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Musculoskeletal complications in long COVID: A systematic review

Swarnakar R *et al*. Long COVID musculoskeletal complications

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19), since early 2020, has crippled humanity for almost two years. Various sequelae of COVID have been reported in different body systems. Musculoskeletal symptoms are widely reported during COVID-19 infection but the symptom following musculoskeletal complications in long COVID are underreported though many times we have encountered post-COVID survivors complaining of persisting or new-onset fatigue, myalgia, arthralgia, arthritis, muscle weakness *etc.* in clinical practice. The well-known detrimental effects of steroids on the musculoskeletal system coupled with their over-the-counter availability can also be anticipated since they were the cornerstone of life-saving management in this pandemic.

AIM

To find out musculoskeletal complications in long COVID.

METHODS

We performed a systematic review of 'systematic reviews and meta-analyses'.

RESULTS

Of 63 articles were screened; 24 articles were included. Two articles discussed specifically children and adolescents. One article discussed rehabilitation intervention. No article addressed rehabilitation on musculoskeletal issues in long COVID in particular. Fatigue is most common musculoskeletal complication.

CONCLUSION

Fatigue is found to be very common along with myalgia, and arthralgia. There are no studies for rehabilitation intervention in musculoskeletal complications specifically. Considering the lacuna in literature and the needs of the current situation, further

studies are warranted to find out effective rehabilitation interventions in musculoskeletal complications. More homogenous studies are needed. Studies on functional impairment due to musculoskeletal involvement are essential.

Key Words: Musculoskeletal complications; COVID-19; Long COVID; Post-COVID syndrome; Rehabilitation; SARS-CoV-2

Swarnakar R, Jenifa S, Wadhwa S. Musculoskeletal complications in long COVID: A systematic review. *World J Virol* 2022; In press

Core Tip: Though musculoskeletal involvement is reported in severe acute respiratory syndrome coronavirus 2 infection but in long coronavirus disease (COVID), literature is limited. Moreover, rehabilitation of each musculoskeletal complaint is not addressed in the most of the reviews. We would like to highlight those keys areas through our review article. Fatigue is the most common musculoskeletal issue in long COVID. Considering the gaps in literature and current needs, future studies are warranted to find out effective rehabilitation interventions in musculoskeletal complications.

INTRODUCTION

Since 2020 the world has witnessed multiple waves of the coronavirus disease 2019 (COVID-19) pandemic caused by different variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at different times and places. As of 1st September 2022, 599 million confirmed cases and more than 6 million death has been reported[1]. The loss of lives, superimposed by the deterioration of the quality of life of a significant number of survivors made this pandemic a huge hurdle for the whole world. A range of long-term effects or complications, involving different body systems has been reported. The respiratory sequelae of COVID-19 have been widely investigated, but musculoskeletal complications are underreported. Here we performed this

systematic review of systematic reviews and meta-analyses to find out those musculoskeletal complications caused by long COVID conditions.

MATERIALS AND METHODS

Here a systematic review of 'systematic reviews and meta-analyses' was conducted (Figure 1). We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com)

Eligibility criteria

PICOS model: (1) Studies that considered patients with long-term COVID-19 symptoms at least > 4 wk of COVID-19 infections (population); (2) Studies where the primary aim was to evaluate long-term COVID-19 symptoms in mild, moderate, severe, and critical patients that have a follow-up of at least 14 d (interventions); (3) Studies with or without a control group (comparisons); (4) Studies that reported the long COVID-19 symptoms (outcomes); and (5) Systematic review and meta-analyses (study designs). From January 2020 to mid-July 2022, any relevant studies that followed above mentioned PICOS model and that reported musculoskeletal complications in long COVID-19 are eligible for inclusion.

Search strategy

Search was carried out by two independent researchers in all electronic databases mainly MEDLINE, EMBASE, Web of Science, and Google Scholar with this time period. We combined search terms and key words related to the population (*e.g.*, "COVID-19", "SARS-CoV-2", "long Covid-19", "long Covid'', "long haulers'') and outcomes (*e.g.*, "fatigue", "pain", "musculoskeletal", "myalgia", "myopathy", "arthralgia'', "arthritis'', "rheumatic'', "joint''). We additionally filtered study designs "systemic review'', and "meta-analyses'' in humans.

Inclusion and exclusion

All the systematic reviews and meta-analyses on long COVID following our above-mentioned PICOS model were included. After the preliminary search, we extracted the musculoskeletal complications that were reported in long COVID studies or in post COVID studies (at least after 4 wk of COVID-19 active infection). We excluded any musculoskeletal issues that occurred after any neurological sequelae of long COVID and also excluded any myocarditis or issues related to smooth muscle dysfunction.

Study selection and data extraction

Titles and abstracts were screened for potentially eligible studies. Following an initial screening, full texts of potentially eligible studies were acquired for detailed evaluation eliminating all duplicates. Manual scanning of key articles and review papers was conducted to identify additional articles missed by the search strategy. Two reviewers assessed the articles independently and in case of any disagreements, the opinion of the third reviewer was consulted.

Analysis

We performed a descriptive analysis of the included reviews.

RESULTS

Of 63 articles were screened; 24 articles were included[2-25]. Two articles discussed specifically children and adolescents. One article discussed rehabilitation intervention. No article addressed rehabilitation on musculoskeletal issues in long COVID in particular. Details of the selected articles are listed in Table 1.

DISCUSSION

According to the National Institute of Health and Care Excellence guidelines, post-acute COVID-19 and post-COVID-19 syndrome both are included in the long COVID. Post-acute-COVID-19 means ongoing symptomatic COVID-19 for people who still have symptoms 4 and 12 wk after acute COVID-19, on the other hand, post-COVID-19

syndrome for people who are having persisting symptoms for > 12 wk after acute symptoms[26]. According to the World Health Organization post COVID-19 conditions occur generally 3 mo from the onset of COVID-19 with symptoms lasting for at least 2 mo and should be unexplained by any alternative diagnosis[27].

Another definition consists of "not recovering several weeks or months following the start of symptoms that were suggestive of Covid-19, regardless individuals were tested or not"[28]. Common symptoms reported are fatigue, shortness of breath, cognitive dysfunction/attention disorder, hair loss and dyspnoea[29,30]. Musculoskeletal symptoms of skeletal muscle, neurological, bone, and joint disorders have also been reported. The proinflammatory responses can impact nearly every organ system, including the musculoskeletal system. Myalgias, arthralgias, fatigue, exercise and intolerance are some of the common musculoskeletal sequelae.

Why musculoskeletal system affected?

SARS-Cov-2 has three structural proteins [membrane protein (M), spike protein (S), and envelope protein (E)]. Spike glycoprotein (S protein) through its subunits S1 and S2 helps in entering the host cells[31]. Angiotensin-converting enzyme 2 (ACE2) receptor acts as the entry receptor using the serine protease transmembrane protease, serine 2 (TMPRSS2) for protein S priming[32]. Following the binding of the receptor, viral S protein is broken down by TMPRRS2 proteolytically which exposes a fusion peptide signal that helps in the fusion of viral and human membranes. It leads to the cytoplasmic release of viral RNA. Interestingly, ACE2 is found in the lung, heart, kidney, liver, gastrointestinal and musculoskeletal systems.

In humans, endothelial cells, smooth muscle cells, pericytes, muscle stem cells, macrophages, B-cells, T-cells, natural killer cells, and myonuclei express TMPRSS2. Furthermore, several cells in the synovium including fibroblasts, monocytes, B cells, and T cells express ACE2 and TMPRSS2. However, only smooth muscle cells and pericytes express ACE2. Articular cartilage (proliferative, hypertrophic, and effector chondrocytes) express ACE2, and only homeostatic chondrocytes (which control

circadian rhythm in cartilage) express TMPRSS2. In the meniscus, a few cartilage progenitors and regulatory fibrochondrocytes express ACE2 (no TMPRSS2 is detected). ACE2 is also found to be present in composite unenriched cortical and trabecular bone and osteoblast enriched tissues. TMPRSS2 was almost absent in composite bone tissue, and TMPRSS2 was detected in all osteoblast-enriched samples.

The presence of these receptors implies that skeletal muscle, synovium, and cortical bone may serve as potential areas of direct SARS-CoV-2 infection and its probable long-term sequelae[33]. The cytokines and signalling molecules are induced by the infection [C-X-C motif chemokine 10 (CXCL10), interferon-gamma (IFN-γ), interleukin (IL)-1β, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha (TNF-α)]. They play a crucial role in the pathogenesis of clinical signs and symptoms and long-term sequelae of COVID-19. IFN-γ, IL-1β, IL-6, IL-17 and TNF-α show a negative impact on skeletal muscle (fiber proteolysis and decreasing protein synthesis). IL-1β and IL-6 may lead to fibrosis after inducing increased muscle fibroblast activity. IL-1β and TNF-α induce muscle fiber growth by inhibiting the differentiation and proliferation of satellite cells, the progenitor cells[34].

COVID therapy sequelae in the musculoskeletal system

Corticosteroids a lifesaving medication in the management of COVID-19 has been overused in many cases. Additionally, long-term corticosteroid use has been known to cause a variety of effects on the bone, including osteonecrosis, reduced bone mineral density (BMD), avascular necrosis of the hip joint and osteoporosis with or without fracture. It implies that steroids might be an important cause of multiple musculoskeletal complications.

Skeletal muscle & fatigue

Many studies have reported fatigue myalgia and generalised weakness as some of the common persisting complaints in symptomatic infections of the disease[35]. In the previous epidemics of SARS, extensive myalgias and muscle dysfunction were also

reported. Direct viral infection and or the cytokine storm could lead to pathological changes in skeletal muscle tissue in addition to deconditioning due to prolonged disuse during the hospitalisation or disease period.

Mayer *et al*[36] showed that a long intensive care unit (ICU) stay is linked with a rapid and significant reduction in the volume of the rectus femoris muscle (average: 18.5%), until the 7th d of hospitalisation. Carfì *et al*[37] in a study to follow up the post-COVID-19 patients in a hospital in Italy, they have found that in recovered patients, 87.4% responded with at least one persistent symptom, especially fatigue. Paneroni *et al*[38] evaluated the muscle strength of the quadriceps and biceps femoris of patients in post-discharge recovered COVID-19 cases. They found that 86% of cases had quadriceps weakness and 73% had biceps femoris weakness. These findings proved muscle dysfunction in individuals with long COVID-19. Jacobs *et al*[39] in their study to assess the persistence of symptoms and quality of life at 35 d after hospitalisation of COVID-19 infection found fatigue as the most common persisting symptom.

Office for the national statistics, census 2021, in the estimates of the prevalence of self-reported long COVID-19 and associated activity limitation, using United Kingdom Coronavirus (COVID-19) Infection Survey data, fatigue was found to be the most common symptom others are shortness of breath (31%), loss of smell (22%), and muscle ache (21%)[40]. Compared with age-matched healthy controls, approximately 2 to 3 mo after discharge moderate to severe cases had a 32% reduction in grip strength and a 13% reduction in the distance walked in 6 min[41].

Aiyegbusi *et al*[42] did a review on symptoms, complications and management of long COVID-19 and found that 47% reporting fatigue as the most common, myalgia (muscle pain) in 25% and joint pain in 20%. Varghese *et al*[43] found that 54% of the patients reported fatigue as one of the persisting symptoms. Huang *et al*[44] did a follow-up study from June 16 to September 3, 2020, to assess 6 mo consequences of COVID-19 in patients discharged from the hospital and they reported fatigue (63%) and sleep difficulties (26%) as the most common symptoms. Miyazato *et al*[45] also reported fatigue as one of the prolonged and late-onset symptoms conducted in patients admitted for

COVID-19 to the Disease Control and Prevention Center and National Center for Global Health and Medicine from February to June 2020. Daher *et al*[46] conducted a follow-up study on 33 confirmed COVID-19 positive patients post-discharge 6 wk to assess the pulmonary and extrapulmonary disease sequelae and found out significant tendency among the patients to suffer from fatigue symptoms with significant limitations of their mobility, which was reflected by reduced six-minute walking test distance among the extrapulmonary sequelae. In their study characterising long COVID-19 in an international cohort: 7 mo of symptoms and their impact, Davis *et al*[47] also reported the patients who have had or are suspicious of COVID-19 reported fatigue as the most common persisting symptom even after 6 mo.

Howsoever multiple aetiologies of fatigue (physical, mental, emotional) could be there and therefore, fatigue should be researched according to the accompanying symptoms or more specific features[48]. Another sequel is intolerance to physical activities associated with a chronic fatigue condition and difficulty in returning to normal daily life[49]. 18 people living with long COVID-19 in the United Kingdom were interviewed with a semi-structured questionnaire in a qualitative study by Humphrey *et al*[50] showing people facing reduced physical function, compounded by the cognitive and psychological effects of long COVID-19.

Arthralgia & myalgia

Arthralgia is pain localized to the joints, while myalgia is pain localized to muscle. Typically present in the early course of the disease, also found in patients experiencing long-term effects of COVID-19 or a prolonged disease course. Studies have described how SARS-CoV-2 infection induces systemic elevations of cytokines and signaling molecules. This 'cytokine storm' is thought to be implicated in musculoskeletal manifestations, among many others. Myalgia and arthralgia are reported as one the most common persistent symptoms in patients with PASC and are more notable in patients who were prone to being positioned during ICU admission[51].

Study of 294 patients hospitalized with COVID-19, Hoong *et al*[52] observed that 30% of patients reported musculoskeletal complaints; 37.5% had myalgia, 5.7% had arthralgia, and 6.8% had new-onset backache and 50% generalized bodyache. Elhiny *et al*[53] reported physical decline was the most common symptom reported in musculoskeletal complications. Patients who also had mild to moderate forms of the infection can experience exacerbated muscle and joint pain. Petersen *et al*[54] in their study of long COVID-19 in a longitudinal study in Faroe islands found out arthralgia is one of the most persistent symptoms following fatigue, loss of smell and taste.

Follow up of adults with non-critical COVID-19 after symptoms onset in a study by Carvalho-Schneider *et al*[55], 13% of the patients who never had arthralgia at the onset of the disease reported arthralgia 30 d after discharge and 21% after 60 d. Chopra *et al*'s study on clinical predictors of long COVID-19 symptoms in patients with mild COVID-19 at 30 d post-discharge (long COVID-19) found myalgia as one of the most common persistent symptoms following fatigue and cough[56]. Stavem *et al*[57] also reported myalgia as one of the most common persisting symptoms in 1.5 to 6 mo after in non-hospitalised patients. Ghosn *et al*[58] in a large prospective cohort study in French among the post-discharge patients at 3 and 6 mo, mostly fatigue, dyspnoea, joint pain and myalgia were the symptoms patients reported persisting. COVID-19 has also been found to cause reactive arthritis and new-onset inflammatory arthritis typically occurring within a month after its diagnosis[59].

There were reported cases of reactive arthritis post discharge from COVID-19[60]. Derksen *et al*[61] in a Dutch study of five patients who presented with inflammatory arthritis 6.6 wk post COVID-19 infection, two patients had strongly positive and another patient had weakly positive anti-CCP antibodies; suggesting post-COVID-19 rheumatoid arthritis development.

BMD

CXCL10, IL-17 and TNF-α induce osteoclastogenesis and inhibit osteoblast proliferation and differentiation causing increased bone fragility[34]. Berktaş *et al*[62] assessed the BMD

of hospitalized COVID-19 patients at diagnosis and follow-up visits using chest computed tomography (CT). BMD was retrospectively measured by quantitative CT. BMD decreased by a mean of 8.6% (± 10.5%) from diagnosis to follow-up. The osteoporosis ratio increased two-fold after hospitalization for COVID-19 because of this substantial bone loss.

An animal experimental study characterized the effects of SARS-CoV-2 infections on bone metabolism in an established golden Syrian hamster model for COVID-19. SARS-CoV-2 causes significant multifocal loss of bone trabeculae in the long bones and lumbar vertebrae of all infected hamsters implicating the same could happen in humans post COVID-19. A multi-center study by Kottlor *et al*[63] showed that COVID-19 patients requiring intensive care had significantly lower BMD than those who were managed in non-intensive care settings.

Researchers at Indiana University School of Medicine discovered that the mouse models infected with the novel coronavirus lost nearly 25% of their bone mass within two weeks of contagion. They also found mouse models with a 63% increase in osteoclasts, the cells that cause the bone to break down.

Neuromuscular

Musculoskeletal manifestations can be a result of underlying neurological disturbances. The central and peripheral nervous systems control our movements *via* the spinal motor neurons, which act as the final common pathway to the muscles[64]. Many studies have reported peripheral neuropathy most commonly Guillain-Barre and related symptoms. Guillain-Barre syndrome and critical illness-induced polyneuropathy/myopathy are two important peripheral neuropathies seen in COVID-19[65].

A follow-up study conducted for 8 mo in Denmark, performed electromyography and conventional nerve conduction study of 20 patients with persistent fatigue. They found out that all patients with myopathic electromyography reported about physical fatigue and 8 patients about myalgia while 3 patients without myopathic changes complained about physical fatigue. Also added long-term COVID-19 does not cause

large fiber neuropathy, but myopathic changes are seen[66]. Acute myopathies are reported in acute COVID-19 infection[67], which may have a detrimental effect in the muscle in the post infective stages.

Rehabilitation perspectives

COVID-19 has multisystem effects including physical as well as psychological effects. And the wholesome evaluation and rehabilitation of such patients require a multifaceted and interdisciplinary approach to cover all the aspects properly. Identification of the pre-existing disabling conditions contributing to the cumulative effect of long COVID-19 is also an important aspect. Reinfection, post-viral bacterial and fungal infections, baseline routine investigations along with C-reactive protein, fibrinogen, D-dimer, troponin, and ferritin can also be considered if clinically indicated. Cardiac function tests (echocardiography) should be done to check cardiopulmonary status before framing the exercise program.

Rehabilitation should be addressed holistically following the domains of the International Classification of Functioning, Disability, and Health. Studies have shown that early mobilisation helps in the reduction of the harmful effects of the disease, especially on muscle and cardiopulmonary function, mobility and function[68], implying rehabilitation of long COVID-19 should start from the beginning. Physical exercise should be individualised specifying intensity, frequency, duration and type of exercise. And exercise should be gradually increased according to one's capacity. The patient should be educated with an emphasis on self-management. The patient should respect the pain and their own capabilities. Energy conservation techniques such as simplifying tasks, pacing the activities over time, and taking breaks should be followed. Repeated practice of functional activities; a set of specific actions according to the patient's priorities, needs and goals may improve the functional aspects. And all such activities need to be evaluated regularly to determine whether they should be continued, changed or stopped[69].

However, no studies on rehabilitation intervention have been investigated in long Covid for musculoskeletal complications in particular[70]. In our systematic reviews, we did only descriptive analysis, we did not address the individual cases or case series study or any cohort or trials, which may miss the characteristics of the individual cases in particular. However, performing a systematic review of all systematic reviews, and meta-analyses, makes a stronger evidence-based medicine.

CONCLUSION

Musculoskeletal involvement is common during active SARS-CoV-2 infection. Fatigue is very common during this phase. Here we have highlighted the musculoskeletal complications in long COVID syndrome. Again, fatigue is found to be very common along with myalgia, and arthralgia. There is a lack of studies on these aspects. Moreover, all the studies are heterogeneous, especially in terms of the duration of post-COVID, and the definition of long COVID. There are no studies for rehabilitation intervention in musculoskeletal complications specifically. This study reinforces the gravity of the current situation. Considering the lacuna in literature and the needs of the current situation, further studies are warranted to find out effective rehabilitation interventions in musculoskeletal complications. More homogenous studies are needed using proper case definition and duration of long COVID. Studies on functional impairment due to musculoskeletal involvement are needed.

ARTICLE HIGHLIGHTS

Research background

Research is lacking in musculoskeletal complications in long coronavirus disease (COVID).

Research motivation

Currently there is many long COVID patients are coming to out patients Department of Rehabilitation for musculoskeletal issues.

Research objectives

To find out musculoskeletal complications in long COVID and relevant rehab interventions.

Research methods

Systematic review of systematic reviews and meta-analyses was done.

Research results

Among many musculoskeletal issues fatigue as found to be the most common complication. Rehab intervention is severely lacking in literature.

Research conclusions

Rehabilitation need identification is of utmost importance in musculoskeletal aspects of long COVID. Fatigue as found to be the most common complication.

Research perspectives

Identification of rehab need following identification of musculoskeletal complications is crucial in long COVID cases.

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