Whole-Body Cryostimulation in Fibromyalgia

Subjects: Medicine, Research & Experimental

Contributor: Jacopo Maria Fontana , Michele Gobbi , Paolo Piterà , Paolo Capodaglio

Currently, all available therapies for the control and management of fibromyalgia (FM) are mostly focused on relieving patients' symptoms and improving their quality of life. Thermal stress caused by cryostimulation induces an analgesic effect, improving pain, redox balance, and inflammatory symptoms in an exercise-mimicking fashion. In addition, it reduces the feeling of fatigue, improves mood, and reduces mental health deterioration with positive consequences on depressive states and improved sleep quality.

whole-body cryostimulation fibromyalgia cryotherapy inflammation pain

1. Introduction

Fibromyalgia (FM) is a medical condition characterized by the combination of complex, sometimes indistinct, symptoms. FM manifestations include chronic widespread musculoskeletal pain and associated fatigue, morning stiffness, sleep disturbances [1][2], depression, anxiety, and cognitive symptoms [3][4], in line with the biopsychosocial model of pain [5], and evidence related to other chronic pain conditions [6][7][8]. In addition, FM is associated with psychological factors, such as neuroticism [9], alexithymia [10], catastrophizing [11], and low health-related quality of life [4], limiting people's daily activities as well as their social, professional, and recreational activities [12][13]. FM is the third most common musculoskeletal condition and is estimated to affect 0.2 to 6.6% of the adult general western population [14][15]. Due to its persistent and debilitating condition, FM imposes enormous economic burdens on society, as patients with FM have relatively high levels of comorbidities and high levels of health care utilization and cost [16].

Despite predisposing factors (genetic, stressful or traumatic events, viral infections, and obesity), the etiopathogenesis of FM is still not fully unraveled, making its diagnostic and classification criteria confusing. One of the most widely held hypotheses regarding the pathogenesis of FM is central sensitization to pain and deficits in endogenous pain-inhibiting mechanisms. Several studies in patients with FM have shown a lower threshold and tolerance for pain [17][18], hyperalgesia and allodynia [19], a slower cognitive processing speed [20], a cortical or subcortical increase in pain processing compared with healthy subjects [21], and evidence of the presence of polyneuropathy in both small and large fibers [22]. All these symptoms suggest a neurogenic common origin characterized by an imbalance in the levels of neurotransmitters and consequently of the peripheral pro- and anti-inflammatory mediators [23]. Due to lack of agreement regarding its diagnosis, classification and etiopathogenesis, no consistently effective treatments are yet available. In many cases, FM has been seen as a "disease of misconnection" at different levels characterized by lack of specific biomarkers [2][24].

In most cases, the therapeutic approach is characterized by multidisciplinary interventions that include patient's education, physiotherapy (including physical agents and exercise), pharmacological treatment, and psychotherapy [2]. Therapies for the management of FM are mainly focused on easing patients' symptoms and improving quality of life [25]. Although some studies have been conducted examining pharmacological and non-pharmacological interventions, treating patients with FM using a multimodal approach appears to be the most effective option even if more trials are needed [26]. Conventional pharmacological therapies usually rely on cyclic or chronic use of antidepressants, muscle relaxants, anti-inflammatories, and antioxidants [27]. Non-pharmacological measures consist of: (i) physiotherapy, including a variety of physical agents and land- or water-based physical exercise, such as aquatic or aerobic-based exercise, strength training (anaerobic exercise), and flexibility training; and (ii) psychotherapy, including cognitive-behavioral interventions, biofeedback, and psychological support [28][29]. With the growing recognition that there are different categories of FM with different clinical features, personalized prescription should be an important target to be achieved among the empirical and constantly evolving approaches that are proposed.

Whole-body cryostimulation (WBC) is a highly effective physical treatment mainly used in sports medicine to relieve pain, inflammatory symptoms, fatigue, and overuse symptoms due to its widely recognized anti-inflammatory and anti-oxidant effects [30]. Presently, it has been used as an add-on therapy in rheumatic (arthritis [30], fibromyalgia [31][32][33][34][35][36][37][38][39][40], and ankylosing spondylitis [41]), neurological (multiple sclerosis [42]) psychiatric (depression) [43], metabolic (obesity) [44], and diabetes [45]. WBC consists of exposure of a part or the whole body to very cold and dry air for generally 2 to 3-min. At present, there are two types of cryostimulation. Partial-body cryostimulation (PBC), where the body, excluding the head, is exposed to a cryogenic fluid injected and vaporized around the body inside a cryosauna, and the whole-body cryostimulation (WBC), performed inside a cryochamber, where the whole body is exposed to cold produced by cryogenic fluids or refrigerants [46]. Given the limited amount of published literature, here adopted studies performed with both a cryochamber and a cryosauna, all reported as "Whole-body Cryostimulation", despite knowing the different physiological reactions after PBC and WBC due to their large differences in internal temperatures measured with PBC having a higher gradient. The thermal stress elicited by cryostimulation generates vasoconstriction and stimulate the thermal receptors of the dermis by lowering skin temperature, and slowing down nerve conduction in pain fibers, which may be a way that cryotherapy induces an analgesic effect, relieving pain and inflammatory symptoms [47][48]. Moreover, it causes changes in the endocrine, circulatory, neuromuscular, and immunological system [49]. It provides homeostatic autonomic responses of thermogenesis and vasoconstriction by stimulating cold receptors and the thermoregulatory center in the hypothalamus from which efferent signals cause activation of the sympathetic system resulting in vasoconstriction followed by release of noradrenaline. Along with endorphins, norepinephrine modulates pain and slow conduction velocity of sensory nerve fibers such as C fibers, disabling the sensory receptors as well as their connections to proprioceptors [50]. An increase in parasympathetic cardiac control also occurs. Indeed, after cryostimulation, as a compensatory mechanism, downregulation of blood pressure [50], even overnight [51], may result in reduced feelings of fatigue, improved mood, and reduced mental health deterioration with possible positive consequences on depressive states, and improved sleep quality [43]. Recent literature has shown that WBC is immunostimulating and yields an anti-inflammatory response, with a decrease of the pro-

inflammatory cytokines and increases of anti-inflammatory mediators [52][53][54][55][56][57]. It also appears to improve the effect on redox balance in a session/treatment number-, age-, and fitness-dependent manner [58], probably through the decrease in the total oxidant production which, consequently, induces antioxidant activity [56][58][59][60][61][62][63]. Thus, due to its widely recognized anti-inflammatory, antioxidant, analgesic, and exercise-mimicking effects [64], WBC is proposed as a promising add-on option in the multidisciplinary treatment of FM, considering also that diffuse inflammation is one of the sub mechanisms of depression [65], and that co-morbid depression is very common among FM patients, with a lifetime prevalence of 62–86% [66].

2. Clinical Effects of WBC in FM

Pain perception involves interconnected physiological and psychological mechanisms that include anatomical, physiological, cognitive, and affective components of pain [67]. There are two neural pathways that regulate pain signals: ascending pathways that transmit sensory signals through peripheral nerves, including nociceptive signals, to the spine and brain for processing; and descending pathways that send modulatory (excitatory and/or inhibitory) signals from the brain to the periphery, regulating ascending nociceptive signals that reach the brain [68]. These physical and noxious chemical signals are detected by nociceptors, specialized receptors in peripheral nerves activated by physical stimuli (i.e., changes in temperature, pressure, and impact). Many neurotransmitters and neurochemicals are involved in the transmission of pain signals such as norepinephrine and serotonin [69].

In FM, these two neural pathways operate abnormally causing an increased activity in the pain matrix which results in central amplification of pain signals, a phenomenon named central sensitization [70]. Several studies of FM-related pain and hyperalgesia have demonstrated the involvement of spinal mechanisms and an enhanced response to somatic and cutaneous stimuli throughout the brain's pain matrix, allodynia and hyperalgesia. In most cases, patients become hypersensitive to pain. The constant hypervigilance to pain can also be associated with psychological problems [71].

Most of the studies included in this review (7 out of 10) hypothesized that WBC should alleviate pain and/or inflammatory processes in FM patients, with the aim of improving health-related quality of life. These studies tested the therapeutic efficacy of WBC and its practicability for clinical routine in FM, also comparing it to other therapies (warm therapy or steam therapy) or treatments (antioxidants and analgesic agents).

All studies reported an analgesic effect of WBC with significant reduction in pain level, but had different settings. Bettoni et al. carried out two studies on the efficacy and safety of WBC in FM patients. The first report showed the superiority of WBC compared to antioxidants and analgesic agents, in terms of pain and fatigue reduction [34]. In the second study, patients performed aerobic exercise (cycle ergometer or treadmill) for 30 min immediately after WBC [33]. Physical activity, which is also used to treat FM, may have masked these results by opposing its induced vasodilation to WBC-induced vasoconstriction. In the cross-over trial of Rivera et al., the individuals' VAS and FIQ scores did not return to baseline after the first treatment with WBC due to too short wash-out periods, so that only results of the first sequence could be reported [40]. Vitenet et al. reported that WBC significantly improved health-reported quality of life, evaluated through the changes in the Medical Outcome Study Short Form-36 (10 sessions

over 8 days) [35]. However, the sample size was limited, as only 11 patients underwent WBC and the control group protocol was not described in detail. This was the same for the study of Metzger et al. that described a decreased pain intensity and a short-term pain relief of about 1.5 h after cold application. No control group receiving a regular rehabilitation program could be compared to a group additionally treated with WBC [36]. Therefore, the reduction in pain could probably be due not only to the analgesic effect of the WBC, but also to the effect of the applications carried out in parallel. However, they described some adjustment time before reaching maximum pain relief, in their case after about two weeks (half of the treatment). Interestingly, most patients rated the effect of WBC as not very effective in the context of the overall treatment, perhaps also due to the session conditions (temperature −105 °C and 2–3 patients in the chamber). Klemm et al. included patients with standard treatment before and during the study, excluding physical activity as a possible confounder of the reduced level of pain found after WBC treatment, but no control group not undergoing WBC was present [37].

Only Rivera et al. [40] and Klemm et al. [37] investigated the effects of WBC on FIQ, and only Vitenet et al. [35] and Klemm et al. [37] included a follow-up, after 1 and 3 months, respectively, showing that the effects of WBC on pain and disease activity after discontinued treatment were no longer reduced. In addition, Klemm et al. demonstrated that serial WBC (between 6 and 10 sessions in a maximum of 3 weeks) elicited effects for more than 1 month after the end of WBC treatment, then decreasing gradually to null effect after 3 months [37].

Two studies compared the effects of WBC with other classic thermotherapy methods. Kurzeja et al. investigated the effect of thermotherapy with WBC (−110 °C) alone compared with mud bath (+40 °C) and hot air (+42 °C) combined in the daily shift. Pain intensity was reduced in all groups with no significant differences between groups [38]. However, the pain scores in the WBC group were lower and the patients described a 2-h pain relief after cold exposure.

The abstract of Sundaram mentions that WBC provides better results in association with physiotherapy than with steam therapy. Improvement in pain, general health, fatigue, and sleep are attributed by the author to the systemic response and serotonin levels stimulated by WBC [39]. However, no information about the temperature was mentioned, the sample was not homogeneous in terms of age and gender, and there were no actual data to corroborate the findings and conclusions.

3. Molecular Effects of WBC in FM

The pathogenesis of FM not only includes pain sensitivity, pain inhibition, or pain amplification, but also an imbalance of pro- and anti-inflammatory cytokines, genetic predisposition, and environmental triggers such as mechanical/physical trauma or injury and psychosocial stressors that ultimately leads to pain and impaired pain processing.

There is growing evidence of neuroinflammation in FM. Several pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and tumor necrosis factor α (TNF-α), have been found to be elevated in animal models of neuropathic pain and in the cerebrospinal fluid (CSF), peripheral tissues, and blood of patients with chronic neuropathic pain

conditions [72]. In addition, pharmacologically lowering or blocking of these pro-inflammatory cytokines has been demonstrated to prevent, reduce, or reverse pain (allodynia and hyperalgesia) in both animal models and clinical studies [73].

Thus, the imbalance of pro- and anti-inflammatory cytokines is assumed to play a role in the induction and maintenance of pain and the occurrence of many of the clinical features of FM (such as swelling, dysesthesia, skin manifestations, fluid retention, and increased levels of fibronectin, which is a tissue marker of endothelial activation) as a result of a neuroinflammatory condition that gives rise to descending pathways that influence predominant symptoms, such as pain, fatigue, and cognitive impairment. In addition, environmental triggers, stress, and emotions are the upstream driving mechanism of neurogenic inflammation in FM [74].

Therefore, the likelihood that FM may have an imbalance in cytokine production and secretion has been confirmed. Ucelyer et al. showed that FM patients have higher serum levels of IL-1ra, IL-6, and IL-8, and higher plasma levels of IL-8, compared to controls [75], while two studies of Lubkowska et al. showed how WBC affects the inflammatory status by inducing an imbalance towards the anti-inflammatory side [55][56]. Consecutive sessions of cryotherapy increased levels of IL-6, which can act both as a pro-inflammatory and anti-inflammatory cytokine, and IL-10, an anti-inflammatory cytokine, and lowered the IL-1α levels. Furthermore, WBC appears to improve the oxidative status already after a limited number of sessions, in a dose-dependent way [58][59].

Klemm et al. integrated the clinical effects with the molecular effects of WBC [37]. In parallel with changes in disease activity and pain reduction, patients with FM showed a significantly different response to WBC compared with healthy controls in terms of changes in IL1, -6, -10, and TNF-α over time to WBCs. FM patients had higher levels of IL-1, -6, -10, and TNF-α at baseline compared to healthy subjects. IL-1, IL-6, and IL-10 levels decreased significantly after three and six sessions and stabilized up to three months after discontinued WBC treatment. Interestingly, IL-6 levels returned to baseline after three months only in healthy controls and showed significantly decreased IL-6 levels at each reading point compared to baseline. WBC had no effect on TNF-α levels, neither in FM patients nor in healthy controls.

Therefore, even if the levels of IL-1, IL-6, and IL-10 in FM patients were higher than healthy controls after 6 WBC sessions and 3 months after the last WBC session, their significant alteration confirms the overall beneficial effects of WBC.

4. Gene Expression after WBC in FM

Drynda et al. investigated the changes in gene expression on peripheral blood cells of patients with FM going through a series of three exposures to WBC within three days [32]. One study correlated the reduced pain intensity with transcripts that were found significantly changed already after a single exposure to WBC. The majority of down-regulated transcripts belonged to a group of small nucleolar RNA (SNORD) while the up-regulated transcripts were a few specific genes, such as PBX1, SFRP2, MAP2K3, and SLC25A39. SNORD molecules belong to so-called non-coding RNAs. Emerging evidence has demonstrated that they are involved in various physiological and

pathological cellular processes acting as internal signals that control various levels of gene expression. However, the sample size and homogeneity were rather limited, as only 10 patients were studied.

Another study from the same group investigated on a larger cohort of 22 patients the changes in the gene expression of selected genes (CCL4, TGFBR3, CD69, and MAP2K3) identified as significantly regulated in cells from peripheral blood of patients with FM going through a series of three exposures to WBC within three days [31]. The expression levels of CCL4 and CD69, two proteins produced upon activation of T-lymphocytes, reduced significantly after the third exposure compared to baseline. In contrast, the expression of MAP2K3, a protein activated by cytokines and environmental stress in vivo, was found to be up-regulated in 13 patients, while the expression levels in the other 9 patients remained almost unchanged. Interestingly, the changes of gene expression were evident already after the first cold exposure, but reached statistical significance after the third exposure. The down-regulation of TGFBR3, a membrane proteoglycan that often functions as a co-receptor with other TGF-β receptors observed in the pilot study, could not be confirmed in the larger cohort. Unfortunately, both studies are scientific abstracts only and do not provide further speculation or discussion of the results.

References

1. Wolfe, F.; Clauw, D.J.; Fitzcharles, M.-A.; Goldenberg, D.L.; Katz, R.S.; Mease, P.; Russell, A.S.; Russell, I.J.; Winfield, J.B.; Yunus, M.B. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. Arthritis Care Res. 2010, 62, 600–610.
2. Sarzi-Puttini, P.; Giorgi, V.; Marotto, D.; Atzeni, F. Fibromyalgia: An Update on Clinical Characteristics, Aetiopathogenesis and Treatment. Nat. Rev. Rheumatol. 2020, 16, 645–660.
3. van Middendorp, H.; Lumley, M.A.; Jacobs, J.W.G.; van Doornen, L.J.P.; Bijlsma, J.W.J.; Geenen, R. Emotions and Emotional Approach and Avoidance Strategies in Fibromyalgia. J. Psychosom. Res. 2008, 64, 159–167.
4. Galvez-Sánchez, C.M.; Montoro, C.I.; Duschek, S.; Reyes Del Paso, G.A. Depression and Trait-Anxiety Mediate the Influence of Clinical Pain on Health-Related Quality of Life in Fibromyalgia. J. Affect. Disord. 2020, 265, 486–495.
5. Turk, D.C.; Wilson, H.; Swanson, K.S. The Biopsychosocial Model of Pain and Pain Management. In Behavioral and Psychopharmacologic Pain Management; Cambridge University Press: Cambridge, UK, 2010; pp. 16–43. ISBN 978-0-521-88434-1.
6. Varallo, G.; Giusti, E.M.; Scarpina, F.; Cattivelli, R.; Capodaglio, P.; Castelnuovo, G. The Association of Kinesiophobia and Pain Catastrophizing with Pain-Related Disability and Pain Intensity in Obesity and Chronic Lower-Back Pain. Brain Sci. 2021, 11, 11.

7. Varallo, G.; Scarpina, F.; Giusti, E.M.; Cattivelli, R.; Guerrini Usubini, A.; Capodaglio, P.; Castelnuovo, G. Does Kinesiophobia Mediate the Relationship between Pain Intensity and Disability in Individuals with Chronic Low-Back Pain and Obesity? Brain Sci. 2021, 11, 684.
8. Picavet, H.S.J.; Vlaeyen, J.W.S.; Schouten, J.S.A.G. Pain Catastrophizing and Kinesiophobia: Predictors of Chronic Low Back Pain. Am. J. Epidemiol. 2002, 156, 1028–1034.
9. Montoro, C.I.; Reyes del Paso, G.A. Personality and Fibromyalgia: Relationships with Clinical, Emotional, and Functional Variables. Personal. Individ. Differ. 2015, 85, 236–244.
10. Montoro, C.I.; Reyes del Paso, G.A.; Duschek, S. Alexithymia in Fibromyalgia Syndrome. Personal. Individ. Differ. 2016, 102, 170–179.
11. Velasco, L.; López-Gómez, I.; Gutiérrez, L.; Écija, C.; Catalá, P.; Peñacoba, C. Exploring the Preference for Fatigue-Avoidance Goals as a Mediator Between Pain Catastrophizing, Functional Impairment, and Walking Behavior in Women with Fibromyalgia. Clin. J. Pain 2022, 38, 182–188.
12. Kramer, S.; Deuschle, L.; Kohls, N.; Offenbächer, M.; Winkelmann, A. The Importance of Daily Activity for Reducing Fibromyalgia Symptoms: A Retrospective “Real World” Data Comparison of Two Multimodal Treatment Programs. Arch. Rheumatol. 2020, 35, 575–583.
13. Farin, E.; Ullrich, A.; Hauer, J. Participation and Social Functioning in Patients with Fibromyalgia: Development and Testing of a New Questionnaire. Health Qual. Life Outcomes 2013, 11, 135.
14. Creed, F. A Review of the Incidence and Risk Factors for Fibromyalgia and Chronic Widespread Pain in Population-Based Studies. Pain 2020, 161, 1169–1176.
15. Marques, A.P.; Santo, A.d.S.d.E.; Berssaneti, A.A.; Matsutani, L.A.; Yuan, S.L.K. Prevalence of Fibromyalgia: Literature Review Update. Rev. Bras. Reumatol. 2017, 57, 356–363.
16. Berger, A.; Dukes, E.; Martin, S.; Edelsberg, J.; Oster, G. Characteristics and Healthcare Costs of Patients with Fibromyalgia Syndrome. Int. J. Clin. Pract. 2007, 61, 1498–1508.
17. de la Coba, P.; Bruehl, S.; Moreno-Padilla, M.; Reyes del Paso, G.A. Responses to Slowly Repeated Evoked Pain Stimuli in Fibromyalgia Patients: Evidence of Enhanced Pain Sensitization. Pain Med. 2017, 18, 1778–1786.
18. de la Coba, P.; Bruehl, S.; Galvez-Sánchez, C.M.; Reyes Del Paso, G.A. Slowly Repeated Evoked Pain as a Marker of Central Sensitization in Fibromyalgia: Diagnostic Accuracy and Reliability in Comparison with Temporal Summation of Pain. Psychosom. Med. 2018, 80, 573–580.
19. Maugars, Y.; Berthelot, J.-M.; Le Goff, B.; Darrieutort-Laffite, C. Fibromyalgia and Associated Disorders: From Pain to Chronic Suffering, from Subjective Hypersensitivity to Hypersensitivity Syndrome. Front. Med. 2021, 8, 666914.

20. Montoro, C.I.; Duschek, S.; Muñoz Ladrón de Guevara, C.; Fernández-Serrano, M.J.; Reyes del Paso, G.A. Aberrant Cerebral Blood Flow Responses during Cognition: Implications for the Understanding of Cognitive Deficits in Fibromyalgia. Neuropsychology 2015, 29, 173–182.
21. Gracely, R.H.; Petzke, F.; Wolf, J.M.; Clauw, D.J. Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia. Arthritis Rheum. 2002, 46, 1333–1343.
22. Martínez-Lavín, M. Fibromyalgia and Small Fiber Neuropathy: The Plot Thickens! Clin. Rheumatol. 2018, 37, 3167–3171.
23. Clauw, D.J.; Arnold, L.M.; McCarberg, B.H. The Science of Fibromyalgia. Mayo Clin. Proc. 2011, 86, 907–911.
24. Perrot, S. Fibromyalgia: A Misconnection in a Multiconnected World? Perrot—European Journal of Pain; Wiley Online Library. 2019. Available online: https://onlinelibrary.wiley.com/doi/abs/10.1002/ejp.1367 (accessed on 7 March 2022).
25. Briones-Vozmediano, E.; Vives-Cases, C.; Ronda-Pérez, E.; Gil-González, D. Patients' and Professionals' Views on Managing Fibromyalgia. Pain Res. Manag. 2013, 18, 19–24.
26. Macfarlane, G.J.; Kronisch, C.; Dean, L.E.; Atzeni, F.; Häuser, W.; Fluß, E.; Choy, E.; Kosek, E.; Amris, K.; Branco, J.; et al. EULAR Revised Recommendations for the Management of Fibromyalgia. Ann. Rheum. Dis. 2017, 76, 318–328.
27. Häuser, W.; Welsch, P.; Klose, P.; Derry, S.; Straube, S.; Wiffen, P.J.; Moore, R.A. Pharmacological Therapies for Fibromyalgia in Adults—An Overview of Cochrane Reviews. Cochrane Database Syst. Rev. 2018, 2018, CD013151.
28. Rolls, C.; Prior, Y. 285 Non-Pharmacological Interventions for People with Fibromyalgia: A Systematic Review. Rheumatology 2018, 57, key075.509.
29. Hassett, A.L.; Williams, D.A. Non-Pharmacological Treatment of Chronic Widespread Musculoskeletal Pain. Best Pract. Res. Clin. Rheumatol. 2011, 25, 299–309.
30. Sadura-Sieklucka, T.; Sołtysiuk, B.; Karlicka, A.; Sokołowska, B.; Kontny, E.; Księżopolska-Orłowska, K. Effects of Whole Body Cryotherapy in Patients with Rheumatoid Arthritis Considering Immune Parameters. Reumatologia/Rheumatology 2019, 57, 320–325.
31. Drynda, S.; Mika, O.; Kekow, J. THU0313 Impact of Whole-Body Cryotherapy on Gene Expression of Peripheral Blood Cells in Patients with Fibromyalgia. Ann. Rheum. Dis. 2015, 74, 309.
32. Drynda, S.; Mika, O.; Koczan, D.; Kekow, J. AB0661 Impact of Whole-Body Cryotherapy on Transcriptome of Peripheral Blood Cells in Patients with Fibromyalgia. Ann. Rheum. Dis. 2013, 72, A990–A991.

33. Bettoni, L.; Bonomi, F.G.; Zani, V.; Manisco, L.; Indelicato, A.; Lanteri, P.; Banfi, G.; Lombardi, G. Effects of 15 Consecutive Cryotherapy Sessions on the Clinical Output of Fibromyalgic Patients. Clin. Rheumatol. 2013, 32, 1337–1345.
34. Bettoni, L.; Bonomi, F.G.; Zani, V.; Indelicato, A.; Banfi, G. THU0347|Efficacy and Safety of Whole Body Cryotherapy in Fibromyalgic Patients|Annals of the Rheumatic Diseases. Available online: https://ard.bmj.com/content/71/Suppl_3/273.1 (accessed on 7 March 2022).
35. Vitenet, M.; Tubez, F.; Marreiro, A.; Polidori, G.; Taiar, R.; Legrand, F.; Boyer, F.C. Effect of Whole Body Cryotherapy Interventions on Health-Related Quality of Life in Fibromyalgia Patients: A Randomized Controlled Trial. Complement. Ther. Med. 2018, 36, 6–8.
36. Metzger, D.; Zwingmann, C.; Protz, W.; Jäckel, W.H. Whole-body cryotherapy in rehabilitation of patients with rheumatoid diseases—Pilot study. Rehabilitation 2000, 39, 93–100.
37. Klemm, P.; Becker, J.; Aykara, I.; Asendorf, T.; Dischereit, G.; Neumann, E.; Müller-Ladner, U.; Lange, U. Serial Whole-Body Cryotherapy in Fibromyalgia Is Effective and Alters Cytokine Profiles. Adv. Rheumatol. 2021, 61, 3.
38. Kurzeja, R.; Gutenbrunner, C.; Krohn-Grimberghe, B. Primäre Fibromyalgie: Vergleich der Kältekammertherapie mit zwei klassischen Wärmetherapieverfahren. Aktuelle Rheumatol. 2003, 28, 158–163.
39. Sundaram, V.M. To Compare the Effectiveness of Whole Body Cryotherapy against Steam Therapy in Patients with Chronic Fibromyalgia. Physiotherapy 2015, 101, e988–e989.
40. Rivera, J.; Tercero, M.J.; Salas, J.S.; Gimeno, J.H.; Alejo, J.S. The Effect of Cryotherapy on Fibromyalgia: A Randomised Clinical Trial Carried out in a Cryosauna Cabin. Rheumatol. Int. 2018, 38, 2243–2250.
41. Romanowski, M.W.; Straburzyńska-Lupa, A. Is the Whole-Body Cryotherapy a Beneficial Supplement to Exercise Therapy for Patients with Ankylosing Spondylitis? J. Back Musculoskelet. Rehabil. 2020, 33, 185–192.
42. Miller, E.; Kostka, J.; Włodarczyk, T.; Dugué, B. Whole-Body Cryostimulation (Cryotherapy) Provides Benefits for Fatigue and Functional Status in Multiple Sclerosis Patients. A Case-Control Study. Acta Neurol. Scand. 2016, 134, 420–426.
43. Rymaszewska, J.; Lion, K.M.; Pawlik-Sobecka, L.; Pawłowski, T.; Szcześniak, D.; Trypka, E.; Rymaszewska, J.E.; Zabłocka, A.; Stanczykiewicz, B. Efficacy of the Whole-Body Cryotherapy as Add-on Therapy to Pharmacological Treatment of Depression—A Randomized Controlled Trial. Front. Psychiatry 2020, 11, 522.
44. Fontana, J.M.; Bozgeyik, S.; Gobbi, M.; Piterà, P.; Giusti, E.M.; Dugué, B.; Lombardi, G.; Capodaglio, P. Whole-Body Cryostimulation in Obesity: A Scoping Review. J. Therm. Biol. 2022, 106, 103250.

45. Kozłowska, M.; Kortas, J.; Żychowska, M.; Antosiewicz, J.; Żuczek, K.; Perego, S.; Lombardi, G.; Ziemann, E. Beneficial Effects of Whole-Body Cryotherapy on Glucose Homeostasis and Amino Acid Profile Are Associated with a Reduced Myostatin Serum Concentration. Sci. Rep. 2021, 11, 7097.
46. Bouzigon, R.; Grappe, F.; Ravier, G.; Dugue, B. Whole- and Partial-Body Cryostimulation/Cryotherapy: Current Technologies and Practical Applications. J. Therm. Biol. 2016, 61, 67–81.
47. Algafly, A.A.; George, K.P. The Effect of Cryotherapy on Nerve Conduction Velocity, Pain Threshold and Pain Tolerance. Br. J. Sports Med. 2007, 41, 365–369.
48. White, G.E.; Wells, G.D. Cold-Water Immersion and Other Forms of Cryotherapy: Physiological Changes Potentially Affecting Recovery from High-Intensity Exercise. Extreme Physiol. Med. 2013, 2, 26.
49. Kellogg, D.L. In Vivo Mechanisms of Cutaneous Vasodilation and Vasoconstriction in Humans during Thermoregulatory Challenges. J. Appl. Physiol. 2006, 100, 1709–1718.
50. Louis, J.; Theurot, D.; Filliard, J.-R.; Volondat, M.; Dugué, B.; Dupuy, O. The Use of Whole-Body Cryotherapy: Time- and Dose-Response Investigation on Circulating Blood Catecholamines and Heart Rate Variability. Eur. J. Appl. Physiol. 2020, 120, 1733–1743.
51. Dugué, B.; Bernard, J.P.; Bouzigon, R.; De Nardi, M.; Douzi, W.; Feirreira, J.J. Whole Body Cryotherapy/Cryostimulation, 39th Informatory Note on Refrigeration Technologies. Available online: https://iifiir.org/en/fridoc/whole-body-cryotherapy-cryostimulation-39-lt-sup-gt-th-lt-sup-gt-informatory-142805 (accessed on 20 January 2022).
52. Ziemann, E.; Olek, R.A.; Kujach, S.; Grzywacz, T.; Antosiewicz, J.; Garsztka, T.; Laskowski, R. Five-Day Whole-Body Cryostimulation, Blood Inflammatory Markers, and Performance in High-Ranking Professional Tennis Players. J. Athl. Train. 2012, 47, 664–672.
53. Lange, U.; Uhlemann, C.; Müller-Ladner, U. Serial whole-body cryotherapy in the criostream for inflammatory rheumatic diseases. A pilot study. Med. Klin. Munich Ger. 1983 2008, 103, 383–388.
54. Banfi, G.; Melegati, G.; Barassi, A.; Dogliotti, G.; Melzi d'Eril, G.; Dugué, B.; Corsi, M.M. Effects of Whole-Body Cryotherapy on Serum Mediators of Inflammation and Serum Muscle Enzymes in Athletes. J. Therm. Biol. 2009, 34, 55–59.
55. Lubkowska, A.; Szyguła, Z.; Chlubek, D.; Banfi, G. The Effect of Prolonged Whole-Body Cryostimulation Treatment with Different Amounts of Sessions on Chosen pro- and Anti-Inflammatory Cytokines Levels in Healthy Men. Scand. J. Clin. Lab. Investig. 2011, 71, 419–425.
56. Lubkowska, A.; Szygula, Z.; Klimek, A.J.; Torii, M. Do Sessions of Cryostimulation Have Influence on White Blood Cell Count, Level of IL6 and Total Oxidative and Antioxidative Status in Healthy Men? Eur. J. Appl. Physiol. 2010, 109, 67–72.

57. Pournot, H.; Bieuzen, F.; Louis, J.; Fillard, J.-R.; Barbiche, E.; Hausswirth, C. Time-Course of Changes in Inflammatory Response after Whole-Body Cryotherapy Multi Exposures Following Severe Exercise. PLoS ONE 2011, 6, e22748.
58. Lubkowska, A.; Dołęgowska, B.; Szyguła, Z. Whole-Body Cryostimulation—Potential Beneficial Treatment for Improving Antioxidant Capacity in Healthy Men—Significance of the Number of Sessions. PLoS ONE 2012, 7, e46352.
59. Wojciak, G.; Szymura, J.; Szygula, Z.; Gradek, J.; Wiecek, M. The Effect of Repeated Whole-Body Cryotherapy on Sirt1 and Sirt3 Concentrations and Oxidative Status in Older and Young Men Performing Different Levels of Physical Activity. Antioxidants 2021, 10, 37.
60. Lubkowska, A.; Dudzińska, W.; Bryczkowska, I.; Dołęgowska, B. Body Composition, Lipid Profile, Adipokine Concentration, and Antioxidant Capacity Changes during Interventions to Treat Overweight with Exercise Programme and Whole-Body Cryostimulation. Oxid. Med. Cell. Longev. 2015, 2015, 803197.
61. Stanek, A.; Cholewka, A.; Gadula, J.; Drzazga, Z.; Sieron, A.; Sieron-Stoltny, K. Can Whole-Body Cryotherapy with Subsequent Kinesiotherapy Procedures in Closed Type Cryogenic Chamber Improve BASDAI, BASFI, and Some Spine Mobility Parameters and Decrease Pain Intensity in Patients with Ankylosing Spondylitis? BioMed Res. Int. 2015, 2015, 404259.
62. Banfi, G.; Lombardi, G.; Colombini, A.; Melegati, G. Whole-Body Cryotherapy in Athletes. Sports Med. Auckl. NZ 2010, 40, 509–517.
63. Lubkowska, A.; Chudecka, M.; Klimek, A.; Szyguła, Z.; Frączek, B. Acute Effect of a Single Whole-Body Cryostimulation on Prooxidant–Antioxidant Balance in Blood of Healthy, Young Men. J. Therm. Biol. 2008, 8, 464–467.
64. Lombardi, G.; Ziemann, E.; Banfi, G. Whole-Body Cryotherapy in Athletes: From Therapy to Stimulation. An Updated Review of the Literature. Front. Physiol. 2017, 8, 258.
65. Berk, M.; Williams, L.J.; Jacka, F.L.; O'Neil, A.; Pasco, J.A.; Moylan, S.; Allen, N.B.; Stuart, A.L.; Hayley, A.C.; Byrne, M.L.; et al. So Depression Is an Inflammatory Disease, but Where Does the Inflammation Come from?|BMC Medicine|Full Text. Available online: https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-11-200 (accessed on 7 March 2022).
66. Veltri, A.; Scarpellini, P.; Piccinni, A.; Conversano, C.; Giacomelli, C.; Bombardieri, S.; Bazzichi, L.; Dell'Osso, L. Methodological Approach to Depressive Symptoms in Fibromyalgia Patients. Clin. Exp. Rheumatol. 2012, 30, 136–142.
67. Marchand, S. Mechanisms Challenges of the Pain Phenomenon. Front. Pain Res. 2021, 1, 574370.

68. Yam, M.F.; Loh, Y.C.; Tan, C.S.; Khadijah Adam, S.; Abdul Manan, N.; Basir, R. General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. Int. J. Mol. Sci. 2018, 19, 2164.
69. Dubin, A.E.; Patapoutian, A. Nociceptors: The Sensors of the Pain Pathway. J. Clin. Investig. 2010, 120, 3760–3772.
70. Latremoliere, A.; Woolf, C.J. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. J. Pain 2009, 10, 895–926.
71. Staud, R. Peripheral Pain Mechanisms in Chronic Widespread Pain. Best Pract. Res. Clin. Rheumatol. 2011, 25, 155–164.
72. Littlejohn, G.; Guymer, E. Neurogenic Inflammation in Fibromyalgia. Semin. Immunopathol. 2018, 40, 291–300.
73. Hung, A.L.; Lim, M.; Doshi, T.L. Targeting Cytokines for Treatment of Neuropathic Pain. Scand. J. Pain 2017, 17, 287–293.
74. Vanderwall, A.G.; Milligan, E.D. Cytokines in Pain: Harnessing Endogenous Anti-Inflammatory Signaling for Improved Pain Management. Front. Immunol. 2019, 10, 3009.
75. Uçeyler, N.; Häuser, W.; Sommer, C. Systematic Review with Meta-Analysis: Cytokines in Fibromyalgia Syndrome. BMC Musculoskelet. Disord. 2011, 12, 245.