



# Long-term Fatigue or Muscle Weakness Outcomes During Post-Covid-19

Jalal J<sup>1</sup>, Hedyeh S<sup>1</sup> and Siavash HC<sup>2\*</sup>

<sup>1</sup>School of Health Sciences, University of Georgia, Georgia

<sup>2</sup>School of Science and Technology, University of Georgia, Georgia

\*Corresponding author: Siavash Hosseinpour Chermahini, University of Georgia, Kostava St. 77a, 0171 Tbilisi, Georgia, Tel: +995595917942; Email: s.chermahini@ug.edu.ge

## Research Article

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## Abstract

The coronavirus pandemic has had a major impact on many areas of life, especially health. After the end, it was found that there were numerous persistent symptoms even after no prolonged infection with COVID-19, called post-acute sequelae of Covid-19 (PASC). Symptoms like depression, muscle weakness and fatigue. The information gathering method used for this paper was searching the PubMed, WHO and Google Scholar databases. To achieve the purpose of this review, it was found that there are factors that increase the risk of PASC specific fatigue, such as diabetes and obesity, by increasing the release of pro-inflammatory cytokines. In addition to other psychological factors that occurred during quarantine, such as anxiety, social isolation and the patient's ability to cope with stressful events and factors beyond the patient's control while in the hospital, such as: E.g., forced inactivity and bed rest, they all increase muscle wasting and reduce blood flow to skeletal muscles. In conclusion, the mechanisms related to fatigue and its causes are still not clearly understood, but early mobilization has been shown to improve fatigue outcomes of hospitalized patients.

**Keywords:** Fatigue; Post-Covid 19; Muscle weakness; Post-Covid syndrome; SARS-CoV-2

**Abbreviations:** PASC: Post-Acute Sequelae; MVC: Maximal Voluntary Contraction; PAL: Physical Activity Level.

## Introduction

Coronavirus disease 2019 (Covid-19) spread as a global pandemic causing diverse clinical signs and symptoms leading to an increase in mortality rates. Unfortunately, this is just the beginning as several patients reported a range of symptoms such as deep vein thrombosis, depression, myalgia, muscle weakness and fatigue in various systems, which persisted even after the patients recovered from Covid-19. The purpose of this review article is to answer these questions by examining the impact of these symptoms

on patients during post-Covid-19, with a greater focus on fatigue and muscle weakness. In this post-pandemic period, it is essential to understand how these post-Covid-19 symptoms develop and how acute or chronic they are, target demographic, age specificity, gender, race, ethnicity, specific patient comorbidities or others. It is important to identify possible factors that indicate that a patient could develop these post-Covid-19 symptoms. What can change the patient's chance of recovering more quickly from these post-Covid-19 symptoms or at least reduce their severity? Many more questions that help us understand exactly how to deal with such symptoms in post-Covid-19 patients and clearly understand the relationships between them and post-Covid-19, if any. Another point explored in this review

article is that Covid-19 is a very recent pandemic.

Therefore, it is necessary to find out what we know about which symptoms persist after Covid-19 and the possible areas in which they appear. They are currently undetected but require further research to develop strategies for managing such symptoms to achieve the most favorable results.

## Methods

This literature search was conducted on December 4, 2022, using PubMed, Google Scholar and the World Health Organization (WHO) databases, examining in-depth search terms corresponding to fatigue or muscle weakness or muscle fatigue or dermatomyositis and post-Covid-19 or post-Covid syndrome or post-Covid-19 syndrome by searching for randomized clinical trials, clinical trials, reviews, systematic reviews, cohort studies, observational studies and qualitative research. The screening was carried out by carefully selecting the relevant titles and abstracts.

## Results and Discussion

The first source said fatigue or muscle weakness is often a result of Covid-19. This was due to some variables such as cortico-therapy, prolonged bed rest and systemic inflammation. The disadvantages of post-Covid 19 infections were also shown to be mitigated by early mobilization and this had an impressive effect on recovery and their quality of life, particularly regarding fatigue [1].

The second source mentions that muscle weakness and exercise intolerance are the most common and important symptoms of Covid 19 and post-acute sequelae of Covid-19 (PASC). These signs and symptoms result from altered blood flow and metabolic activity, decreased ability to generate force, decreased neuronal responses, fiber atrophy, necrosis and fibrosis. Forced inactivity, systemic inflammation and viral infections are the causes of these symptoms. Factors that exacerbate skeletal muscle atrophy in bedridden individuals include malnutrition, hypoxemia and comorbidities. According to the studies, numerous patients report that they suffer from muscle weakness and exercise intolerance up to a year after contracting the virus [2-4].

The third study shows that after following patients for up to three months after Covid-19 in 34 studies, fatigue was the first symptom mentioned by patients and the most frequently mentioned at 28% to 87% and pain (myalgia 4.5%) up to 36%), which is a very significant number. Another point is that women reported greater fatigue and pain than men [5]. In the fourth study, seven patients between the ages of 48 and 77 were examined after Covid-19. This study also

showed that (85.7%) patients experienced Covid-19-related fatigue [6]. In the fifth study, 100 patients were included after discharge from hospital and examined for 4 to 8 weeks after Covid-19. According to the results, the first and most common symptom reported was fatigue and then shortness of breath [7]. The sixth study suggests that a single pathology or disease cannot fully explain fatigue.

However, the pathway that leads to fatigue includes inflammation, mitochondrial dysfunction and sleep problems, all of which are also common in Covid-19 infections and recovered post-Covid-19 patients. In patients with Covid-19, it can be difficult to distinguish between fatigue, sleepiness, mood disorders and depression because they often occur at the same time. Muscle wasting, myalgia and muscle weakness are also frequently observed in Covid-19 patients. A likely explanation for this is that the virus enters the muscle cell directly via the angiotensin-converting enzyme 2 receptor and causes local inflammation, which can lead to mitochondrial dysfunction, which increases the effect of muscle wasting. In addition, due to mitochondrial dysfunction, the impact on endurance is increased, resulting in decreased endurance, whereas its increase causes fatigue.

Covid-19 requires a high catabolic response from the body to fight it. Because of this, weight loss and muscle loss occur, which can also lead to fatigue. Obesity is also a major risk factor for terrible Covid-19 outcomes and is also linked to fatigue. This is caused by the mechanism characterized by increased release of cytokines and adipokines in adipose tissue, which trigger inflammation. Inflammatory mediators can also cause Covid-19 by crossing the blood-brain barrier and acting as stress signals, leading to irregularities such as fatigue.

The improved transmission efficiency of SARS-CoV-2 variants over the main Covid-19 variant results in a reduction in the overall average age of infected individuals, who may also feel tired regardless of their age [8-11]. The seventh study shows that there is an association with the degree of illness of the patient infected with Covid-19 during their hospitalization and deterioration in functional ability and, more importantly, an increase in fatigue [12]. In the eighth study, quadriceps muscle strength was measured in 98 patients hospitalized for Covid-19 and 50 patients recovering from Covid-19 with post-acute sequelae (PASC) over a period of 1 month analyzed for 5 years. The results showed that muscle weakness was noted in 59% of hospitalized patients and 65% of PASC patients after approximately 14 weeks of recovery from Covid- 19.

However, maximal voluntary contraction (MVC) improved slightly, but the prevalence of muscle weakness

remained the same. The possible predictors that played a role in muscle weakness were length of hospital stay and diabetes mellitus after hospitalization due to Covid-19. On the other hand, no predictors of PASC after Covid-19 could be identified. It is also mentioned that long-term improvement in muscle weakness is poor [13]. The ninth study examined the long-term functional status of 801 hospitalized Covid-19 patients 3 to 11 months after hospital discharge.

The average age of the group was 55.35 to 14.58 years, about 70.86% (567 of 800) reported limited daily activity after discharge and 5.62% (45 of 800) of them were severe. An interesting point of this study is that no general fatigue was noted in these patients (mean: 39.18, SD: 9.77; 95% CI: 38.50 to 39.86). The patient's functional level also remained unchanged in the months following hospital discharge [14]. The tenth study is a systematic review that showed that fatigue, myalgia and arthralgia are the most common musculoskeletal symptoms in the acute phase of Covid-19. While the musculoskeletal symptoms of fatigue, muscle weakness, myalgia, arthralgia, new onset back pain and poorer physical performance are present in post-Covid-19 syndrome and persist for more than 12 weeks.

There are some additional manifestations such as osteoporosis, acute sarcopenia, myositis, rhabdomyolysis, etc [15]. The eleventh study analyzed 16 patients with post-Covid-19 symptoms such as fatigue, weakness, or myalgia that lasted 14 months. It was found that 50% of them had muscle weakness and 75% of them had myopathic electromyography. In addition, all patients had histological changes of the 16 patients, 38% had muscle fiber atrophy and 56% showed signs of fiber regeneration. This study also mentions that 62% of them experienced functional changes in mitochondria, loss of cytochrome c oxidase, inflammation and subsarcolemmal enrichment. In addition, fatigue due to reduced energy supply occurred due to mitochondrial changes, inflammation and capillary damage.

One difference between the old variant and the new variant of SARS-CoV-2 is that the new variant may cause milder disease than the old variant as it may still retain the ability to lead to long-term muscle disease [16]. The twelfth study provides an overview of the mechanism that is responsible for the long-term physical effects of a SARS-CoV-2 infection and is of a pathophysiological nature. It mentions that the pathophysiological adaptations that take place during infection lead to symptoms most commonly associated with post-Covid-19 symptoms such as fatigue, chronic diseases and intolerance to physical activity. Given that cardiovascular dysfunction caused by heart damage, vascular and endothelial dysfunction, muscle weakness due to metabolic disorders and O<sup>2</sup> diffusion limitations, easy gas exchange due to impaired pulmonary diffusion and poor V/Q

matching may play a role in the long-term condition.

However, how these mechanisms work is still unknown [17].

The thirteenth study examines the possible factors contributing to fatigue by presenting a hypothetical model. It assumes that physiological and conditioning factors influence fatigue. The environment, the task and the person's physical and mental capabilities are conditional factors, while the peripheral, psychological and central parts of the body are physiological factors. Starting with conditional factors, the task type depends on the cognitive or motor task for the extent of fatigue.

Environmental dependency refers to how, for example, different temperatures or humidity can affect the patient's physical performance. The patient's physical and mental performance is also a factor that influences fatigue. For example, the patient's ability to cope with the stress of self-isolation, social isolation and anxiety due to the pandemic and the lack of physical activity in quarantine may lead to an increase in fatigue. In addition, physiological factors are related to how the physiology of the body is affected. Key factors affecting post-Covid-19 fatigue could be the result of a viral attack on the CNS. This is an example of how this affects normal levels of neurotransmitters such as dopamine and serotonin, demyelination, inflammation and many others.

Psychological factors include anxiety, depression and fear of the measures taken to combat the pandemic, but have negative consequences through post-traumatic stress symptoms, confusion and anger, which increase fatigue in post-Covid-19 patients. For example, in Covid-19, peripheral factors include the ability to infect different tissue types, particularly skeletal muscle, leading to symptoms of skeletal muscle weakness, pain and injury. This raises the possibility that Covid-19 could have a direct deleterious effect on skeletal muscle cells and cause fatigue [11,18-yyy21]. The aim of the fourteenth study was to determine the prevalence of post-Covid-19 symptoms. It was found that of the 817 references, the most reported post-Covid-19 symptoms are fatigue, shortness of breath and pain, with the overall prevalence of post-Covid-19 manifestations ranging from 35% to 90.5% [22].

The fifteenth study examined the long-term effects of 504 patients and the risk factors in the post-Covid-19 period. The study was conducted in three steps. The first was a telephone questionnaire, which revealed that 93.5% of patients were hospitalized and 61.7% of them were found to have a history of pneumonia. In addition, 27.1% showed clinical symptoms at the end of the first year. At 6.3%, the prevalence of fatigue was between the other long-term symptoms.

The third step showed that of 138 patients admitted for an in-person visit after at least the first year, 49.27% experienced any symptom, excluding dyspnea (27.6%) and psychiatric symptoms (18.1%). The most common rate of fatigue was 17.4% in the other study [23,24]. The sixteenth study found that 48 post-Covid-19 patients who recovered halfway from mild to moderate severity had extra pulmonary features. 39.6% of patients had handgrip weakness, while 35.4% had quadriceps weakness. Physical activity level (PAL) was high in 27.1%, moderate in 33.3% and low in 39.6%. Psychological symptoms such as anxiety and depression were observed in 33.3% and 29.2% of participants, respectively [25,26].

### Conclusion and Recommendation

Ultimately, Covid-19 is an infection that causes numerous symptoms and symptoms during and after the illness. The most well-known are the post-acute consequences of Covid-19, which range from shortness of breath to fatigue and muscle weakness and last for months to a year after infection. From the above studies, fatigue and muscle weakness are common in patients recovering from Covid-19, confirmed by a prevalence of 90.5% in patients with fatigue. The other variants of SARS CoV-2 show increased transmission, reducing the overall average age of people who become fatigued and increasing the prevalence of such symptoms. Fatigue and muscle weakness occur due to various underlying mechanisms, most commonly due to the release of pro-inflammatory cytokines that enter various cells, primarily muscles, via the angiotensin-converting enzyme 2 receptor, causing systemic inflammation, which are prone to mitochondrial dysfunction, increasing muscle loss as well as reduced endurance, which increases fatigue.

Additionally, Covid-19 requires the body to have high catabolic needs, which can lead to weight loss and muscle wasting, exacerbating the effects of more fatigue. Risk factors that may influence the effect of Covid-19 include diabetes and obesity by increasing the release of pro-inflammatory cytokines. Another underlying mechanism relies on inflammatory mediators, which can also trigger fatigue by crossing the blood-brain barrier and transmitting stress signals that lead to fatigue. Factors that can cause fatigue include physiological factors such as stress and anxiety caused by quarantine, as well as conditional factors such as the person's mental ability to cope with such stressful events, all of which can lead to fatigue. Hospitalization during infection was also a factor leading to increased fatigue and muscle weakness, resulting from their forced inactivity and reduced blood flow to skeletal muscles.

Therefore, early mobilization is recommended for hospital patients as this will help them recover better from

fatigue. A recommendation for future researchers is that many of the underlying mechanisms describing how fatigue and muscle weakness arise are not clearly understood and there is little evidence to support them. In principle, additional research needs to be carried out in this area to better understand the mechanisms for alleviating such symptoms and improving the quality of life of patients infected with Covid-19 and those who have recovered from it.

### Declaration

#### Ethical approval and consent to participate

Not applicable.

#### Consent to publish

Not applicable.

#### Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

#### Competing interests

The authors declare that they have no conflict of interest.

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#### Author's contributions

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