: a systematic review, J. Rheumatol. 35 (June (6)) (2008) 1130–1144.
[90] J. Bidonde, A.J. Busch, C.L. Schachter, T.J. Overend, S.Y. Kim, S.M. Góes, C. Boden, H.J. Foulds, Aerobic exercise training for adults with fibromyalgia, Cochrane Libr. (January (1)) (2017).
[91] A.M. Alcántara, C.C. Sánchez, EULAR revised recommendations for the management of fibromyalgia, Semergen 43 (September (6)) (2017) 472–473.
[92] K.A. Firestone, J.W. Carson, S.D. Mist, K.M. Carson, K.D. Jones, Interest in yoga among fibromyalgia patients: an international internet survey, Int. J. Yoga Therap. 24 (September) (2014) 117–124.
[93] H. Wahbeh, S.M. Elsas, B.S. Oken, Mind-body interventions: applications in neurology, Neurology 70 (24) (2008) 2321–2328, https://doi.org/10.1212/01.wnl.0000314667.16386.5e.
[94] K. Beri, Breathing to younger skin: "reversing the molecular mechanism of skin aging with yoga.", Fut. Sci. OA 2 (2) (2016), https://doi.org/10.4155/fsoa-2016-0015 fsoa-2016-0015.
[95] F. Saatcioglu, Regulation of gene expression by yoga, meditation and related practices: a review of recent studies, Asian J. Psychiatr. 6 (1) (2013) 74–77, https://doi.org/10.1016/j.ajp.2012.10.002.
[96] J.D. Creswell, E.K. Lindsay, How does mindfulness training affect health? A mindfulness stress buffering account, Curr. Dir. Psychol. Sci. 23 (6) (2014) 401–407, https://doi.org/10.1177/0963721414547415.
[97] K.J. Tracey, Reflex control of immunity, Nat. Rev. Immunol. 9 (6) (2009) 418–428, https://doi.org/10.1038/nri2566.
[98] N. Morgan, M.R. Irwin, M. Chung, C. Wang, The effects of mind-body therapies on the immune system: meta-analysis, PLoS One 9 (7) (2014), https://doi.org/10.1371/journal.pone.0100903.
[99] A. Vijayaraghava, V. Doreswamy, O.S. Narasipur, R. Kunnavil, N. Srinivasamurthy, Effect of yoga practice on levels of inflammatory markers after moderate and strenuous exercise, J. Clin. Diagn. Res. 9 (6) (2015), https://doi.org/10.7860/JCDR/2015/12851.6021 CC08-12.
[100] J.E. Bower, G. Greendale, A.D. Crosswell, et al., Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial, Psychoneuroendocrinology 43 (2014) 20–29, https://doi.org/10.1016/j.psyneuen.2014.01.019.
[101] M.R. Irwin, R. Olmstead, E.C. Breen, et al., Cognitive behavioral therapy and tai chi reverse cellular and genomic markers of inflammation in late-life insomnia: a randomized controlled trial, Biol. Psychiatry 78 (10) (2015) 721–729, https://doi.org/10.1016/j.biopsych.2015.01.010.
[102] G.E. Miller, E. Chen, J. Sze, et al., A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-κB signaling, Biol. Psychiatry 64 (4) (2008) 266–272, https://doi.org/10.1016/j.biopsych.2008.03.017.
[103] J.W. Carson, K.M. Carson, K.D. Jones, R.M. Bennett, C.L. Wright, S.D. Mist, A pilot randomized controlled trial of the Yoga of Awareness program in the management of fibromyalgia, PAIN®. 1 (November (2)) (2010) 530–539.
[104] C. Wang, C.H. Schmid, R.A. Fielding, W.F. Harvey, K.F. Reid, L.L. Price, J.B. Driban, R. Kalish, R. Rones, T. McAlindon, Effect of tai chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial, BMJ 21 (March (360)) (2018) k851.
[105] S. Opasanon, W. Pongsapich, S. Taweepraditpol, B. Suktitipat, A. Chuangsuwanich, Clinical effectiveness of hyperbaric oxygen therapy in complex wounds, J. Am. Coll. Clin. Wound Spec. 6 (1–2) (2014) 9–13, https://doi.org/10.1016/j.jccw.2015.03.003.
[106] D.J. Clauw, L.M. Arnold, B.H. McCarberg, The science of fibromyalgia, Mayo Clin. Proc. 86 (9) (2011) 907–911, https://doi.org/10.4065/mcp.2011.0206.
[107] R. Boussi-Gross, H. Golan, G. Fishlev, et al., Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury – randomized prospective trial, PLoS One 8 (11) (2013), https://doi.org/10.1371/journal.pone.0079995.
[108] N. Üçeyler, D. Zeller, A.-K. Kahn, et al., Small fibre pathology in patients with fibromyalgia syndrome, Brain 136 (Pt 6) (2013) 1857–1867, https://doi.org/10.1093/brain/awt053.
[109] D.J. Clauw, Fibromyalgia, JAMA 311 (15) (2014) 1547, https://doi.org/10.1001/jama.2014.3266.
[110] E. Guedj, S. Cammilleri, J. Niboyet, et al., Clinical correlate of brain SPECT perfusion abnormalities in fibromyalgia, J. Nucl. Med. 49 (11) (2008) 1798–1803, https://doi.org/10.2967/jnumed.108.053264.
[111] S. Akarsu, L. Tekin, H. Ay, et al., The efficacy of hyperbaric oxygen therapy in the management of chronic fatigue syndrome, Undersea Hyperb Med J Undersea Hyperb Med Soc Inc 40 (2) (2013) 197–200 http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=23682549&site=ehost-live.