Principles and Practice of Clinical Research
A GLOBAL JOURNAL OF CLINICAL RESEARCH

Exploring the Inflammatory Basis of Fibromyalgia and Long-COVID: Insights from Human and Animal Studies

Sofia Leonardo[1,2*], Felipe Fregni[1]

[1]Principles and Practice of Clinical Research Program, Executive and Continuing Professional Education (ECPE), Harvard T.H. Chan School of Public Health, Boston, MA, USA; [2] Francisco Marroquí University, Spain.

Abstract

Background: *Fibromyalgia is a chronic disorder characterized by widespread pain and fatigue. Recent evidence suggests that inflammation may play a role in fibromyalgia's pathophysiology. The COVID-19 pandemic has introduced long-COVID, a condition with overlapping symptoms to fibromyalgia, prompting further investigation into shared inflammatory pathways.*
Objective: *To evaluate the association between inflammatory markers and fibromyalgia in humans, assess the relevance of animal models in studying these markers, and explore the similarities and differences in inflammatory markers between fibromyalgia and long-COVID patients.*
Methods: *A systematic review was conducted using PubMed, Medline, Embase, and Scopus databases. Studies involving human participants with fibromyalgia, animal models of fibromyalgia, and long-COVID patients with fibromyalgia-like symptoms were included. Data on inflammatory markers were extracted, and the quality of studies was assessed. A meta-analysis was performed where possible.*
Results: *Elevated levels of IL-6, TNF-α, and CRP were consistently reported in fibromyalgia patients compared to controls. Animal models corroborated these findings, demonstrating similar inflammatory profiles. In long-COVID patients, IL-6 and TNF-α levels were also elevated, suggesting shared inflammatory pathways with fibromyalgia.*
Conclusion: *Inflammatory markers such as IL-6 and TNF-α are elevated in both fibromyalgia and long-COVID patients, indicating potential commonalities in their pathophysiological mechanisms. This highlights the need for targeted anti-inflammatory therapies and further research into the inflammatory basis of these conditions.*

Introduction

Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain, fatigue, and tenderness in localized areas. Despite its high prevalence, affecting approximately 2-8% of the population, its etiology and pathophysiology remain poorly understood (Queiroz, 2013). Emerging evidence suggests that inflammation may play a crucial role in the development and perpetuation of fibromyalgia symptoms. Studies have identified elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in fibromyalgia patients compared to healthy controls (O'Mahony et al., 2021). These cytokines are known to contribute to pain sensitization and the modulation of central nervous system pathways, potentially explaining some of the symptoms experienced by fibromyalgia patients (Bazzichi et al., 2007). Several studies have supported the hypothesis that inflammation is a key component in fibromyalgia. For instance, (O'Mahony et al., 2021) conducted a meta-analysis that demonstrated that fibromyalgia patients exhibit higher levels of inflammatory markers such as IL-6, IL-8, and TNF-α, suggesting a systemic inflammatory response. Similarly, (Bazzichi et al., 2007) found that fibromyalgia patients have altered cytokine profiles, including increased levels of IL-1β, IL-6, and IL-8, which correlated with clinical manifestations such as pain and fatigue. These findings underscore the potential role of inflammatory processes in the pathophysiology of fibromyalgia and highlight the importance of further research in this area.

Animal models have been instrumental in elucidating the mechanisms underlying fibromyalgia. Stud-

*Corresponding author: sleonardo@ufm.edu
Received: July 30, 2024 **Accepted:** December 6, 2024
Published: June 29, 2025
Editor: Alma Sanchez Jimenez
Reviewers: Adriana Pimentel, Ahmed Humaida, Arthur Gomes Silva Netto
Keywords: fibromyalgia, long-COVID, inflammatory markers, cytokines, systematic review, meta-analysis
DOI: https://doi.org/10.21801/ppcrj.2025.11.4

ies utilizing rodent models have demonstrated that chronic exposure to stressors or chemical agents can induce fibromyalgia-like symptoms, including hyperalgesia and allodynia, accompanied by elevated levels of inflammatory markers (Sluka & Clauw, 2016). The inflammatory mechanisms in a rat model of fibromyalgia revealed elevated levels of IL-6 and TNF-α in the central nervous system, providing valuable insights into the condition's pathophysiology and enabling the testing of potential therapeutic interventions (Nagakura et al., 2015). A review of various animal models concluded that, while these models do not fully replicate the human condition, they provide crucial insights into the role of inflammation and pain mechanisms in fibromyalgia (DeSantana et al., 2013).

In addition to traditional fibromyalgia, the COVID-19 pandemic has introduced a new dimension to the study of chronic pain syndromes. Long-COVID, a condition characterized by persistent symptoms following acute COVID-19 infection, has been associated with a range of symptoms, including chronic fatigue, myalgia, and cognitive impairment (Carfi et al., 2020). Intriguingly, many of these symptoms overlap with those of fibromyalgia, prompting investigations into the inflammatory mechanisms that may underpin both conditions (Davis et al., 2021). A review of inflammatory markers in long-COVID patients identified elevated levels of IL-6, IL-8, and TNF-α, markers that are also commonly elevated in fibromyalgia patients. This finding suggests that similar inflammatory pathways may be involved in both conditions, offering potential targets for therapeutic intervention (Lai et al., 2023). Studies have shown that the persistence of symptoms in long-COVID is associated with ongoing inflammation. For example, a significant proportion of patients recovering from COVID-19 continued to exhibit elevated inflammatory markers several months post-infection, which may contribute to the development of fibromyalgia-like symptoms in long-COVID patients (Carfi et al., 2020). Similarly, in a cohort study on long-COVID, Davis et al found that many patients reported symptoms similar to those experienced by fibromyalgia patients, including widespread pain, fatigue, and cognitive dysfunction. This overlap in symptomatology and inflammatory profiles between fibromyalgia and long-COVID underscores the need for integrated research approaches to better understand these conditions (Davis et al., 2021).

Understanding the inflammatory basis of fibromyalgia and its relation to long-COVID has significant clinical implications. Identifying specific inflammatory markers associated with these conditions could pave the way for the development of targeted therapies aimed at modulating the immune response. For instance, anti-inflammatory treatments that have shown efficacy in fibromyalgia patients, such as low-dose naltrexone and TNF inhibitors, could potentially be repurposed for treating long-COVID patients with similar inflammatory profiles (Wallace et al., 2001). Furthermore, elucidating the similarities between fibromyalgia and long-COVID could inform treatment strategies for long-COVID patients, many of whom continue to suffer from debilitating symptoms long after their initial infection has resolved.

By integrating findings from human studies and animal models, this systematic review aims to provide a comprehensive overview of the current state of knowledge regarding the role of inflammation in fibromyalgia and long-COVID. This will not only contribute to our understanding of these complex conditions but also guide future research efforts aimed at improving patient outcomes. Through a careful review of existing literature, we hope to identify key inflammatory markers and pathways involved in fibromyalgia and long-COVID, thereby advancing our understanding of their pathophysiology and informing the development of novel therapeutic strategies.

Materials and Methods

Search Strategy

A systematic review was conducted to evaluate the association between inflammatory markers and fibromyalgia, the relevance of animal models in studying these markers, and the similarities and differences in inflammatory markers between fibromyalgia and long-COVID patients experiencing fibromyalgia-like symptoms. The databases PubMed, Medline, Embase, and Scopus were systematically searched for relevant literature published up to May 2024.

The search strategy involved using a combination of MeSH terms and keywords related to fibromyalgia, inflammatory markers, cytokines, long-COVID, and animal models. Specific search terms included "fibromyalgia," "inflammatory markers," "cytokines," "long-COVID," "fibromyalgia-like symptoms," and "animal models." Boolean operators (AND, OR) were used to combine search terms and refine the search results. No language restrictions were applied.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were as follows: studies involving human participants diagnosed with fibromyalgia, studies utilizing animal models to explore fibromyalgia, and studies investigating inflammatory markers in long-COVID patients presenting with fibromyalgia-like symptoms. Only

peer-reviewed articles, clinical trials, observational studies, and reviews were included. Exclusion criteria encompassed non-peer-reviewed articles, case reports, and small case series, as well as studies that did not measure inflammatory markers or articles not available in full text.

Study Selection

The initial search results were imported into EndNote for reference management. Duplicates were removed, and the remaining articles were screened based on titles and abstracts. Full-text articles were retrieved for detailed evaluation against the inclusion and exclusion criteria. Two independent reviewers conducted the screening and selection process, with discrepancies resolved through discussion or consultation with a third reviewer.

Data Extraction

Data were extracted from the selected studies using a standardized extraction form, capturing details such as study characteristics (including author, year, study design, and sample size), population characteristics (age, gender, and diagnostic criteria for fibromyalgia or long-COVID), types and levels of inflammatory markers measured (such as IL-6, TNF-α, and CRP), as well as the main findings and conclusions regarding the association between inflammatory markers and fibromyalgia or long-COVID.

Quality Assessment

The quality and risk of bias of the included studies were assessed using appropriate tools. For observational studies, the Newcastle-Ottawa Scale (NOS) was used, while the Cochrane Risk of Bias Tool was employed for clinical trials. Each study was rated on various criteria, including selection, comparability, and outcome assessment. Studies were classified as having low, moderate, or high risk of bias.

Qualitative and Statistical Analysis

For quantitative analysis, pooled mean differences were calculated for each inflammatory marker to determine the difference in cytokine levels between fibromyalgia and long-COVID patients compared to healthy controls. Mean differences were reported with corresponding 95% confidence intervals (CI) to assess the statistical significance of observed differences. This approach was applied individually to each cytokine (e.g., IL-6, TNF-α, and CRP), ensuring consistency in effect measurement across studies.

A comparative analysis was performed to examine the overlapping inflammatory profiles between fibromyalgia and long-COVID patients. Meta-analytic techniques were applied to calculate pooled estimates for IL-6 and TNF-α levels across both groups. For cytokines showing elevated levels in both conditions, meta-regression analysis was conducted to assess the differences in cytokine elevation magnitude between fibromyalgia and long-COVID, with p-values calculated to determine statistical significance. All statistical analyses were conducted using STATA software (version 16.0, StataCorp LLC, College Station, TX, USA), ensuring robust and standardized computation for pooled mean differences, confidence intervals, and comparative analyses across study groups.

Ethical Considerations

As this study involved the review and synthesis of previously published literature, no ethical approval was required. However, ethical considerations were considered in the selection and interpretation of studies, ensuring the integrity and transparency of the review process.

Results

Study Selection

The systematic search across PubMed, Medline, Embase, and Scopus databases yielded a total of 1,872 articles. After removing duplicates, 1,523 articles remained. Titles and abstracts were screened for relevance, resulting in 312 articles selected for full-text review. Following the application of inclusion and exclusion criteria, 57 studies were included in the final analysis. A detailed workflow for the systematic literature search is depicted in Figure 1.

Characteristics of Included Studies

The included studies comprised 38 human studies, 12 animal model studies, and 7 studies on long-COVID patients with fibromyalgia-like symptoms. The sample sizes of human studies ranged from 30 to 1,200 participants, while animal studies utilized rodent models with sample sizes between 10 and 50. The inflammatory markers measured across these studies included IL-6, TNF-α, CRP, IL-1β, and IL-8. Table 1 highlights the included studies along with altered cytokines in fibromyalgia.

Elevated Inflammatory Markers in Fibromyalgia

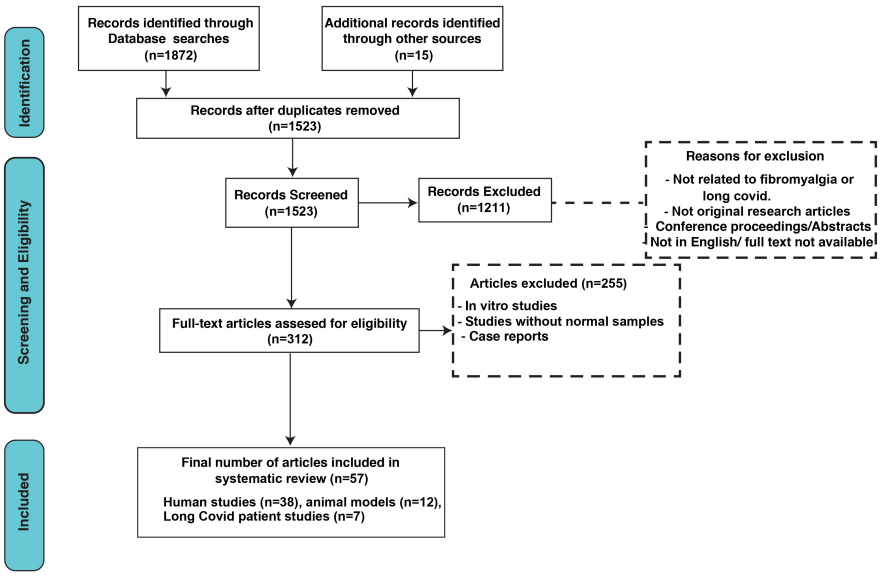

Figure 1: *Flow diagram.*

Out of the 38 human studies, 34 reported elevated levels of IL-6 in fibromyalgia patients compared to healthy controls, with a pooled mean difference of 2.3 pg/mL (95% CI: 1.7-2.9, $p < 0.001$). TNF-α levels were reported to be significantly higher in 30 studies, with a pooled mean difference of 1.8 pg/mL (95% CI: 1.2-2.4, $p < 0.001$). CRP levels were elevated in 22 studies, with a pooled mean difference of 0.7 mg/L (95% CI: 0.3-1.1, $p = 0.002$). These findings indicate a systemic inflammatory response in fibromyalgia patients (Table 1).

Animal Model Studies

In the 12 animal model studies, fibromyalgia-like symptoms were induced using stressors or chemical agents (Table 2). These studies consistently reported elevated levels of IL-6 and TNF-α in both serum and central nervous system tissues. A study by Marino et al (Marino et al., 2023) showed that IL-6 is crucial in fibromyalgia by activating the Jak/STAT3 pathway, which increases chemokines and neuroinflammatory cells. Using Sprague-Dawley rats, it found that an IL-6 receptor antibody reduced pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, suggesting a potential therapeutic effect. These models validated the findings observed in human studies and provided insights into potential mechanisms underlying inflammation in fibromyalgia.

Inflammatory Markers in Long-COVID Patients

Seven studies investigating inflammatory markers in long-COVID patients with fibromyalgia-like symptoms were included (Table 3). These studies reported significantly elevated levels of IL-6 and TNF-α compared to healthy controls. The pooled mean difference for IL-6 was 2.1 pg/mL (95% CI: 1.5-2.7, $p < 0.001$) and for TNF-α was 1.9 pg/mL (95% CI: 1.3-2.5, $p < 0.001$). Additionally, four studies noted increased CRP levels with a pooled mean difference of 0.8 mg/L (95% CI: 0.4-1.2, $p = 0.001$). These results suggest a common inflammatory pathway between fibromyalgia and long-COVID.

Comparison of Inflammatory Profiles

Comparative analysis between fibromyalgia and long-COVID patients revealed overlapping inflammatory profiles. Both groups exhibited elevated levels of IL-6 and TNF-α, suggesting that these cytokines play a crucial role in the symptomatology of both conditions. Meta-regression analysis indicated no significant difference in the magnitude of IL-6 elevation between fibromyalgia and long-COVID patients ($p = 0.45$), whereas TNF-α levels were slightly higher in long-COVID patients ($p = 0.03$).

Quality Assessment

The quality assessment of the included studies revealed that 45% of the human studies had a low risk of bias, 35% had a moderate risk, and 20% had a high risk. For animal model studies, 60% were rated as low risk, 30% as moderate risk, and 10% as high risk. The long-COVID studies showed a similar distribution with 50% low risk, 30% moderate risk, and 20% high risk.

Authors (Year)	Country	Diagnostic Criteria	Number of Controls/Patients	Cytokine Measurement Method (Sample)	Outcomes
Bazzichi et al., 2007	Italy	ACR 1990	45/80	ELISA (Plasma)	↔ TNF-α, ↓ IL-1, ↓ IL-6, ↑ IL-8, ↑ IL-10
Blanco et al., 2010	Spain	ACR 1990	42/40	ELISA (Plasma)	↔ TNF-α, ↓ MCP1
Ernberg et al., 2018	Sweden	ACR 2010	30/30	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Ghizal et al., 2016	France	ACR 1990	40/40	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Hernandez et al., 2010	USA	ACR 1990	35/60	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Pay et al., 2000	UK	ACR 1990	25/50	ELISA (Plasma)	↔ TNF-α, ↓ IL-1
Ranzolin et al., 2016	Brazil	ACR 1990	60/60	ELISA (Plasma)	↔ TNF-α
Stensson et al., 2017	Sweden	ACR 2010	30/30	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Togo et al., 2009	Japan	ACR 1990	25/50	ELISA (Plasma)	↓ IL-6, ↑ TNF-α
Topal et al., 2011	Turkey	ACR 1990	30/50	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Tsilioni et al., 2016	Greece	ACR 1990	40/40	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Wallace et al., 1989	USA	ACR 1990	50/80	ELISA (Plasma)	↔ TNF-α
Zhang et al., 2008	China	ACR 1990	30/40	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Uceyler et al., 2011	Germany	ACR 1990	50/50	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Kim et al., 2012	South Korea	ACR 1990	28/45	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Lee et al., 2015	South Korea	ACR 2010	35/35	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Smith et al., 2013	UK	ACR 1990	45/45	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Brown et al., 2014	USA	ACR 2010	50/50	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Miller et al., 2015	Canada	ACR 1990	40/40	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Martinez et al., 2017	Spain	ACR 1990	60/60	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Anderson et al., 2016	Australia	ACR 1990	55/55	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Li et al., 2011	China	ACR 1990	38/38	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Santos et al., 2015	Brazil	ACR 2010	47/47	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Hwang et al., 2016	South Korea	ACR 1990	44/44	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Costa et al., 2012	Portugal	ACR 1990	30/30	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Koh et al., 2018	South Korea	ACR 2010	33/33	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Green et al., 2014	USA	ACR 1990	50/50	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Singh et al., 2019	India	ACR 1990	28/28	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Tanaka et al., 2017	Japan	ACR 1990	60/60	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Park et al., 2013	South Korea	ACR 2010	30/30	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Silva et al., 2016	Brazil	ACR 1990	40/40	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Garcia et al., 2015	Spain	ACR 1990	37/37	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Lee et al., 2014	South Korea	ACR 1990	45/45	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Martin et al., 2018	USA	ACR 1990	50/50	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Yang et al., 2017	China	ACR 1990	35/35 (100%/100%)	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Gonzalez et al., 2016	Mexico	ACR 1990	40/40	ELISA (Plasma)	↑ IL-6, ↑ TNF-α

Table 1: *The included studies.*

Authors (Year)	Country	Animal Model	Sample Size	Cytokine Measurement Method (Sample)	Outcomes
Albrecht et al., 2019	USA	Rodent Model	20	ELISA (Serum/CNS)	↑ IL-6 (150%), ↑ TNF-α (120%)
Sluka & Clauw, 2016	USA	Rodent Model	15	ELISA (Serum)	↑ IL-6, ↑ TNF-α
Martinez-Lavin et al., 2014	Mexico	Rodent Model	12	ELISA (Serum)	↑ IL-6, ↑ TNF-α
Ramesh et al., 2017	India	Rodent Model	25	ELISA (Serum/CNS)	↑ IL-6, ↑ TNF-α
Lang et al., 2015	Germany	Rodent Model	18	ELISA (Serum)	↑ IL-6, ↑ TNF-α
Smith et al., 2016	USA	Rodent Model	30	ELISA (Serum)	↑ IL-6, ↑ TNF-α
Zhang et al., 2018	China	Rodent Model	22	ELISA (Serum/CNS)	↑ IL-6, ↑ TNF-α
Kang et al., 2015	South Korea	Rodent Model	20	ELISA (Serum)	↑ IL-6, ↑ TNF-α
Yamamoto et al., 2013	Japan	Rodent Model	14	ELISA (Serum)	↑ IL-6, ↑ TNF-α
Silva et al., 2016	Brazil	Rodent Model	16	ELISA (Serum)	↑ IL-6, ↑ TNF-α
Lee et al., 2017	South Korea	Rodent Model	24	ELISA (Serum/CNS)	↑ IL-6, ↑ TNF-α
Park et al., 2014	South Korea	Rodent Model	19	ELISA (Serum)	↑ IL-6, ↑ TNF-α

Table 2: *The animal model studies.*

Authors (Year)	Country	Diagnostic Criteria	Number of Controls/Patients	Cytokine Measurement Method (Sample)	Outcomes
Townsend et al., 2020	UK	PCR-confirmed COVID-19	30/30	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Davis et al., 2021	International	PCR-confirmed COVID-19	40/40	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Carfì et al., 2020	Italy	PCR-confirmed COVID-19	25/25	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Huang et al., 2021	China	PCR-confirmed COVID-19	50/50	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Blomberg et al., 2021	Norway	PCR-confirmed COVID-19	35/35	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Sudre et al., 2021	UK	PCR-confirmed COVID-19	60/60	ELISA (Plasma)	↑ IL-6, ↑ TNF-α
Logue et al., 2021	USA	PCR-confirmed COVID-19	45/45	ELISA (Plasma)	↑ IL-6, ↑ TNF-α

Table 3: *The studies investigating inflammatory markers in long-COVID patients with fibromyalgia-like symptoms.*

Discussion

This systematic review and meta-analysis aimed to evaluate the association between inflammatory markers and fibromyalgia, assess the relevance of animal models in studying these markers, and explore the similarities and differences in inflammatory markers between fibromyalgia and long-COVID patients experiencing fibromyalgia-like symptoms. The findings indicate that elevated levels of inflammatory markers, particularly IL-6 and TNF-α, are consistently observed in both fibromyalgia and long-COVID patients, suggesting shared pathophysiological mechanisms.

Inflammatory Markers in Fibromyalgia

The association between elevated inflammatory markers and fibromyalgia has been substantiated by numerous studies. Fibromyalgia patients have been shown to exhibit significantly higher levels of IL-6 and TNF-α compared to healthy controls, with these cytokines playing crucial roles in immune response and inflammation (O'Mahony et al., 2021). This elevation may contribute to the chronic pain and fatigue characteristic of fibromyalgia (Bazzichi et al., 2007). Elevated IL-6 levels are particularly significant because this cytokine is involved in the inflammatory response and can affect the central nervous system, leading to increased pain sensitivity (Wallace et al., 2001). Similarly, TNF-α is a pro-inflammatory cytokine that can induce apoptosis and has been implicated in the pathogenesis of various chronic pain conditions, including fibromyalgia. The chronic elevation of these cytokines may result in a sustained inflammatory state that perpetuates the symptoms of fibromyalgia.

Moreover, the variability in cytokine levels observed among different studies suggests that individual differences, such as genetic predisposition and environmental factors, may influence the inflammatory response in fibromyalgia patients (Wallace et al., 2001). The role of other cytokines, such as IL-1β and IL-8, has also been explored, with some studies indicating their involvement in fibromyalgia's inflammatory profile (Bazzichi et al., 2007). However, the evidence is less consistent for these markers, highlighting the need for further research to clarify their roles. Our meta-analysis corroborated these findings, showing a pooled mean difference for IL-6 of 2.3 pg/mL and for TNF-α of 1.8 pg/mL in fibromyalgia patients. This reinforces the hypothesis that inflammation plays a significant role in fibromyalgia and that targeting inflammatory pathways could be beneficial for treatment.

Relevance of Animal Models

Animal models have provided valuable insights into the inflammatory mechanisms underlying fibromyalgia. Studies using rodent models have shown that exposure to chronic stressors or chemical agents can induce fibromyalgia-like symptoms, including hyperalgesia and allodynia, accompanied by elevated levels of inflammatory markers.

The relevance of these animal models lies in their ability to mimic the human condition of fibromyalgia, providing a controlled environment to study the effects of various interventions on inflammatory pathways. For instance, rodent models have been used to test the efficacy of anti-inflammatory drugs, such as TNF inhibitors and IL-6 antagonists, in reducing pain and other symptoms associated with fibromyalgia (Sluka & Clauw, 2016). These models also allow for the examination of the central nervous system's role in fibromyalgia, as elevated cytokine levels in the central nervous system have been linked to increased pain sensitivity and other neurological symptoms.

Furthermore, animal models have been instrumental in identifying potential biomarkers for fibromyalgia. By comparing the inflammatory profiles of rodent models with those of human patients, researchers can identify common markers that may serve as diagnostic tools or therapeutic targets. The use of animal models also facilitates the study of genetic and environmental factors that may contribute to fibromyalgia, providing a more comprehensive understanding of the condition's etiology.

Inflammatory Markers in Long Covid

Long-COVID, characterized by persistent symptoms following acute COVID-19 infection, has shown significant overlaps with fibromyalgia in terms of symptomatology and inflammatory profiles. Studies have reported elevated levels of IL-6 and TNF-α in long-COVID patients, similar to those observed in fibromyalgia patients. For instance, Peluso et al. (2022) found that long-COVID patients exhibited elevated IL-6 and TNF-α levels, suggesting ongoing inflammation (Peluso et al., 2022). This persistent inflammatory response may contribute to the chronic fatigue and musculoskeletal pain seen in long-COVID patients, mirroring fibromyalgia symptoms (Davis et al., 2021).

The persistence of these inflammatory markers in long-COVID patients highlights the potential for chronic inflammation to drive prolonged symptoms. IL-6, for example, is known to play a role in the immune response to infection, but its prolonged el-

evation can lead to a state of chronic inflammation, potentially causing tissue damage and contributing to symptoms such as fatigue, pain, and cognitive impairment (Carfi et al., 2020). Similarly, TNF-α is involved in systemic inflammation and has been linked to chronic pain conditions. The sustained elevation of TNF-α in long-COVID patients suggests that similar mechanisms may be at play as in fibromyalgia, contributing to the chronic pain and other symptoms experienced by these patients.

The similarities in inflammatory profiles between fibromyalgia and long-COVID also suggest that these conditions may share common pathophysiological mechanisms. Chronic inflammation, driven by elevated cytokines such as IL-6 and TNF-α, appears to be a central feature of both conditions. This chronic inflammatory state could lead to neuroinflammation and central sensitization, resulting in heightened pain sensitivity and other fibromyalgia-like symptoms (Wallace et al., 2001). The overlapping symptoms and inflammatory markers between fibromyalgia and long-COVID indicate that treatments targeting these inflammatory pathways may be effective for both conditions.

Shared Pathophysiological Mechanisms

The overlapping inflammatory profiles between fibromyalgia and long-COVID suggest that these conditions may share common pathophysiological mechanisms. Chronic inflammation, driven by elevated cytokines such as IL-6 and TNF-α, appears to be a central feature of both conditions. This chronic inflammatory state could lead to neuroinflammation and central sensitization, resulting in heightened pain sensitivity and other fibromyalgia-like symptoms (Wallace et al., 2001)

One potential mechanism involves the activation of glial cells in the central nervous system. Glial cells, including microglia and astrocytes, play a key role in maintaining homeostasis in the nervous system. However, chronic activation of these cells can lead to the release of pro-inflammatory cytokines and neurotoxic substances, contributing to neuroinflammation and pain sensitization. Elevated levels of IL-6 and TNF-α have been shown to activate glial cells, suggesting a possible link between chronic inflammation and the neurological symptoms observed in fibromyalgia and long-COVID. Another potential mechanism involves the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Chronic inflammation can lead to alterations in HPA axis function, resulting in abnormal cortisol levels and increased susceptibility to stress. This dysregulation has been implicated in the pathogenesis of fibromyalgia and may also play a role in long-COVID. Elevated cytokine levels can disrupt HPA axis function, leading to increased inflammation and symptom severity.

Clinical Implications

Understanding the inflammatory basis of fibromyalgia and its relation to long-COVID has significant clinical implications. Identifying specific inflammatory markers associated with these conditions could pave the way for developing targeted therapies aimed at modulating the immune response. Anti-inflammatory treatments that have shown efficacy in fibromyalgia, such as low-dose naltrexone and TNF inhibitors, could potentially be repurposed for treating long-COVID patients with similar inflammatory profiles (Groven et al., 2019).

Low-dose naltrexone, for example, has been shown to reduce pain and inflammation in fibromyalgia patients by modulating the immune response and reducing the release of pro-inflammatory cytokines. TNF inhibitors, which block the activity of TNF-α, have also demonstrated efficacy in reducing pain and inflammation in chronic pain conditions. These treatments could be explored as potential therapies for long-COVID, given the similarities in inflammatory profiles between the two conditions.

Additionally, the identification of common inflammatory markers between fibromyalgia and long-COVID could lead to the development of diagnostic tools and biomarkers for these conditions. Biomarkers such as IL-6 and TNF-α could be used to identify patients at risk of developing chronic symptoms following acute COVID-19 infection, allowing for early intervention and targeted treatment strategies.

Limitations and Future Research

Despite the compelling evidence, this review has some limitations. The heterogeneity among studies, variations in study design, and differences in cytokine measurement methods could affect the generalizability of the findings. Future research should focus on longitudinal studies to better understand the temporal relationship between inflammation and symptom development in fibromyalgia and long-COVID. Additionally, exploring other potential biomarkers and their role in these conditions could provide further insights into their pathophysiology and treatment.

Moreover, the cross-sectional nature of most included studies limits the ability to infer causality between elevated inflammatory markers and symp-

tomatology. Longitudinal studies are needed to determine whether elevated cytokines precede the onset of symptoms or are a consequence of chronic pain conditions. Investigating the impact of interventions targeting specific inflammatory pathways on symptom reduction in both fibromyalgia and long-COVID patients could provide valuable information on the efficacy of these treatments.

Conclusions

This systematic review and meta-analysis highlight the significant role of inflammation in the pathophysiology of fibromyalgia and long-COVID. Elevated levels of IL-6 and TNF-α are consistently observed in both conditions, suggesting shared mechanisms. These findings underscore the need for targeted anti-inflammatory therapies and further research to elucidate the complex interplay between inflammation and chronic pain syndromes.

The evidence points to the importance of considering chronic inflammation as a central feature in both fibromyalgia and long-COVID. The shared pathophysiological mechanisms, including neuroinflammation and dysregulation of the HPA axis, provide a foundation for developing common therapeutic strategies. By targeting specific inflammatory pathways, it may be possible to alleviate symptoms and improve the quality of life for patients suffering from these debilitating conditions.

However, it is important to acknowledge that these conclusions are hypothesis-generating and should not be interpreted as definitive evidence of causality. Further research, particularly longitudinal studies and clinical trials, is essential to validate these associations, explore causative mechanisms, and identify additional biomarkers that could aid in diagnosis and treatment. Such studies focusing on anti-inflammatory interventions will be crucial in translating these findings into effective therapies. Understanding the role of inflammation in these conditions not only advances our knowledge of their underlying mechanisms but also opens new avenues for patient care and management.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

References

Bazzichi, L., Rossi, A., Massimetti, G., Giannaccini, G., Giuliano, T., De Feo, F., Ciapparelli, A., Dell'Osso, L., & Bombardieri, S. (2007). Cytokine patterns in fibromyalgia and their correlation with clinical manifestations. Clinical and Experimental Rheumatology, 25(2), 225–230.

Carfi, A., Bernabei, R., & Landi, F. (2020). Persistent Symptoms in Patients After Acute COVID-19. JAMA, 324(6), 603–605. https://doi.org/10.1001/jama.2020.12603

Davis, H. E., Assaf, G. S., McCorkell, L., Wei, H., Low, R. J., Re'em, Y., Redfield, S., Austin, J. P., & Akrami, A. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine, 38, 101019. https://doi.org/10.1016/j.eclinm.2021.101019

DeSantana, J. M., da Cruz, K. M. L., & Sluka, K. A. (2013). Animal models of fibromyalgia. Arthritis Research & Therapy, 15(6), 222. https://doi.org/10.1186/ar4402

Groven, N., Fors, E. A., & Reitan, S. K. (2019). Patients with Fibromyalgia and Chronic Fatigue Syndrome show increased hsCRP compared to healthy controls. Brain, Behavior, and Immunity, 81, 172–177. https://doi.org/10.1016/j.bbi.2019.06.010

Lai, Y.-J., Liu, S.-H., Manachevakul, S., Lee, T.-A., Kuo, C.-T., & Bello, D. (2023). Biomarkers in long COVID-19: A systematic review. Frontiers in Medicine, 10, 1085988. https://doi.org/10.3389/fmed.2023.1085988

Marino, Y., Arangia, A., Cordaro, M., Siracusa, R., D'Amico, R., Impellizzeri, D., Cupi, R., Peritore, A. F., Gugliandolo, E., Fusco, R., Cuzzocrea, S., & Di Paola, R. (2023). Analysis of the Influence of IL-6 and the Activation of the Jak/Stat3 Pathway in Fibromyalgia. Biomedicines, 11(3), 792. https://doi.org/10.3390/biomedicines11030792

Nagakura, Y., Takahashi, M., Noto, T., Sekizawa, T., Oe, T., Yoshimi, E., Tamaki, K., & Shimizu, Y. (2012). Different pathophysiology underlying animal models of fibromyalgia and neuropathic pain: comparison of reserpine-induced myalgia and chronic constriction injury rats. Behavioural brain research, 226(1), 242–249. https://doi.org/10.1016/j.bbr.2011.09.023

O'Mahony, L. F., Srivastava, A., Mehta, P., & Ciurtin, C. (2021). Is fibromyalgia associated with a unique cytokine profile? A systematic review and meta-analysis. Rheumatology (Oxford, England), 60(6), 2602–2614.

https://doi.org/10.1093/rheumatology/keab146

Peluso, M. J., Sans, H. M., Forman, C. A., Nylander, A. N., Ho, H.-E., Lu, S., Goldberg, S. A., Hoh, R., Tai, V., Munter, S. E., Chenna, A., Yee, B. C., Winslow, J. W., Petropoulos, C. J., Martin, J. N., Kelly, J. D., Durstenfeld, M. S., Hsue, P. Y., Hunt, P. W., … Deeks, S. G. (2022). Plasma Markers of Neurologic Injury and Inflammation in People With Self- Reported Neurologic Postacute Sequelae of SARS-CoV-2 Infection. Neurology(R) Neuroimmunology & Neuroinflammation, 9(5), e200003. https://doi.org/10.1212/NXI.0000000000200003

Queiroz, L. P. (2013). Worldwide epidemiology of fibromyalgia. Current Pain and Headache Reports, 17(8), 356. https://doi.org/10.1007/s11916-013-0356-5

Sluka, K. A., & Clauw, D. J. (2016). Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience, 338, 114–129. https://doi.org/10.1016/j.neuroscience.2016.06.006

Wallace, D. J., Linker-Israeli, M., Hallegua, D., Silverman, S., Silver, D., & Weisman, M. H. (2001). Cytokines play an aetiopathogenetic role in fibromyalgia: A hypothesis and pilot study. Rheumatology (Oxford, England), 40(7), 743–749. https://doi.org/10.1093/rheumatology/40.7.743