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Invited Review

Musculoskeletal involvement: COVID-19 and post COVID 19

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ABSTRACT

The worldwide pandemic of coronavirus disease 2019 (COVID-19) was known to predominantly affect the lungs, but it was realized that COVID-19 had a large variety of clinical involvement. Cardiovascular, gastrointestinal, neurological, and musculoskeletal systems are involved by direct or indirect mechanisms with various manifestations. The musculoskeletal involvement can manifest during COVID-19 infection, due to medications used for the treatment of COVID-19, and in the post/long COVID-19 syndrome. The major symptoms are fatigue, myalgia/arthralgia, back pain, low back pain, and chest pain. During the last two years, musculoskeletal involvement increased, but no clear consensus was obtained about the pathogenesis. However, there is valuable data that supports the hypothesis of angiotensin-converting enzyme 2, inflammation, hypoxia, and muscle catabolism. Additionally, medications that were used for treatment also have musculoskeletal adverse effects, such as corticosteroid-induced myopathy and osteoporosis. Therefore, while deciding the drugs, priorities and benefits should be taken into consideration. Symptoms that begin three months from the onset of the COVID-19 infection, continue for at least two months, and cannot be explained by another diagnosis is accepted as post/long COVID-19 syndrome. Prior symptoms may persist and fluctuate, or new symptoms may manifest. In addition, there must be at least one symptom of infection. Most common musculoskeletal symptoms are myalgia, arthralgia, fatigue, back pain, muscle weakness, sarcopenia, impaired exercise capacity, and physical performance. In addition, the female sex, obesity, elderly patients, hospitalization, prolonged immobility, having mechanical ventilation, not having vaccination, and comorbid disorders can be accepted as clinical predictors for post/long COVID-19 syndrome. Musculoskeletal pain is also a major problem and tends to be in chronic form. There is no consensus on the mechanism, but inflammation and angiotensin-converting enzyme 2 seem to play an important role. Localized and generalized pain may occur after COVID-19, and general pain is at least as common as localized pain. An accurate diagnosis allows physicians to initiate pain management and proper rehabilitation programs.

Keywords: Bone, COVID-19, muscle, post/long COVID-19.

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, at the end of 2019 and had spread all over the world. The World Health Organization declared it as a pandemic.[1] In Türkiye, the first COVID-19 case was diagnosed in March 2020, and it affected 17,042,722 people at the end of 2022.[2] The pandemic has negatively affected the health care system and caused both an economic and social burden almost all over the world. Furthermore, 6.5 million deaths were recorded since the beginning of the pandemic. Initially, it was hard to predict the emerging effects of multisystem involvement. The damage was known to predominantly affect the lungs, but it was realized that COVID-19 has a large variety of clinical involvement. The symptoms are characterized from mild infection to severe pneumonia with respiratory failure. Some patients were hospitalized, and some were admitted to intensive care units (ICUs) and supported by mechanical ventilation.[3] During the pandemic, there are growing evidence that cardiovascular, gastrointestinal, neurological, and musculoskeletal systems are involved by direct or indirect mechanisms with various manifestations.[4-6] Mechanisms of musculoskeletal involvement in COVID-19 can be

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overviewed in three headings: musculoskeletal involvement that manifests *(i)* during the COVID-19 infection, *(ii)* due to medications used for the treatment of COVID-19, and *(iii)* as part of the post/long COVID-19 syndrome.

1. Musculoskeletal involvement during COVID-19 infection

Musculoskeletal symptoms of COVID-19 cannot be underestimated due to their high prevalence. In a meta-analysis involving 51 studies with 11,069 patients, the prevalence of myalgia was 19%, fatigue was 32%, and back pain was 10%.[7] In another meta-analysis with 49 studies and 6,335 COVID-19 patients, the prevalence of myalgia was 86%.[8] A retrospective study with 210 patients diagnosed with COVID-19 evaluated the symptoms of the patients.[9] The major symptom was fatigue (76.6%), followed by pain (69.3%), myalgia/arthralgia (69.2%), back pain (43.6%), low back pain (33.1%), and chest pain (25%). Similarly, a cross sectional study involved 150 patients hospitalized due to COVID-19 and assessed myalgia severity, fatigue, and handgrip strength.[10] Fatigue was reported in 68%, and arthralgia was reported in 43.3%. The most affected joints were the wrist, ankle, and knee. Ischemic myalgia was a common symptom, but it was not related to disease activity and muscle strength. Furthermore, muscle strength was found lower in female patients, which might guide the rehabilitation program.[10] Bone health is another issue for COVID-19 patients that is mostly ignored. Lower bone mineral density, osteoporosis, osteomalasia, and osteonecrosis were reported in COVID-19 patients.[11,12] Although there are studies that express the neurological manifestations in this review, muscular and bone involvement will be the primary focus. Table 1 shows the musculoskeletal involvement of COVID-19 infection.

TABLE 1
Musculoskeletal involvement of COVID-19

Muscle/joint	Bone
Fatigue	Osteoporosis
Myalgia	Osteonecrosis
Arthralgia/arthritis	Heterotopic ossification
Headache	Osteomalasia
Back pain	Fragility fracture
Chest pain	Osteosarcopenia
Low back pain	
Muscle weakness	
Myositis	
Rhabdomyolysis	
Myopathy	
Sarcopenia	
Widespread pain/fibromyalgia	
Chronic pain	

COVID-19: Coronavirus disease 2019.

During the last two years, the number of studies related to musculoskeletal involvement increased, but no clear consensus was obtained about the pathogenesis. However, there is valuable data that supports the hypothesis of ACE2, inflammation, hypoxia, and muscle catabolism.

ETIOPATHOGENESIS AND FACTORS THAT AFFECT MUSCULOSKELETAL SYSTEM INVOLVEMENT

1. Receptors and enzymes

Angiotensin-converting enzyme 2 (ACE2) and serum transmembrane protease 2 (TMPRSS2) are key points of the system. Angiotensin-converting enzyme 2 was demonstrated not only in the pulmonary system but also in some other tissues, such as smooth muscle, cartilage, and kidneys. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein directly interacts with ACE2 receptors. In skeletal muscle, TMPRSS2 is predominantly expressed, and both ACE2 and TMPRSS2 play a role in the binding of the virus. Synovium and bone tissue also include either ACE2 or TMPRSS2, which may result in a potential target in COVID-19-related muscle injury, and COVID-19 may cause bone loss by affecting remodeling since osteoclasts express ACE2 receptors.[11,13-16]

2. Inflammation-cytokine storm

Disease prognosis has a close relationship with systemic inflammation. Proinflammatory and inflammatory cytokines (C-reactive protein, interferon-γ, interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, and IL-17, and tumor necrosis factor-α) increase, and excessive response occurs, which is called cytokine storm.[15-18] Studies showed that cytokine storm is associated with multi organ failure and fatality. One reason is endothelial damage, resulting in micro- or macrotrombosis. Early detection of high levels of CRP and IL-6 was found to be correlated with disease severity and muscular breakdown. Proteolysis of muscle fibers with decrease in protein synthesis leads to muscle damage due to increased inflammatory

cytokines. Increase in IL-10 corrupts the mitochondrial function in muscles and endothelium. In particular, IL-1β and -6 cause muscular fibrosis. Inflammation affects large muscles and multiple sides, including the diaphragm and intercostal muscles, which provide significant support for pulmonary functions.[14,15,17-19] Furthermore, inflammatory cytokines lead to increased bone resorption by interacting with nuclear factor kappa B-RANK-RANKL system and may cause osteoporosis.[11,12]

3. Hypoxia

Hypoxia/hypoxemia is the key point of the SARS-CoV2 infection as the pulmonary involvement was the primary early clinical finding at the beginning of the pandemic. Hypoxia and inflammation interact with each other. Hypoxia also triggers the release of proinflammatory cytokines. Thus, muscle anabolic metabolism changes, anaerobic glycolysis, and lactate dehydrogenase production increases. These alterations trigger the dysfunction of skeletal muscles.[6,20,21] Furthermore, due to hypoxemia, activation of osteoclasts cause an imbalance between bone formation and bone resorption.[6] Additionally, production of reactive oxygen species (ROS) are increased during hypoxia. High levels of ROS play an important role in DNA (deoxyribonucleic acid) damage and cell apoptosis.[22]

4. Muscle catabolism

Sarcopenia: During COVID-19 infection, particularly in older patients, sarcopenia can be seen due to inflammation, malnutrition, and muscle catabolism. There is an increase in oxidative stress and production of ROS, which leads to the impairment of mitochondrial function autophagy and myofibrillar damage. Regarding to inflammation, muscle protein synthesis is altered, and a catabolic process starts. Additionally, hypoxia, bed rest/immobility, low physical activity, inappropriate dietary and vitamin intake, and other systemic diseases, such as diabetes mellitus, also contribute to the development of sarcopenia.[23-26] Paneroni et al.[26] reported the results of muscle strength and physical performance of patients who recovered from COVID-19 pneumonia without having any musculoskeletal disability previously. They found that there was weakness in biceps (73% of patients) and quadriceps muscles (73% of patients). Quadriceps and biceps muscle performances were 54% and 69% of the predicted normal value, respectively. Moreover, muscle weakness had close relationship with physical performance. Similarly, another study investigated the muscle mass and muscle strength in patients with COVID-19 in the ICU. There was a 30.1% and 18.6% decrease in rectus femoris muscle area and thickness, respectively, at the end of 10 days.[25]

Rhabdomyolysis and myositis: Studies showed that COVID-19 patients may develop rhabdomyolysis, which results in muscle disruption with elevated myoglobin and creatine kinase. According to a systematic review during hospitalization, the incidence of rhabdomyolysis was 0.2 to 2.2%, which is related to mortality.[27] In addition, there are case reports of idiopathic inflammatory myopathy, viral myositis, and necrotizing autoimmune myositis in COVID-19 patients.[27-29]

Malnutrition: In COVID-19, excessive inflammation and impaired anabolic protein metabolism result in weight loss. Intensive care unit and hospital stay may prompt cachexia and malnutrition.[17,30,31] Wierdsma et al.[31] reported in a prospective study that one in five patients had weight loss during hospital stay, whereas this ratio was one in three in ICU stay. Additionally, 73% of these patients were under high risk of developing sarcopenia. Loss of smell and taste may contribute to a lack of appetite, which could result in weight loss of over 5 kg. Poor malnutrition with low vitamin D intake affects bone health and may cause osteoporosis.[11,12]

2. Musculoskeletal involvement due to medications used for the treatment of COVID-19

At the beginning of the pandemic, there was no specific drug, and little was known about the treatment. Although latest studies showed no positive effect on the COVID-19 treatment, hydroxychloroquine/chloroquine was one of the main drugs that many patients received. However, it is well known that myopathy is one of the main adverse effect of hydroxychloroquine/chloroquine.[32,33] Azithromycin is mostly preferred for pulmonary infection, but it has a potential adverse effect of muscle weakness. Corticosteroids were one of the life-saver and major treatment drugs used in COVID-19. Some patients used lower doses, and some had pulse therapies. The main musculoskeletal system-related adverse effects are myopathy, atrophy, muscle weakness, and osteonecrosis. Prolonged use of steroids is related to osteoporosis, which is called glucocorticoid-induced osteoporosis.[11,34,35] There are some controversial results about antiviral treatment indicating that lopinavir/ritonavir leads to musculoskeletal pain

and fatigue. Some studies reported that interferon (α and β) itself causes arthralgia/myalgia.[6,32,35] Initially, there was a necessity to find an urgent solution. Therefore, it was necessary to prioritize the benefits of the drugs over their side effects.

3. Post/long COVID-19

During the pandemic, it was noticed that some of the COVID-19 survivors still had the symptoms of the viral infection even after months of recovery. This was challenging on the health care system, and the World Health Organization defined this condition as post/long COVID-19 syndrome. According to the definition, symptoms begin three months from the onset of the COVID-19 infection, last for at least two months, and cannot be explained by another diagnosis.[36] The symptoms may persist, there may be onset of new symptoms, and the symptoms may fluctuate, with at least one symptom of COVID-19 infection. The prevalence of the post/long COVID-19 syndrome is 10 to 30%.[37] The post COVID-19 includes the persistence of symptoms after 12 months of acute infection. Therefore, the long COVID-19 term comprises both post COVID-19 and that the symptoms persist for more than a year.[35] Mostly, the terminology of post COVID-19 and long COVID-19 is used interchangeably. These terms may be redefined in the future as physicians follow up on the patients.

Main symptoms of long COVID-19: Dyspnea, cough, fatigue, musculoskeletal pain, headache, autonomic dysregulation, cognitive problems, and depression are the main symptoms of long COVID-19.[38,39] Most common musculoskeletal symptoms involve myalgia, arthralgia, fatigue, back pain, muscle weakness, sarcopenia, impaired exercise capacity, and physical performance. In addition, immobile patients, such as those requiring mechanical ventilation, had heterotopic ossification at upper and lower extremities.[38-40] A recently published study reported that fatigue, chest pain, and neurocognitive problems were related to difficulty in daily activities.[41]

Clinical predictors: Studies show that the female sex, obesity, elderly patients, hospitalization, prolonged immobility, having mechanical ventilation, not being vaccinated, and comorbid disorders, such as hypertension, can be accepted as clinical predictors for long COVID-19.[38,39,42,43] Furthermore, SARS-CoV-2 variants may present an additional risk factor for developing the post COVID-19 syndrome. Although there are controversial reports, Antonelli et al.[44] published a study reporting that patients infected with the omicron variant had a lower risk of post/long COVID-19 compared to the delta variant. In another study on post COVID-19, the musculoskeletal pain prevalence was compared between patients infected with historical, alpha, and delta variants and found 80.1%, 75.2%, and 79.5%, respectively. Additionally, 40% of hospitalized patients had post/long COVID-19-related musculoskeletal pain, mostly characterized by widespread pain.[45] Similar to COVID-19 involvement, post/long COVID-19 patients mostly had widespread fatigue and myalgia/arthralgia, followed by low back and back pain. Joint pain was located on the knee, ankle, foot, and shoulders.[46-48] Aging was found to be a risk factor for post/long COVID-19 syndrome. Osteosarcopenia is a new terminology that contains both sarcopenia and osteoporosis. Immobility, poor physical performance, malnutrition, low vitamin D levels, high inflammation, and associated metabolic problems seem to be risk factors for osteosarcopenia, which may result in mortality.[49]

Underlying mechanisms: Although there is no accepted reason for post/long COVID-19-related musculoskeletal involvement, there are some hypotheses discussed in the literature. The main one is that inflammatory cytokines cause chronic inflammation, which results in a decrease in muscle protein synthesis.[41] Impaired physical function and muscle strength are other reasons for post/long COVID-19 and have a negative outcome on quality of life.[17,42,50] Effects of SARS-CoV2 on muscle cells by ACE2 and TMPRSS2 may be another reason. Furthermore, permanent viral gene particles may play a role in immune hyperactivation. Studies showed that direct viral entry of muscle and nerve cells has no evidence.[51,52] Recently, patients with high fibrinogen levels were associated with post COVID-19 myalgia. Additionally, serum C-reactive protein, neutrophil/lymphocyte ratio, and neutrophil counts were related to post COVID-19 syndrome with a hypothesis of low-grade inflammation.[53]

Pain in post/long COVID-19: Musculoskeletal pain is getting more and more interest among physicians as there is no consensus on the mechanism. Localized and generalized pain may occur after COVID-19, and general pain is at least as common as localized pain. Some of the patients have fibromyalgia-like symptoms with generalized pain. The exact mechanism is unknown; however, nociceptive, neuropathic, and nociplastic pain and central desensitization may be considered. Persistent inflammation affects dorsal horn neurons, microglia, as well as peripheral and central nerve systems.[54,55] Post/long COVID-

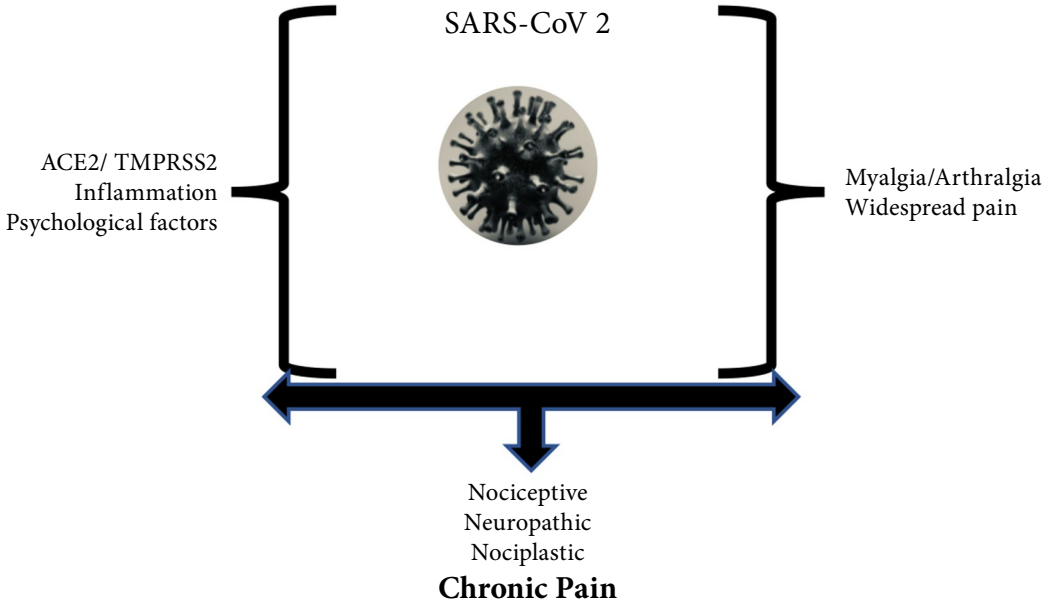

Figure 1. Post/long COVID-19-related pain.

SARS-CoV 2: The severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Serum transmembrane protease 2; COVID-19: Coronavirus disease 2019.

19-related pain tends to be a chronic condition that carries a risk for global disability. Psychological factors, such as depression and anxiety, have an additional negative impact on chronic pain syndrome. Fernández-de-Las-Peñas et al.[55] recently published the phenotypes for nociceptive, neuropathic, and nociplastic pain in post COVID-19 syndrome. They provided a clinical decision-making system for diagnosing nociplastic pain. Finally, they emphasized the phenotyping of pain for planning proper treatment modalities. Figure 1 shows post/long COVID-19-related pain features.

In conclusion, after the acute phase of COVID-19, patients and physicians may deal with chronic complications and post/long COVID-19 syndrome. For physical medicine and rehabilitation specialists, it seems that chronic pain conditions will be a major issue, followed by joint pain, fatigue, and bone loss. The first step should be to correctly diagnose post/long COVID-19 patients. Thus, pain management and proper rehabilitation programs can be implemented.

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