Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19

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Abstract

Skeletal muscle-related symptoms are common in both acute coronavirus disease (Covid)-19 and post-acute sequelae of Covid-19 (PASC). In this narrative review, we discuss cellular and molecular pathways that are affected and consider these in regard to skeletal muscle involvement in other conditions, such as acute respiratory distress syndrome, critical illness myopathy, and post-viral fatigue syndrome. Patients with severe Covid-19 and PASC suffer from skeletal muscle weakness and exercise intolerance. Histological sections present muscle fibre atrophy, metabolic alterations, and immune cell infiltration. Contributing factors to weakness and fatigue in patients with severe Covid-19 include systemic inflammation, disuse, hypoxaemia, and malnutrition. These factors also contribute to post-intensive care unit (ICU) syndrome and ICU-acquired weakness and likely explain a substantial part of Covid-19-acquired weakness. The skeletal muscle weakness and exercise intolerance associated with PASC are more obscure. Direct severe acute respiratory syndrome coronavirus (SARS-CoV)-2 viral infiltration into skeletal muscle or an aberrant immune system likely contribute. Similarities between skeletal muscle alterations in PASC and chronic fatigue syndrome deserve further study. Both SARS-CoV-2-specific factors and generic consequences of acute disease likely underlie the observed skeletal muscle alterations in both acute Covid-19 and PASC.

Keywords   Covid-19; Skeletal muscle; Inflammation; Muscle wasting; Metabolism

Introduction

There is a clear heterogeneity in the clinical presentation of patients with coronavirus disease (Covid)-19.[1,2] The majority of patients with Covid-19 infections are asymptomatic or only experience mild symptoms, do not require hospitalization, and recover relatively quickly.[3] Also, the majority of those with more severe Covid-19 survive hospitalization.[4] A substantial proportion of post-Covid-19 patients, however, suffers from persistent symptoms such as fatigue and exercise intolerance.[5] Recently, this condition has been termed 'post-acute sequelae of Covid-19' (PASC). At 4–7 months following initial onset of Covid-19 in hospitalized patients, the most common symptoms reported in patients with PASC

were dyspnoea, fatigue, and muscle weakness, each seen in approximately 53–63% of patients.[6–8] These symptoms were more common in women and patients with higher disease severity of the acute Covid-19 episode, whereas dyspnoea was not explained by long-term pulmonary abnormalities.[6]

Skeletal muscle-related symptoms are common in both acute Covid-19 and PASC. These include muscle pain (myalgia), muscle weakness (mild to severe), fatigue, and exercise intolerance.[9,10] Myalgia and arthralgia are also common persistent symptoms in patients with PASC and are more notable in patients who were prone positioned during intensive care unit (ICU) admission.[11]

The high prevalence of skeletal muscle-related symptoms hints towards structural and functional alterations in skeletal muscle in patients with Covid-19.[10] Due to the heterogeneity of patients and their clinical presentations, these muscle-related symptoms may vary substantially and are likely to be multifactorial in nature. Patients with Covid-19 may develop an acute myopathy during their acute viral illness, although the myopathy itself is rarely the presenting symptom,[12,13] and muscle weakness can range from mild to severe. Furthermore, during hospitalization, patients with severe Covid-19 are susceptible to the development of an acute myopathy, known as critical illness myopathy.[14,15] Risk factors to developing critical illness myopathy include respiratory failure, severity of the underlying illness, the need for mechanical ventilation, the administration of intravenous corticosteroids or neuromuscular junction blocking agents, and sepsis, most of which are commonly encountered in hospitalized patients with Covid-19.[16,17] It remains unclear whether Covid-19-related myopathy and critical illness myopathy have a common underlying mechanism. Other risk factors such as systemic inflammation, hypoxaemia, extended periods of (forced) inactivity or bed rest, and various medications may promote or exacerbate muscle weakness, fatigue, and exercise intolerance in Covid-19 patients.[10,18–20]

In this narrative review, we focus on the skeletal muscle alterations in acute Covid-19 and PASC. We highlight key clinical findings, describe the cellular and molecular pathways that are involved, and discuss these in the light of the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak of 2003, acute respiratory distress syndrome (ARDS), pneumonitis, post-intensive care syndrome, critical illness myopathy, and post-viral fatigue syndrome. Subsequently, we discuss risk factors and confounding factors in acute Covid-19 and PASC.

Structure and function of the neuromuscular system in Covid-19

This section highlights the specific muscular alterations found in patients with Covid-19, with particular focus on hospital-ized patients with acute Covid-19, as the majority of current studies included patients that required (intensive) hospital care or were deceased.

Skeletal muscle weakness

Patients admitted to the ICU with Covid-19 show significant reductions in skeletal muscle mass and strength over the course of their hospital stay.[20] Bedridden, intensive-care patients with severe Covid-19 showed a 30% decrease in cross-sectional area of the rectus femoris, with a reduction in thickness of the anterior compartment of the quadriceps muscle of almost 20% after 10 days.[20] Knee-extensor and arm-flexor weakness was observed in 75–85% of a cohort of 41 previously hospitalized patients (40–88 years old) recovering from Covid-19.[21] These values for the Covid-19 cohort were comparable with those seen in patients with ARDS, who failed to recover completely even 5 years after initial hospitalization.[22] In hospitalized patients with Covid-19, the impairment in quadriceps strength was significantly associated with a longer hospital stay. In other cohorts, muscle strength negatively correlated with the length of stay in the ICU.[21,23] In general, hospitalized patients, particularly those that require intensive care, require a long rehabilitation process after discharge,[24] and low muscle mass is an independent risk factor for mortality.[25] It is therefore not surprising that patients with Covid-19 with pre-existing sarcopenia took twice as long to discharge and had an eight times higher mortality rate than those without sarcopenia.[26] While it remains unclear whether the SARS-CoV-2 virus directly causes muscle atrophy and weakness, muscle weakness is an evident clinical symptom in patients with Covid-19.

The Covid-19-induced muscle weakness closely resembles that seen in ICU-acquired weakness, which extends hospital stay and mortality in the short term and results in sustained physical disability in the long term.[27] Although comparative studies are needed, it is reasonable to expect that the skeletal muscle alterations in a subgroup of hospitalized patients with Covid-19 fall under this broader category of generic ICU-acquired weakness. Some of the major risk factors for intensive care-acquired muscle weakness are time spent at ICU, age, female sex, systemic inflammation, and sepsis.[28] Muscle weakness can originate from muscle atrophy, reduced specific tension (force relative to size), or both. Qualitative differences in muscle tissue (i.e. fibrosis, fat infiltration, and a selective loss of myosin) and impairments in the neuromuscular activation can contribute to a lower specific tension. The increased echogenicity in rectus femoris muscle in severe Covid-19 patients suggests that indeed qualitative tissue impairments, potentially due to fat infiltration and fibrosis, contribute to muscle weakness.[20]

The molecular mechanisms of ICU-acquired atrophy include an activation of the muscle ubiquitin-proteasome

pathway in the diaphragm and limb muscles of patients on mechanical ventilation,[29] as atrogin and muscle ring finger-1 (MuRF1) are elevated in septic ICU patients.[30] Hyperactivation of autophagy contributes to muscle loss in critical illness myopathy, as it does in cancer cachexia, sepsis, chemotherapy, disuse, and chronic obstructive pulmonary disease (COPD).[31]

Nerve function impairments in acute Covid-19

A wide spectrum of neurological complications have been described in patients with Covid-19[32–35] as well as in Middle East respiratory syndrome (MERS)-related coronavirus.[36] The reported sensory loss and paresthesia, along with the muscle weakness, are in line with an acute inflammatory sensory and motor polyradiculoneuropathy or Guillain-Barré syndrome. This syndrome is thought to be due to viral antigen mimicry resulting in an immune response in peripheral nerves ultimately leading to muscle denervation.[37]

Neuromuscular problems are common ICU-acquired complications, affecting about 40% of all patients,[38] and include a decreased muscle membrane excitability.[39] This causes a prolonged duration of the compound muscle action potential (CMAP) and slowing of motor conduction velocities.[39] Prolonged CMAP duration is one of the most characteristic indicators of critical illness myopathy.[39] Decreased muscle membrane excitability, slowing of nerve conduction velocities, and axonal degeneration directly impact skeletal muscle activation, and thus function.[40] This reduction in the ability of maximal voluntary activation causes muscle weakness independent from a loss of muscle mass. Molecular pathways of axonal degeneration in critical illness remain to be clarified, but pro-inflammatory and neurotoxic mediators produced through nuclear factor-κB (NF-κB)-regulated inflammation signalling have been implicated.[40] As such, it is likely that peripheral nerve damage contributes to a lower voluntary muscle activation in patients with Covid-19.

Muscle histopathologic alterations

Data on histopathologic alterations in patients with Covid-19 or PASC are scarce. An unpublished case from a middle-aged female patient with Covid-19-related critical illness myopathy, but no other comorbidities, is presented in *Figure* 1. The histopathological equivalent of cell death is the presence of necrotic fibres (*Figure* 1A). Necrosis results from toxic, inflammatory or mechanical injury, and infiltrating immune cells (mainly macrophages) clean up the remaining debris. Muscle fibre regeneration, and atrophy (*Figure* 1A + 1B), disruption in sarcomeric ultrastructure, and myosin loss (myosinolysis; *Figure* 1C and 1D) are seen in this patient with Covid-19. A selective loss of myosin directly impairs

crossbridge cycling, force production, and specific tension. These observations resemble those seen in critical illness myopathy,[41–44] and are cellular explanations of muscle weakness in patients with Covid-19. Skeletal muscle from deceased patients following the 2003 outbreak of SARS-CoV-related pneumonitis also showed a heterogeneous presentation of myofibre necrosis, muscle atrophy, myofibrillar disarray, and loss of Z disk organization.[45] Circulating creatine kinase levels are classically elevated in Covid-19 up to levels comparable with those seen in rhabdomyolysis,[46] indicative of rapid skeletal muscle breakdown. Activation of the ubiquitin-proteasome pathway and calpain activation have been suggested as possible contributors to the observed proteolysis and atrophy in critically ill patients,[47] but it is unclear if Covid-19 can also activate these pathways independently.[48]

A comprehensive histopathological, virological, immunological, and ultrastructural study of skeletal muscle samples from people who died of severe Covid-19 showed substantial infiltration of leukocytes, T-cells, and natural killer cells compared with critically-ill patients without Covid-19.[46] This suggests a clear contribution of immune cell involvement in severe Covid-19.

We provide evidence of the occurrence of internalized nuclei in a patient with Covid-19 (*Figure* 1A). Indeed, signs of degenerating muscle fibres were more frequent in autopsy material from deceased Covid-19 patients.[46] Internalized nuclei are a histological indication that muscle regeneration has occurred and are seen in critical illness myopathy[49] and COPD.[50] It is likely that regeneration and repair of injured cells are required to fully recover from Covid-19-related muscle alterations.

An ultrastructural analysis of capillaries showed thickening and multiple layers of basement membranes in patients who died of Covid-19.[46] Endothelial cells frequently had swollen mitochondria and a granular appearance of cytoplasm with numerous ribosomes, indicative of ongoing regenerative processes,[46] which has been previously observed in severe acute respiratory syndrome (SARS).[51] These observations confirm a regenerative process after a primary injury in acute Covid-19. Despite these observations, it remains unknown whether the skeletal muscle regenerative capacity is impaired in Covid-19, as seen in other diseases such as COPD.[50]

Fibrosis

Pulmonary fibrosis is an important clinical observation in patients with severe Covid-19 and is strongly associated with dysregulation of the transforming growth factor β (TGF-β) pathway following SARS-CoV-2 infection.[52] Members of the TGF-β pathway have also been implicated in skeletal muscle fibrosis.[53] Autopsies from 26 patients with Covid-19 showed an increased expression of angiotensin I-converting enzyme 2 (ACE2) and genes involved in fibrosis, as well as a
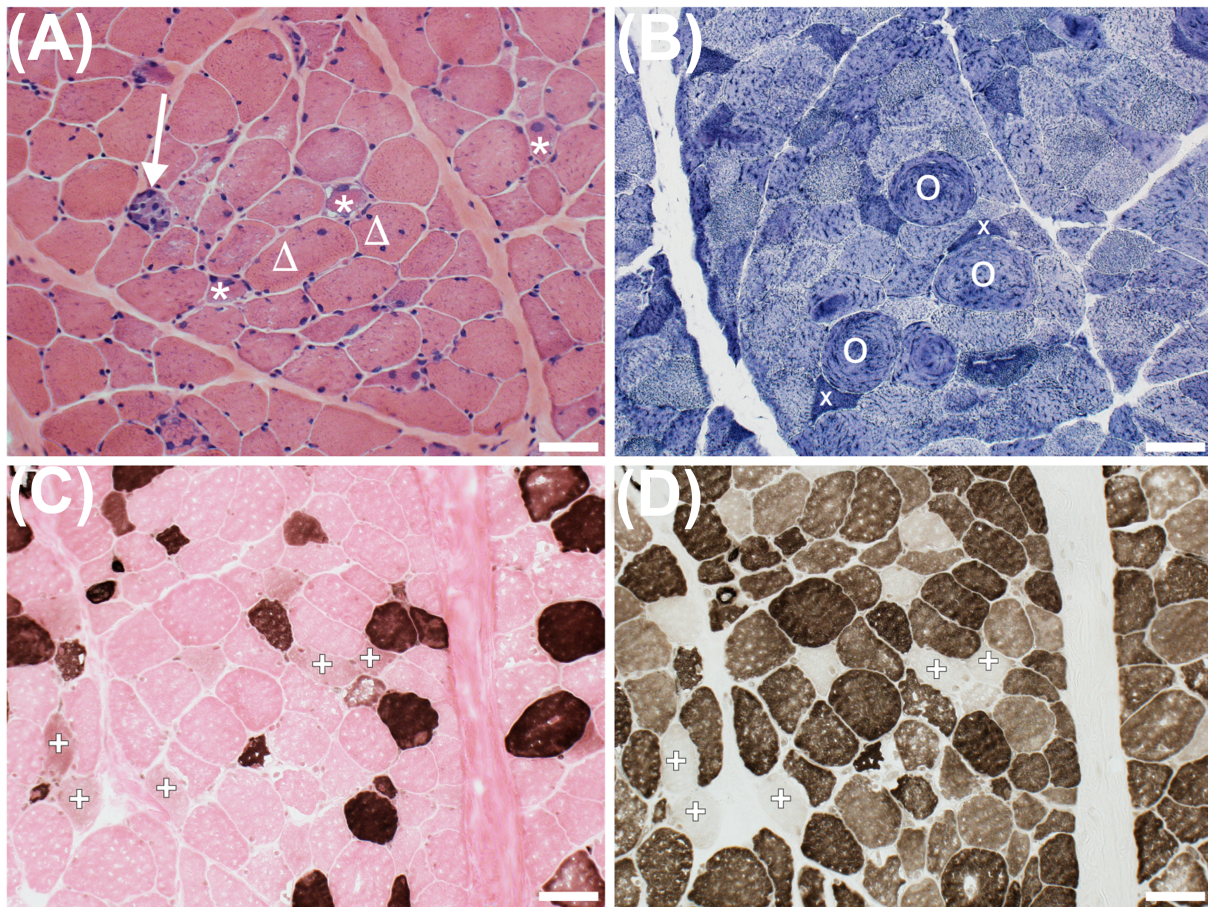
Figure 1 Frozen sections of the vastus lateralis from a young female patient hospitalized with Covid-19. Haematoxylin and eosin stain (*A*) shows a necrotic fibre replaced by macrophages (arrow), regenerating fibres (stars), one of which has subsarcolemmal vacuoles, and fibres with internalized nuclei (triangles). NADH-reacted section (*B*) shows atrophic angulated fibres (x) and a disrupted mitochondrial network (O). ATPase-reacted sections show type I fibres (dark at pH 4.3; *C*). At pH 9.4 (*D*), both type I and type II fibres are stained. Failed staining indicates the absence of functional myosin ATPase, indicative of myosinolysis (+; *C*, *D*). Scale bar = 50 μm.

two-fold higher degree of fibrosis in the diaphragm muscle, compared with ICU patients without Covid-19.[29] This fibrosis contributes to a lower specific force generating capacity of the diaphragm and possibly to dyspnoea.[29] Whether similar results are observed in limb skeletal muscles in patients with Covid-19 is currently unknown. Patients recovering from critical illness myopathy have a distinct gene expression signature where genes involved in skeletal muscle regeneration and extracellular matrix deposition are altered, contributing to the development of fibrosis.[27] This may be an important factor to understand the persistent muscle weakness in patients with PASC.

Exercise intolerance and metabolic alterations

Daily activities require not only an adequate skeletal muscle mass to produce force and power but also an optimal metabolic capacity to sustain function. As fatigue and exercise in-tolerance are common clinical symptoms in patients with Covid-19 and PASC, it is possible that metabolic function of the skeletal muscle is impaired.[54] Post-Covid-19 patients who had been mechanically ventilated for a median of 13 days showed poor cardiorespiratory fitness during clinical rehabilitation, with peak oxygen uptake corresponding to ~50% of predicted values.[55] After 3 months post-hospital dis-charge, recovering patients with Covid-19 were primarily lim-ited by reduced muscle mass, low oxidative capacity or both, rather than by a cardiac or ventilatory exercise limitation.[55]

The ACE2 is generally regarded as the host cell entry point of SARS-CoV-2.[56] Because ACE2 is expressed in endothelial cells, endothelial dysfunction has been implicated in the pathophysiology of Covid-19.[57] SARS-CoV-2-infected endo-thelial cells lead to vascular inflammation and increased permeability, ultimately culminating in a pro-coagulant, pro-inflammatory, and pro-oxidant condition that contributes to endothelial injury and reduces systemic perfusion and oxygen delivery.[58] Indeed, skeletal muscle flow-mediated dilation

during exercise is reduced in young adults with Covid-19 indicating a lower vascular function and a higher arterial stiffness compared with healthy controls,[59] even in a case study of a young pre-symptomatic Covid-19 patient.[60] Autopsy material from patients with SARS showed oedema and infiltration of monocytes and lymphocytes in vessel walls and the circumference of small veins and arteries in striated muscles in the lower limbs.[51]

Mitochondrial dysfunction is not well studied in patients with Covid-19 or PASC. A lower ADP-stimulated mitochondrial respiration and an attenuated sensitivity to ADP have been observed in a young Covid-19 patient before symptoms developed, suggestive of early alterations in skeletal mitochondrial function and substrate utilization.[60] Our example from *Figure* 1 also shows a disrupted mitochondrial network (*Figure* 1B), but it is unclear if mitochondrial density and respiration are altered.

Indirect evidence supports the presence of mitochondrial stress in patients with Covid-19. Growth differentiation factor 15 (GDF15) is released from skeletal muscle upon activation of the mitochondrial unfolded protein response, which is activated upon mitochondrial proteotoxic stress.[61] Circulating GDF15 concentrations were elevated in ~80% of patients hospitalized with Covid-19, compared with age-stratified healthy individuals, and higher concentrations were associated with detectable SARS-CoV-2 viremia, hypoxaemia, soluble ACE2 levels, and a higher risk for mortality and cardiovascular disease.[62] The source of GDF15 in Covid-19 is currently unknown. Release of the myokine GDF15 has been associated with skeletal muscle bioenergetic dysfunction in older people with sarcopenia[63] and sepsis.[64] Plasma GDF15 levels and gene expression in the skeletal muscle are also elevated in patients with intensive care-acquired weakness.[65] GDF15 acts to increase mitochondrial function, fatty acid oxidation, and insulin sensitivity and can also reduce food intake.[61] How GDF15 contributes to skeletal muscle dysfunction and other symptoms in patients with Covid-19 warrants further study.

Mitochondrial dysfunction and metabolic alterations are typically observed in patients with critical illness myopathy.[66] Suppression of fatty acid oxidation and NADH-linked (mitochondrial complex I-supported) respiration occur within days of admission to the ICU.[67] Sepsis triggers profound long-lasting ultrastructural defects in skeletal muscle mitochondria.[68,69] Critical illness is also associated with the loss of mitochondrial complex subunits and lower expression of peroxisome-proliferator activated receptor gamma co-activator (PGC)-1α,[70] suggesting impaired mitochondrial biogenesis. Mitochondrial dysfunction in critical illness myopathy[69] alters the cellular ATP/AMP balance and activates AMPK, which subsequently enhances the transcriptional activity of FoxO3 to induce muscle atrophy.[71] Similarly, alterations in the molecular machinery of mitochondrial dynamics (increasing fission and decreasing fusion) contribute to muscle atrophy.[72]

Recovery from critical illness is strongly associated with restoration of oxidative phosphorylation[67] and the activation of mitochondrial biogenesis,[70] with eventual survivors showing higher intramuscular ATP content than non-survivors.[69] Low muscle mitochondrial content in ICU survivors contributes to long-term weakness.[73] Whether more subtle alterations in oxidative phosphorylation, metabolic flexibility, or mitochondrial redox homeostasis persist in Covid-19 remains to be determined.

Factors contributing to muscle weakness and exercise intolerance in patients with Covid-19

The cause of the exercise intolerance and muscle atrophy seen in patients with Covid-19 and PASC is likely multifactorial. While it is clear that multiple comorbidities exacerbate Covid-19 disease severity and symptoms,[74,75] Covid-19 might act as a second hit, exacerbating muscle weakness and exercise intolerance. Contributing factors are probably similar to those seen in other chronic diseases, critical illness myopathy, and ageing. We describe the most widely acknowledged factors here, namely, systemic inflammation, enforced physical inactivity or disuse, viral infiltration, hypoxaemia, malnutrition, and certain medications (*Figure* 2). Increasing evidence shows that not all patients with PASC were hospitalized during the acute infection.[76] This suggests that other factors than those associated with critical illness may contribute to muscle weakness and exercise intolerance.

Systemic inflammation

Systemic inflammation plays a critical role in Covid-19 morbidity and disease progression.[77,78] Blood plasma levels of C-reactive protein (CRP), interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-2 receptor, soluble tumour necrosis factor receptor-1 (sTNFR1), and tumour necrosis factor-α (TNF-α) were higher in severe cases of Covid-19 compared with those showing mild symptoms.[79,80] These increased levels of pro-inflammatory mediators cause a so-called 'cytokine storm', contributing to excessive and uncontrolled inflammation.[78] The inflammatory profile of patients with severe Covid-19 is different to other inflammatory muscle wasting conditions seen in, for instance, diabetes, cancer, or COPD,[75,81–83] likely because of the viral nature of the disease. Although the link between systemic inflammation and muscle wasting has been widely studied in other diseases and conditions,[81,82,84] the link between circulating cytokines, muscle wasting and altered metabolism has not yet been made in patients with Covid-19. It is, however, likely that the cytokine storm of pro-inflammatory mediators plays an important role in the development of skeletal muscle
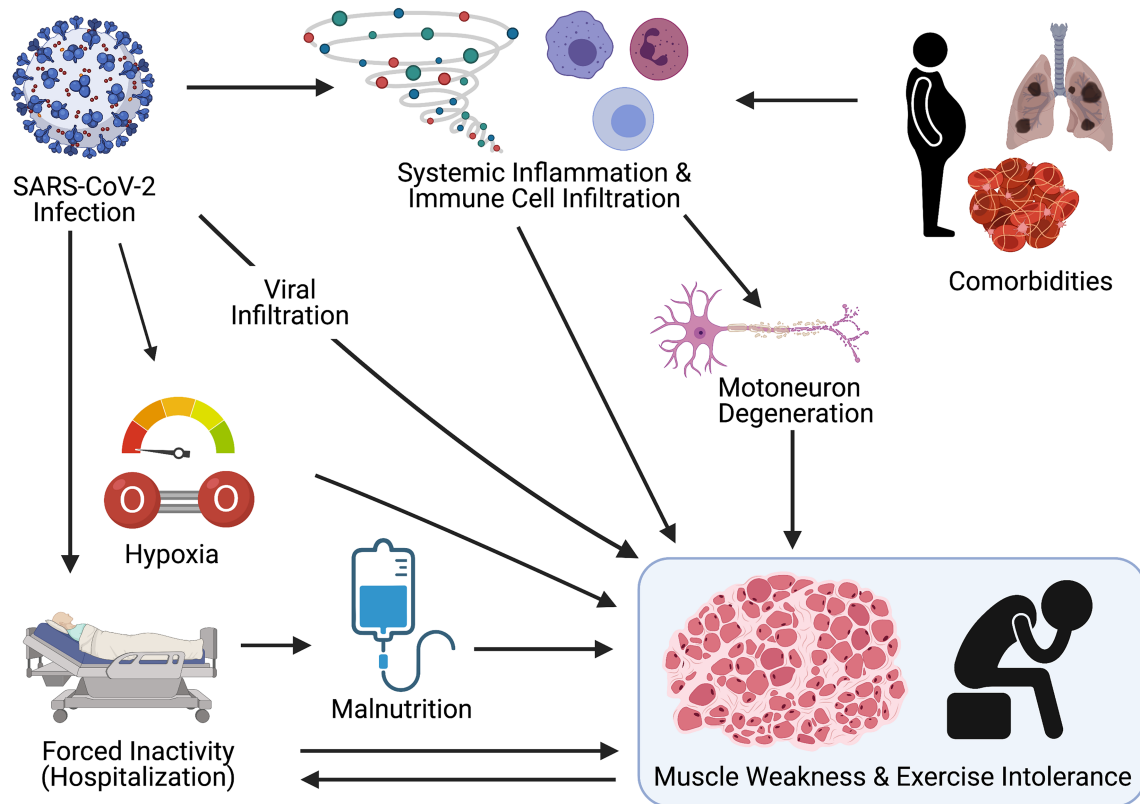
Figure 2 A graphical overview of the factors that contribute to muscle weakness and fatigue in patients with Covid-19. Severe SARS-CoV-2 infection is characterized by a dysregulated host response that can directly affect neuronal function and various inflammatory cytokines and immune cells contributing to muscle atrophy. The concomitant physical inactivity and, in some cases, hypoxaemia and malnutrition are additional factors that likely contribute to alterations in skeletal muscle structure and function. Impaired muscle weakness and exercise intolerance lead to further inactivity at vicious cycle.

atrophy and altered metabolic function in acute patients with Covid-19.

Interleukin-6 has been shown to be the best early biomarker for disease severity, followed by CRP, IL-10, IL-8, and IL-1β.[80,85] Results from patients with severe SARS and MERS have suggested that elevated levels of IL-6 are associated with long-term dependency on mechanical ventilation—likely through disease severity—and may underpin a mechanistic link to the poor clinical outcome of patients with severe Covid-19 after a prolonged stay at the ICU.[86] IL-6, which is markedly elevated in patients with Covid-19, has pleiotropic pro-inflammatory effects.[78] Elevated levels of IL-6 in skeletal muscle promote both uptake and oxidation of glucose and fat oxidation and alter insulin signalling.[87] Further, it has been suggested that IL-6 may acutely alter brain serotonergic function and motor neuron activation, reducing exercise capacity in healthy athletes, independent of other contributing factors.[88]

Systemic TNF-α infusion in healthy volunteers increased protein breakdown and inhibited muscle protein synthesis.[89] Activation of TNF-α receptors induce the NF-κB pathway, regulating expression of the muscle-specific ubiquitin ligase

MuRF-1,[30,82,90] which is involved in protein breakdown. NF-κB also lowers the skeletal muscle regenerative potential by inhibition of satellite cell activation.[30,90] TNF-α induces an NF-κB-dependent reduction in muscle oxidative capacity and transcription of regulators of mitochondrial biogenesis.[91] Lastly, NF-κB contributes to a loss of motoneuron excitation by inducing axonal degradation.[92]

C-reactive protein (CRP) can induce cellular apoptosis, phagocytosis, and lower muscle protein synthesis,[84] and CRP levels correlate with Covid-19-related cachexia.[48] Because CRP does not consistently go back to pre-infection levels 3 months after infection in patients with Covid-19,[5] this may have implications for understanding PASC.

Other, less well-studied cytokines that are elevated in Covid-19 also promote muscle atrophy, metabolic alterations, and neural dysfunction, such as IL-2 receptor.[40] Further research is clearly needed to confirm which inflammatory factors contribute to muscle wasting and dysfunction in patients with Covid-19 and PASC and may provide further mechanistic insight in the cellular and molecular pathways leading to skeletal muscle alterations in Covid-19.

Viral infiltration

Deceased patients with Covid-19 show more myositis in skeletal muscle than patients dying without Covid-19.[29,46] However, while a recent case report described the detection of viral particles in the skeletal muscle 5 weeks following the infection,[93] in a study of autopsy material from deceased patients with Covid-19, the detection of viral load was low or negative in most skeletal and cardiac muscles, probably due to circulating viral RNA rather than genuine infection of myocytes.[46] Nevertheless, a direct cytotoxic effect of viral particles on the skeletal muscle cannot be excluded. Viral particles were also found in diaphragm muscle of deceased patients with severe Covid-19,[29] and post mortem examinations of patients who succumbed to SARS in 2005 showed the presence of viral particles in atrophic skeletal muscle fibres.[45]

While it has been unclear whether viral infiltration is a contributing factor for skeletal muscle adaptations, viral infection in general is known to modulate mitochondrial function and alter gene expression levels of the host cell.[94] Different viruses affect mitochondrial dynamics through mitochondrial fusion or fission proteins and can induce mitophagy to clear damaged mitochondria to enhance cell survival and viral persistence, which is associated with physiological alterations such as oxidative stress, hypoxia, and dysregulated calcium homeostasis.[94,95] Clearly, more fundamental and clinical work is required to better understand viral infiltration of skeletal muscle and the possible functional consequences.

Muscle disuse

Disuse presents a major risk factor for patients with severe Covid-19 who require intensive care and mechanical ventilation.[20] Physical inactivity or (forced) disuse alters muscle contractile properties and metabolic health, leading to further physical inactivity and a vicious cycle. Low physical activity also significantly increases the risk of hospitalization, ICU admission, and mortality.[96]

de Andrade-Junior et al.[20] observed a ~30% reduction in rectus femoris cross-sectional area in patients with severe Covid-19 after ~10 days, which is larger than seen after disuse only. During disuse, muscle atrophy appears rapidly and in a non-linear manner, with a decline in muscle mass of 5% after short-term (10 days) and up to ~20% after long-term disuse (6 weeks).[97] This disuse-related loss of muscle mass and size accounted for ~80% of a decrease in strength of the knee extensor muscles, with the remaining 20% being due to qualitative alterations, such as a lower specific tension.[97] A lower force generating capacity and power is largely attributable to a loss of contractile material due to a decrease in the cross-sectional area of single muscle fibres.[19,97] It is particularly the fast-twitch, type II muscle fibres that show more

atrophy.[30] Because type II fibres produce up to five times more power than type I fibres,[98] this specific type II fibre atrophy results in larger declines in power, thus impacting activities of daily living more than a loss of strength *per se*. Type II atrophy or a lower specific tension are not yet reported in patients with Covid-19 but are described in ICU-acquired weakness.[99]

Not only does disuse cause a loss of muscle mass and strength, disuse also induces alterations in metabolism that ultimately result in increased fatigability, exercise intolerance, and lower VO_{2max}.[100,101] Short-term bed rest resulted in impairments in peripheral oxygen delivery and altered metabolic pathways upstream of mitochondrial respiration,[102] but the location and cause of these are unknown. A lower mitochondrial density and oxidative phosphorylation capacity have been observed following prolonged physical inactivity.[101] Disuse-induced changes in skeletal muscle mitochondrial morphology, such as mitochondrial fission, alterations in transcription, translation and import of mitochondrial proteins, as well as changes in membrane lipid profiles, reactive oxygen species emission, and impaired Ca^{2+} handling can underlie the lower oxidative phosphorylation capacity.[101]

Hypoxaemia

Pulmonary abnormalities are present in virtually all patients with severe Covid-19, as hypoxia is a criterion for marking Covid-19 as severe. Hypoxia poses a challenge for tissue oxygen delivery, and common features of the human response to hypoxia include weight loss, muscle wasting, and tissue metabolic alterations.[103] The molecular response to hypoxia is primarily initiated by activation of the hypoxia-inducible factor (HIF) family of transcription factors and associated regulatory proteins, which orchestrate angiogenesis and erythropoiesis as means to combat tissue hypoxia.[104] Stabilization of HIF1α activates the glycolysis[104] and suppresses oxidative metabolism.[105] It has been postulated that either tissue hypoxia or oxidative stress, and the consequent downstream activation of HIF signalling, might explain the metabolic responses reported in muscle samples from ICU patients and that this pathway might therefore be a novel target for therapeutic intervention.[106] There has been intense speculation on the possible roles played by HIF pathway activation in the pathogenesis of Covid-19,[107,108] and these hypotheses warrant further investigation.

Malnutrition

Proteins and amino acids are important substrates for muscle build-up and maintenance. As such, appropriate nutrition of patients with acute Covid-19 is required. A multicentre study

in the Netherlands revealed a high prevalence of malnutrition in patients with Covid-19.[109] While 67% of patients with Covid-19 were overweight, 36% were found to be malnourished at hospital admission. One in five patients (and more than one-third of ICU patients) showed serious acute weight loss of more than 5 kg during hospitalization. In total, 73% of patients were at high risk of developing sarcopenia. Contributing factors to this high incidence of malnutrition were the high prevalence of nutritional complaints, including loss of appetite (58%), feeling of being full (49%), loss and change of taste (both 33%), and loss of smell (27%). Notably, just 7% of patients did not experience any nutritional complaint. Because nutritional abnormalities may persist long after discharge, dietary counselling should be considered in hospitalized patients with Covid-19. Although it is less clear how malnutrition affects Covid-19 outcome and recovery, it is clear that nutritional complaints in patients with Covid-19 contribute to the weight loss observed during the acute phase of the infection.[110]

Adverse effects of medication

Several medications used in the management of patients with acute Covid-19 are known to have side effects on skeletal muscle structure and function. Chloroquine and its derivative hydroxychloroquine have been used in the first year of the Covid-19 pandemic. Its use can lead to myopathy, characterized by the accumulation of autophagic vacuoles with abnormally increased acid phosphatase (lysosomal enzyme) reactivity, and detection of myeloid or curvilinear bodies.[111] In patients with Covid-19 admitted to the ICU, correlations between hydrocortisone dose with handgrip strength and walking distance were indicative of possible links between medication and skeletal muscle function.[20] The absence of a correlation between hydrocortisone dose with rectus femoris cross-sectional area, thickness of the anterior compartment of the quadriceps muscle, and echogenicity, however, suggests that confounding factors such as disease severity, duration at the ICU, and other factors may play a more important role.

Skeletal muscle adaptations in patients with post-acute sequelae of SARS-CoV-2

Persisting skeletal muscle-related symptoms may exist throughout Covid-19 severity grades. Classically, critical illness myopathy is only seen in ICU-admitted patients, but also non-admitted patients with mild disease show low exercise capacity and low fat-free mass index.[5] Symptoms in patients with PASC are remarkably similar to those seen with (post-viral) chronic fatigue syndrome (CFS), including profound fatigue, sleep disturbances, neurocognitive changes, and post-exertional malaise.[112] CFS, or myalgic encephalomyelitis (ME), is a debilitating disease of unknown aetiology or therapy. Viral infections are sometimes mentioned as trigger. A more pronounced immune response to exercise and altered muscle metabolic function are evident in CFS/ME, with a larger reliance on glycolysis for energy production.[113] Because exercise intolerance and muscle weakness are complex phenomena, with interaction between physical and psychological factors,[6,11] it is currently unknown what the possible mechanisms are that can explain these symptoms in patients with PASC. Likely, other mechanisms than those traditionally described above are involved, but no systematic study has been published yet. It is speculated that hypoxia, malnutrition, and medication may play a smaller role, and other factors such as low-grade systemic inflammation, physical inactivity, persisting viral load, and possibly specific genotypes (such as higher skeletal muscle ACE protein content in women[114]) might play important roles.

Improving skeletal muscle function after Covid-19

There is not yet a consensus on optimal management strategies to improve fatigue and exercise tolerance in patients with acute Covid-19 and PASC. Detailed clinical recommendations for hospital-based physical therapists managing patients with Covid-19 have been published,[115,116] but recommendations for exercise therapy are still suboptimal. Rehabilitation, in the form of regular physical exercise, has proven to be effective in avoiding and improving the debilitating effects of critical illness myopathy. Immediate ambulation in ICU-admitted patients has proven to be feasible and results in positive effects.[117,118] Recent work has highlighted the potential effectiveness of neuromuscular electrical stimulation on the recovery of ICU-admitted patients with Covid-19.[119]

Physical therapy after acute Covid-19 infection may be beneficial in the respiratory and physical rehabilitation of patients with Covid-19. Physical exercise reduces local and systemic inflammation and can induce whole-body metabolic alterations, mainly induced by various myokines.[82,120] Symptoms of under-strain and over-strain should, however, be closely monitored in both ICU and non-ICU Covid-19 patients. Particularly in patients with PASC, post-exertional malaise is a complicating factor for optimizing exercise therapy. Clearly, a better clinical and fundamental understanding of post-exertional malaise will provide important new avenues for a more optimal, personalized rehabilitation process.

Conclusions

Muscle weakness and exercise intolerance are key symptoms of patients with acute Covid-19 and PASC. Our current evidence base suggests that reduced force generating capacity, decreased neural activation, fibre atrophy, necrosis, fibrosis, and alterations in blood flow and metabolic function may underlie these symptoms. Contributing factors will vary between patients, but likely include systemic inflammation, viral infection, and (forced) inactivity. Comorbidities, malnutrition, hypoxaemia, and certain medications can worsen skeletal muscle atrophy and metabolic alterations in some (hospitalized) patients. The observation that a significant subgroup of patients reports clinical symptoms of exercise intolerance and muscle weakness for up to a year post-infection suggests this to be a multifactorial problem. Clearly, future studies across larger cohorts and from different genetic backgrounds are required to completely disentangle the molecular signature of Covid-19-related skeletal muscle alterations and its pathogenicity. Tailored interventions based on a more in-depth, fundamental understanding of skeletal muscle alterations and the underlying determinants are needed in order to attenuate clinical symptoms and improve quality of life in patients with acute Covid-19 and PASC.

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Conflict of interest

Madu N. Soares, Moritz Eggelbusch, Elie Naddaf, Karin H. L. Gerrits, Marike van der Schaaf, Bram van den Borst, W. Joost Wiersinga, Michele van Vugt, Peter J. M. Weijs, Andrew J. Murray, and Rob C. I. Wüst declare that they have no conflict of interest.

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