MYOPATHY AND COVID-19: LITERATURE REVIEW.

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Abstract

The myopathies produce impairment of the striated skeletal muscle in its structure or development, distinguishing two categories: genetic myopathies and acquired myopathies. COVID-19 has been categorized as a disease which acute respiratory manifestation is caused by the SARS-CoV-2 virus. In very severe cases, patients are admitted to Intensive Care Units (ICU), where they receive invasive, complex, and long-term treatments that can have negative consequences for recovery, making the risk-benefit balance a very complex factor. The purpose of this work is to address the relationship between myopathy and COVID-19 in severely ill patients admitted to the ICU, observing the set of factors that cause the conditions and the impact on the clinical evolution of these patients. For the development of the project, a search was carried out in the following databases: Medline, Scielo - Scientific Electronic Library Online, Google Scholar and Redalyc, using appropriate descriptors and selecting a total of 54 articles. It is concluded that myopathy and COVID-19 are closely related in patients hospitalized in the ICU, also showing the presence of neurological problems associated with multisystemic involvement, among which are polyneuropathy in critical patients, myopathy in critical patients, Guillain-Barré Syndrome, among others.

Palabras clave: COVID-19, Myopathies, Intensive Care Unit, Treatment, Consequences. (Mesh).

Resumen

MIOPATÍA Y COVID-19: REVISIÓN DE LITERATURA

Las miopatías producen afectación del músculo esquelético estriado en su estructura o desarrollo, distinguiéndose dos categorías: Miopatías genéticas y miopatías adquiridas. La COVID-19 ha sido catalogada como una enfermedad cuya manifestación respiratoria aguda es causada por el virus SARS-CoV-2, en casos muy severos, los pacientes son ingresados en las Unidades de Cuidados Intensivos (UCI), donde reciben tratamientos invasivos, complejos y prolongados que pueden traer consecuencias negativas para la recuperación, haciendo del balance riesgo beneficio un factor muy complejo. El objetivo de este trabajo es abordar la relación existente entre la miopatía y COVID-19 en pacientes críticos internados en UCI, observando el conjunto de condiciones que provocan las afectaciones y el impacto en la evolución clínica. Para el desarrollo de la investigación se realizó una búsqueda en las bases de datos Medline, Scielo – Scientific Electronic Library Online, Google Académico y Redalyc, utilizando descriptores adecuados y seleccionándose en total 54 artículos. Se concluye que la miopatía y COVID-19 están estrechamente relacionados en pacientes internados en UCI, evidenciándose además la presencia de problemas neurológicos asociados con afectación multisistémica dentro de los que se encuentran la polineuropatía del paciente crítico, la miopatía del paciente crítico, el Síndrome de Guillain-Barré, entre otros.

Keywords: COVID-19, Miopatías, Unidad de Cuidados Intensivos, Tratamiento, Secuela. (Mesh).

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INTRODUCTION

Myopathies are considered neuromuscular diseases characterized by the impairment of the striated skeletal muscle in its structure or development, distinguishing two categories: genetic myopathies (inherited) and acquired myopathies [1]. The first data in the literature referring to inherited myopathies (IM) was in 1852, where Edward Meryon described granular degeneration in postmortem muscle. Idiopathic inflammatory myopathies (IIM) directly affect skeletal muscle and can sometimes involve the skin and other organs to varying degrees [2].

Weakness associated to critical illness is a general term describing neuromuscular disorders related to a severe disease such as COVID-19. It is divided into three groups depending on the damage location: polyneuropathy due to critical illness (CIP), myopathy due to critical illness (CIM) and, polyneuromyopathy due to critical illness (CIPNM) [3].

Although it has been described in the literature that among the clinical symptoms caused by the SARS-CoV-2 virus are respiratory manifestations, fever, gastrointestinal problems, among others, since the beginning of the pandemic, neurological symptoms such as headache, anosmia, myalgia, insomnia and confusion have also been observed [4].

ICUs are part of the last step in the integrated patient care system and their main objective is the diagnosis and treatment of critically ill patients, those with very deteriorated health conditions and high risk of suffering severe complications in the short and medium term [5]. The consequences of admission to the ICU may be the result of the different and aggressive treatments or secondary to other aspects of the disease itself, such as fatigue, asthenia, weight loss, cognitive shortcomings, myopathy and polyneuropathy [6].

The current relationship between myopathy and COVID-19 in critical patients admitted to the ICU, observing the set of conditions that cause the impairment and functional decline in these patients has particular importance given the current circumstances, and constitutes a relevant aspect for future research.

RESEACH STRATEGIES

An unstructured search was carried out in the following databases: Medline (https://www.ncbi.nlm.nih.gov/pubmed/), Scielo – Scientific Electronic Library Online (http://www.scielo.org), Académic Google (https://scholar.google.es) y Redalyc (https://www.redalyc.org), using descriptors and key words: "*COVID-19*", "COVID-19, Myopathies , "Intensive Care Unit", "Treatment", "Consequences".

A total of 147 related articles were obtained; giving emphasis on those of an original nature, specifically systematic reviews, case studies and experimental studies; 63 publications prior to 2012 were rejected, resulting in 84 articles in the sampling phase, 12 were not relevant or were duplicates, for a total of 72 to choose from. Finally, the 54 most updated and best documented publications were selected (**Figure 1**).

Literature Review

While CIM, CIP and CIPNM are similar in their clinical presentation, there are important differences in their pathophysiology. CIP is a sensorimotor axonal polyneuropathy characterized by the loss of individual nerve fibers, whereas the weakness in CIM is attributed

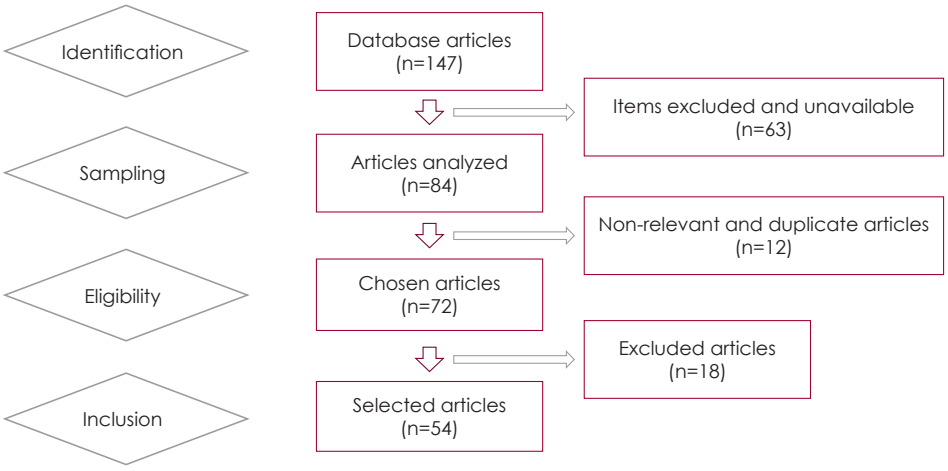

Figure 1 . Flow chart for articles selection.
Source: Author.

to a decrease in thick myofilaments leading to the death of skeletal muscle myofibers [7].

CIP shows worse results when compared to CIM [8]. Although substantial progress has been made to improve understanding of the mechanisms related to these conditions, age and length of ICU stay are important indicators of long-term outcomes [9].

ACE2 RECEPTORS IN STRIATED MUSCLE

ACE2 receptors serve as a protective molecule, maintain physiological homeostasis, and prevent the development of numerous diseases. Binding of SARS-Cov2 to ACE2 not only initiates the entry of the virus into the human body, but also disrupts the protective action of ACE2 in affected organs. Therefore, it is important to re-evaluate the impact of ACE2 in modulating organ function and human health [10].

Skeletal muscle plays an extremely important role in the regulation of the motor system and metabolic homeostasis. Through activation of the classical RAS pathway, the ACE-Ang II-AT1 axis participates in muscle pathogenesis by promoting disturbances in the motor system and insulin sensitivity, that is, muscle wasting accompanied by pathological muscle remodeling or insulin resistance, respectively [11].

Regarding the ACE2-Ang 1-7 pathway as a counter-regulatory system of the ACE-Ang II-AT1 axis, previous studies in skeletal muscle mention a protective role of Ang 1-7 in pathological muscle remodeling and insulin resistance [12],[13].

Riquelme et al. investigated the role of ACE2 in the existing pathological muscle modulation, suggesting that ACE2 activity and protein levels in skeletal muscle were increased by genetic induction of muscular dystrophy, which could imply a compensatory mechanism of the RAS protective pathway against muscle injury [14],[15].

PATHOPHYSIOLOGICAL MECHANISMS OF MUSCLE WEAKNESS IN COVID-19

Myopathy can be caused by several factors such as: direct viral damage to skeletal muscle or secondary disorders such as motor neuron involvement, malnutrition, systemic inflammatory response, prolonged bed rest and insufficient O2 supply [16],[17].

Atrophy and fibrosis are caused by pathological muscle remodeling of skeletal muscle, secondary to endothelial dysfunction in the microcirculation and RAS system in the musculature [18].

Muscle atrophy is caused by an imbalance in protein metabolism, especially by inhibition of the IGF-1-AKT-mTOR pathway due to the alteration caused by AngII in muscle protein synthesis, which can indirectly induce cell apoptosis [13]. This damaged or atrophied muscle tissue directly influenced by AngII is replaced by connective tissue producing muscle fibrosis with a subsequent decrease in skeletal muscle [19].

To shorten, it can also be mentioned that SARS-COV2 can induce muscle atrophy through dysregulation of the renin-angiotensin-aldosterone system (RAS) in interaction with other processes secondary to hospitalization in the ICU (**Figure 2**) [20],[11].

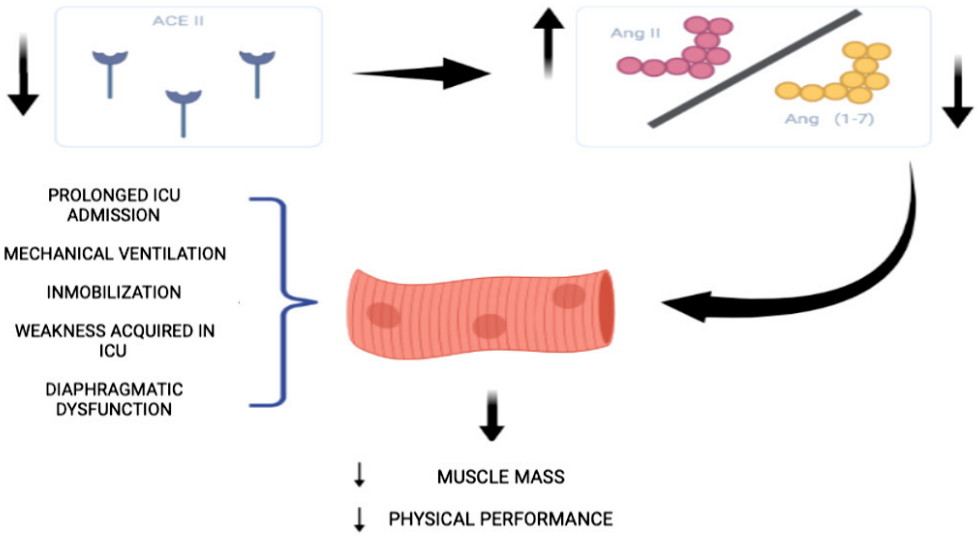

Figure 2 . Summary of the etiopathogenesis of COVID myopathy – 19
Source: Author

PATIENTS WITH COVID-19 AND MYOPATHY

During the COVID-19 pandemic, neuromuscular complications have been evident [21]. Between 30% and 50% of ICU patients present during hospitalization neuromuscular weakness apparently secondary to CIM and CIP or their combination, causing an increase in the number of days of mechanical ventilation and ICU stay [22].

Mao et al. (2020) stated that 36.4% of patients had neurological manifestations that were directly related to the severity of the clinical picture of COVID-19 [23],[24].

Markussen et al. (2019) state that it is predictable and logical that patients who have been hospitalized in the ICU for a longer period of time will present physical consequences, such as myopathy, polyneuropathy, musculoskeletal retractions, among others [25],[26].

Authors such as Céspedes et al. (2021) report that in the advanced phase of COVID-19, there is clinical manifestations related to peripheral nerve involvement, dysautonomias and myopathies [27]. Muscle weakness due to post-ICU immobility has been considered as the sequela that most affects the quality of life and recovery time of these patients. (**Figure 3**) [28].

OTHER MYOPATHY CAUSES IN COVID-19 PATIENTS

A large number of patients with COVID-19 require admission and long-term stay in intensive care units (UCI) [29], therefore, the chance of complications and the development of CIM was highly possible [30],[31].

- Guillain Barré syndrome (GBS) andCOVID-19

GBS is one of the most common causes of paralysis worldwide, manifesting as an acute inflammatory polyradiculoneuropathy. Among the usual clinical features are symmetrical ascending weakness, painful paresthesias, decreased or absent osteotendinous reflexes, alteration of cranial nerves and in severe cases even respiratory muscle weakness may occur [32]. It can appear as a heterogeneous disease and different variants have been reported [33].

Gigli et al. (2021) reported 47 patients with classical GBS or its variants in patients diagnosed with COVID-19, suggesting a marked increase in its frequency during the pandemic [34]. Zuberbuhler et al. (2021) assume that respiratory failure in patients with COVID-19 is secondary to the relationship between muscle weakness and viral lung infection [35].

- Transverse myelitis and encephalomyelitis in COVID-19

Transverse myelitis leads to the destruction of the myelin of nerve cells causing the interruption of the messages that the spinal cord sends throughout the body via the peripheral nerves, resulting in pain, muscle weakness, paralysis, sensory problems or bladder and bowel dysfunction [36]. SARS-CoV-2 has clinical features that are not only limited to the respiratory tract, but also involve the nervous system. Several authors have studied the indirect and direct mechanisms involved in the complications and neurological manifestations reported in COVID-19 and have identified the possible mechanisms of direct invasion of SARSCoV-2 into the CNS [36]. This is why isolated cases of encephalopathy, encephalitis, encealomyelitis, necrotizing hemorrhagic encephalopathy, among others, have been described [37].

- Cerebrovascular disease (ECV) and COVID-19

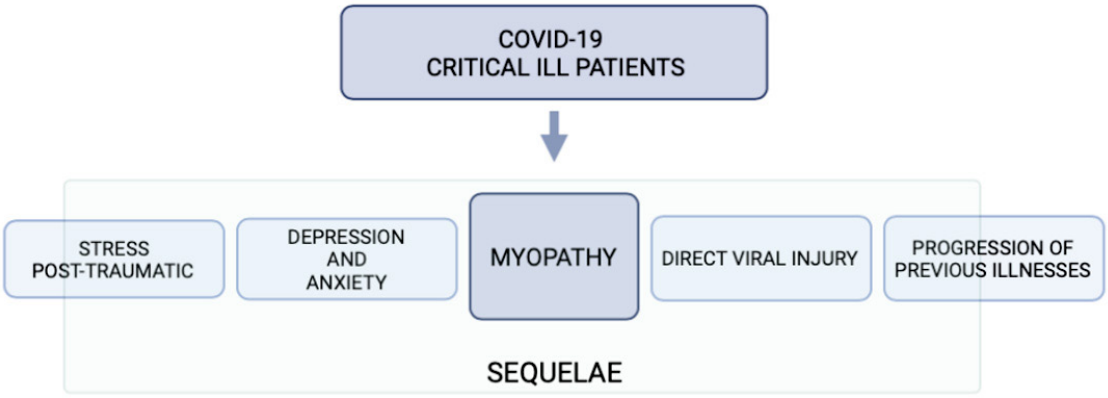

Figure 3 . Consequences of COVID-19 in patients admitted to the ICU
Source: Author

Related to the prothrombotic phenotype of severe COVID, ischemic cerebrovascular events have been reported with an incidence that can reach up to 5% of hospitalized patients [38].

Another mechanism that has been mentioned is endothelial dysfunction, SARS-CoV-2 binds and invades vascular endothelial cells through ACE2 present in the endothelium, triggering endothelial inflammatory cell death (pyroptosis) [39],[40].

DIAGNOSTIC

CIP, CIM and CIPNM are usually diagnosed during the recovery phase of the disease and while all are known to share common clinical signs, the diagnosis also depends on the correct interpretation of those data related to the clinical presentation and electrodiagnostics, with standard laboratory tests showing little significance [3].

Sagging and generally symmetrical weakness are aspects found in CIP, CIM and CIPNM, a potential differentiating factor may be no or diminished response to pain, vibration or temperature sensitivity in those with CIP, whereas these functions would be seen in CIM [41]. Muscle atrophy is generally more evident in CIM, which is difficult to diagnose due to the condition of critically ill patients. In awake patients, muscle strength can be assessed using the Medical Research Council (MRC) scale, which rates muscle weakness in six muscle groups, giving a score between 0 (no contraction) and 5 (normal strength). CIPNM is defined when the total MRC score is less than 48, other causes of weakness having been previously ruled out [3].

Laboratory tests are not considered indispensable for the diagnosis of CIAW, however, it has been recognized that plasma IL-6 is an early marker of membrane dysfunction for CIM [3]. GDF-15 is a critical disease mediator stimulated by the stress of muscle atrophy and is considered a potential biomarker candidate; however, further studies will be needed to confirm its usefulness [8].

Needle electromyography can help clarify the diagnosis, among the findings are described: early recruitment and small amplitude polyphasic waves in the different affected muscles (biceps brachii, rectus femoris and tibialis anterior muscles), reduced amplitude and duration of the motor unit potential and sometimes the presence of fibrillations and fasciculations [42].

Muscle biopsy in the case of CIP shows atrophy due to denervation of muscle fibers type 1 and 2. In CIM, atrophy of myofibers, focal or diffuse loss of thick filaments, angulated fibers, fatty degeneration, and necrosis are described.

With imaging techniques such as computed tomography and nuclear magnetic resonance it is possible to observe the degree of muscle loss and the infiltration of muscle by adipose tissue. It also allows the evaluation of deeper muscle groups; however, among the main disadvantages of these techniques are described their high cost, exposure to radiation and the need to transport the patient out of the ICU [30].

THERAPEUTICS

Treatment model provides for minimization of associated risk factors, symptom management and physical rehabilitation [26].

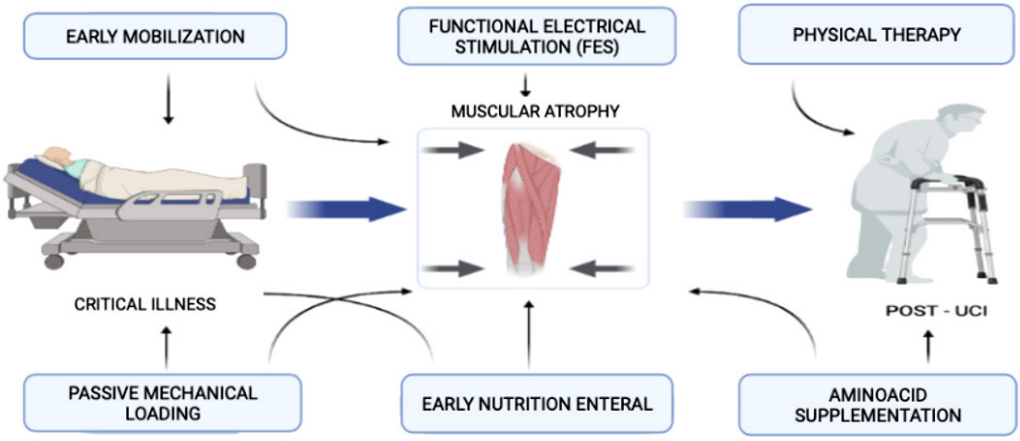

Figure 4 . Therapeutics recomended to myopathy

Source: Author

Some authors state that there are no recommended pharmacological treatments to prevent or treat CIAW [43]. However, euglycemia has been shown to improve some outcomes in critically ill patients. Insulin therapy greatly reduced CIP and CIM rates, including mechanical ventilation time, hospitalization days, and mortality rate [44].

Functional electrical stimulation (FES) is reported to be beneficial in patients who have not been admitted to the ICU by promoting increased muscle strength [45],[46].

However, there is discordance among the results, so more and better studies are needed to support its efficacy [47],[48].

Early passive and active mobilization plus sedation breaks may aid recovery, especially in patients admitted to the ICU for COVID-19 [49], being relevant, safety from a procedural point of view with a low risk of adverse events [50]. Zhou et al. (2014) report that early mobilization leads to a lower incidence of CIAW, improving functional capacity and increasing the ability to stand upright [51]. The proposals studied have focused on: transfers (from supine to sitting), walking and cycloergometry adjacent to the bed [22].

Yang et al. (2018) mention that malnutrition is the leading cause of "critical illness polyneuropathy," emphasizing the harmful effects of parenteral nutrition in critically ill patients and supporting early enteral feeding [52].

McGlory et al. (2020) report that omega-3 fatty acid supplementation improved skeletal muscle anabolism [53], also showing strong anti-inflammatory properties [54].

CONCLUSIONS

Myopathies are an important aspect to consider for the development of complications and consequences associated with COVID-19 in critically ill patients admitted to the ICU. Among the most important neurological problems associated with COVID-19 with multisystemic involvement are polyneuropathy in the critically ill patient, myopathy in the critically ill patient and Guillain-Barré syndrome, so there is a close relationship between myopathy and COVID-19, an aspect of particular importance in the present circumstances.

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