

Effects of COVID-19 on the Musculoskeletal System: Clinician's Guide

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Abstract: The global pandemic caused by SARS-CoV-2, or COVID-19, continues to impact all facets of daily life. Clinical manifestations of COVID-19 commonly include musculoskeletal symptoms such as myalgias, arthralgias, and neuropathies/myopathies. The inflammatory response and its impact on the respiratory system have been the focus of most studies. However, the literature is more limited regarding the inflammatory response and its implications for other organ systems, specifically the musculoskeletal system. Previous studies have described how systemic inflammation may play a role in bone and joint pathology. Furthermore, it is important to understand the effects current therapeutics used in the treatment of COVID-19 may have on the musculoskeletal system. In this study, we will review the current understanding of the effect COVID-19 has on the musculoskeletal system, provide an overview of musculoskeletal symptoms of patients infected with the virus, and address key issues for clinicians to address during the care of COVID-19 patients.

Keywords: COVID-19, musculoskeletal system, SARS-CoV-2

Introduction

The global pandemic caused by SARS-CoV-2, or COVID-19, continues to impact all facets of daily life. Those infected with COVID-19 can vary widely in presentation, ranging from asymptomatic to severely ill and in critical condition. While COVID-19 is primarily a respiratory disease, numerous studies have documented and reported the various extra-pulmonary manifestations and symptoms. Clinical manifestations of COVID-19 commonly include musculoskeletal (MSK) symptoms such as myalgias, arthralgias, and neuropathies/myopathies. One study observed that of 12,046 patients, myalgia and/or arthralgia were present in 15.5% of patients. Consequently, it is crucial for clinicians to understand further and investigate the musculoskeletal symptoms and presentation of those infected with COVID-19.

Additionally, it is imperative to investigate the pathology, and potential mechanisms of the impact COVID-19 has on the musculoskeletal system. Previous studies have demonstrated that infection with the virus induces a proinflammatory state in patients with systemic effects as a result. The inflammatory response and its impact on the respiratory system have been the focus of most studies. However, the literature is more limited regarding the inflammatory response and its implications for other organ systems, specifically the musculoskeletal system. Previous studies have described how systemic inflammation may play a role in bone and joint pathology. Inflammation has also been linked to damage and disease of skeletal muscle. Therefore, investigating the potential impact COVID-19 induced

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inflammation has on musculoskeletal health is essential to adequately understand and treat these symptoms.

Furthermore, it is important to understand the effects current therapeutics used in the treatment of COVID-19 may have on the musculoskeletal system. Current therapy for COVID-19 includes medications such as chloroquine, hydroxychloroquine, colchicine, specific antivirals, and corticosteroids. Many of these medications are associated with toxic myopathies, arthralgias, and other various side effects. Given that the side effect profile of many of these medications overlaps and can potentially mask symptoms that can present with COVID-19, it is important to keep these drug interactions in mind.

In this study, we will review the current understanding of the effect COVID-19 has on the musculoskeletal system, provide an overview of musculoskeletal symptoms of patients infected with the virus, and address key issues for clinicians to address during the care of COVID-19 patients.

Clinical Effects of COVID-19 Infection on Musculoskeletal System Neuromuscular Involvement: Neuropathies & Myopathies

Reports in the literature have described cases of COVID-19 causing neuromuscular damage and symptoms in patients, especially those that are critically ill or of older age with reports of myopathy, polyneuropathy, and Guillain-Barre syndrome. Notably, in a systematic review and meta-analysis of 11,069 patients infected with COVID-19, Abdullahi et al found that there are more neurologic symptoms than musculoskeletal symptoms in COVID-19 patients. Intensive care unit (ICU)-acquired weakness (ICUAW) is an umbrella term used to describe common neuromuscular symptoms in critically ill ICU patients, encompassing critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and the combination of both, critical illness polyneuromyopathy (CIPM). This is especially relevant for COVID-19 patients admitted to the ICU that have undergone invasive ventilation and pronation cycles for respiratory distress, with reports describing cases of patients experiencing critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) as a result. One case series reported that of 225 COVID-19 patients in the ICU in Spain, 12 patients were referred to the neurophysiology department for suspicion of ICUAW, and 11 cases of CIM and CIP were confirmed.

This reported rate of ICUAW in ICU patients with COVID-19 is thought to be underestimated due to patient death prior to diagnosis, the delay and cancellation of non-essential studies due to the infectious nature of the disease, and limited availability of neurophysiology staff and resources. It is essential that clinicians can identify and properly diagnose COVID-19 patients with ICUAW so that these patients may receive early rehabilitation and treatment to improve functional outcomes after recovery. Additionally, it is important to recognize that CIM has a better prognosis than CIP according to published studies and younger patients with CIM are found to have more positive outcomes and recovery of motor skills.

The exact pathophysiology of CIP and CIM is not well understood, especially as it pertains to COVID-19. Risk factors for ICUAW of general causes include multiple organ failure, sepsis, hyperglycemia, mechanical ventilation, and parenteral nutrition. These risk factors are highly prevalent in COVID-19 patients in the ICU. It has also been described how COVID-19-induced inflammation may result in a cytokine storm. CIM is thought to be caused by serious injury to the body with sequential overproduction of cytokines causing microvascular derangement, and metabolic and electrical (channel) alterations. It has been proposed that CIP may be caused by either a storm of systemic inflammation factors (cytokines, nitric oxide and oxygen radicals), creating hypoxic conditions that decreased circulation of local axonal survival factors or by increased vascular permeability from chronic inflammation causing vasogenic edema.

In COVID-19 patients, ICUAW can be diagnosed by assessing peripheral and/or respiratory muscles. The challenge in diagnosing infected patients is that the patients must be awake and cooperative. However, many COVID-19 patients are uncooperative due to sedation-induced delirium. In these cases, electromyography and single nerve conduction studies can be used for differential diagnosis. Cabanes et al reported on 12 COVID-19 patients in the ICU that presented with weakness in their upper and lower extremities, accompanied with elevated creatine kinase (CK) levels, elevated D-dimer and lymphopenia. The authors did not find any difference in the presentation of COVID-19-related CIM/CIP from other causes. However, they observed a noticeable degree of spontaneous muscle activity in patients COVID-19 patients with CIM.

In a single-center study looking into differences in outcomes for COVID-19 patients with ICUAW patients,

Van Aerde et al found that patients with ICUAW spent more days on ventilation ($p < 0.001$) and had longer stays in the ICU ($p = 0.008$), had higher average glycemia in the morning ($p = 0.041$), lower mobility scores at ICU discharge ($p < 0.001$), and more treatment with corticosteroids, sedatives and analgesics compared to patients without weakness. COVID-19 patients with CIM and CIP also tend to have difficulty weaning from a ventilator due to respiratory muscle weakness. COVID-19-related CIM studies have also highlighted symptoms of severe hypotrophy of the shoulder girdle and/or peroneal district. Studies have found that ICUAW of various etiologies is associated with lower physical functioning at 6 months after discharge from the ICU and higher rates of mortality after discharge from the hospital at 6-months and 1-year post-ICU. The likelihood of post-ICU mortality is even more striking with more severe weakness (MRC sum score < 36) or weakness that continues until the time of discharge. COVID-19 studies of ICUAW, however, have not found any difference in ICU readmission or ICU-related mortality rates between ICUAW patients and patients without weakness ($p = 0.225, 0.491$). More studies are needed to determine the long-term functional outcomes of COVID-19 patients with ICUAW.

Therapeutic intervention of COVID-19-associated CIM and CIP focus on both prevention and treatment with the goal of increasing patients' chances of returning to their baseline, pre-infection state of function. The prevention aspect of intervention focuses on reducing the time a patient spends in an immobilized state. The treatment aspect focuses on pulmonary rehabilitation and early mobilization. Interventions for pulmonary prevention include incentive spirometry and patient positioning to increase ventilation. Early mobilization of conscious patients and passive mechanical loading for unconscious or sedated patients have been found to increase post-discharge function. One meta-analysis showed that early rehabilitation with mobilization to reduce time spent immobile and/or neuromuscular electrical stimulation to lessen muscle atrophy was associated with a decreased likelihood of developing ICUAW. The authors also found that early rehabilitation had a better effect in studies with patients that spent more time in the ICU. They also found that length of stay in the ICU was numerically shortened in patients with early rehabilitation. Additionally, early rehabilitation in the ICU reduced the odds of developing ICUAW in 37% of patients that were screened and 29% in randomized populations. Caution should be taken for

patients suffering from sedation-induced delirium, as this can interfere with the ability to complete pulmonary and mobilization intervention due to decreased patient ability, motivation, and cooperation.

There have also been several documented cases of Guillain Barre Syndrome (GBS) arising in hospitalized COVID-19 patients. Studies have described how similar to typical GBS, COVID-19-related GBS affects a broad age range but has a higher reported incidence and less favorable outcomes in older patients. Patients with COVID-19-related GBS also tended to have accompanying pneumonia, acute respiratory distress syndrome, and more extensive demyelinating neuropathy.

Inflammation Impact on MSK

COVID-19-induced inflammation has been found to negatively affect the musculoskeletal system through numerous proposed mechanisms. SARS-CoV-2 utilizes ACE2, a receptor present on many tissue types including smooth muscle, synovial tissue, and cartilage, to enter cells and undergo viral replication. ACE2 has many functions including anti-inflammatory properties and restriction of bone resorption. Tao et al proposed that when SARS-CoV-2 uses the ACE2 receptor to enter cells and blocks receptor function leading to decreased bone mass and joint inflammation. Apoptosis of virally infected cells can lead to more local inflammation. Especially important for COVID-19 patients being treated with a ventilator, long times spent on a ventilator can cause proinflammatory signals that can lead to muscle and bone fragility measured by decreased bone mineral density. Furthermore, COVID-19 induces hypoxia which can cause the overproduction of inflammatory cytokines such as receptor activator of nuclear factor- κ B ligand (RANKL), vascular endothelial growth factor (VEGF), and macrophage colony stimulating factor (M-CSF). Studies have described how these hypoxia-induced molecules may activate osteoclasts and block osteogenesis of osteoblasts, which can lead to increased bone resorption and restricted bone formation.

The inflammatory response to SARS-CoV-2 in the respiratory tract may lead to systemic inflammation that impacts many organ systems including the musculoskeletal system. Studies have described how SARS-CoV-2 infection induces systemic elevations of cytokines and signaling molecules such as CKCL19, IFN- γ , IL-1 β , IL-6, IL-8, IL-17 and TNF- α . These inflammatory molecules have numerous potential mechanisms by which they may cause musculoskeletal symptoms. IFN- γ , IL-1 β , IL-6, IL-

IL-17 and TNF- α are known to directly impact skeletal muscle by inducing fiber proteolysis and decreasing protein synthesis. IL-1 β and IL-6 may cause fibrosis by inducing increased muscle fibroblast activity. IL-1 β and TNF- α have been described to inhibit the differentiation and proliferation of satellite cells, the progenitor cells involved in muscle fiber growth. CXCL10, IL-17 and TNF- α induce osteoclastogenesis and inhibit osteoblast proliferation and differentiation causing increased bone fragility. IL-1 β , IL-6, and TNF- α induce chondrolysis leading to arthralgia and/or the progression of osteoarthritis. IL-1 β , IL-17 and TNF- α may contribute to tendinopathy by impairing the biological activity of tenocytes. Therefore, these inflammatory molecules may be involved in the decreased muscle strength and endurance and increased bone fragility associated with COVID-19 infection.

COVID-19 may also be a cause of inflammatory reactive arthritis, which presents similarly to rheumatoid arthritis. One case report described 5 patients presenting with polyarthritis following COVID-19 infections with negative RA factor and anti-CCP, suggesting a diagnosis of inflammatory reactive arthritis. The authors proposed that the inflammatory reactive arthritis arose secondary to the involvement of pro-inflammatory markers, IL-6 and TNF- α , that are released due to COVID-19-related respiratory and musculoskeletal inflammation. These patients were treated with low-dose corticosteroids (prednisone 10 mg/d), etoricoxib, disease modifying anti-rheumatic drugs (DMARDs), leflunomide (20mg/d) and hydroxychloroquine (400 mg/d).

Corticosteroids may be given to COVID-19 patients for acute inflammation, but these medications can lead to muscle atrophy, muscle weakness, and decreased bone mineral density. Current studies are looking into the efficacy of tocilizumab, a monoclonal antibody against IL-6. This drug is currently approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis to modulate joint inflammation, bone loss, and other manifestations of these diseases. Tocilizumab is being used in the treatment of COVID-19 because IL-6 believed to be a key cytokine leading to an inflammatory cytokine storm. The goal of this treatment is to reduce the effects of COVID-19-induced cytokine storms.

Arthralgias & Myalgias

Arthralgias or myalgias have been reported as symptoms in those infected with COVID-19, with one study finding that myalgia and/or arthralgia were present in 15.5% of

patients. A systematic review and meta-analysis of 11,069 infected patients found the prevalence of myalgia to be present in 19% of patients. However, reporting of these two symptoms in the literature have often wrongly been grouped together or used interchangeably. It is important to make the distinction between arthralgia and myalgia as they are unique in the locations they present and their underlying physiology. Arthralgia is localized to the joints, while myalgia is localized to muscle. The literature has described how arthralgia and/or myalgia typically present in the early course of the disease, with some studies observing they present more commonly in females. Studies have also suggested that the presence of arthralgia may have an association with disease severity, although the evidence for this is scarce. One study found that the onset of arthralgia sometimes occurred days before or after the onset of fever and pulmonary symptoms in contrast to myalgia which has been reported to coincide with the occurrence of viral illness, which is an important distinguishing factor for clinicians to recognize. Furthermore, in patients experiencing long-term effects of COVID-19 or a prolonged disease course, 27% report ongoing joint pain. Patients with arthralgia also reported higher pain levels and required more analgesia. Therefore, it is imperative for clinicians to recognize this when diagnosing and managing patients with a history of COVID-19 infection who present with arthralgia and to adequately discern this finding from reactive arthritis.

The prevalence of arthralgia or myalgia in infected patients varies in the literature. In a single-center retrospective cohort study of 294 patients hospitalized with COVID-19, Hoong et al observed that 30% of patients reported musculoskeletal complaints. The authors found that of those with musculoskeletal complaints, 37.5% had myalgia, 5.7% arthralgia, 6.8% new-onset backache and 50% generalized body ache. Interestingly, the authors also found that patients with musculoskeletal symptoms had a higher prevalence of fever ($p < 0.01$) and a higher CRP level ($p < 0.01$), and that the presence or absence of musculoskeletal symptoms was not a significant predictor of the risk of developing pneumonia. This highlights the importance of recognizing and understanding arthralgia and myalgia in patients at risk of COVID-19, even in the absence of pulmonary symptoms. In a retrospective study of 615 patients hospitalized for COVID-19 in Italy, De Rosa et al found that 2.8% of patients reported myalgia and/or arthralgia. Of note, the authors in that study did not find a statistically significant association with elevated serum creatine kinase (CK) levels.

The authors also found that patients with history of falls had higher CK levels ($p < 0.002$) even if there was no clinical evidence of muscle trauma on ER reports and consequently may be an important factor for clinicians to consider. In a prospective observational cohort study of 1150 patients hospitalized for COVID-19 in New York City, Cummings et al found that 26% of patients reported myalgia. Another epidemiologic study of 1420 patients in Europe with mild-to-moderate COVID-19 infections found that 62.5% reported myalgia.

The mechanism behind the presence of myalgia or arthralgia with COVID-19 infection remains poorly understood. As a close relative to COVID-19, studies on SARS-CoV-1 may provide insight into potential mechanisms of injury to the musculoskeletal system caused by COVID-19 infections. Previous studies on the SARS-CoV-1 virus have described how infection can lead to muscle damage or dysfunction, decreases in body mass, muscle fiber atrophy, or focal muscle fiber necrosis and immune cell infiltration. Studies have also described reports of patients with avascular necrosis, mostly in the femoral head, following SARS-CoV-1 infection, which may be due to the infection itself or the corticosteroid use in its treatment.

Furthermore, the inflammatory response to COVID-19 infection may be a contributor to myalgia and/or arthralgia in infected patients. Studies have described how those infected with COVID-19 can experience an aggressive inflammatory response, with elevated levels of proinflammatory signaling molecules such as CRP, IFN- γ , IL-1 β , IL-6, IL-17, and TNF- α . These inflammatory signaling molecules have been linked to muscle fiber damage and consequently may play a role in causing or contributing to arthralgia and/or myalgia during COVID-19 infection.

The management of myalgia and/or arthralgia in patients infected with or having a history of COVID-19 remains largely unchanged and consists of NSAIDs and/or rehabilitation such as physical therapy. Caution should be taken in determining the etiology of the arthralgia and/or myalgia, and other causes such as reactive arthritis or inflammatory disease processes should be adequately explored.

Musculoskeletal Sequelae of COVID Therapy

Understanding the potential musculoskeletal sequelae of therapies used to treat and manage COVID-19 is imperative. Numerous medications are being investigated as

potential therapeutic options for COVID-19 patients, including new investigational drugs and therapies being repurposed for COVID-19. Repurposed therapies, each with their unique side effect profile, include drugs such as chloroquine/hydroxychloroquine, Lopinavir/Ritonavir, Ribavirin, Interferon (IFN) - α and - β , and corticosteroid use. Studies have described how IFN- β and IFN- α are associated with arthralgia and myalgia in patients undergoing its therapy. It has also been reported that, rarely, myopathy and neuromyopathy may occur following treatment with chloroquine and hydroxychloroquine. Although rare, it has been reported that Lopinavir-ritonavir treatment is associated with arthralgia, back pain and osteonecrosis. One study on the pharmacological profile of ribavirin found that for patients being treated with the drug, >10% of patients reported arthralgia and musculoskeletal pain. Furthermore, a population cohort-based study in South Korea investigating pain medication use found that patients with comorbid musculoskeletal disorders who are infected with COVID-19 were not associated with increased in-hospital mortality. However, the authors found that strong opioid use was associated with higher in-hospital mortality among patients, whereas use of other pain medications (paracetamol, gabapentin, pregabalin, glucocorticoids, NSAIDs, weak opioid, and benzodiazepine) did not show a significant association with in-hospital mortality.

Corticosteroid use in the management of COVID-19 patients has increased, thus understanding its wide side effect profile is essential. Prolonged corticosteroid use, especially in critically ill patients, has been associated with a variety of effects on bone, including associations with osteonecrosis, reduced bone mineral density (BMD), and osteoporosis. Studies have described how corticosteroids can also lead to muscle atrophy and muscle weakness. Whether these effects are due to the use of corticosteroids specifically remains poorly understood, as it has also reported these effects occur in critically ill patients without the use of corticosteroids. As clinicians managing patients with musculoskeletal complaints, caution and consideration should be given to the use or history of corticosteroid therapy, and these patients should be monitored for long-term effects.

Rehabilitation and Recovery

Equally important for clinicians is understanding the potential long-term impact COVID-19 infection may have on patients and their recovery. In a single-center cohort study following the recovery of 300 patients

hospitalized from COVID-19 infection, Karaarslan et al found that 56.3% of patients reported musculoskeletal complaints 1 month after discharge. The authors also found that the most common musculoskeletal complaints of patients recovering from infection included fatigue, followed by back pain, arthralgia, myalgia, low back pain, and neck pain. Notably, the authors also observed that the persistence of fatigue, myalgia, and arthralgia was associated with a higher BMI. In another case series following patients discharged from COVID-19 hospitalization in Italy, Carfi et al found that 23.7% of patients had persistent complaints of joint pain over a month following discharge. Another study of 110 patients reported that 22.7% of patients experienced ongoing myalgia following infection. Therefore, it is important for patients to consider a history of COVID-19 infection when managing patients with musculoskeletal complaints.

Rehabilitation programs may prove beneficial for patients with persistent musculoskeletal complaints recovering from COVID-19 infection. Past studies investigating recovery following SARS-CoV-1 infection have observed improvement of symptoms in recovering patients. In one randomized control trial evaluating the effect of an exercise training program on cardiorespiratory and musculoskeletal recovery following SARS-CoV-1 infection, Lau et al found that exercise training program was effective in improving both the cardiorespiratory and musculoskeletal fitness. Consequently, there may be similar benefit for patients recovering from COVID-19 infection. Additionally, preventing prolonged physical inactivity in recovering patients may prove beneficial in preventing muscle disuse atrophy and loss in functional performance. Furthermore, long-term monitoring and follow-up chest imaging may be warranted for patients

Table 1 Summary of COVID-19 Effects on the Musculoskeletal System

Neuromuscular involvement: neuropathies & myopathies	<ul style="list-style-type: none"> • COVID-19 patients admitted to the ICU that have undergone invasive ventilation and pronation cycles are at increased risk of critical illness myopathy (CIM) and critical illness polyneuropathy (CIP), and more rarely Guillain Barre Syndrome. • In cases of uncooperative or sedated patients, electromyography and single nerve conduction studies can be used for diagnosis. • Management of CIM and CIP includes reducing the time a patient spends in an immobilized state and pulmonary rehabilitation/early mobilization.
Inflammation impact on MSK	<ul style="list-style-type: none"> • COVID-19 induced proinflammatory state may lead to inflammatory reactive arthritis, muscle fibrosis, increased bone fragility, tendinopathy, and muscle weakness.
Arthralgias & myalgias	<ul style="list-style-type: none"> • Arthralgia and myalgia commonly present early in COVID-19 patients, even in the absence of pulmonary symptoms, with myalgia occurring more commonly. • Studies have suggested that arthralgia can precede the onset of fever and pulmonary symptoms in infected patients. • Management of myalgia and/or arthralgia in patients with a history of COVID-19 consists of NSAIDs and/or rehabilitation.
Musculoskeletal sequelae of COVID therapy	<ul style="list-style-type: none"> • The use of IFN-β and IFN-α as therapy for COVID-19 may be associated with arthralgia and myalgia in patients. • It has been reported that in patients being treated with ribavirin, >10% of patients reported arthralgia and musculoskeletal pain. • Care should be given with opioid use, as strong opioid use was associated with higher in-hospital mortality, whereas other pain medications did not show a significant association with in-hospital mortality. • Prolonged corticosteroid use has been associated with various effects on bone and muscle, including associations with osteonecrosis, reduced bone mineral density, osteoporosis, muscle atrophy, and muscle weakness.
Rehabilitation and recovery	<ul style="list-style-type: none"> • Musculoskeletal symptoms may continue to persist following recovery from COVID-19, with the most common complaints including fatigue, back pain, arthralgia, myalgia, low back pain, and neck pain. • Rehabilitation can improve persistent musculoskeletal symptoms, including exercise training programs and/or physical therapy. • Prevention of prolonged physical inactivity may assist in minimizing muscle disuse atrophy and loss in functional performance.

recovering from severe illness. One study of patients recovering from both SARS-CoV-1 and Middle East respiratory syndrome (MERS) found fibrosis was a common finding in patients who experienced persistent pulmonary symptoms. Therefore, special attention should be paid to patients experiencing persistent pulmonary symptoms.

Conclusion

As the global pandemic caused by COVID-19 continues to leave its mark on the world, special attention must be given to its musculoskeletal effects. Infection with the virus can cause a range of musculoskeletal symptoms such as arthralgias, myalgias, neuropathies/myopathies, and potential bone and joint damage (Table 1). Importantly, current therapeutics used in the management of COVID-19 patients can also cause musculoskeletal effects that clinicians should be aware of. Finally, understanding the need for effective rehabilitation is critical in helping patients return to pre-infection mobility and function.

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Disclosure

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