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REVIEW

Role of inflammation in the pathogenesis and treatment of fibromyalgia

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Abstract

Fibromyalgia is a multifaceted disease. The clinical picture of fibromyalgia covers numerous comorbidities. Each comorbidity stands as a distinct condition. However, common pathophysiologic factors are occupied in their background. Along with the genetic, environmental and neuro-hormonal factors, inflammation has been supposed to have role in the pathogenesis of fibromyalgia. The aim of the present article was to review the current literature regarding the potential role of inflammation in the pathogenesis and treatment of fibromyalgia. A literature search was conducted through PubMed/MEDLINE and Web of Science databases using relevant keywords. Recent evidence on this highly studied topic indicates that fibromyalgia has an immunological background. Cytokines/chemokines, lipid mediators, oxidative stress and several plasma-derived factors underlie the inflammatory state in fibromyalgia. There are potential new therapeutic options targeting inflammatory pathways in fibromyalgia patients. In conclusion, there is evidence to support the inflammation-driven pathways in the pathogenesis of fibromyalgia. However, further research is required to fully understand the network of inflammation and its possible role in diagnosis and/or treatment of fibromyalgia.

Keywords Cytokines · Fibromyalgia · Inflammation · Inflammatory markers · Neurogenic inflammation · Treatment

Introduction

Fibromyalgia is a chronic rheumatic condition characterized by widespread pain and various comorbidities. The prevalence of fibromyalgia ranges between 2 and 8% depending on the criteria used for diagnosis. Fibromyalgia is seen either alone or as a comorbidity in other rheumatic diseases such as rheumatoid arthritis, osteoarthritis and systemic lupus erythematosus. Main clinical features of fibromyalgia are generalized pain, sleep impairment, mood disorders, irritable bowel syndrome, headache, genitourinary symptoms and fatigue. Although each seems as a distinct condition, they are connected closely to each other like pieces of a "jigsaw puzzle" [1–4].

Due to its over-complicated nature, treatment is often challenging in fibromyalgia. Chronic generalized pain is the primary target of management. Nevertheless, numerous comorbidities in fibromyalgia require a more comprehensive look [1–4]. Since, not only chronic pain, but also fatigue, psychological comorbidities and sleep disturbances might contribute to functional limitation, absence from work and social isolation in patients with fibromyalgia.

What is the trigger of these events in fibromyalgia? There are many factors identified and many still being studied. These are classified as (1) genetic, (2) environmental, (3) hormonal and (4) neural factors [1, 5]. There might also be immunological alterations that consequently lead to an inflammatory state in fibromyalgia [5–8]. Over the past decade, extensive research has been conducted on the immunologic background of fibromyalgia. Findings, in general, contradict with the knowledge that 'fibromyalgia is a non-inflammatory rheumatic condition' [9–14]. What is the role of inflammation in fibromyalgia pathogenesis? Does it stand at the very beginning of the disease? Does it relate to the comorbid conditions? Does it provide new insights to the treatment of fibromyalgia?

With these questions in mind, the objective of the present article is to review the current knowledge regarding the potential role of inflammation in the pathogenesis and management of fibromyalgia.

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Search strategy

The present article followed the search strategy recommended for narrative reviews [15]. Accordingly, PubMed/MEDLINE and Web of Science databases were searched through MeSH-recognized terms including "fibromyalgia" and "inflammation". Observational studies, randomized controlled trials and case–control studies written in English and published within the past 7 years till 9th September, 2018 were included. Case reports, animal studies, review articles, editorials, letters, conference papers and unpublished data were excluded. Reference lists of included articles were scanned. Articles were added if they met the inclusion criteria and were not included in earlier stages of the review (Fig. 1).

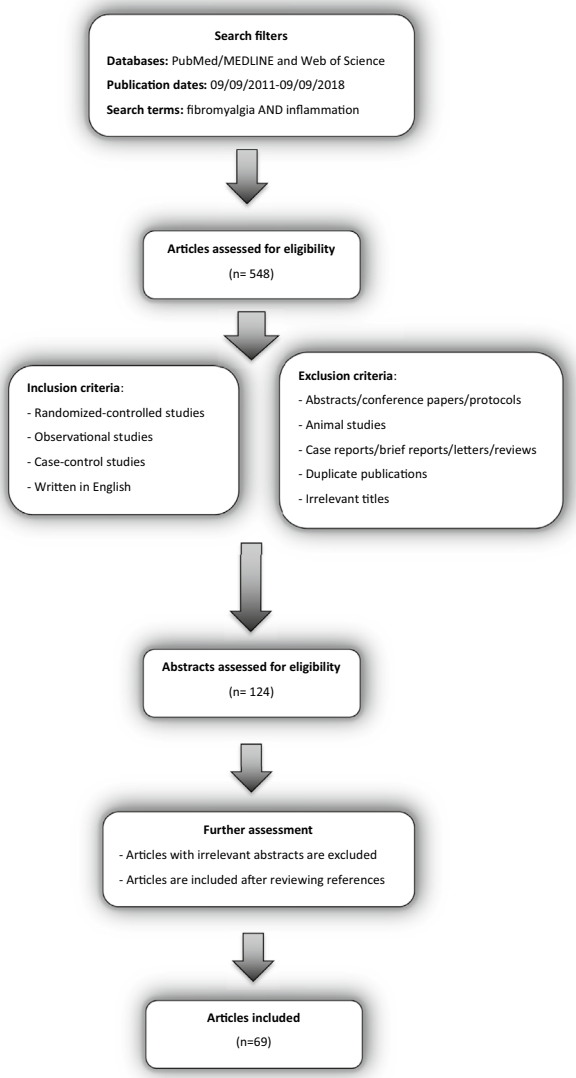

Fig. 1 Flowchart of the narrative review

What is inflammation?

Inflammation is a defensive process that is necessary for human life. Without inflammation, response to endogenous/exogenous insults and tissue repair after any kind of injury would not be possible. The crosstalk among innate/adaptive immunity, coagulative/fibrinolytic pathways and the nervous system is necessary for proper inflammatory cascade. This crosstalk is enabled with messengers called 'inflammatory mediators'. Mediators of inflammation can be classified as cell-derived and plasma-derived mediators [16, 17]. Several cells including macrophages, leucocytes, lymphocytes, endothelial cells, mast cells and platelets play role in inflammation. Cell-derived mediators vary in nature and include the cytokines (interleukins, tumor necrosis factor, and chemokines), lysosomal components (proteases, collagenase, and elastase), arachidonic acid derives (cyclooxygenase and lipoxygenase), oxygen-derived free radicals, reactive oxygen species, nitric oxide, neuropeptides, growth factors, platelet-activating factor, lipid mediators (adiponectin, leptin, and endocannabinoids), and vasoactive amines (serotonin and histamin). On the other hand, plasma-derived inflammatory mediators are synthesized in the liver and include the coagulation factors, acute phase proteins and complement proteins [17].

Cell-derived inflammatory mediators in fibromyalgia

Cell-driven inflammatory pathways in fibromyalgia are illustrated in Fig. 2.

Cytokines

Cytokines are small polypeptides released from both immune (monocytes, T cells, and macrophages) and non-immune cells (Schwann cells, fibroblasts, microglias, and astrocytes) [18, 19]. Cytokines are classified as anti-inflammatory and pro-inflammatory cytokines. In fibromyalgia, the balance between pro- and anti-inflammatory cytokines is suggested being disrupted in favor of pro-inflammatory cytokines. Distinct gene variants are supposed to be associated with cytokine release and the inflammatory state in fibromyalgia [20–22]. The upregulation of pro-inflammatory cytokines including TNF, IL-1,

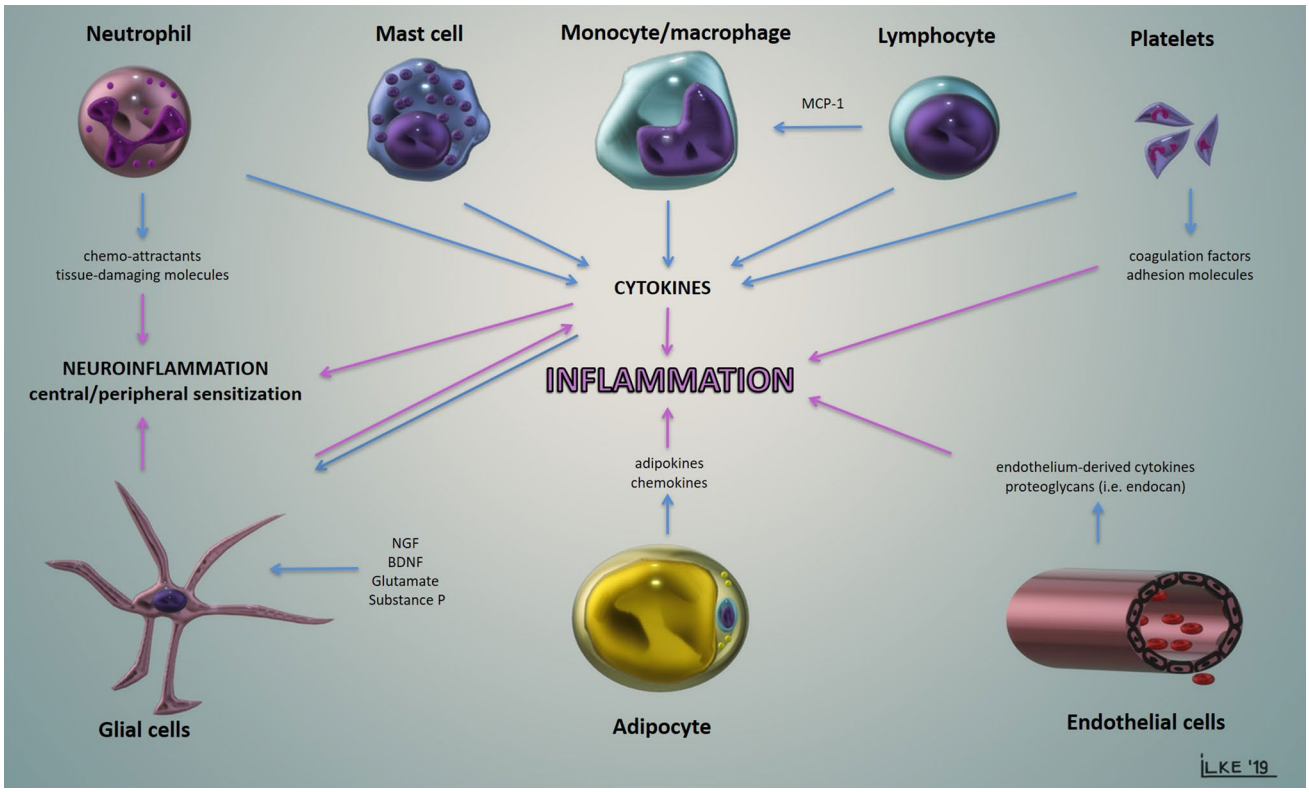

Fig. 2 Cell-driven inflammation in fibromyalgia (Illustrated by the Author Ilke Coskun Benlidayi; *MCP-1* monocyte chemoattractant protein-1, *BDNF* brain-derived neurotrophic factor, *NGF* nerve growth factor)

IL-6, and IL-8 might be related to several disease-related comorbidities in fibromyalgia.

Cytokines act their role through peripheral or central mechanisms. They modify the peripheral neuroimmune interactions, as well as the neuroinflammation process in the spinal cord and brain. Central neuroinflammation and central sensitization are connected closely in fibromyalgia [18]. Central neuroinflammation is triggered by the increased levels of cytokines and neurotrophic factors in cerebrospinal fluid. Substance P, brain-derived neurotrophic factor, glutamate, nerve growth factor and several inflammatory mediators activate glial cells. Activated glial cells produce pro-inflammatory cytokines and lead to neuroinflammation. This phenomenon increases the central processing of nociceptive input and contributes to chronic pain, allodynia and hyperalgesia in fibromyalgia. As an evidence of central neuroinflammation, intrathecal concentration of IL-8 is elevated in fibromyalgia patients when compared to healthy controls [9]. However, similar increase is not the case for IL-1β which is another pro-inflammatory cytokine. The increase in IL-8 level might be related to glial cell activation, which is an important determinant of central sensitization and hyperalgesia, since glial cells are activated by the excitatory substances of the central nervous system or by pro-inflammatory cytokines released from peripheral immune cells. This vicious cycle can be amplified by stress and can explain the stress-induced symptom aggravation in fibromyalgia. While IL-8 production is mediated by the activation of sympathetic nervous system, IL-1β is related to the cyclooxygenase activity. The elevated IL-8 concentration with the lack of IL-1β increase indicates that symptoms in fibromyalgia are mediated by sympathetic nervous system, instead of the prostaglandin-related pathways [9, 10]. The combination of autonomic dysfunction and elevated stress levels in fibromyalgia is also in line with this finding [10]. Management in fibromyalgia should take these sympathetically mediated disease features into consideration. Medications targeting beta-adrenergic receptors should be preferred instead of non-steroidal anti-inflammatory drugs targeting the cyclooxygenase pathway.

Several studies focused on serum/plasma cytokine concentrations in fibromyalgia [11, 12, 23, 24]. A number of studies showed elevated levels of IL-6, IL-8, IL-1β or TNF-alpha in fibromyalgia [11–14]. However, there are studies with conflicting results as well [23, 25, 26]. Ranzolin et al. found no difference in biomarker levels (except for IL-10) between fibromyalgia patients and controls. No correlation was detected between biomarkers and disease severity [23]. On the other hand, there is evidence that IL-10 level increases in fibromyalgia [13, 23]. IL-10 is an

anti-inflammatory cytokine also known as human cytokine synthesis inhibitory factor. High IL-10 levels in fibromyalgia patients may be related to the effort on compensating the inflammatory state [13].

Cytokines may involve in comorbidities related to fibromyalgia [11]. Supporting this hypothesis, IL-6 showed positive correlation with the severity and sensation of pain in fibromyalgia [12]. Patients with fibromyalgia also revealed increased plasma levels of IL-17 when compared to healthy controls. Moreover, IL-17 was found to be correlated with other pro-inflammatory cytokines including TNF, IFNγ, IL-2, IL-4 and IL-10 [24]. On the other hand, T_H2 cytokines including IL-4, IL-5 and IL-13 are suppressed in fibromyalgia. Analgesic properties of IL-4 and IL-13 highlight the potential role of T_H1-T_H2 imbalance in generalized pain [27]. A microdialysis study evaluated the inflammatory response to repetitive dynamic muscle contraction in fibromyalgia patients. Samples were collected from the most painful point of the vastus lateralis and analyzed in terms of pro-inflammatory cytokine (IL-1β, IL-6, IL-8, and TNF) concentrations. The results revealed no correlation between cytokine level and pain or fatigue [19].

Mast cells are implicated in allergy and immunity. These cells have also been considered as potential contributors of inflammation in fibromyalgia [2]. IL-6 and TNF-alpha, two main pro-inflammatory cytokines secreted from mast cells are significantly higher in fibromyalgia patients when compared to controls. Serum levels of neuropeptides such as neuropeptide Y, corticotropin-releasing hormone, substance P and its structurally related hemokinin-1 levels are also elevated in fibromyalgia. These peptides can stimulate mast cells to secrete cytokines. Pro-inflammatory cytokines can further stimulate neurons to release more neuropeptides [28, 29]. Thus, a vicious cycle of inflammation is established in fibromyalgia through neuron-inflammatory cell interaction.

Monocytes are precursors of pro-inflammatory cytokines. At the beginning of an inflammatory process, monocyte count increases in peripheral circulation. As cells migrate in tissues to produce pro-inflammatory cytokines, monocyte number shows a decrease. Taylor et al. examined the potential role of monocytes in fibromyalgia. Total percentage of circulating monocytes was not different from that in healthy controls. However, percentages of circulating monocyte subtypes (intermediate and classical) were inversely correlated with perceived pain [30].

Chemokines

Chemokines are small cytokines produced by various stimuli. Chemokines are divided in four categories as CC-, CXC-, CX_3C- and XC- chemokine ligands. Chemokine receptors are highly distributed in glial cells, neurons, neural progenitor cells and leukocytes. Chemokines play role in pain modulation and regulation through direct or indirect mechanisms. Direct action is related to the activation of neurons, whereas indirect action is due to leukocyte activation. Both peripheral and central nervous system cells can be activated by chemokines. Therefore, chemokines play important role in peripheral and central sensitization [31]. This phenomenon might be of value for the pathogenesis of fibromyalgia, as there is some evidence that the chemoattractant chemokine levels are higher than healthy population [32]. Wallace et al. undertook a comparative analysis as to test the cytokine/chemokine profile in fibromyalgia [33]. Concentrations of IL-6 and IL-8, macrophage inflammator cerebrospinal fluid y protein-1 alpha and beta were combined to a single score and compared among patients with fibromyalgia, rheumatoid arthritis, systemic lupus erythematosus and healthy controls. Each group revealed distinct cytokine/chemokine profile and fibromyalgia group demonstrated less response to mitogenic stimulation. The unique cytokine/chemokine pattern in fibromyalgia showed diagnostic sensitivity and specificity [33]. Instead of examining a limited number of predetermined chemokines/cytokines, Bäckryd et al. used a multiplex protein panel to simultaneously analyze 92 inflammation-related proteins in fibromyalgia [34]. Neuroinflammation and systemic inflammation were assessed in cerebrospinal fluid and plasma, respectively. High levels of fractaline (a chemokine released from the first-order neurons) and IL-8 in cerebrospinal fluid certified central inflammation in fibromyalgia. On the other hand, high plasma IL-8 level was consistent with systemic inflammation [34].

Neutrophils participate as mediators of inflammation. There is some evidence that neutrophil count is higher in patients with fibromyalgia than that in healthy population [35]. These cells secrete a variety of cytokines, chemoattractants and tissue-damaging molecules [36]. The neutrophil to lymphocyte ratio (NLR) is proposed as a prognostic marker for systemic inflammation. Patients with fibromyalgia have significantly higher NLR than healthy population, indicating the potential role of neutrophil-related inflammation in fibromyalgia [37, 38]. Endothelial cells and endothelium-derived cytokines are other modulators of inflammation. A study by Mertoglu et al. showed that level of endocan, a proteoglycan produced by endothelial cells, was significantly higher in patients with fibromyalgia when compared to healthy controls [39].

Cytokine/chemokine profile in fibromyalgia should be evaluated within the framework of aging, since inflammatory response changes in elderly/older adults regardless of fibromyalgia. On the other hand, menopause is another milestone in female-specific cytokine production. In postmenopausal women with fibromyalgia, pain catastrophizing, pain-related anxiety and depression are correlated with IL-8 level

[40]. Therefore, researchers should pay specific attention on age-related factors including current menstrual status.

Lipid mediators

Adipokines have crucial role in immune response and inflammation. Passing through the brain–blood barrier, adipokines can also modulate central activity and central pain regulation. Adiponectin is considered as an anti-inflammatory adipokine. Visfatin, lesitin and leptin have been described to have pro-inflammatory features [41]. Leptin increases the number and vitality of T lymphocytes and also attracts macrophages via monocyte chemoattractant protein-1 [42]. Moreover, leptin enhances pain sensitivity through neuropeptide Y-dependent mechanism and considered as a pro-nociceptive adipokine. In patients with fibromyalgia, cerebrospinal leptin level is higher and adiponectin level is lower than serum levels [41]. This finding can be important for explaining central-mediated comorbidities in fibromyalgia.

Adipocytes are sources of adipokines and chemokines. Therefore, adipocytes bear a great potential to enhance inflammatory response [43]. Adipose tissue that is composed of preadipocytes, adipocytes and immune cells has been considered as a regulator of pain and inflammation in fibromyalgia. However, the recent literature has conflicting results with increased, decreased and unchanged levels of leptin in patients with fibromyalgia [42, 44–46]. Studies showed no correlation between leptin level and clinical variables (pain threshold, tender point count, quality of life, and mood) or inflammatory parameters (monocyte chemoattractant protein-1 and C-reactive protein) [42, 44]. On the other hand, smoking is associated with higher pain experience in fibromyalgia. This effect is partly driven by the deregulation of leptin-neuropeptide Y interaction [41].

Endocannabinoid system modulates immune cell function. Stensson et al. evaluated the relation between endocannabinoidome lipid mediators and symptoms of fibromyalgia. The results revealed higher levels endocannabinoid lipids in patients with fibromyalgia when compared to controls. However, their biologic roles on comorbidities remained uncertain [47].

Reactive oxygen species and free radicals

Oxidative stress and inflammation are interconnected. In inflammatory disease, inflammation increases the energy demand and contributes to a hypoxic state. On the other hand, mitochondrial dysfunction in inflammatory diseases leads to an increase in reactive oxygen species. Oxidative damage causes further inflammation, creating a vicious cycle [48]. With their high-lipid content, neural cells are sensible to reactive oxygen species and lipid peroxidation. Therefore, oxidative stress can be regarded as a confounder of neuroinflammation [49]. Several studies showed increased levels of oxidative stress markers in fibromyalgia [50, 51]. Mitochondrial dysfunction, impaired bioenergetics and reduced anti-oxidant enzyme levels are considered as underlying factors of oxidative stress and inflammation in fibromyalgia [50]. Blood mononuclear cells of fibromyalgia patients have reduced mitochondrial DNA content and coenzyme Q10 and contain high levels of reactive oxygen species [51]. Reactive oxygen species lead to lipid peroxidation and increase in oxidative products such as lysophosphocolines. Lysophosphocolines, acting through platelet-activating factor receptor, can contribute to inflammation and pain [52]. Adenosine monophosphate-activated protein kinase (AMPK) plays regulatory role in all these events [50]. Modulation of AMPK can reduce inflammatory response by inhibiting the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome [53].

Skin is a tissue that is involved in nociception. Skin-related symptoms are associated with small fiber neuropathy in fibromyalgia. Besides, skin biopsies from fibromyalgia patients reveal mitochondrial dysfunction, decreased coenzyme Q10 level, reduced mitochondrial DNA content and enzyme activity [54]. Damaged mitochondrial DNA accumulation in a cell leads to an innate inflammatory response. Accordingly, mitochondrial DNA content in fibromyalgia is inversely correlated with TNF-alpha levels.

Plasma-derived inflammatory mediators in fibromyalgia

Plasma-derived mediators of inflammation include the complements, coagulation factors and acute phase proteins:

Complements and coagulation factors

Evidence regarding the role of complement and coagulation systems in fibromyalgia pathogenesis is relatively limited. A recent study examined the plasma proteome profile of patients with fibromyalgia. Moreover, the study analyzed the molecular network/pathways related to the overexpressed proteins in fibromyalgia. Researchers determined 33 differently expressed proteins, majority of which were related to inflammatory pathways such as coagulation system, complements and acute phase response signaling [34]. As an important finding, the results highly overlapped with those reported by Gerdle et al. in their cross-sectional study on chronic widespread pain [55].

Complement and coagulation systems play crucial roles in inflammation. Pathways related to complement proteins are mainly triggered by immunoglobulin M- and G-antigen complexes. High immunoglobulin M level in patients with

fibromyalgia is consistent with this knowledge [5]. Several coagulation factors are overexpressed in fibromyalgia and most of these proteins can activate the complement cascade. The extrinsic and intrinsic plasminogen-activating systems are related to these coagulation factors. Therefore, fibromyalgia can be considered as a pro-coagulant condition. Higher expression of fibrinogen and alterations in platelet distribution in fibromyalgia support this theory [5, 37].

Acute phase proteins

Acute phase proteins are categorized as positive and negative acute phase reactants. As indicators of inflammation, positive acute phase reactants are upregulated in fibromyalgia, while negative acute phase proteins are decreased. As an indirect measure of this finding, there is some evidence that erythrocyte sedimentation rate is higher in fibromyalgia than that in healthy controls [5]. However, there is also evidence showing that erythrocyte sedimentation rate is unchanged in patients with fibromyalgia [25, 37, 56]. Data on C-reactive protein are also conflicting [13, 25, 37, 57, 58]. A study with a large sample size revealed a positive association between C-reactive protein and fibromyalgia. However, this association was attenuated after adding body mass index and comorbidities in the model. Sleep impairment and mood disorders also attenuated, but did not eliminate this relationship [57]. The results revealed that obesity and comorbid conditions are partly responsible for the inflammatory status in fibromyalgia [25, 57, 59].

Platelets are positive acute phase reactants that are highly produced in response to inflammatory conditions, whilst decreased lymphocyte number is related to an uncontrolled inflammatory state. Therefore, platelet to lymphocyte ratio might be considered as an indicator of inflammation. As a sign of inflammatory status, platelet to lymphocyte ratio shows increase in fibromyalgia [38].

Potential therapeutic options targeting inflammation

The clinical importance of inflammation in fibromyalgia is related to its potential role in diagnostic and therapeutic decision making. Certain cytokines (IL-6, IL-8 and TNF-alpha), cytokine/chemokine profile, acute phase reactants and adipokines are suggested as diagnostic markers in fibromyalgia. There are also cell-based markers such as NLR, platelet count, platelet to lymphocyte ratio and mitochondrial DNA content. Each can provide some insight on the inflammatory state in fibromyalgia patients. However, knowledge so far indicates that none of these inflammation markers alone are diagnostic/predictive biomarkers for fibromyalgia. As for management of the patient, there are several potential therapeutic options targeting inflammation-related pathways in fibromyalgia (Fig. 3).

Anti-cytokine therapy

Pro-inflammatory cytokines are main confounders of inflammation. These molecules can also contribute to the initiation/progression of comorbidities such as generalized pain, fatigue, sleep impairment and mood disorders in fibromyalgia. Therefore, pro-inflammatory cytokines have been considered as potential targets of treatment. Mastrangelo et al. suggested that anti-inflammatory cytokines such as IL-37 could serve therapeutic benefits by inhibiting IL-1 and TNF-alpha [2]. However, literature so far does not specify any monoclonal antibodies or other biologic drugs in fibromyalgia treatment. Future research is needed to evaluate the potential role of biologics in the management of fibromyalgia.

Evidence so far confirms that low-dose naltrexone has beneficial effects in patients with fibromyalgia [60, 61]. Baseline inflammatory status defined by erythrocyte sedimentation rate, predicts the response to naltrexone [60].

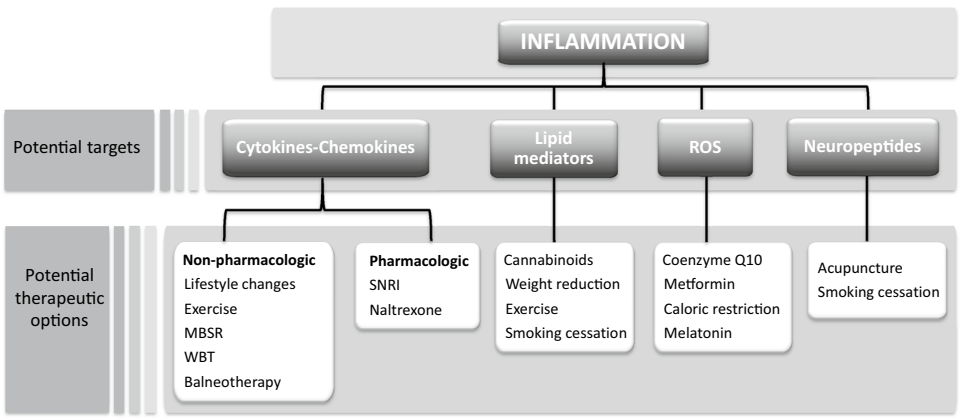

Fig. 3 Potential therapeutic options targeting inflammation in fibromyalgia (*ROS* reactive oxygen species, *MBSR* mindfulness-based stress reduction, *WBT* whole-body cryotherapy, *SNRI* serotonin and norepinephrine reuptake inhibitor)

Therefore, a potential immunomodulatory effect of naltrexone might be possible. Confirming this suggestion, a single-blind, crossover trial revealed that 8 weeks administration of low-dose naltrexone was related to the reduction of cytokine levels in plasma. It is noteworthy to state that the cytokines most suppressed by low-dose naltrexone were those involved in nociception, allodynia and hyperalgesia [61].

Palmitoylethanolamide is a fatty acid amine that provides anti-inflammatory effects by inhibiting mast cell degranulation, release of cytokines and immune-related activation of glial cells. An open-label non-randomized, non-blinding study showed that palmitoylethanolamide therapy in combination to pregabaline and duloxetine provided additional benefit in terms of pain relief [62]. As potent inhibitors of inflammation, glucocorticoids might be considered to have therapeutic effect in fibromyalgia. However, a clinical study on fibromyalgia showed reduced sensitivity of circulating monocytes to the immunosuppressive effects of glucocorticoids [35]. Besides, it was shown that higher dexamethasone dose was required to inhibit IL-6 production in fibromyalgia patients. This finding is in line with the hypothesis that main clinical features of fibromyalgia (fatigue and pain) are associated with disturbed glucocorticoid receptor signaling pathway, instead of reduced glucocorticoid levels, as the reduction in glucocorticoid sensitivity is accompanied by increased fatigue frequency [35]. On the other hand, reduced sensitivity of monocytes to the immune-suppressive effects of glucocorticoids has also potential importance for treatment strategies in fibromyalgia. Although glucocorticoids are potent anti-inflammatory molecules, disturbed glucocorticoid receptor signaling pathway blocks this potency in fibromyalgia.

Serotonin and norepinephrine reuptake inhibitors are recommended treatment options for fibromyalgia [63]. Researchers have focused on their anti-inflammatory potentials through serotonin- and noradrenaline-related pathways [64]. Milnacipran, a dual reuptake inhibitor, acts its therapeutic effect partly by targeting glial activation and thereby inhibiting neuroinflammation. It reduces ventricular lactate, which serves as a proxy for central inflammation [65].

In terms of non-pharmacological treatment options, lifestyle modifications (smoking cessation, regular physical activity and healthy dieting) would be of value. Since, gastrointestinal dysbiosis, vitamin D insufficiency/deficiency and obesity are potential contributors of inflammatory diseases [66]. Dietary weight loss alone can reduce IL-6 levels in fibromyalgia [67]. Whole-body cryotherapy has been suggested as a therapeutic modality for inflammatory conditions. Research on fibromyalgia revealed favorable results, as well. In a comparative study by Bettoni et al., patients treated with cryotherapy reported more improvement in pain perception, fatigue and quality of life than those in the non-cryotherapy group [68]. The effectiveness might be in part related to the immunomodulatory effects of cold therapy. On the other hand, a number of studies showed that mud-bathing therapy and/or balneotherapy were effective in reducing inflammatory markers in patients with fibromyalgia [69, 70]. Acupuncture is another non-pharmacological option for fibromyalgia. Acupuncture was shown to drive its pain modulatory effect by decreasing neuropeptide Y levels in patients with fibromyalgia [29]. Overall, further research is needed to support the limited evidence regarding non-pharmacological therapies.

Stress induces pro-inflammatory cytokine production. Therefore, mindfulness-based stress reduction might be a reasonable therapeutic option for suppressing inflammation in patients with fibromyalgia. Mindfulness meditation improves psychological comorbidities in fibromyalgia. It has been proven that mindfulness-based stress reduction reduces anger and anxiety, thereby improves mood and social isolation in fibromyalgia. Mindfulness meditation can also be beneficial in relieving generalized pain [71, 72]. However, further studies are required to clarify the biologic background of mindfulness-based symptom relief in fibromyalgia.

Anti-oxidants and mitochondrial protector drugs

Mitochondrial dysfunction is supposed to play crucial role in fibromyalgia pathogenesis. Mitochondrial biogenesis activators and mitochondrial protector drugs may serve as new therapeutic options. AMPK is one of the regulators of oxidative stress and peripheral sensitization of nociceptors. Therefore, new therapeutic strategies such as metformin and caloric restriction might help restoring this master regulatory molecule. Since, it was already shown that metformin and caloric restriction enhance AMPK function and improve defense against oxidative stress [50]. Besides, in a series of fibromyalgia patients, oral supplementation of coenzyme Q10 (a powerful free radical scavenger) was found effective in reducing TNF-alpha levels and improving clinical outcomes including headache and pain [51, 73]. This finding might be related to the inhibitory effect of coenzyme Q10 on NLRP3 inflammasome [74]. Melatonin and its precursor serotonin are also important in removing oxygen radicals [75]. A phase II, randomized, double-dummy, controlled trial showed that 10 mg/day melatonin potentiated the inhibitory endogenous pain-modulating system, with better responses than amitriptyline alone in improving pain [76]. Hyperbaric oxygen therapy is supposed as a new therapeutic option in fibromyalgia. A prospective, active control, crossover trial revealed that hyperbaric oxygen was effective in relieving symptoms, improving quality of life and rectifying abnormal brain activity in patients with fibromyalgia [77].

Exercise

Exercise is strongly recommended as a non-pharmacological treatment option for fibromyalgia [63]. There are several underlying mechanisms of exercise-related benefits. The potential role of exercise on inflammation has attracted attention in recent years [78–83]. Research mainly focused on aerobic exercise [78–80]. Even a single bout moderate cycling enabled decrease in IL-8, cortisol and heat shock protein levels, as well as in neutrophil chemotaxis and monocyte's cytokine release [80]. Results regarding aquatic exercise are also favorable [82, 83]. Aquatic exercise for 8 months (two sessions per week, 60 min per session) provided a neuro-immuno-endocrine adaptation as evaluated through neutrophil chemotaxis, monocyte's cytokine production, IL-8, C-reactive protein and noradrenaline levels [82, 83]. Contradicting these findings, no anti-inflammatory effect was obtained by progressive resistance exercise [84]. However, response to resistance exercise was prominent in lean patients, with significant changes in IGF-1 and leptin levels following 15 weeks of exercise program [79]. A recent study evaluated the effect of a single session of whole-body vibration on inflammatory biomarkers. Adiponectin and soluble TNF receptor 1 levels reduced after treatment. This finding is consistent with the exercise-enhanced adaptation to stress response [85].

Concluding remarks

Fibromyalgia has a multifaceted pathophysiology. Research so far confirms that immune system is an important part of this complex pathogenesis. Pro-inflammatory cytokines, reactive oxygen species and plasma-derived inflammatory factors play distinct roles in inflammatory response. There have been attempts to find new therapeutic options targeting the inflammatory network and potential confounders of inflammation. Further research is required to clarify the role of inflammation in fibromyalgia-related comorbidities, as well as to shed light on potential therapeutic options.

Author contributions ICB contributed to the conception and design of the study; collection and interpretation of data; drafting and revising the article; and approval of the final version.

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Compliance with ethical standards

Conflict of interest The author declares that she has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

References

1. Clauw DJ (2019) Fibromyalgia and related syndromes. In: Hochberg MC, Gravallese EM, Silman AJ, Smoşen JS, Weinblatt ME, Weisman MH (eds) Rheumatology, 7th edn. Elsevier, Philadelphia, pp 736–745
2. Mastrangelo F, Frydas I, Ronconi G, Kritas SK, Tettamanti L, Caraffa A, D Ovidio C, Younes A, Gallenga CE, Conti P (2018) Low-grade chronic inflammation mediate by mast cells in fibromyalgia: role of IL-37. J Biol Regul Homeost Agents 32:195–198
3. Coskun Benlidayi I (2018) Fibromyalgia as a challenge for patients and physicians. Rheumatol Int 38:2345. https://doi.org/10.1007/s00296-018-4138-4136
4. Kozanoglu E, Coskun Benlidayi I, Eker Akilli R, Tasal A (2016) Is there any link between joint hypermobility and mitral valve prolapse in patients with fibromyalgia syndrome? Clin Rheumatol 35:1041–1044. https://doi.org/10.1007/s10067-015-3024-3029
5. Ramírez-Tejero JA, Martínez-Lara E, Rus A, Camacho MV, Del Moral ML, Siles E (2018) Insight into the biological pathways underlying fibromyalgia by a proteomic approach (. J Proteomics 186:47–55. https://doi.org/10.1016/j.jprot.2018.07.009
6. Sluka KA, Clauw DJ (2016) Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience 338:114–129. https://doi.org/10.1016/j.neuroscience.2016.06.006
7. Littlejohn G, Guymer E (2018) Neurogenic inflammation in fibromyalgia. Semin Immunopathol 40:291–300. https://doi.org/10.1007/s00281-018-0672-2
8. Metyas S, Rezk T, Arkfeld D, Leptich T (2017) Autoinflammation and immunomodulation in inflammatory fibromyalgia syndrome- a review. Curr Rheumatol Rev 13:98–102. https://doi.org/10.2174/1573397112666160919120530
9. Kadetoff D, Lampa J, Westman M, Andersson M, Kosek E (2012) Evidence of central inflammation in fibromyalgia-increased cerebrospinal fluid interleukin-8 levels (. J Neuroimmunol 242:33–38. https://doi.org/10.1016/j.jneuroim.2011.10.013
10. Kosek E, Altawil R, Kadetoff D, Finn A, Westman M, Le Maître E, Andersson M, Jensen-Urstad M, Lampa J (2015) Evidence of different mediators of central inflammation in dysfunctional and inflammatory pain-interleukin-8 in fibromyalgia and interleukin-1 β in rheumatoid arthritis. J Neuroimmunol 280:49–55. https://doi.org/10.1016/j.jneuroim.2015.02.002
11. Mendieta D, De la Cruz-Aguilera DL, Barrera-Villalpando MI, Becerril-Villanueva E, Arreola R, Hernández-Ferreira E, Pérez-Tapia SM, Pérez-Sánchez G, Garcés-Alvarez ME, Aguirre-Cruz L, Velasco-Velázquez MA, Pavón L (2016) IL-8 and IL-6 primarily mediate the inflammatory response in fibromyalgia patients. J Neuroimmunol 290:22–25. https://doi.org/10.1016/j.jneuroim.2015.11.011
12. Malhotra D, Saxena AK, Dar SA, Kumar V, Nasare N, Tripathi AK, Banerjee BD (2012) Evaluation of cytokine levels in fibromyalgia syndrome patients and its relationship to the severity of chronic pain. J Musculoskelet Pain 20:164–169. https://doi.org/10.3109/10582452.2012.704141
13. Bote ME, García JJ, Hinchado MD, Ortega E (2012) Inflammatory/stress feedback dysregulation in women with fibromyalgia. Neuroimmunomodulation 19:343–351. https://doi.org/10.1159/000341664
14. Imamura M, Targino RA, Hsing WT, Imamura S, Azevedo RS, Boas LS, Tozetto-Mendoza TR, Alfieri FM, Filippo TR, Battistella LR (2014) Concentration of cytokines in patients with

osteoarthritis of the knee and fibromyalgia. Clin Interv Aging 9:939–944. https://doi.org/10.2147/CIA.S60330
15. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31:1409–1417. https://doi.org/10.1007/s00296-011-1999-3
16. Manicone AM, McGuire JK (2008) Matrix metalloproteinases as modulators of inflammation. Semin Cell Dev Biol 19:34–41
17. Porth CM (2011) Inflammation, the inflammatory response and fever. In: Porth CM (ed) Essentials of pathophysiology, 3rd edn. Wolters Kluwer Health|Lippincott Williams & Wilkins, China, pp 51–72
18. Bjurstrom MF, Giron SE, Griffis CA (2016) Cerebrospinal fluid cytokines and neurotrophic factors in human chronic pain populations: a comprehensive review. Pain Pract 16:183–203. https://doi.org/10.1111/papr.12252
19. Christidis N, Ghafouri B, Larsson A, Palstam A, Mannerkorpi K, Bileviciute-Ljungar I, Löfgren M, Bjersing J, Kosek E, Gerdle B, Ernberg M (2015) Comparison of the levels of pro-inflammatory cytokines released in the vastus lateralis muscle of patients with fibromyalgia and healthy controls during contractions of the quadriceps muscle—a microdialysis study. PLoS One 10:e0143856. https://doi.org/10.1371/journal.pone.0143856
20. Feng J, Zhang Z, Wu X, Mao A, Chang F, Deng X, Gao H, Ouyang C, Dery KJ, Le K, Longmate J, Marek C, St Amand RP, Krontiris TG, Shively JE (2013) Discovery of potential new gene variants and inflammatory cytokine associations with fibromyalgia syndrome by whole exome sequencing. PLoS One 8:e65033. https://doi.org/10.1371/journal.pone.0065033
21. Smith SB, Maixner DW, Fillingim RB, Slade G, Gracely RH, Ambrose K, Zaykin DV, Hyde C, John S, Tan K, Maixner W, Diatchenko L (2012) Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia. Arthritis Rheum 64:584–593. https://doi.org/10.1002/art.33338
22. Iacob E, Light AR, Donaldson GW, Okifuji A, Hughen RW, White AT, Light KC (2016) Gene expression factor analysis to differentiate pathways linked to fibromyalgia, chronic fatigue syndrome, and depression in a diverse patient sample. Arthritis Care Res (Hoboken) 68:132–140. https://doi.org/10.1002/acr.22639
23. Ranzolin A, Duarte AL, Bredemeier M, da Costa Neto CA, Ascoli BM, Wollenhaupt-Aguiar B, Kapczinski F, Xavier RM (2016) Evaluation of cytokines, oxidative stress markers and brain-derived neurotrophic factor in patients with fibromyalgia—a controlled cross-sectional study. Cytokine 84:25–28. https://doi.org/10.1016/j.cyto.2016.05.011
24. Pernambuco AP, Schetino LP, Alvim CC, Murad CM, Viana RS, Carvalho LS, Reis D (2013) Increased levels of IL-17A in patients with fibromyalgia. Clin Exp Rheumatol 31(6 Suppl 79):S60-63
25. Xiao Y, Haynes WL, Michalek JE, Russell IJ (2013) Elevated serum high-sensitivity C-reactive protein levels in fibromyalgia syndrome patients correlate with body mass index, interleukin-6, interleukin-8, erythrocyte sedimentation rate. Rheumatol Int 33:1259–1264. https://doi.org/10.1007/s00296-012-2538-6
26. Behm FG, Gavin IM, Karpenko O, Lindgren V, Gaitonde S, Gashkoff PA, Gillis BS (2012) Unique immunologic patterns in fibromyalgia. BMC Clin Pathol 12:25. https://doi.org/10.1186/1472-6890-12-25
27. Sturgill J, McGee E, Menzies V (2014) Unique cytokine signature in the plasma of patients with fibromyalgia. J Immunol Res 2014:938576. https://doi.org/10.1155/2014/938576
28. Tsilioni I, Russell IJ, Stewart JM, Gleason RM, Theoharides TC (2016) Neuropeptides CRH, SP, HK-1, and inflammatory cytokines IL-6 and TNF are increased in serum of patients with fibromyalgia syndrome, implicating mast cells. J Pharmacol Exp Ther 356:664–672. https://doi.org/10.1124/jpet.115.230060
29. Iannuccelli C, Guzzo MP, Atzeni F, Mannocci F, Alessandri C, Gerardi MC, Valesini G, Di Franco M (2017) Pain modulation in patients with fibromyalgia undergoing acupuncture treatment is associated with fluctuations in serum neuropeptide Y levels. Clin Exp Rheumatol 105:81–85
30. Taylor AG, Fischer-White TG, Anderson JG, Adelstein KE, Murugesan M, Lewis JE, Scott MM, Gaykema RP, Goehler LE (2016) Stress, inflammation and pain: a potential role for monocytes in fibromyalgia-related symptom severity. Stress Health 32:503–513. https://doi.org/10.1002/smi.2648
31. Kiguchi N, Kobayashi Y, Kishioka S (2012) Chemokines and cytokines in neuroinflammation leading to neuropathic pain. Curr Opin Pharmacol 12:55–61. https://doi.org/10.1016/j.coph.2011.10.007
32. Furer V, Hazan E, Mor A, Segal M, Katav A, Aloush V, Elkayam O, George J, Ablin JN (2018) Elevated levels of eotaxin-2 in serum of fibromyalgia patients. Pain Res Manag 2018:7257681. https://doi.org/10.1155/2018/7257681
33. Wallace DJ, Gavin IM, Karpenko O, Barkhordar F, Gillis BS (2015) Cytokine and chemokine profiles in fibromyalgia, rheumatoid arthritis and systemic lupus erythematosus: a potentially useful tool in differential diagnosis. Rheumatol Int 35:991–996. https://doi.org/10.1007/s00296-014-3172-2
34. Bäckryd E, Tanum L, Lind AL, Larsson A, Gordh T (2017) Evidence of both systemic inflammation and neuroinflammation in fibromyalgia patients, as assessed by a multiplex protein panel applied to the cerebrospinal fluid and to plasma. J Pain Res 10:515–525. https://doi.org/10.2147/JPR.S128508
35. Geiss A, Rohleder N, Anton F (2012) Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology 37:671–684. https://doi.org/10.1016/j.psyneuen.2011.07.021
36. Wright HL, Moots RJ, Bucknall RC, Edwards SW (2010) Neutrophil function in inflammation and inflammatory diseases. Rheumatology (Oxford) 49:1618–1631. https://doi.org/10.1093/rheumatology/keq045
37. Aktürk S, Büyükavcı R (2017) Evaluation of blood neutrophil-lymphocyte ratio and platelet distribution width as inflammatory markers in patients with fibromyalgia. Clin Rheumatol 36:1885–1889. https://doi.org/10.1007/s10067-017-3647-0
38. Al-Nimer MSM, Mohammad TAM (2018) Correlation of hematological indices and ratios derived from them with FIQR scores in fibromyalgia. Pak J Med Sci 34:1219–1224. https://doi.org/10.12669/pjms.345.15169
39. Mertoglu C, Gunay M, Yerligok O (2018) Could endocan, a marker of inflammation and endothelial dysfunction, be a new diagnostic marker for fibromyalgia? Clin Lab 64:405–410. https://doi.org/10.7754/Clin.Lab.2017.171024
40. Sturgeon JA, Darnall BD, Zwickey HL, Wood LJ, Hanes DA, Zava DT, Mackey SC (2014) Proinflammatory cytokines and DHEA-S in women with fibromyalgia: impact of psychological distress and menopausal status. J Pain Res 7:707–716. https://doi.org/10.2147/JPR.S71344
41. Bokarewa MI, Erlandsson MC, Bjersing J, Dehlin M, Mannerkorpi K (2014) Smoking is associated with reduced leptin and neuropeptide Y levels and higher pain experience in patients with fibromyalgia. Mediators Inflamm 2014:627041. https://doi.org/10.1155/2014/627041
42. Paiva ES, Andretta A, Batista ED, Lobo MMMT, Miranda RC, Nisihara R, Schieferdecker MEM, Boguszewski CL (2017) Serum levels of leptin and adiponectin and clinical parameters in women with fibromyalgia and overweight/obesity. Arch Endocrinol Metab 61:249–256. https://doi.org/10.1590/2359-3997000000248
43. Bordoni B, Marelli F, Morabito B, Cavallaro F, Lintonbon D (2018) Fascial preadipocytes: another missing piece of the puzzle

to understand fibromyalgia? Open Access Rheumatol 10:27–32. https://doi.org/10.2147/OARRR.S155919
44. Ataoglu S, Ankarali H, Samanci R, Ozsahin M, Admis O (2018) The relationship between serum leptin level and disease activity and inflammatory markers in fibromyalgia patients N Clin Istanb 5:102–108. https://doi.org/10.14744/nci.2017.31644
45. Olama SM, Elsaid TO, El-Arman M (2013) Serum leptin in Egyptian patients with fibromyalgia syndrome: relation to disease severity. Int J Rheum Dis 16:583–589. https://doi.org/10.1111/1756-185X.12155
46. Ablin JN, Aronov N, Shimon I, Kanety H, Pariente C, Aloush V, Elkayam O, Levartovsky D (2012) Evaluation of leptin levels among fibromyalgia patients before and after three months of treatment, in comparison with healthy controls. Pain Res Manag 17:89–92
47. Stensson N, Ghafouri B, Gerdle B, Ghafouri N (2017) Alterations of anti-inflammatory lipids in plasma from women with chronic widespread pain—a case control study. Lipids Health Dis 16:112. https://doi.org/10.1186/s12944-017-0505-7
48. McGarry T, Biniecka M, Veale DJ, Fearon U (2018) Hypoxia, oxidative stress and inflammation. Free Radic Biol Med 125:15–24. https://doi.org/10.1016/j.freeradbiomed.2018.03.042
49. Fais A, Cacace E, Atzori L, Era B, Ruggiero V (2017) Plasma phospholipase, γ-CEHC and antioxidant capacity in fibromyalgia. Int J Rheum Dis 20:550–554. https://doi.org/10.1111/1756-185X.12787
50. Alcocer-Gómez E, Garrido-Maraver J, Bullón P, Marín-Aguilar F, Cotán D, Carrión AM, Alvarez-Suarez JM, Giampieri F, Sánchez-Alcazar JA, Battino M, Cordero MD (2015) Metformin and caloric restriction induce an AMPK-dependent restoration of mitochondrial dysfunction in fibroblasts from Fibromyalgia patients. Biochim Biophys Acta 1852:1257–1267. https://doi.org/10.1016/j.bbadis.2015.03.005
51. Cordero MD, Díaz-Parrado E, Carrión AM, Alfonsi S, Sánchez-Alcazar JA, Bullón P, Battino M, de Miguel M (2013) Is inflammation a mitochondrial dysfunction-dependent event in fibromyalgia? Antioxid Redox Signal 18:800–807. https://doi.org/10.1089/ars.2012.4892
52. Caboni P, Liori B, Kumar A, Santoru ML, Asthana S, Pieroni E, Fais A, Era B, Cacace E, Ruggiero V, Atzori L (2014) Metabolomics analysis and modeling suggest a lysophosphocholines-PAF receptor interaction in fibromyalgia. PLoS One 9:e107626. https://doi.org/10.1371/journal.pone.0107626
53. Bullón P, Alcocer-Gómez E, Carrión AM, Marín-Aguilar F, Garrido-Maraver J, Román-Malo L, Ruiz-Cabello J, Culic O, Ryffel B, Apetoh L, Ghiringhelli F, Battino M, Sánchez-Alcazar JA, Cordero MD (2016) AMPK phosphorylation modulates pain by activation of NLRP3 inflammasome. Antioxid Redox Signal 24:157–170. https://doi.org/10.1089/ars.2014.6120
54. Sánchez -Domínguez B, Bullón P, Román-Malo L, Marín-Aguilar F, Alcocer-Gómez E, Carrión AM, Sánchez-Alcazar JA, Cordero MD (2015) Oxidative stress, mitochondrial dysfunction and, inflammation common events in skin of patients with Fibromyalgia. Mitochondrion 21:69–75. https://doi.org/10.1016/j.mito.2015.01.010
55. Gerdle B, Ghafouri B, Ghafouri N, Bäckryd E, Gordh T (2017) Signs of ongoing inflammation in female patients with chronic widespread pain: a multivariate, explorative, cross-sectional study of blood samples. Medicine (Baltimore) 96:e6130. https://doi.org/10.1097/MD.0000000000006130
56. Halilоğlu S, Carlioglu A, Sahiner E, Karaaslan Y, Kosar A (2014) Mean platelet volume in patients with fibromyalgia. Z Rheumatol 73:742–745. https://doi.org/10.1007/s00393-013-1330-7
57. Feinberg T, Sambamoorthi U, Lilly C, Innes KK (2017) Potential mediators between fibromyalgia and c-reactive protein: results from a large US Community Survey. BMC Musculoskelet Disord 18:294. https://doi.org/10.1186/s12891-017-1641-y
58. Metyas SK, Solyman JS, Arkfeld DG (2015) Inflammatory fibromyalgia: is it real? Curr Rheumatol Rev 11:15–17. https://doi.org/10.2174/1573397111666150522095004
59. Rus A, Molina F, Gassó M, Camacho MV, Peinado M, del Moral ML (2016) Nitric oxide, inflammation, lipid profile, and cortisol in normal- and overweight women with fibromyalgia. Biol Res Nurs 18:138–146. https://doi.org/10.1177/1099800415591035
60. Younger J, Noor N, McCue R, Mackey S (2013) Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Arthritis Rheum 65:529–538. https://doi.org/10.1002/art.37734
61. Parkitny L, Younger J (2017) Reduced pro-inflammatory cytokines after 8 weeks of low-dose naltrexone for fibromyalgia. Biomedicines 5:E16. https://doi.org/10.3390/biomedicines5020016
62. Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S (2015) Palmitoylethanolamide in fibromyalgia: results from prospective and retrospective observational studies. Pain Ther 4:169–178. https://doi.org/10.1007/s40122-015-0038-6
63. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT (2017) EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 76:318–328. https://doi.org/10.1136/annrheumdis-2016-209724
64. Maes M, Ringel K, Kubera M, Berk M, Rybakowski J (2012) Increased autoimmune activity against 5-HT: a key component of depression that is associated with inflammation and activation of cell-mediated immunity, and with severity and staging of depression. J Affect Disord 136:386–392. https://doi.org/10.1016/j.jad.2011.11.016
65. Natelson BH, Vu D, Mao X, Weiduschat N, Togo F, Lange G, Blate M, Kang G, Coplan JD, Shungu DC (2015) Effect of milnacipran treatment on ventricular lactate in fibromyalgia: a randomized, double-blind, placebo-controlled trial. J Pain 16:1211–1219. https://doi.org/10.1016/j.jpain.2015.08.004
66. Vasquez A (2016) Neuroinflammation in fibromyalgia and CRPS is multifactorial. Nat Rev Rheumatol 12:242. https://doi.org/10.1038/nrrheum.2016.25
67. Senna MK, Sallam RA, Ashour HS, Elarman M (2012) Effect of weight reduction on the quality of life in obese patients with fibromyalgia syndrome: a randomized controlled trial. Clin Rheumatol 31:1591–1597. https://doi.org/10.1007/s10067-012-2053-x
68. Bettoni L, Bonomi FG, Zani V, Manisco L, Indelicato A, Lanteri P, Banfi G, Lombardi G (2013) Effects of 15 consecutive cryotherapy sessions on the clinical output of fibromyalgic patients. Clin Rheumatol 32:1337–1345. https://doi.org/10.1007/s10067-013-2280-9
69. Maeda T, Kudo Y, Horiuchi T, Makino N (2018) Clinical and anti-aging effect of mud-bathing therapy for patients with fibromyalgia. Mol Cell Biochem 444:87–92. https://doi.org/10.1007/s11010-017-3233-4
70. Bazzichi L, Da Valle Y, Rossi A, Giacomelli C, Sernissi F, Giannaccini G, Betti L, Ciregia F, Giusti L, Scarpellini P, Dell'Osso L, Marazziti D, Bombardieri S, Lucacchini A (2013) A multidisciplinary approach to study the effects of balneotherapy and mud-bath therapy treatments on fibromyalgia. Clin Exp Rheumatol 31(6 Suppl 79):S111–S120
71. Davis MC, Zautra AJ (2013) An online mindfulness intervention targeting socioemotional regulation in fibromyalgia: results of a randomized controlled trial. Ann Behav Med 46:273–284. https://doi.org/10.1007/s12160-013-9513-7

72. Amutio A, Franco C, Pérez-Fuentes Mde C, Gázquez JJ, Mercader I (2015) Mindfulness training for reducing anger, anxiety, and depression in fibromyalgia patients. Front Psychol 5:1572. https://doi.org/10.3389/fpsyg.2014.01572
73. Cordero MD, Cano-García FJ, Alcocer-Gómez E, De Miguel M, Sánchez-Alcázar JA (2012) Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q_{10} effect on clinical improvement. PLoS One 7:e35677. https://doi.org/10.1371/journal.pone.0035677
74. Cordero MD, Alcocer-Gómez E, Culic O, Carrión AM, de Miguel M, Díaz-Parrado E, Pérez-Villegas EM, Bullón P, Battino M, Sánchez-Alcazar JA (2014) NLRP3 inflammasome is activated in fibromyalgia: the effect of coenzyme Q_{10}. Antioxid Redox Signal 20:1169–1180. https://doi.org/10.1089/ars.2013.5198
75. Sánchez A, Calpena AC, Clares B (2015) Evaluating the oxidative stress in inflammation: role of melatonin. Int J Mol Sci 16:16981–17004. https://doi.org/10.3390/ijms160816981
76. de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, Xavier F, de Souza IC, Deitos A, Torres IL, Caumo W (2014) Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol 15:40. https://doi.org/10.1186/2050-6511-15-40
77. Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, Fishlev G, Ablin JN, Bergan J, Volkov O, Friedman M, Ben-Jacob E, Buskila D (2015) Hyperbaric oxygen therapy can diminish fibromyalgia syndrome-prospective clinical trial. PLoS One 10:e0127012. https://doi.org/10.1371/journal.pone.0127012
78. Bjersing JL, Dehlin M, Erlandsson M, Bokarewa MI, Mannerkorpi K (2012) Changes in pain and insulin-like growth factor 1 in fibromyalgia during exercise: the involvement of cerebrospinal inflammatory factors and neuropeptides. Arthritis Res Ther 14:R162. https://doi.org/10.1186/ar3902
79. Bjersing JL, Larsson A, Palstam A, Ernberg M, Bileviciute-Ljungar I, Löfgren M, Gerdle B, Kosek E, Mannerkorpi K (2017) Benefits of resistance exercise in lean women with fibromyalgia: involvement of IGF-1 and leptin. BMC Musculoskelet Disord 18:106. https://doi.org/10.1186/s12891-017-1477-5
80. Bote ME, Garcia JJ, Hinchado MD, Ortega E (2013) Fibromyalgia: anti-inflammatory and stress responses after acute moderate exercise. PLoS One 8:e74524. https://doi.org/10.1371/journal.pone.0074524
81. Torgrimson-Ojerio B, Ross RL, Dieckmann NF, Avery S, Bennett RM, Jones KD, Guarino AJ, Wood LJ (2014) Preliminary evidence of a blunted anti-inflammatory response to exhaustive exercise in fibromyalgia. J Neuroimmunol 277:160–167. https://doi.org/10.1016/j.jneuroim.2014.10.003
82. Bote ME, García JJ, Hinchado MD, Ortega E (2014) An exploratory study of the effect of regular aquatic exercise on the function of neutrophils from women with fibromyalgia: role of IL-8 and noradrenaline. Brain Behav Immun 39:107–112. https://doi.org/10.1016/j.bbi.2013.11.009
83. Ortega E, Bote ME, Giraldo E, García JJ (2012) Aquatic exercise improves the monocyte pro- and anti-inflammatory cytokine production balance in fibromyalgia patients. Scand J Med Sci Sports 22:104–112. https://doi.org/10.1111/j.1600-0838.2010.01132.x
84. Ernberg M, Christidis N, Ghafouri B, Bileviciute-Ljungar I, Löfgren M, Bjersing J, Palstam A, Larsson A, Mannerkorpi K, Gerdle B, Kosek E (2018) Plasma Cytokine levels in fibromyalgia and their response to 15 weeks of progressive resistance exercise or relaxation therapy. Mediators Inflamm 2018:3985154. https://doi.org/10.1155/2018/3985154
85. Ribeiro VGC, Mendonça VA, Souza ALC, Fonseca SF, Camargos ACR, Lage VKS, Neves CDC, Santos JM, Teixeira LAC, Vieira ELM, Teixeira Junior AL, Mezêncio B, Fernandes JSC, Leite HR, Poortmans JR, Lacerda ACR (2018) Inflammatory biomarkers responses after acute whole body vibration in fibromyalgia. Braz J Med Biol Res 51:e6775. https://doi.org/10.1590/1414-431X20176775