# Fibromyalgia: could hyperbaric oxygen therapy make the difference? Our experience.

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**Introduction**

Fibromyalgia (FM) is defined as a "syndrome of central sensitisation with dysfunction of the neuronal circuits involved in the perception, transmission and processing of nociceptive afferents, with pain predominantly expressed in the musculoskeletal system"[1]. It is an incurable syndrome of unknown origin with signs and symptoms often similar and overlapping with those of other syndromes. This condition, unfortunately with high frequency, delays its diagnosis. The pathogenetic mechanism underlying the clinical picture is alteration of the nociceptive system.

Several hypotheses have been proposed concerning the pathogenesis of FM and the management of FM patients requires a multidisciplinary approach.

Accumulating evidence suggests that hyperbaric oxygen therapy (HBOT) is a non-invasive modality with lasting efficacy to treat FM[2]. HBOT is defined by the Undersea and Hyperbaric Medical Society (UHMS) as a treatment in which a patient intermittently breathes 100% oxygen while the treatment chamber is pressurised to above sea level pressure (1 atmosphere absolute, 1 ATA = 760 mmHg)[3]. HBOT is able to induce many interesting effects on plasma oxygen concentration. Based on Henry's Law, increased pressure will cause more gas to go into solution, and therefore,more oxygen will be transported in the plasma. As a result a lot of oxygen becomes available for the microcirculation, resulting in significant improvement of all metabolic parameters, which have also been shown in several works to influence neurological functions[4]. We report about a case of woman affected by FM and treated with HBOT as adjuvant, experimental and non conventional therapy.

**Case Presentation**

In January 2021 a 54-year-old Caucasian woman with a negative medical past history reported pain in her left arm 24 hours after receiving the first dose of the Pfizer SARS-Covid 19 vaccine. Localised pain in the injection zone (the triceps muscle of the left arm) was accompanied by the onset of high fever (40°C), intense headache with vomiting and abdominal pain. After 48 hours there was defervescence with return to normothermia but progressive appearance of fatigue. Subsequently patient report a relief of pain in the left arm with progressive development of constant, severe and persistent pain in occipital and back neck area, low back and legs with a marked sense of heaviness in the lower limbs. The patient also complained of progressive

difficulty in walking, for which the use of nordic walking sticks was necessary. Furthermore, she reported stiffening of the facial muscles with pain defined as intense, mental fogginess, severe short-term memory involvement and progressive depression, symptoms that had undoubtedly caused a significant impairment in her quality of life.

The patient underwent routine blood sample tests (blood count, ESR, PCR, protein electrophoresis, AST, ALT, gamma GT), as well as more specific immuno-enzymatic tests (serum kappa and lambda chains, IgG, IgA, IgM, anti-nuclear antibodies, ENA, ANA with subclasses). The exams showed no values outside the standard range. Only a slight increase in ESR and a reduction in 25-OH-vitamin D levels was shown. The patient also performed total body CTs, spine MRI, femoral and lumbar bone densitometry from which no structural morphological alteration was highlighted except for an initial picture of osteoporosis. The exclusion of inflammatory disease, although some rheumatic diseases could coexist, suggested a possible diagnosis of FM and thus rheumatologists have sought its diagnostic criteria[5]. The persistence of pain was well over 3 months (the patient reported the onset of symptoms about 18 months ago).

The following questionnaires were administered: Widespread Pain Index (WPI), Symptom Severity Scale (SSS), Revised Fibromyalgia Impact Questionnaire (FIQR), Pittsburgh Sleep Quality Index (PHQI), Generalized Anxiety Disorder Screener (GAD-7), Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F). The scores reported from each individual questionnaires carried out before the start of HBOT were as follows: WPI=18, SSS=10, FIQR=96, PHQI=17, GAD-7=14, FACIT=12.

Thus she started a multidisciplinary therapeutic course based on antalgic therapy, physiotherapy, psychological support, relaxation techniques and healthy nutrition.

Among the various therapies, HBOT was indicated as an experimental non-conventional treatment. The patient underwent forty sessions of HBOT at 2.4 ATA (absolute atmospheres), total oxygen time 60 minutes per session, once a day, five times a week, performed at the multi-place chamber (Sistemi Iperbarici Integrati-Camera Iperbarica Mod 2000) of the Hyperbaric Medicine Centre of ARNAS Ospedale Civico Di Cristina Benfratelli, Palermo, Italy. Therapy started in the first week of September and ended in mid-November 2022. Throughout each session, the patient showed stable vital parameters (blood pressure, heart rate, oxygen saturation and body temperature). Blood tests, markers of flogosis and haematochemical examinations carried out at mid term and at the end showed no change in values outside the normal range.

The patient underwent 40 sessions of HBOT. The clinical improvement achieved was evident and affected all symptom areas reported before treatment. In particular, there was a complete recovery of mobility with the avoidance of walking sticks, an increase in muscular strength evidenced by the ability to climb several flights of stairs and to walk long distances independently. The patient reported a drastic reduction in pain symptoms evident from the moment she woke up in the morning, a significant improvement in sleep quality, previously reported as light, non-restorative and with multiple breaks. The highly debilitating sense of fatigue was reported after treatment as markedly reduced and in any case easily manageable. In addition, a significant change in cognitive abilities was reported, with disappearance of mental fogginess and recovery of short-term memory. In summary, there was a significant improvement in quality of life with the disappearance of the depression into which the patient had plunged, a condition confirmed by psychological advice at the end of the hyperbaric treatment. The scores reported by each individual test at the end of HBOT are shown below: WPI=6, SSS=3, FIQR=13, PHQI=2, GAD-7=3, FACIT=42.

**Discussion**

FM is characterised by chronic pain at multiple specifical anatomical sites lasting for more than 3 months and is usually accompanied by clinical manifestations such as fatigue, muscle and joint stiffness, sleep disturbance, irritative bowel syndrome, low energy, cognitive dysfunction and depressive symptoms[6]. FM affects more frequently female and it is estimated that between 2% and 8% of the world's population is afflicted[7]. The age range in which FM generally appears is between 30 to 35 years[8]. The quality of life in people with FM is severely impaired and the risk of suicide associated with depression and global worsening of the mental state are quite common in these individuals[9].

The hypothesis that reduced oxygen availability could be the cause of the structural and functional degeneration affecting the muscles of FM patients dates back to the first half of the 1970s[10]. Several works have shown that in FM patients, there is a reduction in oxygen availability, either absolute or linked to a low tissue extraction fraction, resulting in hypoperfusion/ischemia, which in turn could play a key role in the onset of muscle pain, an element that dramatically characterises the clinical picture of fibromyalgia patients[11].

Subsequently, research produced in order to define the pathogenesis of FM piled up and several ideas were proposed. Enviromental, psychosocial and genetic aspects have been implicated as being responsible for reduced resilience to adverse stressful events, a condition that would seem to make these individuals more vulnerable[12]. It has been hypothesised that environmental factors such as adverse events occurring early in lifetime, psychosocial stress, trauma and medical diseases (as Lyme disease, Epstein Barr Virus infection, viral hepatitis, Q fever) can trigger the development of FM[13].

Another work involves thalamic mast cells that seem to play a role in the onset of inflammation and pain through the release of pro-inflammatory mediators (interleukin, TNF-alpha) and the stimulation of thalamic nociceptor neurons by direct and indirect pathways[14]. Trauma and infection often precede the onset of FM, suggesting a potential role for immune-mediated pathways. Another fascinating theory being evaluated suggests changes in the serum levels of certain neurotransmitters (serine and glutamate) linked in turn to altered gut-brain cross talk[15]. Several works have shown that a reduced level of biogenic amine, an impaired regulation of the hypothalamus-pituitary axis combined with an increased concentration of excitatory neuromolecules (in particular Substance P) may play a central role in the onset of the clinical pattern[16-17].

To date, the dysfunction of the neurocircuits involved in the perception, transmission and processing of nociceptive afferents is considered a key element in the onset of FM symptoms, and indeed several works have shown that impairments in the neurotransmission system are able to affect pain perception, fatigue, sleep disturbances, anxiety symptoms and depression. FM patients show high levels of norepinephrine and glutamate, low levels of serotonin and dopamine[18-19]. As noted above Substance P reaches three times higher levels in the cerebral spinal fluid of FM patients than in the healthy population[20].

The extreme variety of symptoms and associated comorbidities make the diagnosis of FM problematic. It is pretty frequent to observe the association between FM and other diseases such as osteoarthritis, rheumatoid arthritis and lupus. Many physicians are unfamiliar with the diagnostic criteria, have no clinical experience with these patients and are unaware of potential treatment options. These factors, as described by Choy et al., lead to a diagnosis that often takes more than 2 years and involves an average of 3.7 physicians per patient[21]. It is clear that early diagnosis of FM is essential in order to avoid aggravation of initial symptoms and the development of vicious circles such as pain with immobility and/or pain with mood disorders, conditions that can further complicate the management of these patients. The diagnostic criteria for FM have evolved progressively from the seminal work of the American College of Rheumatology (ACR)[22]to the critical review published by the same author in 2016[5]which is currently considered the reference point for the diagnosis of FM. Briefly, the diagnosis is based on the finding of the following clinical symptoms:

- Widespread Pain Index (WPI) [?] 7 and Symptom Severity Scale (SSS) [?] 5 or WPI of 4-6 and SSS [?]9

- Generalised pain, present in at least 4 of the 5 topographically defined areas

- Symptoms must have been generally present for at least 3 months

The anatomo-topographical areas considered are defined as right and left upper area, right and left lower area and axial area. Some authors recently stated that patients should be screened for WPI and that those with positive WPI should be further screened for the presence of the main symptoms of FM in accordance with the 2016 criteria of the ACR[23].

Unfortunately, to date there is no generally accepted and effective cure, the treatment is multidisciplinary and, consequently, the different pieces of the therapeutic puzzle employed focus on controlling and managing the pain symptoms. Therapy is based on the combined use of different categories of drugs (antidepressants, anticonvulsants, muscle relaxants, analgesics, hypnotics, antipsychotics, cannabis and cannabinoids) along

with non-pharmacological therapies such as fitness, psychotherapy, spa therapy, tai chi, qigong, yoga, mindfulness, hypnosis, acupuncture, thermal and electrical energy. In fact, their combined use has been shown to alleviate pain with variable and time-limited efficacy.

HBOT is a procedure in which patients breathe 100 % oxygen inside a pressurised multiplace hyperbaric chamber at a level above sea level. The Undersea and Hyperbaric Medical Society (UHMS) has determined that HBOT can only be defined as such if the pressure achieved in the hyperbaric chamber is 1.4 ATA or higher[24]. In clinical setting, applied pressures usually range from 2 to 3 ATA. Under hyperbaric conditions, in patients with healthy lungs and normal arterial flow, alveolar partial pressure of oxygen (PaO2) is acutely elevated in proportion to atmospheric pressure, and at 2 ATA, PaO2 and tissue oxygen pressure increase to 1500 mmHg and 200 mmHg, respectively.

HBOT is based on several physiological principles relating to the response of gases to pressure and, more precisely, the response of oxygen to pressure. Indeed, the concentration of dissolved oxygen in the plasma can be strongly influenced by HBOT. In line with Henry's law, an increase in pressure causes more gas to go into solution and hence more oxygen to be carried into the plasma. The rise in partial pressure increases the driving force of diffusion and thus increases the diffusion range, as defined by Fick's law. Furthermore, it is the oxygen dissolved in the plasma that is more bioavailable to the tissue. At 3 ATA, HBOT increases the level of oxygen dissolved in plasma from 0.3 ml/dL to 6 ml/dL assuring the amount of oxygen needed for metabolism independently of the amount chemically bound to haemoglobin.

Although to date there aren't official guidelines supporting the use of HBOT in the treatment of FM patients, the first report on its use in FM is from 2004[25]. Since then, a large number of papers have been conducted to validate the effectiveness of HBOT as a treatment option in FM sufferers, and to clarify the molecular mechanisms by which HBOT is able to produce positive effects.

HBOT represents a non invasive potential therapeutic option, as it is able to reduce the oxidative stress occurring in hypoxic tissues. Indeed, numerous data show an alteration in the pro- and anti-oxidative balance in FM patients characterised by a reduced function of super oxide dismutase (SOD), nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and catalase (CAT) data that correlate well with the severity of pain and fatigue assessed by FIQR[26]. HBOT is able to deactivate caspase 3 and caspase 9 and increases the expression of the Bcl-2 gene, which consequently increases regulated apoptosis. This finding suggests that the increased oxygen availability produced by HBOT reduces mitochondrial apoptosis and preserves mitochondrial function[27]. Furthermore, in animal models HBOT is able to reduce lipoperoxidation and pro-oxidative processes[28]. Research in animal models has revealed that muscle tissue ischemia is a severe activator of unmyelinated muscle nociceptors, which can facilitate central sensitisation[29]. Reduced oxygen availability in the muscle tissue of FM patients influences structural and functional changes, which in turn play a role in the sensitisation of central and peripheral pain receptors, with altered central pain perception and processing. This finding also supports the therapeutic role that HBOT may play in these patients[30]. Moreover, HBOT has anti-inflammatory action, promotes neuroplasticity, optimises mitochondrial functioning and stimulates nitric oxide, actions that may reduce hyperalgesia and facilitate the release of endogenous opioids[31]. Furthermore, Guggino et al[32] reported how the immune system may play a role in the pathogenesis of FM and outlined the therapeutic impact of HBOT by describing changes in the production of proinflammatory cytokines (IL- 1RA, IL-6, IL-8) by CD4 T-cell subpopulations. These results support the idea that HBOT is an effective, safe and rapid means of treating the various symptoms of FM.

Criticism of this treatment is related to the overproduction of oxygen free radicals that could be responsible for an exaggerated pro-oxidative response. In our clinical experience, the oxidative stress produced by weighted use according to HBOT guidelines did not lead to adverse effects. A possible explanation could be the so-called "hyperoxic-hypoxic paradox" [33]. Let us try to elucidate its meaning concisely. Cellular respiration is a complex biochemical process based at the mitochondrial level and involving the complete oxidation of a glucose molecule with formation of CO2, H2O and production of adenosine tri-phosphate (ATP) molecules. Hypoxia results in reduced production of ATP. It is also one of the most strong inducers

of gene expression capable of influencing changes in metabolic structure, regenerative processes, including angiogenesis, as well as mobilisation migration and differentiation of stem cells [34]. Variations in oxygen levels in hyperoxic-hypoxic sense are detected by chemoreceptors and are able to induce metabolic changes by molecular mechanisms. Of more interest is that at the cellular level, is fluctuations in free oxygen that are recognised and interpreted as a reduction in oxygen availability rather than absolute oxygen values. In patients undergoing HBOT there is a fluctuation in oxygen concentration, which in hyperbarism rises from 21% to 100% and then returns to basal levels at the end of treatment. The adaptive response to repeated hyperoxia leads to an up-regulation in scavengers production with a concomitant increase in ROS production. The return to physiological oxygenation levels (ambient air) is characterised by a low ROS/Scavengers ratio and this is related to the different half-lives that ROS and Scavengers have (the former having a half-life that is about half that of the latter). This up regulation of scavengers could play a protective role by counterbalancing the overproduction of oxygen free radicals. Thus, repeated exposure to hyperoxia mimics at the molecular level the hypoxic scenario by triggering the transcriptional cascade underlying the molecular effects induced by HBOT. However, to date HBOT has produced positive effects in several clinical trials, with an overall increase in neurological functions affected by FM [35-36].

It is evident that the results of a case report have limitations related to the individual experience reported, which clearly cannot be considered reproducible with absolute reliability on large populations. In this perspective, one must consider the enormous difficulty with which researchers manage to produce clinical trials that enrol large populations of patients, and this is unfortunately linked to several factors such as the lack of knowledge that many doctors have about the indications for HBOT, the low level of information that they have about the powerful role that HBOT may plays as adjuvant in the treatment of this kind of patients, the scarce territorial spread of hyperbaric chambers, and the difficulties linked to managing the economic costs that hyperbaric treatment requires, especially for a pathology such as FM that is not supported by any guidelines to date. Since the conclusion of the hyperbaric treatment, the patient has been following the multi-structurated therapy proposed by the rheumatology and report that she is feeling well, no longer reporting the alterations in the psycho-neuro-sensory and functional spheres that had severly impaired her quality of life before HBOT.

## Conclusion

We report on our experience with the use of HBOT in the treatment of a patient suffering from FM. FM is a very invalidating disease often afflicting young people. The impaired quality of life of these patients has serious ripercussions on public economy. HBOT is a asafe therapy to experiment with FM because it could improve the quality of life of these patients and reduce its economic impact on society. Further studies are needed to improve our understanding of the mechanisms underlying the effects of HBOT and clarify its role in the treatment of these chronic disorders.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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