Musculoskeletal involvement of COVID-19

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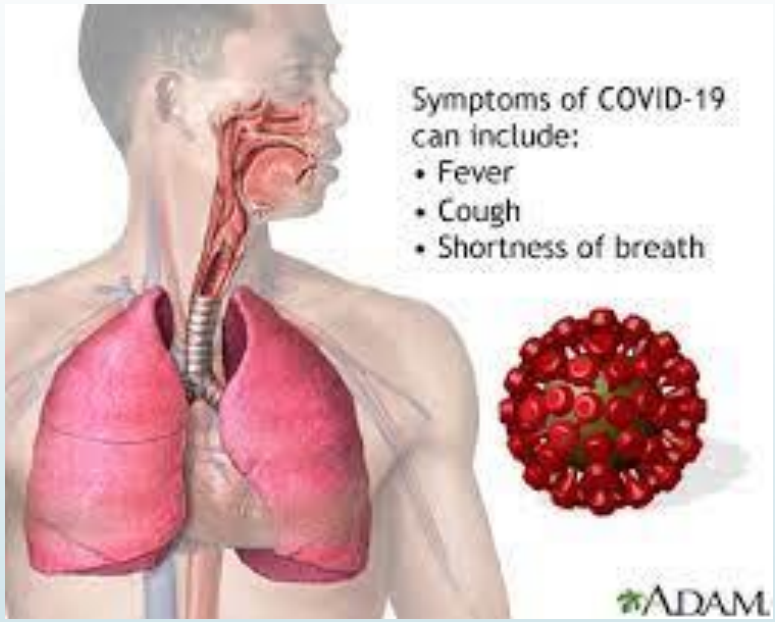
Introduction

- The Coronavirus Disease 2019 (COVID-19) caused by a novel Coronavirus type (SARS-CoV-2) has threatened the health and lives of millions of people around the world since it began in the Chinese city of Wuhan at the end of 2019
- The World Health Organization has declared the COVID-19 outbreak a global pandemic on 11 March 2020
- COVID-19 clinical features range from asymptomatic patients to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction

Con…

- An estimated 5% of COVID-19 patients have severe symptoms that require intensive care
- Older age and comorbidities such as cardiovascular disease, diabetes mellitus, and obesity are risk factors for developing severe disease.
- The most common symptoms in patients with mild to moderate clinical presentation of the condition are fever, fatigue, and dry cough, followed by other symptoms including headache, nasal congestion, sore throat, myalgia, and arthralgia



- Musculoskeletal disorders cause pain and functional disability [4–6], and their burden on individuals and society has been increasing worldwide.
- Therefore, public interest in musculoskeletal disorders during the coronavirus disease 2019 (COVID-19) pandemic should be assessed to develop effective measures for the management of musculoskeletal disorders

- The outbreak of COVID-19 has affected people's mental and physical health.
- Health anxiety means worrying and experiencing anxiety due to a perceived threat to health and is one of the most predominant psychological symptoms during the pandemic

physical activity

- Musculoskeletal symptoms are presumed to increase during the COVID-19 pandemic due to the fact that people have lost their normal daily activity patterns through the lockdown and have become less physically active
- However, the relationship between the amount of physical activity and musculoskeletal symptoms during the pandemic is unknown.

physical activity

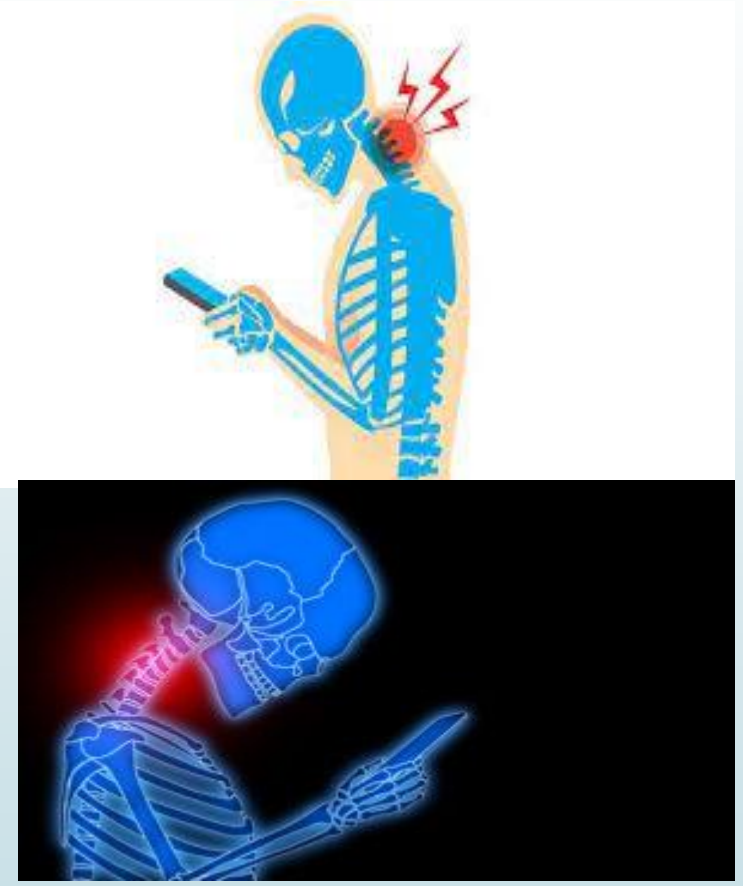
- Fallon et al. reported that the COVID-19 lockdown causes an increase in pain levels in people with chronic pain
- They also identified pain catastrophizing and self-perceived changes in physical activity as important predictors of self-perceived changes in pain
- Furthermore, Celenay et al. found that people who stayed at home during the COVID-19 pandemic have more musculoskeletal complaints than those who continued to work, suggesting that it may be due to the alterations of daily life activities with increased time spent at home and physical inactivity.

Females and severity of symptoms

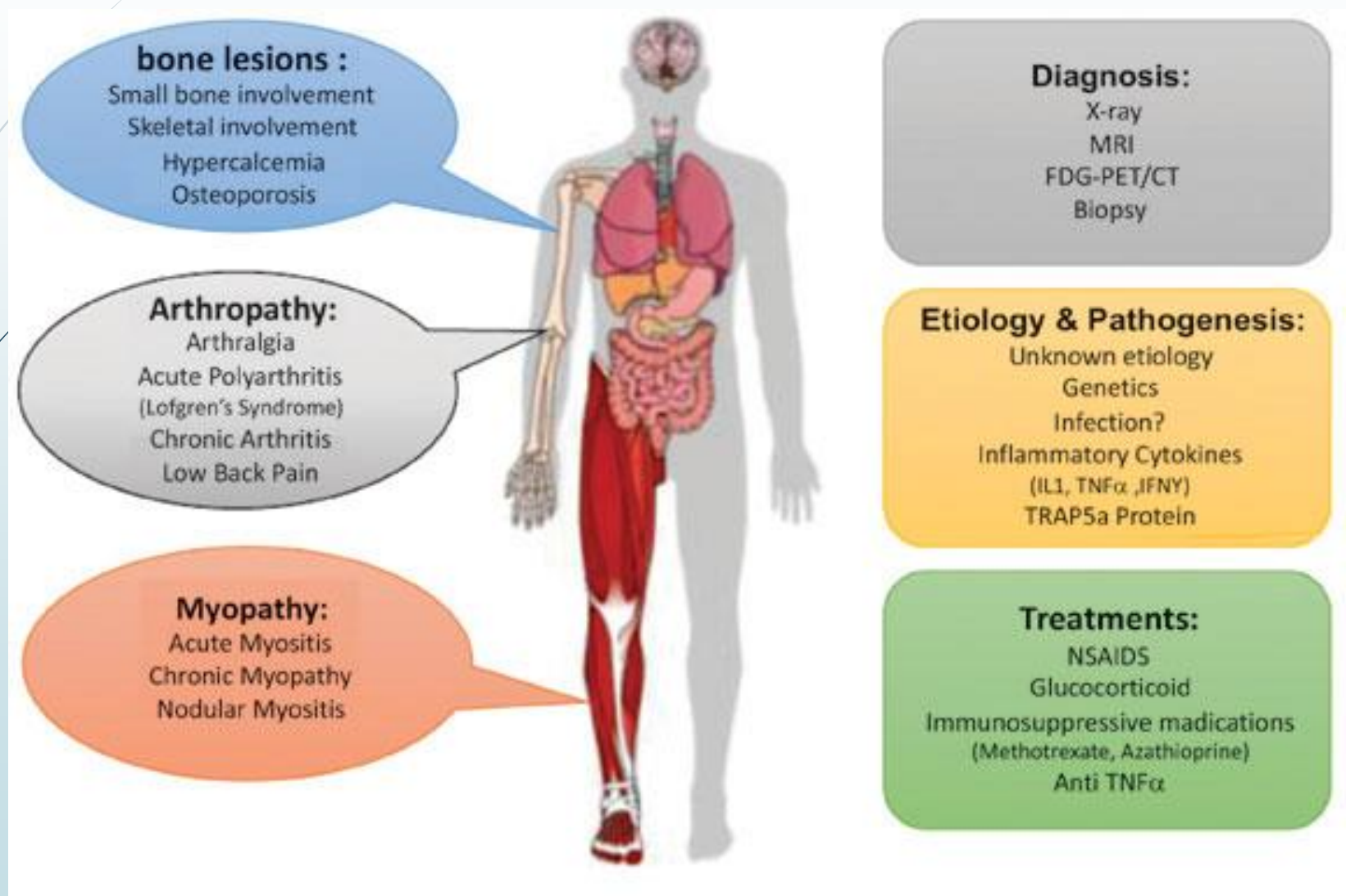
- RCT results also showed that females have more musculoskeletal symptoms than males.
- Females have been frequently reported to have a lower pain threshold and pain tolerance compared to males.
  - higher level of health anxiety in females
- Sfendla et al. reported that people who are more physically active have a lower level of anxiety than people who are insufficiently active during the COVID-19 period.

Thus, the amount of physical activity can be accepted as one of the factors related to health anxiety during the pandemic.

- Moretti et al. have suggested that working from home during the COVID-19 pandemic causes worsening of musculoskeletal problems, particularly affecting the spine
- Regarding musculoskeletal disorders, low back pain was referred by 41.2%of home workers and neck pain by 23.5% of them. Neck pain worsened in 50% of home workers. Home workers with musculoskeletal pain reported a lower job satisfaction
- Depending on our data, the home environment seems to be not adequate in the mobile worker population, with an increased risk for mental health and MSK problems, particularly affecting the spine



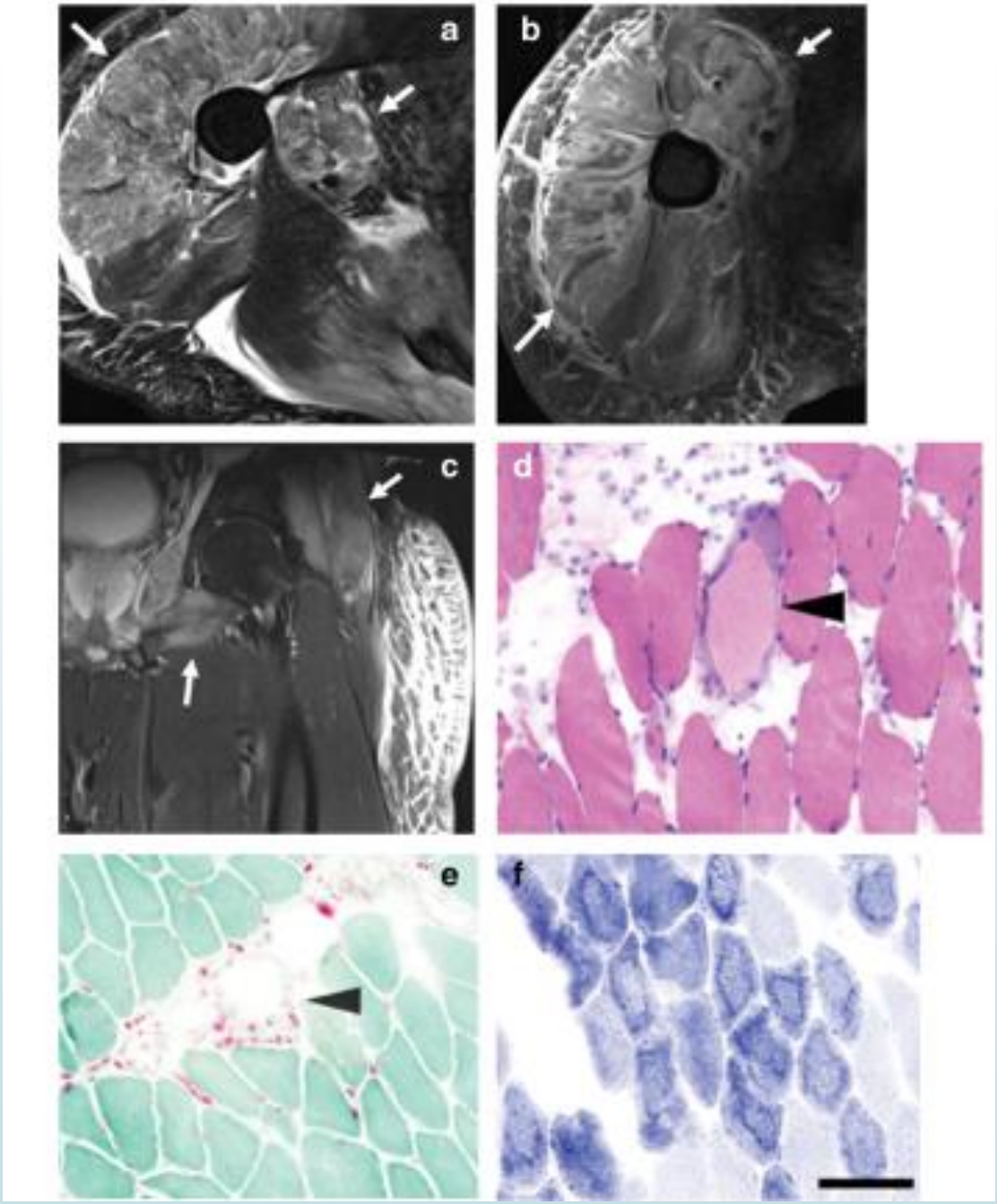
Musculoskeletal symptoms



Musculoskeletal manifestations of sarcoidosis

Muscle

- Myalgia, defined as muscle aches and pain, has been frequently reported in COVID-19 patients with a prevalence ranging from 11 to 50% in large cohort studies
- Several case reports have described myositis and rhabdomyolysis in COVID-19 patients, both as a late complication and as a presenting symptom.
- Rare cases of SARS-CoV-2 triggering necrotizing utoimmune myositis have been described
- Mechanisms of muscular involvement in COVID-19 are not fully understood
- Serum CK level elevations depend on the severity of the disease, ranging from mild to frank rhabdomyolysis.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Con…

- Myositis broadly refers to inflammation of muscles and is associated with SARS-CoV-2 as well as other viral infections such as influenza A/B, hepatitis, and HIV
- Rhabdomyolysis is a complication of myositis involving infarction of muscle (myonecrosis) and high levels of myoglobin in the blood (myoglobinemia).
- Rhabdomyolysis is a life-threatening condition that can lead to acute kidney failure, compartment syndrome, and intravascular coagulation

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- Clinical findings of myositis/rhabdomyolysis generally include myalgia/weakness and elevated creatine phosphokinase kinase levels, both of which have been reported in COVID-19 patients with myositis/rhabdomyolysis

Con…

- Electrodiagnostic studies, such as electromyography (EMG), and nerve conduction studies can be helpful to confirm a myopathic process and exclude mimickers such as motor neuron disease
- Imaging can support diagnosis and delineate sites for muscle biopsy, which is the gold standard for diagnosis
- Findings of myositis include muscle edema, identified as increased signal intensity on T2-weighted or short tau inversion recovery (STIR) sequences

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- In severe disease, areas of necrosis or loss of normal muscle architecture may be seen
- Intramuscular hemorrhage may be present, identified as T1 hyperintense signal or blooming artifact on gradient echo sequences

important

- Clinical presentation of critical illness myopathy includes symmetric and generalized weakness or acute flaccid quadriplegia.
- Critical illness myopathy is a primary myopathy with non-specific imaging findings of multifocal muscle edema and atrophy

Imaging of musculoskeletal involvement

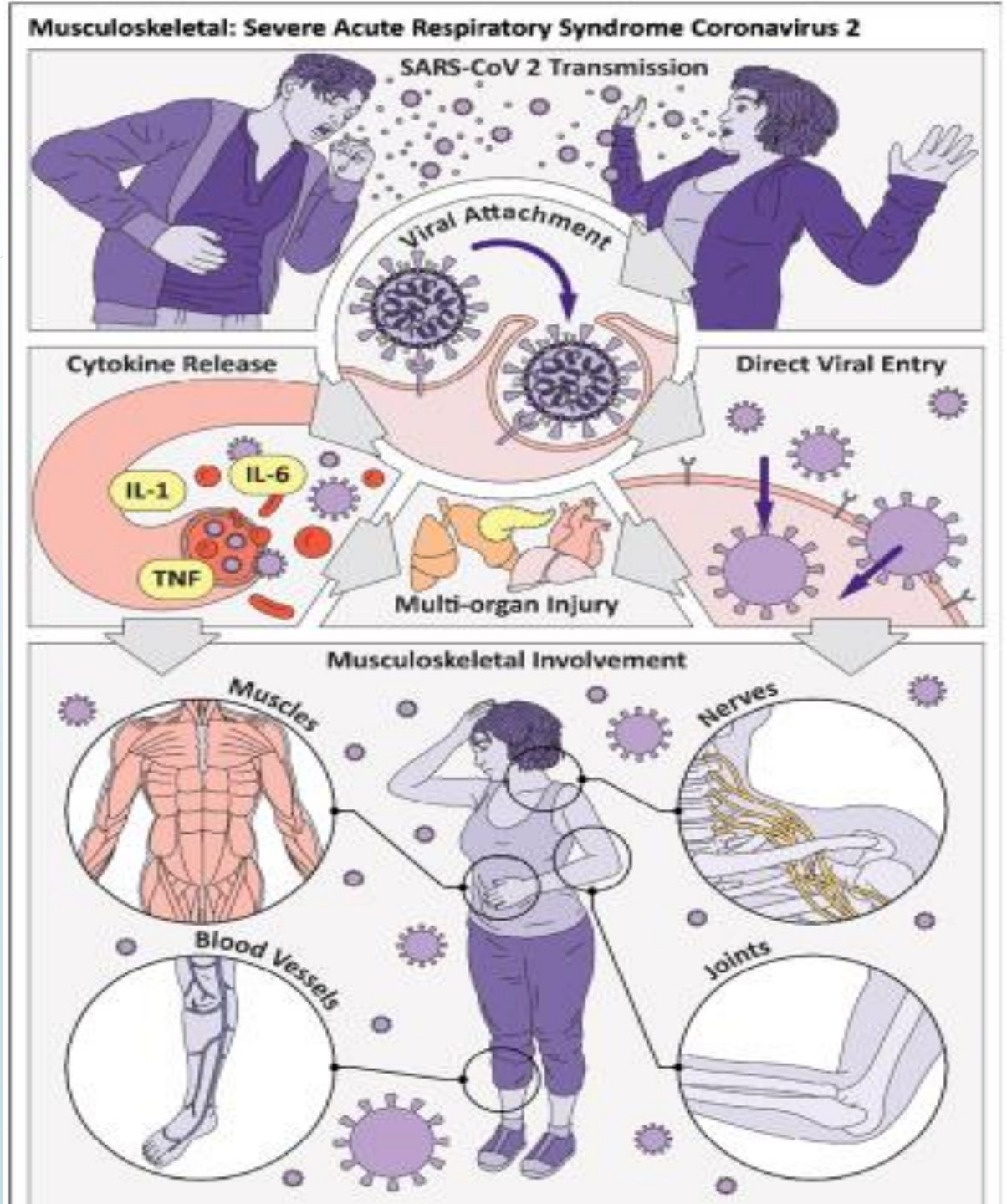
- Imaging, including magnetic resonance (MR) imaging, computed tomography (CT), and ultrasound, can support diagnosis and evaluation of musculoskeletal manifestations and iatrogenic complications of COVID-19

Table 1 Imaging of musculoskeletal involvement in COVID-19

Organ system	Imaging modalities	Imaging findings
Muscle	MRI +/− contrast	Muscle edema, necrosis
		Muscle atrophy
	Ultrasound	Diaphragm dysfunction
Nerve	MR neurography	Nerve enlargement, signal hyperintensity, loss of fascicular architecture
		+/− muscle denervation
	High-resolution ultrasound	Nerve enlargement, hypoechogenicity, loss of fascicular architecture
Joints	MRI +/− contrast	Joint effusion with enhancement, +/− erosions
	Ultrasound with Doppler	Synovitis, hyperemia
Soft tissues	MRI, CT, ultrasound	Hematomas, gangrene, "COVID toes," atypical pressure ulcers from prone positioning
Bone	Radiography, CT, MRI	Osteoporosis, osteonecrosis

Pathophysiology

- SARS-CoV-2 is an RNA virus with a viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor on human cells.
- There is high expression of the ACE2 receptor in lung epithelial cells as well as in the heart, kidney, pancreas, spleen, gastrointestinal system, bladder, cornea, and blood vessels.
- The ACE2 receptor is also found in the central and peripheral nervous systems and in skeletal muscle
- Hematogenous spread and direct invasion of skeletal muscle by SARS-CoV-2 through the ACE2 receptor have been proposed


Musculoskeletal: Severe Acute Respiratory Syndrome Coronavirus 2
SARS-CoV 2 Transmission
Viral Attachment
Cytokine Release
Direct Viral Entry
IL-1
IL-6
TNF
Multi-organ Injury
Musculoskeletal Involvement
Muscles
Nerves
Blood Vessels
Joints

Con …

- COVID-19–induced musculoskeletal manifestations can develop through direct and indirect mechanisms.
- In direct mechanisms, SARS-CoV-2 directly targets ACE2 expressed cells in the musculoskeletal system.
- Studies on ACE2 expression of the musculoskeletal system indicated skeletal muscle, synovium, and cortical bone as a potential site of direct SARS-CoV-2 infection.
- The indirect mechanism of COVID-19–induced musculoskeletal manifestations is caused by over activated immune responses and COVID-19–induced cytokine storm (mainly arising from inflammatory and/or immune response)
- Elevated levels of pro-inflammatory molecules including IFN-g, IL-1b, IL-6, IL-17, and TNF-a can directly impact skeletal muscle by muscle fibers proteolyzing and disturbing protein synthesis.
- Furthermore, corticosteroids that are used for the reduction of inflammation in COVID-19 patients can induce musculoskeletal impairments.
- Reduced bone mineral density has been also reported in patients as an adverse effect of corticosteroid which is dependent on the extent and duration of treatment with corticosteroids.

Con…

- Critical illness myopathy is typically a non-necrotizing diffuse myopathy associated with fatty degeneration of muscle fibers, fiber atrophy, and fibrosis, and may represent an antecedent to acute necrotizing myopathy.
- This is distinguishable by the extensive myonecrosis with the vacuolization and phagocytosis of muscle fibers and is related to multiple organ dysfunction. Nevertheless, these functional disabilities in the muscles can be a result of ICU-acquired muscle loss and weakness and not due to the infection.
- The limb pains are associated with the complications in their large blood vessels which lead to a mismatch between blood supply and demand.
- Therefore, any mechanism that causes ischemia can be followed by limb pain

Con…

- Ischemia can be caused by cardiopulmonary or vascular manifestations of the novel coronavirus.
- In some clinical trials performed on COVID-19 patients, lower limb pains are accompanied by the absence of dorsalis pedis, posterior tibial pulses, and initial skin marbling of the forefoot.
- These demonstrations can be caused by the thrombotic obstruction of the tibial arteries of the lower limb.
- Furthermore, myositis is another disorder in COVID-19 patients.

Diaphragm muscle dysfunction

- Diaphragm muscle dysfunction can occur in COVID-19patients secondary to critical illness myopathy, ventilator-induced diaphragm dysfunction, or phrenic nerve injury, possibly from placement of chest support devices.
- Hypothetically, direct neuromuscular involvement of the SARS-CoV-2 virus may contribute to diaphragm dysfunction

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- A recent autopsy study, in fact, found ACE2 expression in the human diaphragm and SARS-CoV-2 viral RNA in a subset of COVID-19 patients, with increased fibrosis of the diaphragm muscle and a unique myopathic phenotype compared to control ICU patients.
- Diaphragm dysfunction can lead to deteriorating respiratory status and/or difficulty in weaning from mechanical ventilation

Long-term muscular sequelae of COVID-19

- Long-term muscular sequelae of COVID-19 include
  - sarcopenia and cachexia which have been described in COVID-19 patients with prolonged illness.
  - Sarcopenia (or myopenia) is defined as muscle loss, typically associated with aging although other contributing factors include inactivity and poor nutrition
  - Cachexia entails muscle wasting secondary to chronic illness.
  - MR imaging findings of muscle atrophy, as seen in sarcopenia and cachexia, include decreased muscle size and fat infiltration

Con…

- Various chronic rheumatologic diseases triggered by SARS-CoV-2 have been reported, including systemic lupus erythematosus, dermatomyositis, Graves' disease, rheumatoid arthritis, and psoriatic spondyloarthritis
- Inflammatory arthropathies may be triggered by SARS-CoV-2 even in patients with mild or no respiratory symptoms with the acute viral infection, thereby necessitating correlation with COVID-19 testing to establish the association


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