ORIGINAL RESEARCH

A review of Post COVID-19 musculoskeletal effects

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ABSTRACT
The novel coronavirus, SARS CoV-2, was first discovered in Wuhan, China in December 2019 and resulted in a worldwide pandemic spreading to at least 226 countries and territories with > 500 million confirmed cases, and causing > 6 million deaths.
The global pandemic of COVID -19 caused by severe acute respiratory syndrome coronavirus [SARS-CoV 2] had patients presenting with Post-COVID syndrome which refers to the presence of a variety of symptoms that range beyond the acute phase of COVID-19 infection.
These chronic sequelae diminish the individual's functional capacity. Data from the SARS pandemic of 2002 to 2004 identified muscular and bone dysfunction in moderate and severe infections. Studies have shown musculoskeletal dysfunction in some patients with COVID-19 however the exact mechanism of this has not yet been identified.
The purpose of this article is to summarise the proposed musculoskeletal effects involving skeletal muscle, bone, joint, cartilage, and tendon, following SARS CoV-2 infection and the pathophysiology related to these effects.
Keywords: SARS CoV-2, musculoskeletal, coronavirus, effects

INTRODUCTION

The novel coronavirus, SARS CoV-2, was first discovered in Wuhan, China in December 2019 and resulted in a worldwide pandemic spreading to at least 226 countries and territories with > 500 million confirmed cases, and causing > 6 million deaths. It belongs to the coronavirus family of positive sense, single-stranded RNA viruses having 6 strains among which SARS CoV-1 and SARS CoV-2, showing a high degree of genetic homology, have been known to infect humans with similar pathological responses. The symptoms vary from mild to more critical and severe cases.

Most of the infected individuals recovered completely without sequelae or consequences, however clinical studies on some of the convalesced patients showed considerable post-COVID manifestations, commonly called "Post COVID syndrome", namely, fatigue, headache, difficulty in sleeping and concentration, muscle and joint pain, and cough. Post-COVID syndrome may affect COVID-19 patients at all levels, even younger adults, children, and outpatients. There is limited literature available postulating the pathophysiology and treatment of Post COVID syndrome, hence effective management of its effects requires awareness.[1]

There is ample evidence suggesting that regular exercise presents short and long-term health benefits, preventing, delaying, and even reversing metabolic, pulmonary, cardiovascular, inflammatory, rheumatic, and musculoskeletal diseases [2] [3] [4] [5] [6] [7].Isolation of older people during COVID-19 reduced immobility which when prolonged can cause muscular myopathy and atrophy and reduce bone mineral density along with increased pro-inflammatory macrophage activity [8] [9]. This resulted in reduced functional capacity of the affected patients along with a decrease in quality of life. Only 40% of patients returned to work by 2-3 months following COVID infection. This article provides a coherent conceptual framework for understanding the pathophysiology of post-COVID-19 musculoskeletal effects to appreciate a better prognosis and treatment for the affected patients.

DISCUSSION

The receptor for SARS CoV-2 entry into the cell is ACE 2 (Angiotensin Converting Enzyme 2) using the serine protease TMPRSS 2 (Transmembrane Protease Serine 2). ACE 2 is most commonly expressed by the type 2 pneumocytes in the lungs and the expression is variable in men and women. The proteolytic cleavage of the viral S protein by the TMPRSS 2 results in the release of a fusion peptide signal which causes the mixing of human cell and viral membranes. Consequently, the viral RNA is released into the cell. Viral replication within the human host cells is followed by viral release through cell destruction. There is an inflammatory cell (macrophages) influx which leads to a release of cytokines, IFN, IL 1-β, IL 6, IL 8, IL 17, and TNF-α. This cytokine storm results in systemic manifestations and inflammation-induced respiratory epithelium damage [10].

POTENTIAL MUSCULOSKELETAL TARGETS

Back pain was the most common post-COVID musculoskeletal manifestation among fatigue, arthralgia, myalgia, and muscle weakness which have been reported as initial and common symptoms [11] [12][13][14][15][16][17]. Musculoskeletal symptoms can be observed as initial complaints of infection, even before respiratory symptoms like dry cough, sore throat, or dyspnoea set in.

Secondary analysis of human genetic sequencing data allowed the identification of expression of ACE 2 and TMPRSS 2 in musculoskeletal tissue [18].

Human skeletal muscle, endothelial cells, smooth muscle cells, pericytes, muscle stem cells, macrophages, adaptive immune cells, and myonuclei express TMPRSS 2. However, only smooth muscle cells and pericytes express ACE 2 dominantly. In the synovium, fibroblasts, monocytes, B cells, and T cells express ACE 2 and TMPRSS 2. In the articular cartilage, homeostatic chondrocyte expresses TMPRSS 2 while proliferative, hypertrophic and effector chondrocyte express ACE 2. [Table 1,3]

TABLE 1

	ACE 2	TMPRSS 2
RBC	-	-
Endothelial cell	-	+
Smooth muscle cell	+	+
Pericytes	+	+
Myonuclei	-	+
Muscle stem cells	-	+
Inflammatory Macrophages	-	+
B/T/Natural killer cells	-	+

TABLE 2

	ACE 2	TMPRSS 2
B cells	+	+
Fibroblasts	+	+
Monocytes	+	+
T cells	+	+

TABLE 3

	ACE 2	TMPRSS 2
Homeostatic cartilage	-	+
Proliferative cartilage	+	-
Hypertrophic cartilage	+	-
Effector cartilage	+	-

SARS CoV 2 has not been specifically detected in these tissues, however, these serve as potential sites for direct infection (skeletal muscle, synovium, cortical bone).

SKELETAL MUSCLE

Patients with both acute and post-acute sequelae of COVID 19 experience skeletal muscle symptoms. [18]

25% - 50% of symptomatic patients reported myalgia/muscle weakness[21]. Myositis and rhabdomyolysis are known presenting symptoms or late complications of COVID-19 patients. Myositis is the inflammation of muscle tissue caused by an injury, infection, or autoimmune disease [19]. The condition is rare and usually gets worse over time [20]. It is of two types: Polymyositis and Dermatomyositis causing progressive proximal muscle weakness. Rare cases of SARS-CoV-2 which trigger necrotizing autoimmune myositis have been published [21]. Rhabdomyolysis is the breakdown of muscle tissue that releases muscle fiber contents such as myoglobin into the bloodstream which are toxic to the kidneys. Rhabdomyolysis is

most commonly caused by a crush injury or any other injury that damages the skeletal muscle [22]. Clinical findings of myositis/rhabdomyolysis are myalgia with increased creatine phosphokinase levels, both of which are reported in COVID-19 patients.

MECHANISM OF MUSCULAR INVOLVEMENT

The first proposal is hematogenous spread and direct invasion of skeletal muscle by SARS CoV-2 using ACE 2 receptor. Alternatively, an immune-mediated mechanism secondary to cytokine storm and activation of immune cells is more widely accepted [23].

The increased cytokine levels after COVID-19 have been directly associated with decreased muscle strength. Studies performed on SARS-induced mouse models and postmortem humans suggested muscle atrophy, muscle necrosis and the presence of inflammatory infiltrate and showed that the virus had crossed the blood-brain barrier into the hypothalamus, providing knowledge about SARS-related muscle dysfunction.Electron micrograph showed myofibril disarray, and z disc streaming which disrupts force transmission.Neuronal demyelination was observed which could be responsible for the muscle weakness and fatigue complaints. [24-28]

IFN-γ, IL-1b, IL-6, IL-17, and TNF-α are associated with muscle fiber proteolysis and decreased protein synthesis[29]. IL-1b and TNF-α block the proliferation and differentiation of satellite cells which are progenitor cells and contribute to muscle fiber growth [30]. Further, IL-1b and IL-6 induce fibroblast activity in the muscle leading to fibrosis.

Increased cytokines and increased lymphocytes are seen in patients with myalgia. Increased cytokines should be cautionary against muscle damage and extremely high values may indicate a progressive myopathic process. Increased lymphocytes may cause immune cell activation and over-expression of pro-inflammatory cytokines.

Direct neuromuscular involvement of SARS CoV-2 may be associated with diaphragm dysfunction which leads to deteriorating respiratory status and dependence on mechanical ventilation. Increased ventilator use has been associated with pro-inflammatory conditions causing muscle and bone frailty. Muscle weakness in extremities is approximately double of weakness in inspiratory and expiratory muscles after 1 day of mechanical ventilation. Sarcopenia and cachexia may manifest as long-term consequences of COVID-19 [31]. Sarcopenia is muscle loss while cachexia is muscle wasting secondary to chronic illness.

Treatment regimes involving the use of corticosteroids directly induce muscle atrophy and weakness, therefore CDC has advised against corticosteroid use for COVID-19 management [32]. Other COVID-19 therapies used during the initial waves of the pandemic like hydroxychloroquine, colchicine, and specific antivirals are associated with toxic myopathies and arthralgia [33]. Frequent use of anticoagulant drugs and extended hospital stays have resulted in intramuscular hematomas and ischiosacral decubiti [34].

BONE & JOINT

ACE2 is expressed locally in the human bone marrow-derived stem or progenitor cells (BMSPCs). Published texts suggest that ACE2 is essential in maintaining bone structure[35]. Invasion of the virus leading to deficiency of ACE2 may cause decreased bone matrix.

Arthralgia as an independent symptom has been reported in 2.5% of the patients. Though osseous complications have not been fully studied, decreased Bone Mineral Density (BMD) secondary to corticosteroid use for SARS treatment is often responsible for arthralgia. A very significant finding in COVID-19 patients is hyper-coagulability of blood which along with leukocyte aggregation, and vessel inflammation impair the bone microvasculature and blood flow causing osteonecrosis(5%-58%), most common sites being the femoral head. Knee, humeral head, talus, and calcaneus were affected infrequently.

The cytokines CXCL10, IL-17, and TNF-α are known to cause osteoclastogenesis and decrease osteoblastic proliferation. This results in a net decrease in BMD. IL-1β, IL-6, and TNF-α can cause arthralgia or aggravation of osteoarthritis in some patients.

Though viral arthritis secondary to COVID-19 was reported infrequently, SARS COV-2 may aggravate inflammatory arthropathies even in patients with mild or no respiratory symptoms. [36]

CARTILAGE & TENDON

Cartilage is potentially a target though this would require viral priming and entry of SARS COV-2 in a non-cell autonomous paracrine manner.IL-1β, IL-6, and TNF-α may cause chondrolysis. A direct effect of SARS COV-2 on chondrocytes expressing both TMPRSS-2 and ACE-2 may lead to cartilage breakdown.

IL-1β, IL-17, and TNF-α can impair the normal biological activity of tenocytes and may increase inflammation in tendinopathy.

Further studies involving RNA in situ hybridization or immunohistochemistry using antibodies against viral proteins would help elucidate the presence or absence of virus in these tissues.

The treatment may involve pharmacological and non-pharmacological modalities [37]. Osteopathic manipulative treatment (OMT), with its effects on regulating the immune system, could reduce the symptoms and chronic effects of COVID-19 and increase the quality of life of the affected. OMT complements the efficacy of conventional care. A specific category of OMT techniques known as 'pump techniques' affect lymphatic circulation which is

known to decrease inflammation through cytokine regulation and inhibit macrophage activity [38]

CONCLUSION

Clinical studies and reported findings in COVID-19 patients have identified musculoskeletal involvement. The genetic and pathological similarities between SARS CoV-1 and SARS CoV-2 indicate expected short-term and long-term effects on skeletal muscle, bone, joints, cartilage, and tendon.

Decreased lymphocyte and higher D-dimer levels were reported in patients who showed aggravated musculoskeletal symptoms after COVID-19 as compared to patients whose symptoms did not change with COVID-19.

Statistical studies reported that 92.3% of COVID-19 patients reported any musculoskeletal symptom at hospitalization whereas 72.7% and 56.3% of patients reported such symptoms at two weeks and one month respectively. [39]

SARS CoV2 entry into the cell is facilitated by the ACE-2 receptor using the serine protease TMPRSS 2. The inflammatory cell influx following viral replication through cell destruction is responsible for the systemic manifestations. Musculoskeletal involvement produces a wide range of symptoms including arthralgia, myalgia, and fatigue.

The most common site for involvement is skeletal muscle while bone and joints are less frequently involved. Skeletal muscle involvement may present as muscle weakness, myositis, or rhabdomyolysis. Arthralgia and osteonecrosis were also noted with bone and joint involvement.

Studies aimed at understanding the mechanism underlying the noted symptoms are required in addition to the currently ongoing projects and reports. Further research studies are required in this field to provide new insights and for understanding the Post COVID syndrome.

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