

Review Article: Musculoskeletal Problems in Patients With COVID-19: A Review Study

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ABSTRACT

Introduction: SARS-CoV-2 is a coronavirus, primarily targets the human respiratory system and causes symptoms similar to those of pneumonia. However, these patients do not only experience respiratory problems. Those with COVID-19 infection may show various signs and symptoms, including fever, shortness of breath, dry cough, nasal congestion, sore throat, nausea, vomiting, myalgia, arthralgia, fatigue (muscular and mental), joint swelling, headache, diarrhea, as well as some musculoskeletal symptoms. Therefore, this article aimed to investigate the major musculoskeletal problems in patients with COVID-19 through a review study.

Materials and Methods: This study gathered the related published studies in PubMed, Web of Science, and Science Direct. The main keywords were “COVID-19”, “coronavirus”, and “musculoskeletal problem”.

Results: The major musculoskeletal symptoms include muscle fatigue, myalgia, arthralgia, joint swelling (reactive arthritis), and such conditions as joint limitations, tendon shortening, and muscle weakness due to prolonged bed rest. However, their prevalence rates have not been investigated systematically.

Conclusion: Our findings revealed that attention to musculoskeletal rehabilitation of patients with COVID-19 is as essential as their respiratory rehabilitation. Besides, it would be effective in reducing the physical complications of hospitalization, returning to independence and functional activities, and improving the quality of the patients' life.

Keywords: Musculoskeletal pain, Myalgia, Arthralgia, Fatigue, COVID-19

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1. Introduction

SARS-CoV-2 is a coronavirus belonging to the beta coronavirus category [1]. Coronavirus is one of the main pathogens that primarily targets the human respiratory system and causes symptoms similar to pneumonia [2].

Patients with COVID-19 suffer mostly from respiratory problems, and their clinical symptoms range from none to severe pneumonia. However, they may show a variety of symptoms, including fever, shortness of breath, dry cough, nasal congestion, sore throat, nausea, vomiting, myalgia, arthralgia, fatigue (muscular and mental), joint swelling (as reactive arthritis), headache, diarrhea, and rarely arthritis [3-8]. The major musculoskeletal symptoms include arthralgia, myalgia, chronic fatigue, and joint swelling (as reactive arthritis); however, their prevalence rates have not yet been systematically studied [6, 7]. Thus far, the reports have revealed no signs of COVID-19 in skeletal muscle, joint, or bone. According to the reports, musculoskeletal symptoms result from indirect effects of COVID-19 and are mainly due to immune or inflammatory responses. However, other mechanisms can also be considered, such as direct virus damage to the endothelium or peripheral nerves [9]. The onset of symptoms of COVID-19 depends on the patient's age, state of the immune system, and underlying diseases. The symptoms are less severe in patients under 70 [10]. Notably, in some specific diseases such as SARS or COVID-19, there are two distinct stages: the first acute stage is associated with common respiratory symptoms, and the second stage is accompanied by a gradual improvement in respiratory symptoms but along with the musculoskeletal problems and pain due to relatively long-term bed rest and inactivity (such as back pain). Therefore, rehabilitation of patients with COVID-19 not only includes attention to respiratory, infectious, or neurological problems but also contains other medical measures in cases of bedsores, peripheral muscle weakness, and muscle contractions. Notably, joint limitations, balance, postural disturbances, and physical weakness due to prolonged bed rest can significantly reduce the chances of returning to pre-infection functional status, which can profoundly affect the rehabilitation care of patients and the medical team as well [11]. Therefore, the improvement of patients with COVID-19 can be made through improving respiratory function, coping with immobility and its complications, reducing long-term complications, and improving cognitive and emotional states to improve life's quality [12]. Accordingly, adopting a multi-purpose approach to rehabilitation is a fundamental strategy (especially in patients with

advanced age, obesity, multiple chronic diseases, and organ failure). Therefore, each patient requires a specific musculoskeletal and respiratory rehabilitation program that should be adjusted according to his/her characteristics and health conditions [11]. Considering the clinical conditions which cause prolonged immobility and musculoskeletal problems, these patients need different rehabilitation treatments, even after discharge from the inpatient ward, to increase the chance of recovery. These rehabs include respiratory rehabilitation, musculoskeletal rehabilitation, and sometimes neuromuscular rehabilitation. In cases where the complications of COVID-19 disease are not severe and patients are at home, they may also need home or outpatient rehabilitation mainly to restore motor skills and improve their mental state. In both cases, the rehabilitation program should focus on each patient's specific disorders [13]. Because of various musculoskeletal problems in pandemics such as COVID-19 and SARS, this article investigates the major musculoskeletal problems in patients with COVID-19 through a review study.

2. Materials and Methods

This study gathered the related published studies in PubMed, Web of Science, and Science Direct. The main keywords were COVID-19, SARS-CoV-2, and coronavirus combined with the terms of pain and musculoskeletal problem in adults among English publications from 2020 to early 2021. Our search found a total of 60 articles. The inclusion criteria were published papers in the scientific journals in the valid motor search such as Google Scholar and Science Direct based on keywords. The exclusion criteria were papers that were not indexed in the PubMed or Web of Science and the papers which not reported, especially the musculoskeletal pain related to COVID-19. Figure 1 shows the flowchart of the study selection. Thirteen articles were related to musculoskeletal problems prevalence in people with COVID-19. The included articles are listed in Table 1.

3. Discussion

We examined the musculoskeletal problems in patients with COVID-19 through a review study. Notably, the problems of patients with COVID-19 do not only include respiratory ones. They may have various symptoms, including fever, shortness of breath, dry cough, nasal congestion, sore throat, nausea and vomiting, myalgia, arthralgia, fatigue (muscular and mental), headache, diarrhea, and rarely arthritis [3-8]. Their major musculoskeletal symptoms include arthralgia, myalgia, chronic fatigue, and joint swelling (reactive arthritis) [6,

7]. It should be noted that some symptoms such as joint limitations, balance, postural disturbances, and muscular (physical) weakness due to prolonged bed rest can also dramatically reduce the chance of returning to a pre-infection functional state and profoundly affect the rehabilitation care of the affected patients [11]. The improvement of COVID-19 patients is made by improving respiratory function, coping with immobility and its complications, reducing long-term complications, and improving cognitive and emotional states to improve the quality of life [12]. Accordingly, their rehabilitation should be multi-purpose and based on the needs of each patient and his/her characteristics [11].

Arthralgia

Nine of the studies listed in Table 1 reported the accompanied arthralgia with COVID-19 [7, 14, 15, 18-20, 24, 25]. The causes of arthralgia (joint pain) vary from degenerative and destructive processes, such as osteoporosis and sports injuries, to inflammation of the tissues around the joints such as bursitis. This symptom may also be caused by other conditions such as infection or vaccination [26]. Arthralgia is an essential clinical complaint seen in many patients affected by viral infections, including COVID-19 as an emerging infectious disease [27]. Notably, information on its rheumatic manifestations is limited. In a clinical, epidemiological report published in the Lancet, no data on arthralgia were reported as a common complaint among the patients with COVID-19 [28, 29]. However, in Thailand, several patients (2.5%) complained of joint pain [30]. This result could indicate the importance of rheumatoid arthritis in COVID-19 patients. In cases where the disease has been transmitted from an arthropod (an invertebrate animal such as an insect, spider, or crustacean), the symptoms of arthralgia with COVID-19 might be quickly relieved [31]. Low back pain can also be treated with over-the-counter medications, ice packs, hot baths and stretching. But more severe cases of joint pain may require special medical procedures such as steroid injections, the use of non-steroidal anti-inflammatory drugs, joint aspiration or physical therapy (such as physiotherapy, splints, etc.).

Myalgia

Myalgia is caused by viral infections such as the new 2019 Coronavirus (COVID-19) and influenza, indicating a general inflammation and cytokine response (an immune system response) displayed as the onset of symptoms in 36% of patients with COVID-19 [32]. Ten studies listed in Table 1 reported myalgia as a symptom accompanied by COVID-19 [14-18, 20-24]. Low back

pain in COVID-19 may be an indication of pneumonia. COVID-19-induced myalgia may last longer and be more severe than other viral infections, so that it may not respond to conventional analgesics. Usually, along with reducing the viral load by treating the virus, muscle pain may also be reduced. Notably, COVID-19 can cause musculoskeletal pain with a completely different mechanism compared to the known mechanisms of myalgia in viral infections [33]. Recently, a metallopeptidase has been identified as a functional receptor for SARS-CoV, called angiotensin-converting enzyme 2 (ACE2) [34].

ACE2 binds to the membranes of the lung, artery, heart, kidney, and intestine cells [34]. It acts as an entry point into the cells for such coronaviruses as HCoV-NL63, SARS-CoV, and SARS-CoV-2 [35]. Regarding COVID-19 and penetrating ACE2 in the areas with low cytosolic pH, the virus enters the cell and causes infection in the pulmonary system [36]. Recently, it has been found that lactate levels increase due to the damage caused by cell overuse during COVID-19 infection [37]. The capacity of the oxygen cells to carry oxygen is disrupted in hyperlactatemia, and, therefore, the tissues remain hypoxic. Another point worth mentioning is the capacity of this virus to spread through the bloodstream or vascular endothelium, causing infection in all tissues containing ACE2, such as the heart and brain. Therefore, the musculoskeletal system can also become infected. The increased creatinine kinase levels during COVID-19 infection demonstrate muscle involvement [33]. Since lactate begins to accumulate when muscle tissue cannot produce enough energy during aerobic exercise, the Monocarboxylate Transfer (MCT) mechanism is activated to prevent lactate accumulation [38]. In hyperlactatemia, the capacity of red blood cells to carry oxygen is also greatly reduced. It seems that if intense exercise is done, the musculoskeletal system may come across a deficiency in oxygen uptake, and the muscles may develop ischemia due to COVID-19 infection. Therefore, it may cause pain in residual ischemic muscle with a mechanism similar to sickle cell disease. Besides, pain can be caused during hypoxic ischemia because of an increase in growth factors, cytokine levels, ischemic conditions and microvascular changes, by the dorsal root ganglion overexpression [39]. As a result, Lactate Dehydrogenase (LDH) increases by damaging the virus. Then, the increased LDH and anaerobic glycolysis may lead to highly elevated lactate levels in other muscles and tissues. The cytosolic pH may also decrease further. Then, due to the increase in lactate levels, low pH, and low oxygen levels, muscle pain may increase. Therefore, to treat these kinds of pain, it is necessary to eliminate the cause of hypoxia. It should be noted that the use

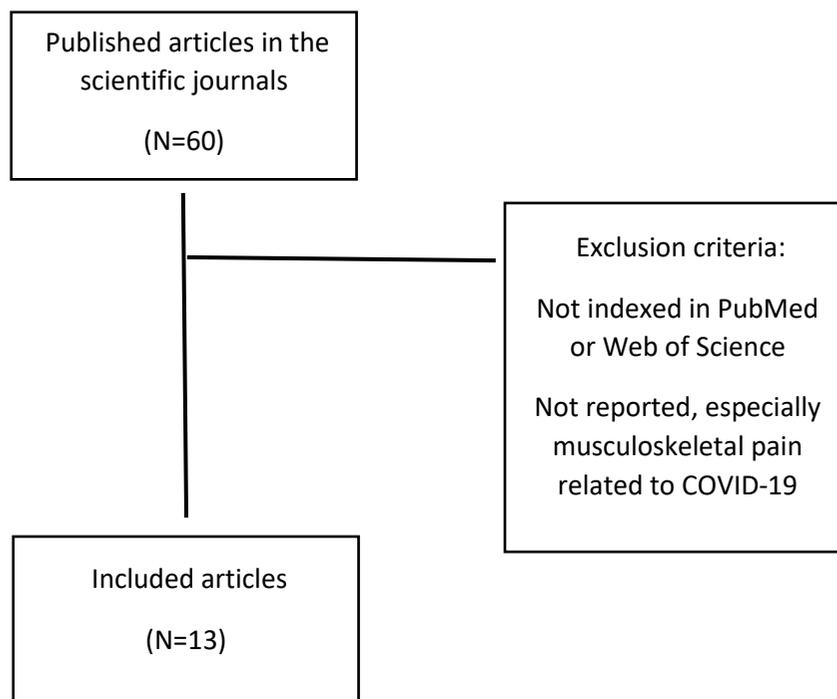


Figure 1. The flow chart of the study

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of analgesics may not be effective in these cases. In fact, through reducing the virus load, oxygen delivery by red blood cells increases, the muscle lactate level decreases, then the pain disappears.

Muscular fatigue

Symptoms such as fatigue, heart palpitations, muscle aches, tingling sensations, and some other symptoms have been reported as side effects in patients with COVID-19. About 10% of 3.9 million patients participating in the “COVID-19 Symptom Study” program had experienced the mentioned effects even for more than four weeks [40]. The WHO report showed that 38% of patients developed fatigue due to COVID-19. A study in Wuhan (China) showed that this symptom was so common that 70% of the participating patients developed fatigue [41]. Nine studies listed in Table 1 reported the fatigue related to COVID-19 from 18% to 85% [14-18, 20, 21, 24]. Since chronic fatigue (takes more than six weeks) can be diagnosed in different clinical cases, from cancer treatment to inflammatory arthritis, COVID-19 is not the only cause. For example, it also occurs after other viral infections such as the Epstein-Barr virus, known as glandular fever. Notably, in a study done in Hong Kong in 2003, a quarter of infected patients with the original SARS virus showed post-infection fatigue syndrome. Since there is no specific treatment for most viral infections, we still do not know how to manage post-infection fatigue of this very new coronavirus [40].

The cause of fatigue after COVID-19 infection

Although different viral infections can sometimes cause persistent fatigue, we know very little about its underlying mechanism. One of the probable reasons might be the continual presence of a viral infection in the lungs, brain, adipose, or other tissues. Besides, prolonged and improper immune response after clearing the infection may be another cause. In patients with hepatitis C, using interferon α as a treatment led to the development of a flu-like illness and, in a few patients, post-viral fatigue. Investigating the very artificial response, the researchers found that the basal level of interleukin-6 and interleukin-10 causes inflammation and subsequent chronic fatigue. The same anti-inflammatory molecules have been observed in the “cytokine storm” of patients with COVID-19, depending on the severity of the disease [28]. The overreaction of the immune system leads to the release of cytokines disproportionately to the threat or for a longer period after the virus threat has ended. After the cytokine storm, the immune system causes significant damage by invading the tissues. This exaggerated inflammatory reaction may cause severe injuries to the liver, blood vessels, kidneys, and lungs, as well as forming blood clots in the body. Therefore, this damage might be greater than that of the coronavirus itself [42]. All indicate a pattern of immune system activation during viral infection that results in persistent symptoms

Table 1. The prevalence rates of musculoskeletal pain in COVID-19

Authors [Ref.]	Year	Type of Musculoskeletal Pain	Number of Samples	Number of People With Symptoms (%)
Ma et al. [14]	April 2020	Fatigue, arthralgia, myalgia	37	8 (21.6)
Zheng et al. [15]	2020	Fatigue, arthralgia, myalgia	99	84 (85.0)
Mo et al. [16]	March 2020	Fatigue, arthralgia, myalgia	155	60 (73.2)
Jin et al. [17]	March 2020	Fatigue	651	119 (18.2)
Guan et al. [18]	2020	Fatigue, arthralgia, myalgia	1099	419 (38.0)
Escalera-Antezana et al. [19]	2020	Arthralgia, myalgia	12	5 (42.0)
Lechien et al. [20]	April 2020	Fatigue, arthralgia, myalgia	417	246 (59.0)
Tian et al. [21]	2020	Fatigue	262	69 (26.0)
Yang et al. [7]	2020	Arthralgia	52	5 (9.8)
Dreher et al. [22]	2020	Myalgia	50	10 (20.0)
Huang et al. [23]	2020	Myalgia	41	8 (20.0)
Tuzun et al. [24]	Jan 2020	Fatigue, arthralgia, myalgia, low back pain	150	102 (67.0)
Hoong et al. [25]	Mar 2021	Fatigue, arthralgia, myalgia, low back pain	294	88 (30.0)

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in infected individuals. Therefore, the successful use of tocilizumab reduces the inflammatory effect of interleukin-6 in patients with severe COVID-19. Indeed, some tips for people with chronic fatigue could be to manage the fatigue and save energy. The important point is that going to the gym and putting your body under pressure is the wrong thing to do, which can significantly increase chronic fatigue. Therefore, low activities (mental or physical) should be done with a long enough rest interval. Returning to work should be through a gradual and graded process. Besides, the patients should learn how to speed up their daily activities [40].

Joint swelling or reactive arthritis

Joint swelling usually occurs shortly after infection and, in most cases, resolves within three to six months without causing any long-term problems. Seemingly, it occurs when the immune system overreacts to an infection and attacks healthy tissues, causing inflammation. However, the exact cause is still unknown. Another probable cause of this disease is HLA-B27 gene. Although reactive arthritis can affect women and men of all ages, it is more common in men aged between 20 and 40. It can affect any joint, but most often knees, feet, toes, hips, and ankles. It causes pain, tenderness, swelling in

the joints, pain, and tenderness in some tendons (especially in heels), back and hip pain, sausage-like swelling in the fingers and toes, and joint stiffness (especially in the morning). Although there is no specific test to diagnose reactive arthritis, such tests as blood and urine tests, genital swab, scan, sonography, and X-rays might be used. Notably, its treatment usually includes antibiotics to remove any factors that may cause reactive arthritis, the use of analgesics such as ibuprofen to alleviate the pains, and medications such as steroids or anti-rheumatic drugs to manage different levels of this disease [43].

4. Conclusion

Patients with COVID-19 do not only have respiratory problems. Their major musculoskeletal problems include muscle fatigue, myalgia, arthralgia, and arthritis. The prevalence of musculoskeletal pain reported in patients with COVID-19 was between 10% to 85%. The tissue inflammation and impairment of oxygen supply related to COVID-19 can be the sources of musculoskeletal pain. Attention to musculoskeletal rehabilitation of patients with COVID-19 is essential, along with their respiratory rehabilitation. In addition, it would be effective in reducing the physical complications of hospitaliza-

tion, returning to independence and functional activities, and improving the quality of patients' life.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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Authors contributions

All authors pass the four criteria for authorship contribution based on the International Committee of Medical Journal Editors (ICMJE) recommendations.

Conflict of interest

The authors declared no conflict of interest.

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