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REVIEWS

Musculoskeletal involvement of SARS-CoV-2 infection with clinical implications

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Abstract

The COVID-19 pandemic is the deadliest disease of the modern medicine era. Internationally, governments are enforcing measures such as travel bans, quarantine, isolation, and social distancing leading to an extended period of time at home. This has resulted in reductions in physical activity and changes in dietary intakes that have the potential to accelerate sarcopenia, a deterioration of muscle mass and function (more likely in older populations), as well as increases in body fat. These changes in lifestyle, diseases including cardiovascular disease (CVD), diabetes, osteoporosis, frailty, cognitive decline, and depression have appeared much more frequently. Furthermore, CVD, diabetes, and elevated body fat are associated with greater risk of COVID-19 infection and more severe symptomology. The potential of low physical activity and isolation lead to an increased muscle loss and chronic disease.

Keywords: SARS-CoV-2 infection, musculoskeletal rehabilitation, osteosarcopenia.

Introduction

The new SARS-CoV-2 virus, which belongs to the coronavirus family, is a single-stranded RNA virus that marks our era and severely affects people's quality of life. This family also includes MERS and SARS-CoV-1 (Disser et al., 2020; Cui et al., 2019). SARS-CoV-2 caused the death of about 3.4 million people by May 19, 2021, triggering the first pandemic in the era of modern medicine, according to information reported on the World Health Organization (WHO) website.

It has been observed that infected people with moderate or severe illness develop more severe symptoms, including skeletal muscles, joints, bones and nerves (Disser et al., 2020).

COVID-19 infection not only causes problems in the acute phase due to its symptoms and lung damage with the onset of acute respiratory distress syndrome (ARDS), but also in the long term regarding the rehabilitation of patients affected either directly or indirectly by the pandemic (Welch et al., 2020; De Biase et al., 2020).

Osteosarcopenia is defined by loss of muscle and bone mass, manifesting by a decrease in muscle strength with the appearance of difficulties in performing daily activities and the occurrence of disabilities with a decrease in quality of life (Welch et al., 2020; Cruz-Jentoff et al., 2019; Beadart et al., 2015).

SARS-CoV-2 has a similar mechanism of action to SARS-CoV-1; we can expect some long-term effects after this pandemic. Studies during SARS-CoV-1 infection in 2009 showed that impairment of lung and musculoskeletal capacity was significant at one year after healing, compared to a control group with uninfected subjects. After regression of the viral infection, patients' functionality improves significantly but remains below that of the control group (Hui et al., 2009).

Pathogenesis

The direct effects of SARS-CoV-2 infection on the musculoskeletal system have received special attention especially in the last period of the pandemic. Initially, the main concerns were for lung damage, respectively life support. Subsequently, it was observed that the involvement of the infection is multisystemic and each system requires a particular approach.

Respiratory infection with SARS-CoV-2 has type II pneumocytes as the first starting point, which line the respiratory epithelium (Cheng et al., 2020).

Common symptoms in hospitalized patients include fever (70%-90%), dry cough (60%-86%), shortness of

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breath (53%-80%), fatigue (38%), myalgias (15%-44%), nausea/vomiting or diarrhea (15%-39%), headache, weakness (25%), and rhinorrhea (7%). Anosmia or ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19 (Mao et al., 2020).

Following accumulation of the authors' clinical experience, after a year of monitoring the evolution and therapy of patients with COVID-19 infection, it has been observed that many patients present with a variety of extra-pulmonary symptoms such as musculoskeletal disorders, digestive tract and metabolic disorders, especially for diabetes. These observations are described in a number of articles.

Even if lung cells are primarily involved, all cells can be affected primarily if they have ACE receptors by viremia and indirectly, e.g. by "cytokine storm".

Cellular mechanism

Both SARS-CoV-1 and SARS-CoV-2 enter cells via the angiotensin-converting enzyme 2 (ACE2) receptor using the serine transmembrane protease, serine 2 (TMPRSS2) (Hoffmann et al., 2020).

Following receptor binding, proteolytic cleavage of the S protein using TMPRSS2 occurs with exposure to fusion peptide signal which allows mixing of viral and human membranes and release of viral RNA into the cytoplasm (Fehr & Perlman, 2015).

The ACE2 receptor is found on all cells in the body, in different concentrations, which at first sight explains why the symptoms are so varied through pulmonary, digestive, neurological manifestations, myalgias, arthralgias (Morley et al., 2020; Lin et al., 2020). It is a multifunctional transmembrane protein with a role in maintaining cellular homeostasis and protection against pathogens. There are two ways to activate it, through the renin-angiotensin system (a process by which Ang2 is cleaved in Ang 1-7) and a pathway through which Ang 1 to Ang 1-9 is cleaved (Yamamoto et al., 2020).

The virus-laden pneumocytes release many different cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumor necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α). This 'cytokine storm' acts as a chemoattractant for neutrophils, CD4 helper T cells and CD8 cytotoxic T cells, which then begin to get sequestered in the lung tissue (Parasher, 2020; Yuki et al., 2020).

Muscle involvement

Due to restrictions, isolation and hospitalization, eating and sports habits have changed over the past year. All this had a strong impact on skeletal muscles.

The World Health Organization recommended during the pandemic a minimum physical activity of 150 min / week, at least 2 days / week. The recommendation is made for all infected people or not, regardless of age or gender. This underscored the importance of avoiding physical deconditioning to prevent long-term complications (***, 2020).

Weakness and myalgia are among the most common musculoskeletal manifestations in COVID-19 infection, up to ¼ of patients having these symptoms. There was a reduction in muscle strength by 32% and in the distance traveled in 6 minutes by 13%, 2-3 months after the acute episode. Return to work was slow and long delayed for 40% of patients who had severe forms. Inability to move from homes or hospitals that required prolonged bed rest led to severe decline in physical activity, loss of appetite and eventually overweight / obesity, hypertension, dyslipidemia, decreased muscle mass (Disser et al., 2020).

The biological mechanisms that lead to muscle loss are still insufficiently known; the possible explanations are: 1. Neuronal demyelination; 2. Cytokine storm that determines a pro-inflammatory status; 3. IFN-gamma, IL-1beta, IL-6, IL-17, TNF-alpha directly induce proteolysis and decrease protein synthesis, 4. Corticosteroids have a direct effect on muscles, causing atrophy and muscle weakness, 5. Vitamin D deficiency causes atrophy of type II muscle fibers (Disser et al., 2020).

Sarcopenia has been considered an age-related condition, manifesting by a qualitative and quantitative decrease in muscle mass and strength. It often begins in people over the age of 40, being one of the most common causes of disability, mortality and morbidity (Kirwan et al., 2020; Welch et al., 2020; Beaudart et al., 2015; Landi et al., 2015).

COVID-19 infection mainly affects the elderly who have other diseases that weaken the body's immune system (diabetes, high blood pressure, obesity), causing more severe forms of the disease and further accentuating sarcopenia through immobilization, isolation and hospitalization (Morley et al., 2020; Lin et al., 2020).

Another factor independent of the disease itself is the social effect of distancing and quarantine, lockdown and restrictions implemented by governments, thus lowering the level of physical activity and increasing the level of sedentary lifestyle. All these factors enhance the degree of disability, with low function, loss of muscle mass, bone, mobility and joint stability (functionality) in the short and long term, by increasing the level of social and medical care.

Due to musculoskeletal impairment, a personalized physiotherapy and rehabilitation plan was added to the drug treatment protocol for each patient, taking into account age and the form of disease (Welch et al., 2020; Deniz et al., 2020).

SARS-CoV-1 and influenza virus have more frequently caused myositis, through an insufficiently known mechanism. SARS-CoV-2 mainly affects the skeletal muscles and heart muscle. There have been cases of infection in children that have resulted in heart failure, followed by death. Autopsy revealed various changes in muscle fibers: atrophy, fibrosis, focal necrosis, changes in myofibrils and Z disc (Casey et al., 2021).

Many studies have shown the presence of rhabdomyolysis, observed by increased values of creatine kinase (CK) and lactate dehydrogenase (LDH), including in patients who did not show respiratory manifestations. Consequently, myalgia and muscle weakness were among the main changes at the onset of COVID-19 infection. Rhabdomyolysis is a complication of myositis

and involves a heart attack (myonecrosis) and elevated levels of myoglobin in the blood (myoglobinemia). Rhabdomyolysis is a life-threatening condition that may cause kidney failure, compartment syndrome and intravascular coagulation (Revzin et al., 2020).

Diaphragm muscle dysfunction causes impaired respiratory function and difficulty accepting mechanical ventilation. Imaging helps diagnose and monitor this muscle dysfunction in COVID-19 patients. The fluoroscopy sniff test offers a quick and real-time assessment of diaphragm excursion. Ultrasound brings additional information about the presence or absence of signs of muscle atrophy, calculation of muscle thickness, and evaluation of muscle excursion. HR-US is used to identify peripheral nerve damage in the neck, which ultimately helps differentiate diagnosis, determining the cause of diaphragmatic dysfunction (Ramani et al., 2021).

The increased incidence of thrombotic events has led to the appearance of painful manifestations in the muscle, both acutely and chronically, rehabilitation taking into account this aspect.

The recommended rehabilitation methods for myalgias during the pandemic include:

- Rest, ice, compression and elevation of the painful limb (RICE rule)

Impairment of muscle and peripheral vessels caused by inflammatory reactions has the effect of edema and pain. These manifestations can be reduced by applying the RICE rule in the first 72 hours after onset.

- Protective technique

Through kinesiology tapes, it protects the joints and reduces pain and edema, improves lymphatic circulation and fascia function.

In the first days after the onset of pain, the passive movement of the limb is indicated. Thus, the mobility of the joint can be maintained and prevents its stiffening. At the same time, peripheral vascularization is improved, so it can help the healing process. Stretching exercises can be applied gradually to maintain the elasticity of the tendons. If pain has subsided, active exercises can be started.

Bone involvement

The effects of viral infections in general on bones have been less studied than on other tissues. We do not know very well how SARS-CoV-2 acts on bone tissue. Rather, we know the consequences of disease, therapy, and isolation / immobilization on bones.

RNS sequencing identified receptors for ACE2 in each sample of unenriched cortical and trabecular bone composites and in osteoblast-enriched samples. TMPRSS2 was expressed in osteoblast samples. This information indicates that the bone structure may also be the site of COVID-19 infection (Disser et al., 2020).

Literature studies have revealed that osteoblasts and osteoclasts express angiotensin-converting enzyme 2 / angiotensin- (1–7) / mitochondrial assembly receptor [ACE2 / Ang- (1–7) / MasR] and have illustrated how the ACE2 / Ang- (1–7) / MasR axis can affect bone metabolism. More specifically, the activation of ACE2 / Ang- (1–7) / MasR axis restrains bone resorption and exhibits anti-inflammatory properties (Nozato et al., 2019).

ACE2 / Ang- (1–7) / MasR is a renin-angiotensin system (RAS) axis with osteoprotective effect in animals with induced postmenopausal osteoporosis. These data suggest that ACE2 is essential in maintaining bone structure. Once ACE2 has been targeted by SARS-CoV-2, the block of ACE2 may give occasion to a decrease in bone mass and joint inflammation (Abuohashish et al., 2017; Tao et al., 2020).

The listed cytokines, and especially IL-1, IL-6, and TNF-α, stimulate bone resorption both directly and indirectly through the RANKL system. In COVID-19 infection, it would be useful to measure the bone metabolism markers (CTX, P1NP, alkaline phosphatase) (Salvio et al., 2020).

From clinical observations in Whuan, China, we know that SARS-CoV-2 infection if associated with fractures has a much poorer prognosis in terms of survival rate (Mi et al., 2020).

A multicenter observational study from 13 hospitals in Spain looked at the survival rate in a pandemic in patients with a femoral neck fracture. Mortality was 30.4% in those with a positive test and 10.3% in those with a negative test for COVID-19 over a 14-day follow-up period (Muñoz Vives et al., 2020).

Decreases in bone mineral density (BMD) have been reported in previous outbreaks of SARS-CoV-1 and MERS. At the beginning of the pandemic, it was considered that the decreases in BMD are due to glucocorticosteroid therapy, so essential in fighting inflammation, but later it was analyzed as occurring independently of treatment (Orford et al., 2019; van Niekerk & Engelbrecht, 2018).

We also know from previous SARS epidemics that osteonecrosis occurs much more frequently and is closely related to glucocorticosteroid therapy. Over up to 3 years of follow-up, the frequency was 58%, the hip bones being the most often incriminated, followed by the talus, the calcaneus (Lv et al., 2009).

In addition to treatment with glucocorticosteroids, the state of hypercoagulability with an increased risk of thrombosis may also contribute to osteonecrosis.

The occurrence of the cytokine storm and especially CXCL10, IL-17, and TNF-α have a well-known role in osteoclastogenesis with decreased osteoblastogenesis by reducing proliferation and differentiation, which will ultimately lead to a reduction in BMD (Liu et al., 2017; Kotake et al., 1999; Gilbert et al., 2000; Wang et al., 2020).

Joint involvement

Arthralgia is a common symptom in viral infections. The association of arthralgias with myalgias makes it difficult to differentiate between them (Vasiliadis et al., 2021). The presence of symptoms seems to persist in most patients after the cure of the viral infection. The remaining symptoms after the acute episode are: fatigue, dyspnea, joint pain and chest pain. This will increase the need for physical and emotional rehabilitation (Mahase, 2020).

The pandemic and lockdown had a negative impact

on patients with advanced arthrosis scheduled for arthroplasties, but delayed due to the pandemic. High levels of osteoarthritis and decreased physical activity have led to increased pain scores and decreased quality of life for patients (Endstrasser et al., 2020).

Patients with arthralgia have a significantly elevated C-reactive protein (CRP) level and fever more frequently than patients without joint manifestations. However, the risk of developing pneumonia is the same, with or without arthralgia (Hoong et al., 2021).

A cohort study reported that 30% of hospitalized patients had an episode of arthralgia. This may be an independent manifestation of lung damage, with arthralgia occurring either before the viral prodrome or in time, after the lung damage has healed. The mechanism of the disease is not known, among the suspected mechanisms being the direct infection of the synovial membrane that has ACE receptors. However, the absence of the virus in the synovial fluid tends to disprove this mechanism. Another proposed mechanism is the doping of immune complexes that trigger inflammation, which is also found in other viral disorders (Hoong et al., 2021).

In another study, half of the patients developed arthralgia in a large joint, which was undetectable biologically or by imaging. A suspected mechanism is neurological or a small degree of synovitis undetectable by imaging (Griffith, 2011).

Cases of reactive arthritis have been reported, all subjects being male, with predominant damage to the lower limb, knee, ankle, metatarsal, interphalangeal joints, with a single case of shoulder and wrist. In the analysis of synovial fluid, the only pathological elements discovered were a large number of polymorphonuclear cells and a small number of mononuclear cells, being negative for rheumatoid factor (FR), anti-CCP antibodies, human leukocyte antigen (HLA B27), COVID, bacteria and other antibodies. All cases responded well to nonsteroidal anti-inflammatory or steroidal anti-inflammatory drugs (Hønge et al., 2021).

Nervous involvement

Neurological symptoms are commonly reported in patients infected with COVID-19. It affects both the CNS, manifesting by headache, dizziness, visual disturbance, crisis, drowsiness, encephalopathy, ataxia, stroke, and peripheral nerves through anosmia, dysgeusia, Guillain-Barre syndrome, Miller-Fisher syndrome, polyneuritis cranialis, axonal demyelination (Zhao et al., 2020; Machhi et al., 2020).

The ACE2 receptor is present in the neuron, astrocyte and oligodendrocyte. Expression of ACE2 was also highly concentrated in the substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb (Zubair et al., 2020). The mechanism of action is not fully elucidated, among the possible pathways being transsynaptic transfer across infected neurons, entry via the olfactory nerve, and infection of vascular endothelium or leukocyte migration across the blood-brain barrier (Chen et al., 2020).

Daia et al. (2021) analyzed people cured of COVID-19, but who still have symptoms, namely generalized fatigue, especially in the lower limbs. Patients who did not have such symptoms before and who are not familiar with neurological pathology were selected. In these patients, following a nerve conduction study (NCS), they found demyelination at the anterior tibial nerve level, supported by slight prolonged distal latency, partial or total conduction block, and rare or absent F-waves on NCS examination. Demyelination was found in a lower percentage at the level of the common fibula nerve. A small number of patients also presented demyelination at the level of the upper limb on the median and ulnar nerves (Daia et al., 2021). Guillain-Barré syndrome (GBS) is an immune-mediated inflammatory pathology of polyneuropathic demyelination. The suspected mechanism is mimetic, otherwise the virus contains epitopes similar to some components of the peripheral nerve. Activation of T and B lymphocytes will lead to the synthesis of antibodies that bind to peripheral nerve components, with the appearance of neuronal dysfunction. Zhao et al. support GBS by the disappearance of F waves associated with prolonged distal latency and slow motor conduction velocity (Zhao et al., 2020). Patients showed only motor nerve damage, without sensitive damage, the rare form in GBS, which can lead us to think of either MMN or an independent entity of peripheral nerve damage in SARS-CoV-2 infection (Daia et al., 2021).

One such case was a patient in Wuhan in January 2020 who showed signs of generalized weakness without respiratory symptoms. Following the examinations, he was diagnosed with GBS and received intravenous treatment with immunoglobulins, with a favorable response (Zhao et al., 2020).

Edward et al. objectified the onset of mononeuritis multiplex in 1 in 6 patients who required prolonged mechanical ventilation. Patients required an average of 36 days of mechanical ventilation ranging from 16 to 73 days. Nerve damage has been observed to occur after withdrawal from sedation, suggesting that the time of injury should be during ventilation. The average nerve affected in these patients is slightly above 3 (Needham et al., 2020).

Another neurological condition of the peripheral nerves observed is Bell's palsy, which appears from a few days after the diagnosis of the infection until 4 weeks after diagnosis. The mechanisms that may lead to nerve damage are direct injury, autoimmunity, and ischemia of the vasa nervorum or inflammatory demyelination. Patients responded favorably to steroid treatment (Oke et al., 2021; Lima et al., 2020).

Conclusions

1. The effects of COVID-19 infection on the musculoskeletal system were neglected at the beginning of the pandemic due to the overwhelming number of new cases when all health systems had to respond to emergencies.

2. It was later observed that COVID-19 infection causes multisystemic impairment, the musculoskeletal system being primarily involved. The consequences of the disease are multiple and affect all structures in varying proportions through a mechanism partially described so far.

3. The means of medical rehabilitation are effective and can act on this side as well. The follow-up time of patients with COVID-19 must be long-lasting because many of the musculoskeletal disorders appear late, with consequences that can cause significant disability.

Conflict of interests

Nothing to declare.

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