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Musculoskeletal pain related to COVID-19 survivors after hospitalization: A short review

Dolor musculoesquelético en supervivientes del COVID-19 tras la hospitalización: Una breve revision

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Abstract. Objective: This review aimed to provide an update on the characterization and impact of musculoskeletal pain in COVID-19 survivors. Methods: It is considered articles on subjects who had been recovered from COVID-19 infection after hospitalization (COVID-19 survivors) with secondary musculoskeletal pain. Results: Six articles (one editorial, one consensus statement, one letter to the editor, one case-control study, one cohort study and one review) showed the polyhedral effects of the SARS-CoV-2 on musculoskeletal pain. This short review was not able to clearly identify what the pathogenesis of musculoskeletal pain was in COVID-19 survivors. Conclusion: Preliminary data showed that widespread pain similar to the pattern compatible with pain of musculoskeletal origin could characterize symptoms after SARS-CoV-2 infection.
Keywords: COVID-19, Pain, Musculoskeletal, SARS-CoV-2, Musculoskeletal Disease, Myofascial Pain Syndrome.

Resumen. Objetivo: Esta revisión tuvo como objetivo proporcionar una actualización sobre la caracterización y el impacto del dolor musculoesquelético en los supervivientes de COVID-19. Métodos: Se consideraron artículos sobre sujetos que se recuperaron de la infección por COVID-19 tras la hospitalización (supervivientes de COVID-19) con dolor musculoesquelético secundario. Resultados: Seis artículos (un editorial, una declaración de consenso, una carta al editor, un estudio de casos y controles, un estudio de cohortes y una revisión) mostraron los efectos poliédricos del SARS-CoV-2 sobre el dolor musculoesquelético. Esta breve revisión no pudo identificar claramente cuál era la patogénesis del dolor musculoesquelético en los supervivientes del COVID-19. Conclusión: Los datos preliminares mostraron que el dolor generalizado similar al patrón compatible con el dolor de origen musculoesquelético podría caracterizar los síntomas después de la infección por SARS-CoV-2.
Palabras clave: COVID-19, Dolor, Musculoesquelético, SARS-CoV-2, Enfermedad Musculoesquelética, Síndrome de Dolor Miofascial.

Introduction

COVID-19 infection causes various clinical manifestations in patients, including neurological ranging from headaches, dizziness, neuralgias, neuropathies, and skeletal, muscular injuries and myalgias (Fernández-de-Las-Peñas & Palacios-Ceña et al., 2021). Musculoskeletal impairment causes pain symptoms in COVID-19 patients (Widyadharma, et al., 2020). Symptoms seem to be similar across countries (Kluge et al., 2020). Prolonged immobilization and mechanical ventilation (MV), and restoration of respiratory and physical functions can either be delayed after discharging the patient from the intensive care unit (ICU), or only a partial recovery is achieved, resulting in a decreased quality of life (Pedersini, et al., 2020). ICU-acquired weakness (ICUW) impairs the peripheral skeletal and respiratory muscles of critically ill patients. This is one of the most serious consequences of long-term immobilization, resulting in a delay in MV weaning and prolonged length of hospital stay (LOS). Song et al. detailed that patients hospitalized with COVID-19 infection presented mild to moderate widespread pain that resembled the pattern of musculoskeletal pain (myalgias or COVID-19-induced muscle pain) (Song et al., 2020). Therefore, knowledge on the presence and origin of possible sequelae experienced by COVID-19 survivor patients should be an emerging priority for researchers and clinicians.

Based on these underlying mechanisms of COVID-19 infection, it is highly plausible that one potential

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post-COVID outcomes would be the development of chronic pain (Kemp, Corner, & Colvin, 2020). Chronic pain represents another pandemic crisis in modern society due its high burden (Rice, et al., 2016) and its high prevalence within the general population (Fayaz et al. 2016). There are few data available on post-COVID-19 sequelae related to the development of pain and the potential musculoskeletal repercussions, in contrast to research that highlights other dimensions of health (Almonacid-Fierro, et al., 2021; Almonacid-Fierro, & Almonacid Fierro, 2021; Almorza Gomar, & César, 2021; Baena-Morales, et al., 2020; Carballo-Fazanes, & Abelairas-Gómez, 2021; Carcamo-Oyarzun, et al., 2021; Cerda, et al., 2021; Intelangelo et al., 2021; Marco-Ahulló, et al., 2021; Mujica Johnson, & Orellana Arduiz, 2021; Ricart Luna et al., 2021; Santos-Miranda, et al., 2021; Zamarripa et al., 2021). In this context, rehabilitation should be started immediately after the acute phase to avoid the progression of hospital-acquired weakness and to achieve a rapid functional recovery. The pathogenesis of widespread musculoskeletal pain in survivors of COVID-19 remains unclear, possibly involving the peripheral and central nervous systems. We aimed to review the literature on the characterization and impact of musculoskeletal pain in COVID-19 survivors.

Materials and methods

We conducted a literature review to identify all available articles published from their inception through June 30, 2021 that evaluated the characterization and impact of musculoskeletal pain in COVID-19 survivors. A primary search on MEDLINE through PubMed, CINAHL, Web of Science and Cochrane Central Register of Controlled Trials databases using the following MeSH terms and free terms combined with Boolean operators AND, OR, NOT. The MeSH terms used were: «COVID-19», «SARS-CoV-2», «acute pain», «chronic pain», «musculoskeletal pain». The free terms used were: «infection», «neuropathic pain», «neuropathy». The reviewers independently selected the articles, performed quality assessments, and extracted the results (Fernández-Aljoe, et al., 2020; Fernández-Espínola, & Almagro, 2019; Fonseca, et al., 2021; González Valero et al., 2017; Miras Moreno, 2019; Navarro Mateos, Pérez López, & Marzo, 2021; Ortiz Rodriguez et al., 2018; Pastor-Vicedo, et al., 2020).

The flow chart of the data selection and extraction process is shown in Figure 1 (PRISMA flow diagram).

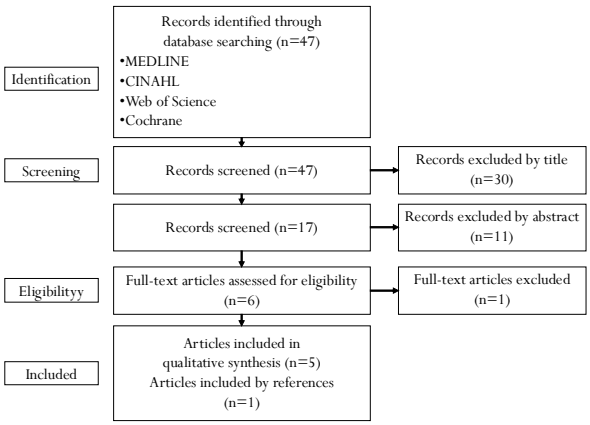

Figure 1. PRISMA Flowchart

Results

Forty-seven records were identified through the database search. We excluded 30 articles after analyzing the titles of the records. From the remaining 17 articles, an abstract evaluation excluded another 11 papers. Of the seven articles considered eligible, two other articles were excluded after full-text analysis. Finally, we included six articles—five of them during a qualitative assessment, and one after the appreciation of its bibliographical reference list.

The musculoskeletal pain related COVID-19 survivors

It is considered articles on subjects who had been recovered from COVID-19 infection after hospitalization (COVID-19 survivors) with secondary musculoskeletal pain. Most published articles comparing subjects with COVID-19 related musculoskeletal pain do not evaluate physiological muscle characteristics after recovery.

This literature review identified few articles that evaluate the characteristics and impact of musculoskeletal pain in COVID-19 survivors. Six articles (one editorial, one consensus statement, one letter to the editor, one case-control study, one cohort study and one review) showed the polyhedral effects of the SARS-CoV-2 on musculoskeletal pain. Those articles presented clinical features, symptoms related to the immobilization, biological and immunological mechanisms, psychological impact, and general rehabilitation recommendations of musculoskeletal pain.

Kucuk et al., reported myalgia in patients with COVID-19. As this symptom is a common feature present in 36% of patients with such viral infection, it is crucial to understand the mechanism underlying muscle pain. Kucuk et al., hypothesis relies on the association between the viral load and muscle pain. According to

the authors, the pain is related to the oxygenation of erythrocytes and muscle lactate level. The authors also state that the pain may resolve with treatment of the virus (Kucuk, et al., 2020).

Barker-Davies et al., published a consensus statement to provide evidence-based recommendations for post-Covid-19 rehabilitation targeted at active subjects. Their consensus was developed using a systematic review conducted by experts organized in seven teams to appraise the veracity of the following dimensions e related to COVID-19 rehabilitation criteria: pulmonary, cardiac, mental health, musculoskeletal, neurorehabilitation, and general medicine (Barker-Davies, et al., 2020).

Disser et al., compared studies of patients presenting with moderate and severe SARS-CoV-2 disease who developed significant musculoskeletal disorders (including skeletal muscle, neurological, skeletal, bone, and joint). They found that clinical data on patients with COVID-19 after the acute episode of care are limited. However, early signs and symptoms of musculoskeletal dysfunction are evident in patients recovering from COVID-19. In vitro experimental studies have demonstrated a large similarities between the pathophysiological changes in those tissues (Disser et al., 2020).

Fernandez-de-las-Peñas et al., researched the relationship between COVID-related myalgia in 738 post-COVID-19 patients (369 with myalgia during admission and 369 without). The patients were admitted at hospital emergency and the occurrence of post-COVID-19 symptoms. They found the existence of 3 or more post-COVID symptoms and post-COVID musculoskeletal pain in the myalgia group at hospital admission. Fifty percent of patients with pre-existing musculoskeletal pain suffered an aggravation of their symptoms after developing COVID- 19. They also associated the acute-phase myalgia to musculoskeletal pain as a long-term symptom after COVID-19. Half of the patients with pre-existing disorders suffered a continuing aggravation of their pre-existing syndromes (Fernández-de-Las-Peñas & Rodríguez-Jiménez et al., 2021).

Kemp et al., in a recent editorial, commented the clear association between COVID-19 with painful symptoms, including myalgia, arthralgia, abdominal pain, headache, and chest pain. Even patients who are not located in critical care settings may have pain that needs to be treated with opioids to improve symptoms. Besides, they stated that the COVID-19 appears to have the capacity to induce painful parainfectious disease, as Guillain-Barré syndrome and polyneuritis (Kemp, et al., 2020).

Al-Aly et al., analyzed the U.S. Department of Veterans Affairs national health care databases in a cohort of 73,435 patients with COVID-19 who survived for at least the first 30 days after their COVID-19 diagnosis and who were not hospitalised, and 4,990, 835 patients who did not have COVID-19 and were not hospitalised to systematically and comprehensively identify 6-month incident sequelae in patients with COVID-19 who survived for at least 30 days after diagnosis, demonstrating that beyond the first 30 days of illness, patients with COVID-19 are at increased risk of death and healthcare resource use. They showed musculoskeletal symptoms (including malaise and fatigue, muscle disorders and musculoskeletal pain) as well as several other disorders in the respiratory system, nervous system and neurocognitive disorders, mental health disorders, metabolic disorders, cardiovascular disorders, gastrointestinal disorders, malaise, fatigue, and anaemia. They also found that these patients demand treatment with opioid and non-opioid analgesics as well as antidepressants, anxiolytics, antihypertensives, and oral hypoglycaemic agents, as well as evidence of laboratory abnormalities in various organ systems (Al-Aly et al., 2021).

Discussion

Musculoskeletal injury leads to pain symptoms in COVID-19 patients (Al-Aly et al., 2021; Barker-Davies et al., 2020; Disser et al., 2020; Fernández-de-Las-Peñas & Rodríguez-Jiménez et al., 2021; Kemp et al., 2020; Kucuk et al., 2020). The virus appears to affect muscle and joint tissue, inducing an inflammatory response similar to that elicited by a generalised viral infection caused by another pathogen. SARSCoV-2 detected in the cerebrospinal fluid of infected patients is another potential mechanism of SARS-CoV-2-induced pain in COVID-19. The rehabilitation of post-acute and chronic patients recovering from COVID-19 should be standardised (Ballesteros-Reviriego et al., 2020). According to Barker-Davies et al., a functional assessment for residual musculoskeletal impairments should be performed in all patients requiring rehabilitation after COVID-19. Patients who have been admitted to the ICU should be managed in rehabilitation by a multidisciplinary team (Pancera et al., 2020; Pancera et al., 2021). Especially for patients presenting with

post-intensive care syndrome, rehabilitation efforts should be considered in all three domains of impairment: psychological, physical and cognitive. The authors note in their consensus that physical rehabilitation after COVID-19 can be performed in inpatient or outpatient settings, telemedicine, or targeted exercises to address the patient's individual needs.

Disser et al. support these findings by stating that conservative rehabilitation protocols are effective in facilitating functional rehabilitation in patients with SARS-Cov-1 and are needed in patients with other critical illnesses as well. According to the authors, more research focused on assessing and treating the musculoskeletal health of patients recovering from COVID-19 is needed. This will help to identify long-term outcomes. Patients with COVID-19 have reported musculoskeletal disorders related to this condition. Epidemiologic data from SARS patients during the 2002 to 2004 pandemic, pathological and genetic resemblances among SARS-CoV-1 and SARS-CoV-2. The common occurrence of sarcopaenia and osteoporosis reported in other critical illnesses provide enough data to predict short- and long-term musculoskeletal disease complications in patients with moderate and severe COVID-19.

Kucuk et al. explained the role of erythrocytes' oxygen-carrying capacity and lactate dehydrogenase (LDH) during the COVID-19 infection. During the infection, oxygen delivery to tissues is greatly diminished. The musculoskeletal system may remain deoxygenated and muscles may become ischaemic during COVID-19 infection, as in the case of intense exercise. They concluded that LDH is increased when the virus harms muscles and other tissues. Due to both mechanisms, the increased LDH, and anaerobic glycolysis, lactate levels may increase excessively. The pH of the cytosol decreases, and the muscle pain increases due to higher lactate, low pH, and low oxygen levels. The cause of hypoxia should be eliminated to treat this type of pain, so painkillers may not be effective, and the pain may reduce with treatment of the virus. Erythrocyte oxygenation increases and muscle lactate level decreases when viral load decreases, contributing to the pain relief. Kemp et al. reported a high prevalence of painful symptoms like myalgias, arthralgias, abdominal pain, headaches and chest pain in patients affected by COVID-19. In this context, the same characteristics related to the development of severe COVID-19 coincide with those related to chronic pain after critical illness, including multiple morbidities and older age.

Those with pre-existing multi-morbidity may be at increased risk of chronic pain prior to infection. This may predispose them to an exacerbation of current pain conditions or development of new symptoms (Fernández-de-Las-Peñas & Rodríguez-Jiménez et al., 2021). Contrary to other authors, Kemp et al. found the therapeutic effects of rehabilitation protocols after ICU admission on exercise tolerance and health-related quality of life are contradictory to the pre-COVID era. However, the effect of post-ICU rehabilitation on pain has never been formally evaluated even though pain is a key dimension of health-related quality of life measures. Most studies on the efficacy of pain management and post-critical illness rehabilitation have focused on face-to-face delivery, often in a group-based setting.

Authors like Fernández-de-Las-Peñas et al. (Fernández-de-Las-Peñas & Palacios-Ceña et al., 2021), by conducting a multicenter observational study in 4 hospitals with a total of 1142 patients who were hospitalized with a positive diagnosis of SARS-CoV-2 by RT-PCR and radiological findings during the first wave of the pandemic (March 10 to May 31, 2020), found patients with signs and symptoms that are beyond the scope of the present review such as dyspnea, fatigue, anosmia, ageusia, hair loss, chest pain, palpitations, diarrhea, skin rashes, brain fog, memory loss, cough. The same research group (Fernández-de-Las-Peñas & Guijarro et al., 2021) evaluated 1,950 recovered COVID-19 patients from three hospitals one year later after hospital discharge by telephone interview those who were asked about the symptoms of fatigue, dyspnea, chest pain, and cough, reporting that the most prevalent symptom was fatigue 61.2%.

Finally, it should be noted that the SARS-Cov-2 pandemic presents the health care system with challenges that require a fast response in a short period (Global Burden of Disease 2020 Health Financing Collaborator Network, 2021).

Conclusions

We were unable to clearly identify the pathogenesis of musculoskeletal pain in COVID-19 survivors. Increased inflammatory mediators could be the pathogenesis of the muscle damage. Patients with COVID-19 frequently experience arthralgia, muscle pain or general weakness caused by the impact of the virus. Pain may continue for longer than that in other viral infections and may not respond to conventional

analgesics in patients affected by COVID-19. The SARS-Cov-2 pandemic presents the health care system with challenges that require a fast response in a short period. The lack of information related to all fields of post-COVID-19 infection rehabilitation creates the need for a broad collaborative network to provide urgent answers related to this disease.

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Abbreviations

ICU: Intensive Care Unit; ICUAW: ICU Acquired Weakness; MV: Mechanical Ventilation; LOS: Hospital Length of Stay.

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