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PERSPECTIVES IN RHEUMATOLOGY

The relationship between COVID-19 and fibromyalgia syndrome: prevalence, pandemic effects, symptom mechanisms, and COVID-19 vaccines

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Abstract

On March 11, 2020, the World Health Organization, realizing the level of spread worldwide and the severity of the condition, accepted coronavirus disease 19 (COVID-19) as a pandemic. Subsequently, quarantine conditions were implemented around the world, and these triggered particular results. Like all other individuals, fibromyalgia syndrome (FMS) patients were affected by these conditions. The stress load in pandemic conditions, difficulties in accessing healthcare services, changes in exercise compliance, variations in physiotherapy programs, and remote work conditions all had an impact on FMS patients. Although general expectations were negative, some FMS patients were able to manage the pandemic conditions and even turn them in their favor. This is thought to be due to this patient group having established strategies to cope with stress in the pre-pandemic period, and they had sufficient ability to adapt to changing situations. FMS-related symptoms occur in a subset of individuals following COVID-19. One of the factors is the increased psychological burden after COVID-19. There is evidence that neuroinflammatory pathways affect neuroplasticity in the central nervous system and trigger the onset of FMS-related symptoms. Among the probable mechanisms are alterations in inflammatory and anti-inflammatory pathways. Changes in the autonomic nervous system with the effect of SARS-CoV-2 may induce the emergence of FMS-related symptoms. FMS and COVID-19 can coexist, and FMS may create a tendency to vaccine hesitancy. Future studies should focus on elucidating FMS-related symptoms occurring post-COVID-19. There is a need to determine distinctions between the FMS clinical status that emerged following COVID-19 and the regular patient group in terms of diagnosis, treatment, and follow-up.

Key Points

- *Conflicting results have been observed in studies investigating the impacts of COVID-19 on FMS patients. In addition to studies revealing unfavorable effects, there are also articles reporting a steady course and even positive impacts.*
- *No significant difference was detected between the groups with and without a diagnosis of FMS in terms of hospitalization and mortality outcomes related to COVID-19.*
- *Several mechanisms have been proposed to explain the onset of FMS-related symptoms following COVID-19. During periods of lock-down and self-isolation, individuals are influenced biopsychosocially. Activation of some inflammatory pathways, changes in plasticity-central sensitization, and alterations in pain pathways are also plausible explanations.*

Keywords COVID-19 · Fibromyalgia syndrome · Post-COVID-19 syndrome

Introduction

Fibromyalgia syndrome (FMS) is a chronic rheumatic disorder in which widespread body pain is at the center of the disease and can be accompanied by symptoms that profoundly affect the quality of life, such as fatigue, disturbed sleep, psychiatric-mental abnormalities, and stiffness. Contrary to the wide range of signs, physical examination findings are limited [1]. There are still many controversial issues in the

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etiopathogenesis of FMS. However, studies using functional neuroimaging techniques have demonstrated the importance of central sensitization with alterations in functional brain connectivity and neurotransmitters in the central nervous system. Hormonal changes, familial predisposition, and genetic factors have also been described [2–4]. In addition, viral infections are one of the emphasized factors in the etiopathogenesis of FMS. HIV infection, hepatitis C, Epstein-Barr virus infection, and Parvovirus B19 are the most focused viral infections in this respect [5]. A multidisciplinary treatment protocol with a combination of pharmacological and non-pharmacological treatment modalities is recommended to relieve FMS-related symptoms. According to the European League Against Rheumatism (EULAR), physical exercise is an intervention with a strong recommendation rating, with particular emphasis on aerobic exercises and resistance training [6].

Since its emergence in December 2019, SARS-CoV-2, as the agent of coronavirus disease 2019 (COVID-19), has demonstrated catastrophic potential, leading to more than five hundred million cases and more than six million deaths worldwide [7]. In addition to the clinical impacts of acute disease and its long-term consequences, the pandemic caused concern of being infected, changes in daily routine activities, decreased opportunities for social and outdoor activities, deaths of family members or close friends from COVID-19, work-related stress, and financial problems [8]. Moreover, in individuals with chronic diseases, clinical worsening may occur due to delayed medical assessments, disruption of routine examinations, and difficulty in accessing healthcare services [9]. All these biopsychosocial effects can create a devastating burden on all individuals, particularly on FMS patients. This burden may exacerbate widespread pain and other somatic signs by altering the pathways involved in central sensitization and pain inhibition in FMS patients [10].

In this review, the link between COVID-19 and FMS is presented. On this basis, evaluations were made of the prevalence of FMS during the COVID-19 pandemic, disease severity of FMS patients during the pandemic, the mechanisms of FMS-related symptoms after COVID-19, and the link between COVID-19 vaccination and FMS.

Search strategy

A systematic search was conducted on the Web of Science, Scopus, and PubMed/MEDLINE using the following keyword combinations: "Fibromyalgia and COVID 19" or "Fibromyalgia and SARS-CoV-2 Infection" or "Fibromyalgia and 2019 Novel Coronavirus Disease" or "Fibromyositis-Fibromyalgia Syndrome and COVID 19" or "Fibromyositis-Fibromyalgia Syndrome and SARS-CoV-2 Infection" or "Fibromyositis-Fibromyalgia Syndrome and 2019 Novel Coronavirus Disease" or "Fibromyalgia and COVID 19 Vaccines" or "Fibromyalgia and SARS-CoV-2 Vaccines" or "Fibromyalgia and 2019 Novel Coronavirus Vaccines" or "Fibromyositis-Fibromyalgia Syndrome and COVID 19 Vaccines" or "Fibromyositis-Fibromyalgia Syndrome and SARS-CoV-2 Vaccines" or "Fibromyositis-Fibromyalgia Syndrome and 2019 Novel Coronavirus Vaccines" or "Fibromyalgia and COVID 19 and survey" or "Fibromyalgia and SARS-CoV-2 Infection and Survey" or "Fibromyalgia and 2019 Novel Coronavirus Disease and Survey" or "Fibromyositis-Fibromyalgia Syndrome and COVID 19 and Survey" or "Fibromyositis-Fibromyalgia Syndrome and SARS-CoV-2 Infection and Survey" or "Fibromyositis-Fibromyalgia Syndrome and 2019 Novel Coronavirus Disease and Survey." The keywords were selected from Mesh terms. Inclusion criteria were established to classify the controlled clinical studies, the observational studies, and papers written in English. Exclusion criteria were determined as duplicated articles, reviews, case reports, case series, meeting abstracts, posters, editorials, commentaries, letters, non-English articles, and off-topic articles. The current search strategy was created in line with the recommendations of Gasparyan et al. [11]. The last update was made on April 15, 2022. The numbers of excluded and included articles are shown in Fig. 1.

Prevalence of fibromyalgia syndrome during the COVID-19 pandemic

Several articles have been published on the prevalence of FMS during the COVID-19 pandemic. Different populations were evaluated in these articles. AlEnzi et al. [12] evaluated healthcare employees in Saudi Arabia, and the Fibromyalgia Rapid Screening Tool (FiRST) and London Fibromyalgia Epidemiological Study Screening Questionnaire (LFESSQ) tools were used to assess the prevalence of FMS. Participants had no diagnosis of COVID-19. In that study, which included 992 participants, the prevalences were reported as 12.6% and 19.8%, respectively, according to FiRST and LFESSQ data. Bileviciute- Ljungar et al. [13] evaluated 100 post-COVID-19 individuals and reported that 40 (40%) met the 2016 diagnostic criteria for FMS. Foti et al. [14] enrolled 171 rheumatoid arthritis and 129 psoriatic arthritis patients in a study. FiRST was administered to the participants and was found to be positive in 21.1% of the rheumatoid arthritis patients and 24% of the psoriatic arthritis patients. Ursini et al. [15] investigated 616 participants who had recovered from COVID-19, and 189 (30.7%) fulfilled the ACR FMS survey criteria. It is remarkable that these results are higher than the literature data [16, 17]. This can be attributed to the

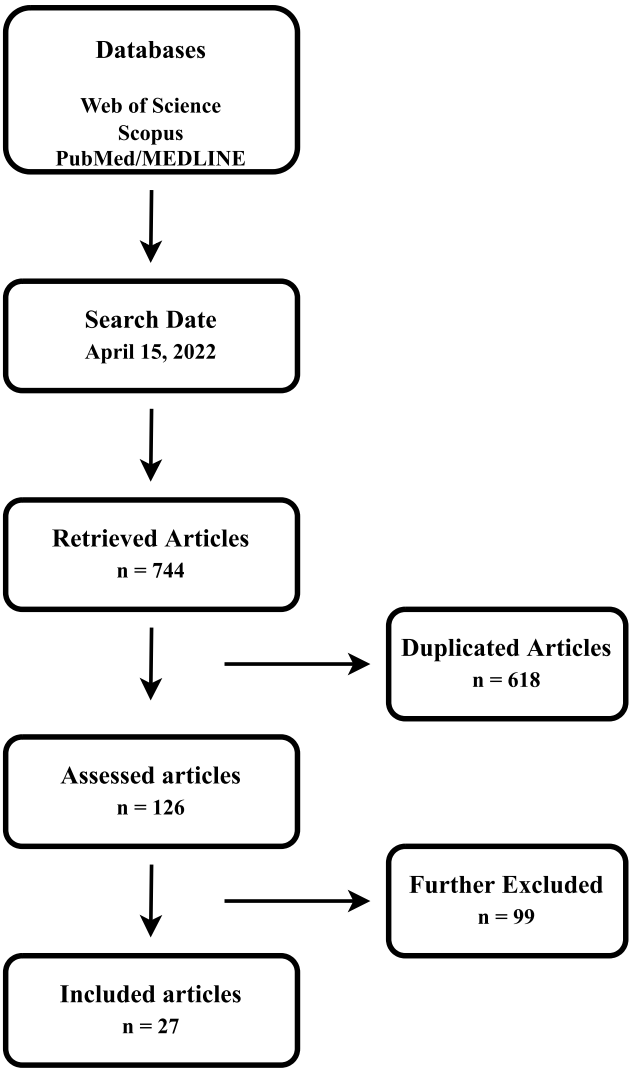

Fig. 1 Flowchart of the review

specific characteristics of the population in focus, as well as the impact of COVID-19 on individuals.

Effects of the pandemic on patients diagnosed with fibromyalgia syndrome before COVID-19

Conflicting results have been reported in studies evaluating the effects of COVID-19 on FMS patients. In addition to studies reporting unfavorable effects on FMS patients [18–25], there are also articles reporting a stable course and even positive impacts [26–29].

At the etiological level, FMS is a disorder in which various triggers play a role, from infections to physical trauma and psychological stress, and there is also an underlying genetic predisposition [30]. In this context, a pandemic that deeply affects the whole world, the implementation of strict quarantine conditions, social distancing rules, and ambiguity in future projections cause a psychological burden that cannot be overlooked, with potentially devastating impacts on the symptoms and quality of life of vulnerable FMS patients [18]. Facing economic challenges, difficulties in accessing healthcare services, and obstacles to obtaining complementary therapies and medicines may also play a role in the exacerbation of FMS symptoms under pandemic conditions [20]. Furthermore, a decline in outdoor activities, a deterioration in compliance with physiotherapy sessions, and a disruption in exercise programs may also be variables that impair the clinical status [19]. Consistent with all these mechanisms, 15 different rheumatic diseases were evaluated in the REUMAVID trial, and the highest risk of anxiety was found in patients with systemic sclerosis and FMS. In addition, the highest risk of depression was detected in patients with polymyalgia rheumatica and FMS [21]. Hruschak et al. [22] evaluated patients with FMS, spinal disorders, and post-surgical pain, and all had chronic pain. Regression analysis revealed that female gender, nonwhite race, lower education level, disability, fibromyalgia, and higher pain catastrophizing were independently associated with worsening pain scores. FMS was reported as one of the factors associated with increased pain scores.

Contrary to the view that FMS patients are adversely affected under pandemic conditions, Bacon et al. [26] reported no deterioration in FMS-related symptoms and an improvement in wellbeing during the study. While this unexpected outcome deals with chronic health problems and related stress, FMS patients may have developed coping strategies to maintain well-being in ways that could not be observed in the general population. FMS patients may have learned adaptation strategies and ways to manage the ever-changing symptom profile specific to the condition. Conversely, the general population may have been more concerned with maintaining a sense of normality during the pandemic. Another hypothesis for the lack of considerable change in somatic symptoms during the pandemic is that COVID-19 prompted individuals to pay attention to external pressures and behavioral variances. This may have had a positive impact on pain perception by moving the focus of patients with central sensitization away from internal sensorimotor states and psychological alterations and toward environmental issues [27, 31]. During the pandemic, fibromyalgia patients reported that their recovery was due to the beneficial effects of working from home and the opportunity to exercise more regularly as a result of increased free time [28, 32]. Under pandemic conditions, FMS patients were able to modify their daily rhythms according to symptom variations, and FMS did not take center stage in their lives. These circumstances may explain

the potential improvement [28, 33]. The negative and positive effects of COVID-19 on FMS patients are summarized in Fig. 2.

The potential for FMS patients to be affected by pandemic conditions varies, with results influenced by factors such as the level of coping with stress, adaptation to pandemic conditions, compliance with regular exercise, access to healthcare institutions, and continuing treatment processes. While COVID-19 was a major stressor that exacerbates FMS symptoms for some patients, for others it was an environmental factor that distracted them from focusing on FMS.

Are patients with fibromyalgia syndrome more severely affected by COVID-19?

Amital et al. [34] investigated the hospitalization of FMS patients due to COVID-19. The researchers analyzed morbidity and mortality patterns in a large cohort of FMS patients ($n = 571$) diagnosed with COVID-19 and examined whether this cohort was more vulnerable to the devastating effects of COVID-19. There was no significant difference between the groups with and without a diagnosis of FMS in terms of hospitalization and mortality outcomes associated with COVID-19. Older age, male sex, and hypertension were identified as risk factors for hospitalization in FMS patients.

Mechanisms and management of fibromyalgia-related symptoms after COVID-19

The effects of COVID-19 on mood symptoms have been frequently described as a consequence of the psychological burden. Therefore, individuals with COVID-19, as well as those with a history of suspected contact, have increased levels of depression and anxiety [35, 36]. Periods of lockdown and self-isolation may also trigger this condition. In addition to this mechanism, the activation of inflammatory and anti-inflammatory pathways may be a part of the process. There is also evidence that neuroinflammatory pathways alter neuroplasticity in the central nervous system and cause mood disorders. Therefore, it may be appropriate to consider that neuroinflammatory pathways are involved in the process, if only partially, in COVID-19-related mood disorders [35]. Post-COVID-19 individuals often experience fatigue (physical and mental), difficulty in concentrating, impaired neurocognitive functions, and myalgia. Similarly, in mood disorders, increased levels of pro- and anti-inflammatory mediators, acute phase response, and numerous markers of nitro-oxidative destruction may be linked to the above-mentioned symptoms [35]. Al-Jassas et al. [35] reported that aberrant chest computed tomography scans and impaired SpO2 levels were linked to the emergence of

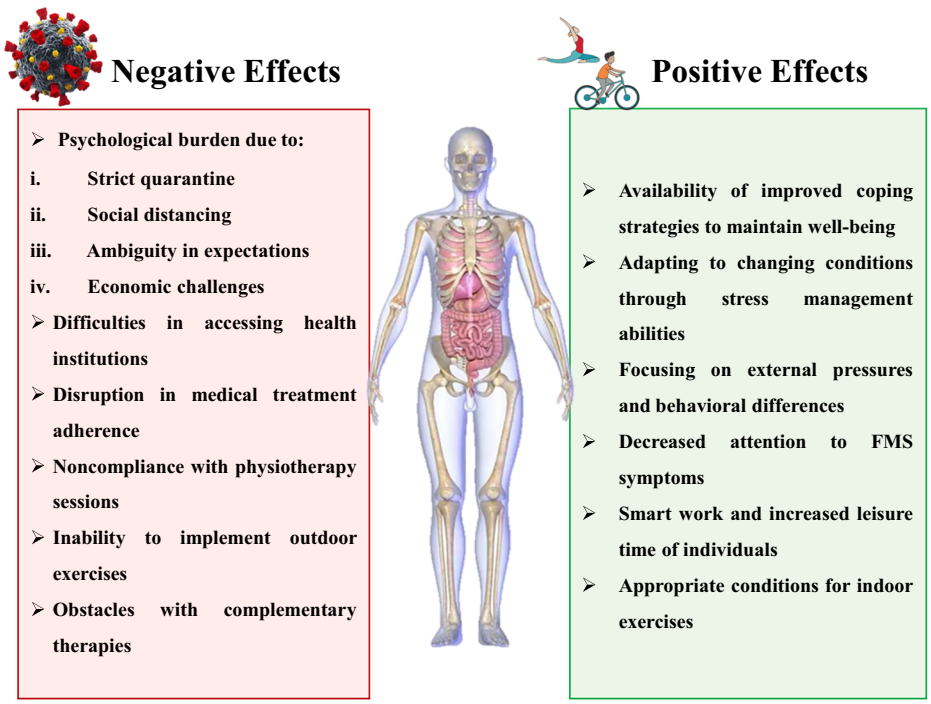

Fig. 2 The negative and positive effects of COVID-19 on FMS patients

the physio-affective core, as well as melancholia, cognitive problems, and sleeplessness. The plasma levels of IL-6, IL-10, C-reactive protein, and soluble receptor for advanced glycation end products were evaluated in the same study, and a significant relationship was revealed between the immunological response and the physio-affective core. Furthermore, SARS-CoV-2 may spread to the brain and trigger neuroinflammation, which is thought to be the source of various neuropsychiatric findings, including chronic fatigue following recovery [37]. Dhatt et al. [38] demonstrated the relationship between low vitamin D levels and flared FMS scores during the lockdown period. Gavrilova et al. [39] reported that post-COVID-19 patients with FMS had a more tolerable level of pain scores, but autonomic dysfunction, depression, and anxiety were prominent, and higher levels were determined of antinuclear antibody, C-reactive protein, and erythrocyte sedimentation rate. The relationship between FMS and autonomic nervous dysfunction has been previously demonstrated. A particular impact on the autonomic nervous system with the effect of the virus may trigger the emergence of FMS-related symptoms [24].

Various confounding factors may be involved during the pandemic. Pain, fatigue, and decreased functional capacity can occur in individuals due to immobilization, tendency to sedentary life, and sarcopenia. It should be emphasized at this point that the exercise habits of individuals change and it becomes more difficult to perform physical activity, particularly outdoor activities. Changes in exercise routines and physical activity patterns can trigger symptomatology. Post-COVID 19 kinesiophobia and anxiety can also play a role as confounding factors.

The first mechanism that comes to mind in terms of FMS-related symptoms after COVID-19 is the psychological burden on individuals. The role of external stressors in the development of FMS has been demonstrated previously. However, it appears to be a complex process in which COVID-19-related inflammation, central nervous system invasion, neuro-inflammation, and autonomic nervous system dysfunction are involved.

Although there is no clear consensus on the management of FMS-related symptoms after COVID-19, the most accurate data can be obtained from studies conducted on the long COVID-19 concept. Key recommendation points are multidisciplinary evaluation and treatment, management of particular symptom groups, and support of individualized rehabilitation [40]. There have been studies revealing the positive effects of comprehensive rehabilitation programs and aerobic exercise on post-COVID-19 fatigue, anxiety, impaired functional capacity, and kinesiophobia [41]. Psychological interventions-support, self-management strategies, and behavioral modification are also thought to be effective in symptom management. There is no agreement on pharmacological treatment choices [42].

COVID-19 vaccination and fibromyalgia syndrome

The safety of COVID-19 vaccines in patients with autoimmune rheumatological disease is a major concern. In this context, Cherian et al. [43] compared autoimmune rheumatic diseases and other rheumatic diseases in terms of COVID-19 vaccine safety, with 57 (27.01%) FMS patients in the other rheumatic disease group. There was no significant difference between the two groups in terms of adverse effects. In rheumatic disorders, the frequency of adverse effects following COVID-19 immunization was similar to the overall population. COVID-19 vaccine safety in inflammatory and non-inflammatory rheumatic diseases was investigated in the COVAX study [44], which included 36 FMS patients. The frequency of serious adverse effects in non-inflammatory rheumatic diseases was 1.9% ($n = 10$). Of these 10 serious adverse events, 3 occurred in FMS patients (2 patients were classified in the neurological (drowsiness, vertigo, dizziness, nausea, tinnitus, migraine, hallucination, and hemiparesis) group and one patient in the gastrointestinal (liver injury) group). Despite the small number of FMS patients, that study suggests that the frequency of serious adverse events of neurological origin is high in FMS patients. Considering that central sensitization, neuroinflammation, pain pathways in the central nervous system, and neuroplasticity are involved in the pathogenesis of FMS, there may be an increase in the frequency of adverse effects of neurological origin.

Vieira Rezende et al. [45] assessed COVID-19 vaccine hesitancy in patients with immune-mediated inflammatory diseases. Concurrent fibromyalgia was identified as an independent risk factor for COVID-19 vaccine hesitancy in that study. There may be various reasons underlying this result. High depression and anxiety levels in FMS patients may have increased the questioning against vaccines. Vaccine hesitancy may have developed as a result of the fact that individuals with FMS and immune-mediated inflammatory disorders have a higher rate of disability and poor quality of life, or fear of clinical deterioration after COVID-19 vaccination may have triggered this hesitancy.

There are several limitations that should be noted. The authors focused only on articles in English. Although major and reputable databases were examined, articles not listed in these databases were neglected. In some articles, the sample size is small and this may prevent the generalization of the results.

Conclusion

The main clinical symptoms of FMS are common in individuals under pandemic conditions, whether or not they have had symptomatic COVID-19. Various mechanisms have been suggested for the emergence of FMS-related symptoms after COVID-19. Individuals are affected biopsychosocially during periods of quarantine and self-isolation. In addition, the activation of some inflammatory pathways, alterations in neural plasticity-central sensitization, and variations in pain pathways are possible mechanisms. Another issue to be emphasized is that concomitant FMS in inflammatory rheumatological diseases is a risk factor for vaccine hesitancy. Considering the importance of vaccination in inflammatory rheumatic disorders, this patient group may require particular attention. Clinicians are confronted with a new clinical picture. At this point, a more in-depth research is needed to elucidate the etiopathogenesis. Is the treatment of this patient group the same as for standard FMS patients? Which scales and parameters should be preferred in the diagnosis and follow-up of this patient group? Future studies should focus on these questions.

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Data acquisition and review of the literature: BFK and AA.
Making interpretations: BFK and AA.
Drafting the manuscript: BFK.
Critically reviewing the manuscript: BFK and AA.
Final approval: BFK and AA.

Declarations

Disclosures None.

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