Coronavirus disease and the musculoskeletal system: a narrative review

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Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome-coronavirus-2). This virus uses as receptors the angiotensin-converting enzyme 2 and the transmembrane protease serine 2, which are also present in cells of the musculoskeletal system. Their presence can explain how coronavirus disease 2019 can cause general symptoms such as myalgia and arthralgia, as well as chronic back pain and articulation-specific symptoms such as shoulder capsulitis and hip and knee osteonecrosis.

Keywords:
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Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [1]. This virus originated in Wuhan, China, and rapidly became a global pandemic with significant medical and economic burden [2]. This virus can target proteins that can disrupt cellular functions and lead to apoptosis which will contribute and amplify local inflammation [1]. Studies have shown that patients who had COVID-19 experienced some musculoskeletal symptoms [3–5], reaching the skeletal muscle, the bone, and the joints. The inflammatory response first localized in the airways can become systemic and affect the musculoskeletal system [6,7]. To add to that, extended use of ventilation can also lead to bone and muscle frailty [8,9].

In individuals recovering from COVID-19 and those with known musculoskeletal disorders, there are convincing early symptoms of musculoskeletal dysfunction. There was no report of musculoskeletal dysfunction after COVID infection. The purpose of this article was to review the literature and shed light on the musculoskeletal symptoms associated with COVID-19.

General

SARS-CoV-2 is thought to infect type-II pneumocytes that border the respiratory epithelium and express angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) [1]. Smooth muscle cells, pericytes, muscle stem cells, fibroblasts, homeostatic chondrocytes, osteoblast-enriched bone samples, and myonuclei are among the cell types that express TMPRSS2 [1]. Smooth muscle cells, fibroblasts, proliferative, hypertrophic and effector chondrocytes, cartilage progenitors, meniscal regulatory fibrochondrocytes, pericytes unenriched cortical and trabecular bone samples, and osteoblast-enriched bone samples express ACE2 [1]. This similarity leads to a lot of musculoskeletal consequences in patients with COVID-19. Patients with this disease exhibited sporadic and focal necrosis of muscle fibers, widespread muscle atrophy, and infiltration of immune cells [3,10]. Myofibril disarray was also noted using electron micrographs, and this may impair force transmission [2]. Neuronal demyelination which was also reported can contribute to the musculoskeletal symptoms of COVID-19 [11]. Pro-inflammatory cytokines that are elevated in this infection can decrease protein synthesis and induce proteolysis of muscle fibers [12–16], block the differentiation as well as the proliferation of satellite cells which are crucial in the process of muscle fiber growth to recover from the infection [13,17,18], and induce fibrosis leading to muscle force impairment and a higher injury susceptibility [19,20]. The use of corticosteroids as a treatment for severe SARS-CoV-2 infections may also cause muscle atrophy and weakness [21]. Other than that, the muscular functional stage prior to the infection, the muscular damage path, the nutritional state, the comorbidities, the age, the elevation in blood sugar, and the use of neuromuscular blocking agents may play a part in the generation of musculoskeletal consequences of COVID-19 [22].

The most common musculoskeletal presentations of COVID-19 are generalized weakness and myalgia, which were reported to occur in ~25–50% of patients

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[23–26], and myalgia was noted to be a predictive factor of the disease's overall severity [27]. A cohort by Villa *et al.* [28] even showed that patients may have subclinical myopathies with the myopathic pattern being only in certain areas of the affected muscle, suggesting a patchy involvement of myofibers. This disease has also been shown to cause muscle weakness and impair endurance as it exhibited a 32% loss of grip strength and 13% reduction in a 6-min walking distance in patients with moderate to severe SARS-CoV-2 infection [29]. Arthralgia and a reduced bone mineral density are also consequences of COVID-19, with the latter not being dependent of the use of corticosteroids [5,8,30,31]. The cause of arthralgias may be due to pro-inflammatory cytokines, which may cause chondrolysis, resulting in this pain or even the progression of a preexisting osteoarthritis [32–34]. Tendinopathy and degenerative tendon disorders may also occur because of the impairment of the biological activity of tenocytes by the cytokines [35–37]. Distal paresthesia and fire-burning sensations may occur as signs of small fiber neuropathies induced by COVID-19 [26]. Rhabdomyolysis can also occur during the acute phase of the infection, and it is usually associated with poor outcomes[38,39]. Sarcopenia may also occur as a consequence of COVID-19, and it may be due to multiple factors such as the pre-infectious state; the inflammatory involvement of SARS-CoV-2; immobility and bedrest; diet; the gut microbiota; COVID-19-related medications such as tocilizumab, steroids, and antibiotics; and the other organs' involvement such as the cardiovascular system, hypoxia, pressure ulcerations, and delirium [40].

Shoulder

Shoulder pain in COVID-19 survivors can be associated with multiple factors such as age, preexisting pain, comorbidities, the number of days spent in the ICU especially if it exceeds 15 days, thus reducing joint mobility and inducing muscle mass loss [41]. In contrast to the supine posture, there are also anatomo-functional issues connected to prolonged placement during protracted ICU stays, which can cause nerve compression and rotator cuff pinching, thus increasing shoulder impingement [41,42]. When shoulder ultrasounds were performed, they showed inflammation and rotator cuff tendinopathies [43]. These results affect the biomechanics of the shoulder joint during abduction [44], which include upward and laterally subluxation with abduction beyond 90°, which makes the rotator cuff muscles contract to prevent the luxation. The weight exercised by the scapular belt can also cause this excessive tension [45].

On the contrary, Parsonage-Turner syndrome has also been reported four times in association with COVID-19 [46–49] with only once being associated with diaphragmatic paralysis.

Finally, a series of patients reported by Ascani *et al.* [50] showed a relation between adhesive capsulitis and COVID-19. They reported that asymptomatic patients from COVID had more pain and range of motion limitations than mild to symptomatic patients. This correlation between the infection and this pathology may be owing to many factors. First of all, it may be due to the viremia of the SARS-CoV-2 and the presence of the receptors required for entry of the virus in the synovium and the fibroblasts causing fibrosis of the capsular and pericapsular tissue in adhesive capsulitis [1,50]. The host's response to this virus is another factor contributing to the development of this pathology [50]. It has also been shown that TNF-a, IL-1, and IL-6 are high in the subacromial bursa, joint capsule, and joint fluids in patients with frozen shoulder, and these are the cytokines induces by SARS-CoV-2 [51,52]. Other factors such as the lifestyle modifications due to the pandemic, such as lockdowns, can have a hand in inducing adhesive capsulitis [53,54].

Hip and knee

Cytokine storm is a consequence of COVID-19. To fight it, a daily treatment of 6 mg of dexamethasone for a duration of 10 days is recommended, and following the treatment, it decreases 28-day mortality [55]. By administrating supraphysiological doses of corticosteroids, the risk of osteonecrosis of the femoral head increases [56]. Higher cumulative doses and longer duration of treatment are correlated with a higher risk of osteonecrosis [57]. A retrospective study by Guo *et al.* [58] showed that 24.1% of patients treated with steroids for SARS-CoV-2 developed osteonecrosis of the femoral head. Therefore, patients with COVID-19 who received high doses of corticosteroids should be evaluated by their physicians. If there is a high degree of suspicion for osteonecrosis, MRI should be performed [59]. To further reduce the risk of this complication, corticosteroids should be cautiously administered and both doses and durations must be minimized, and the use of multiple types of corticosteroids is not recommended [56]. Combined pharmacotherapy and physical therapy can also be used to prevent the collapse in the early stage of osteonecrosis of the femoral head [60].

The same complication can be seen in the knee. Knee osteonecrosis has been reported after COVID-19 [5,61]. It is also associated with a higher and longer dose of corticosteroids [5,58,62]. Hypercoagulability noted in patients infected by SARS-CoV-2 which along with leukocyte aggregation and vessel inflammation can

impair the microvascular blood flow of the bone, thus contributing to the development of osteonecrosis [1].

Spine

There has been several reports of spine symptoms in the spine. Sabouri *et al.* [63] reported a case of COVID-19-induced hematomyelia. Polyneuropathy was the major neurological manifestation in this case. Within 2 days, it had progressed to acute flaccid paralysis with a differentiated sensory level [63]. Therefore, it is recommended that every new neurological symptom in patients with COVID-19 infection should elicit a thorough study based on the clinical picture [63]. Cervical imaging should also be included in the usual workup for COVID-19-infected patients with acute neurological symptoms so that the optimal treatment plan for the patients can be determined as soon as possible [63].

Chronic back pain is also a symptom of COVID, and there appears to be a link between financial difficulty and chronic back pain [64]. A study by Bronheim *et al.* [65] showed that COVID-19 caused approximately half of their group to cancel medical appointments and a small percentage of their responders reported they had trouble getting their drugs, which were mostly opioids. Psychological, social, and environmental elements have all been shown to influence a patient's perception of pain [64,66]. Average back and leg pain levels dramatically worsened between respondents' most recent clinic visit and the commencement of the COVID-19 epidemic [65]. Increased walking during postoperative recovery has been linked to a larger chance of meaningful improvement in back and leg pain [67]. Walking and other such activities were likely limited among individuals due to pandemic restrictions [65]. Moreover, preoperative anxiety and depression affect one-third of spine surgery patients, according to a systematic review, and its presence is an important predictor of increased pain, and physical disability in patients undergoing spine surgery [68].

Conclusion

COVID-19-related musculoskeletal symptoms are multiple. Both the ACE2 and the TMPRSS2 are present in cells of the musculoskeletal system. These similarities, the cytokine storm induced by the virus, and the lifestyle change induced by the lockdown will cause symptoms such as myalgia, arthraglia, fatigue, chondrolysis, tendinopathies, distal neuropathies, and sarcopenia. An association between COVID-19 and shoulder pain, Parsonage-Turner syndrome, and adhesive capsulitis has also been reported. This virus can also cause osteonecrosis of the femoral head as well as osteonecrosis of the knee which may lead to the required caution while administrating corticosteroids in the management of this infection. Hematomyelia and chronic back pain can as well be symptoms of this disease.

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Conflicts of interest

There are no conflicts of interests to disclose.

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