

## Post-acute COVID-19 syndrome and musculoskeletal manifestations: an overview

Síndrome pós-COVID-19 aguda e manifestações musculoesqueléticas: uma visão geral

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Received: 03/20/2023 | Revised: 03/30/2023 | Accepted: 04/04/2023 | Published: 04/09/2023

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### **Abstract**

Post-acute COVID-19 syndrome (also known as long COVID) refers to the persistence of COVID-19 symptoms for at least four weeks following the acute phase of the disease caused by SARS-CoV-2 infection. This study aims to provide a narrative review of the musculoskeletal manifestations of long COVID-19. While prevalence rates varied among studies, chronic fatigue, myalgia, arthralgia, and arthritis were consistently reported as the most common manifestations. Notably, a positive correlation was observed between the length of hospital stay and the likelihood of experiencing long COVID-19 symptoms. Moreover, women were found to be more susceptible to this condition than men.

**Keywords:** COVID-19; SARS-CoV-2; Fatigue; Musculoskeletal system; Musculoskeletal pain; Musculoskeletal diseases.

### **Resumo**

A síndrome pós-COVID-19 aguda (também conhecido como síndrome de COVID-19 longa) refere-se à persistência dos sintomas de COVID-19 por pelo menos quatro semanas após a fase aguda da doença causada pela infecção pelo SARS-CoV-2. Este estudo tem como objetivo fornecer uma revisão narrativa das manifestações musculoesqueléticas do COVID-19 prolongada. Embora as taxas de prevalência variem entre os estudos, a fadiga crônica, mialgia, artralgia e artrite foram consistentemente relatadas como as manifestações mais comuns. Notavelmente, foi observada uma correlação positiva entre a duração da internação hospitalar e a probabilidade de experimentar sintomas prolongados de COVID-19. Além disso, descobriu-se que as mulheres são mais suscetíveis a essa condição do que os homens.

**Palavras-chave:** COVID-19; SARS-CoV-2; Fadiga; Sistema musculoesquelético; Dor musculoesquelética; Doenças musculoesqueléticas.

### **Resumen**

El síndrome post-COVID-19 agudo (también conocido como COVID-19 de larga duración) se refiere a la persistencia de los síntomas de COVID-19 durante al menos cuatro semanas después de la fase aguda de la enfermedad causada

por la infección por SARS-CoV-2. Este estudio tiene como objetivo proporcionar una revisión narrativa de las manifestaciones musculoesqueléticas del COVID-19 de larga duración. Si bien las tasas de prevalencia variaron entre los estudios, la fatiga crónica, la mialgia, la artralgia y la artritis se informaron consistentemente como las manifestaciones más comunes. Cabe destacar que se observó una correlación positiva entre la duración de la estancia hospitalaria y la probabilidad de experimentar síntomas de COVID-19 de larga duración. Además, se encontró que las mujeres son más susceptibles a esta condición que los hombres.

**Palabras clave:** COVID-19; SARS-CoV-2; Fatiga; Sistema musculoesquelético; Dolor musculoesquelético; Enfermedades musculoesqueléticas.

## 1. Introduction

Recent studies suggest that COVID-19 can affect the musculoskeletal system and neurological functions, even after acute infection, which is referred to as long COVID (Brüssow & Timmis, 2021; Coluzzi, et al., 2020). According to the US Department of Health and Human Services, long COVID refers to signs, symptoms, and conditions that persist or develop after primary infection with SARS-CoV-2 for four weeks or more. It can present with multisystem manifestations, and a relapsing-remitting pattern, and can progress over time, potentially resulting in serious and fatal events after months or years. Among patients with long COVID-19, 77.3% reported musculoskeletal manifestations (Pires et al., 2022). Epidemiological studies have identified risk factors for post-acute COVID-19 syndrome, including acute disease severity, female sex (in patients aged 50-60 years), smoking or alcohol consumption, and comorbidities such as hypertension, diabetes, obesity, cardiovascular disease, and asthma (Nalbandian et al., 2021; Şahin et al., 2021). The presence of myalgia since the beginning of the acute disease has also been identified as a risk factor (Garg et al., 2021).

This study aims to provide an overview of possible musculoskeletal manifestations of post-acute COVID-19 syndrome, highlighting the main risk factors, clinical presentations, and mechanisms described so far.

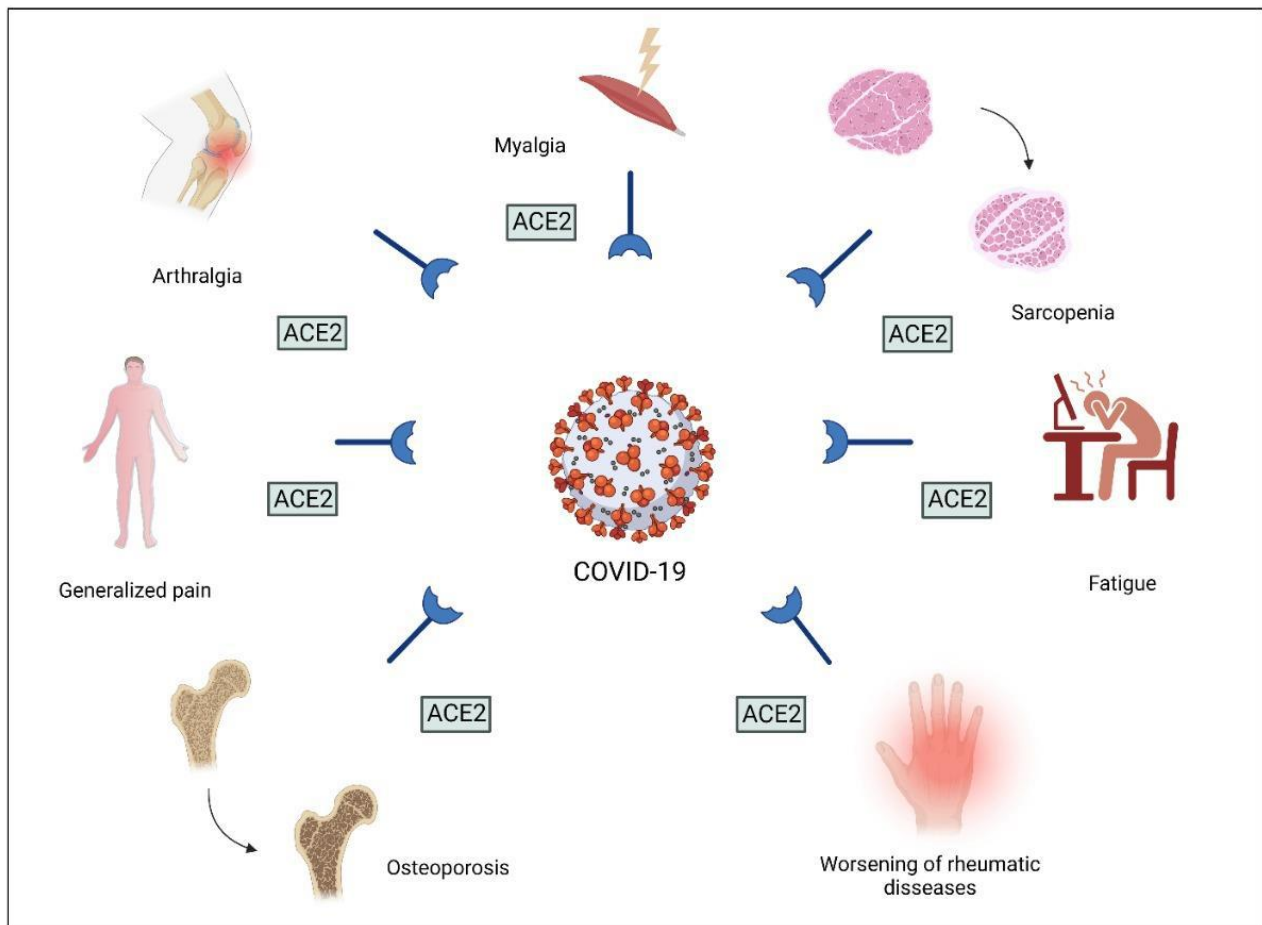
## 2. Methodology

This study was conceived as a narrative review and was performed for all scientific literature written in English and published between January 2020 and September 2022 referenced on PUBMED, concerning the musculoskeletal manifestations of post-acute COVID-19. The following search words or descriptors were used: “long COVID” or “post-COVID” or “musculoskeletal pain” or “fatigue” or “myalgia” or “arthralgia” or “arthritis” or “bone mineral density” or “osteoporosis” or “osteonecrosis” or “osteopenia” or “sarcopenia” or “rhabdomyolysis” or “myositis” or “muscle pain” or “back pain” or “cervical pain”. References from identified articles also were selected.

## 3. Results and Discussion

The most prevalent musculoskeletal manifestations in post-acute COVID-19 are described below and illustrated in Figure 1.

Figure 1 -



The ACE2 receptor serves as the entry point for the SARS-CoV-2 virus to invade cells in multiple organs. This can result in various forms of damage and chronic symptoms. The figure above provides an overview of the primary musculoskeletal manifestations observed in individuals experiencing post-acute COVID-19 syndrome. Source: authors.

### 3.1 Fatigue

Fatigue is characterized by a persistent feeling of tiredness, resulting in decreased energy, motivation, and concentration. Up to 60% of patients experience chronic fatigue after contracting COVID-19 (Crook et al., 2021). It is the most common musculoskeletal symptom, affecting both acute and post-acute COVID-19 manifestations (Bakılan et al., 2021). In one case series, fatigue was reported in up to 98% of patients, with a higher prevalence among women and those with anxiety or depression (Townsend et al., 2020). A study evaluating potential predictors for fatigue following COVID-19 infection found that the persistence and severity of fatigue were not associated with the severity of the acute phase of COVID-19 (hospital stay, ICU admission, or use of supplemental oxygen) or laboratory inflammation markers (Fernández-de-Las-Peñas, et al., 2021).

### 3.2 Myalgia

Myalgia is characterized by muscle pain and discomfort in soft tissues, including tendons, muscles, bones, and organs (Marshall, 2021). Trauma, adverse effects of medications, muscle exhaustion, and other illnesses may contribute to myalgia in individuals (Beydon et al., 2021; Salamanna, et al., 2021; Tuzun, et al., 2021). Myalgia has been reported in up to 25% of patients with COVID-19, similar to long COVID-19 cases. Some patients experience myalgia for 2 to 3 months after the acute manifestations of COVID-19, significantly impairing their health-related quality of life (Gawronska & Lorkowski, 2021). The pathophysiological mechanisms that explain this symptom are not fully understood. However, previous studies suggest that

infection-induced cytokines and pro-inflammatory molecules may damage the musculoskeletal system (Wiersinga, et al., 2021). Muscle involvement in long COVID-19 is still unknown, but SARS-COV-2 has been associated with hematogenous spread and direct muscle invasion via the ACE2 receptor. Hypercytokinemia and immune cell activation are associated with immune-mediated pathways that are activated after an inflammatory response and may be an explanation for muscle involvement. The release of myotoxic cytokines, deposit of immune complexes, and damage caused by extensive similarity between the viral antigen and myocytes are alternative proposals for immune system-mediated muscle damage (Wiersinga et al., 2021). A considerable number of patients experience generalized myalgia during the acute period of the disease and in long COVID-19. Risk factors include female sex, older age, previous comorbidities, and severity of the acute disease (Gawronska & Lorkowski, 2021). Access to healthcare and socioeconomic status also play a crucial role in the persistence of myalgia, as delays or avoidance in care and limitations of possible treatments may impact prognosis (Fernández-de-Las-Peñas et al., 2021).

### **3.3 Arthralgia and arthritis**

Arthralgia is a common symptom in long COVID-19 and primarily affects the wrists, ankles, and knees (Gawronska & Lorkowski, 2021). It affects 10 to 15% of patients, especially women, and is associated with higher levels of pain and greater use of analgesics (Jiang et al., 2021). While some studies suggest a link between disease severity and the presence of arthralgia, there is limited evidence to support this (Disser et al., 2020).

Arthritis observed in individuals infected with coronavirus is a reactive form of arthritis and is likely due to increased pro-inflammatory molecules and cytokines in joint synovial fluid (Montani et al., 2022). There is also evidence to suggest a direct association between long COVID-19 and the exacerbation of previously diagnosed rheumatological diseases (Disser et al., 2020). Several case reports have suggested an association between various rheumatologic conditions and long COVID-19, including seronegative rheumatoid arthritis, psoriatic arthritis, dermatomyositis, systemic erythematous lupus, spondylarthritis, and reactive arthritis. The mechanism of injury has been described as a trigger point for rheumatologic diseases (Cincinelli, et al., 2021).

### **3.4 Reduced bone mineral density, osteoporosis, and sarcopenia**

Reduced bone mineral density has been widely observed in patients who chronically use corticosteroids to treat general diseases and long COVID-19 (Disser et al., 2020; Ramani et al., 2021). Sedentary lifestyle, low sunlight exposure, poor eating habits, irregular sleep patterns, and prolonged hospital stays have also been associated with these manifestations (Lim & Kurniawan, 2021; Lisco et al., 2021). Additionally, fractures are reported, significantly impacting the quality of life of patients (Lim & Kurniawan, 2021). This may also significantly impact morbidity and mortality rates, especially among the elderly. The mortality rate within 30 days of a fracture in patients with acute COVID-19 was twice the pre-pandemic rate (Lim & Kurniawan, 2021). However, there is a lack of studies on this topic from the perspective of long COVID-19 and its complications.

Acute sarcopenia has been found in approximately 28% of patients with long COVID-19 (Pires et al., 2022). It is an important cause of morbidity and mortality in the elderly, and its main risk factors include prolonged hospital stays, prolonged bed rest, and the use of corticosteroids (Gawronska & Lorkowski, 2021).

### **3.5 Osteonecrosis**

Osteonecrosis is a frequently observed complication in patients with severe acute respiratory syndrome, with reported rates ranging from 5% to 58%. It is also an important entity to monitor in individuals with long-lasting COVID-19 symptoms (Hoong, et al., 2021). The head of the femur is the most commonly affected region, although the knee, humeral head, talus,

calcaneus, and other anatomical sites can also be affected (Lim & Kurniawan, 2021). Similar to osteoporosis, corticosteroid use in the acute and chronic stages of the disease is associated with osteonecrosis. Additionally, a higher predisposition to hypercoagulability, leukocytic aggregation, and vascular inflammation may interrupt blood flow to the affected bone region, resulting in osteonecrosis (Ramani et al., 2021). Endothelial dysfunction induced by SARS-CoV-2 may also play a role in the pathophysiology of osteonecrosis (Ciaffi, et al., 2022).

### 3.6 Rhabdomyolysis and Myositis

Rhabdomyolysis and myositis have also been reported in COVID-19 patients. Rhabdomyolysis was observed in up to 14.5% of patients, most of whom had severe acute disease requiring hospitalization (Pires et al., 2022; Ramani et al., 2021). Viral myositis caused by SARS-CoV-2 is presumed to be the cause of rhabdomyolysis (Zacharias, et al., 2021). Cytokines such as interleukin-6 (IL-6), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-8 (IL-8 or CXCL-8), interferon-gamma (IFN- $\gamma$ ), interferon-gamma-inducible protein 10 (IP-10 or CXCL10), and tumor necrosis factor-alpha (TNF- $\alpha$ ) are associated with rhabdomyolysis, as they induce muscle fiber breakdown and reduce protein synthesis (Cipollaro, et al., 2020; Disser et al., 2020; Morley, et al., 2020).

## 4. Conclusion

It is unequivocal that COVID-19 symptoms go beyond the respiratory system. Chronic fatigue and myalgia are among the primary musculoskeletal symptoms, which can have a significant impact on the individual's quality of life. Over the past few years, research on post-acute COVID-19 syndrome has been intensifying, but many knowledge gaps still need to be addressed. In this sense, it is important to carry out in-depth studies on the pathophysiology of the disease and its repercussions over the years, thus being a relevant cause of morbidity and mortality in the post-COVID-19 pandemic world.

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