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Opinion

Skeletal muscle adaptations and post-exertional malaise in long COVID

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When acute SARS-CoV-2 infections cause symptoms that persist longer than 3 months, this condition is termed long COVID. Symptoms experienced by patients often include myalgia, fatigue, brain fog, cognitive impairments, and post-exertional malaise (PEM), which is the worsening of symptoms following mental or physical exertion. There is little consensus on the pathophysiology of exercise-induced PEM and skeletal-muscle-related symptoms. In this opinion article we highlight intrinsic mitochondrial dysfunction, endothelial abnormalities, and a muscle fiber type shift towards a more glycolytic phenotype as main contributors to the reduced exercise capacity in long COVID. The mechanistic trigger for physical exercise to induce PEM is unknown, but rapid skeletal muscle tissue damage and intramuscular infiltration of immune cells contribute to PEM-related symptoms.

Highlights

Long COVID occurs when symptoms persist for more than 3 months after acute SARS-CoV-2 infection. Symptoms include fatigue, brain fog, myalgia, and post-exertional malaise (PEM), which worsens with physical, mental, or cognitive exertion.

Long COVID shares many characteristics with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), particularly PEM, which is necessary for ME/CFS diagnosis.

Long COVID is associated with intrinsic skeletal muscle mitochondrial dysfunction, endothelial abnormalities, and a shift towards more glycolytic muscle fibers, which contribute to a lower exercise capacity.

Several potential mechanisms may explain skeletal muscle abnormalities in long COVID, including local hypoxia, deconditioning, autoimmunity, electrophysiological changes, and central fatigue.

There are no treatments for long COVID or PEM, but ongoing trials include immunoadsorption, dietary supplements, and anti-inflammatory/antiviral drugs.

Long COVID: persistent symptoms after acute infection

Since 2020, acute infections with severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) have affected 775 million people worldwide [1]; in ~10% of these people symptoms do not completely resolve after 3 months [2]. The persistence of one or multiple symptoms beyond 3 months is known as post-acute sequelae of coronavirus disease 2019 (COVID-19) (PASC) or 'long COVID', which cannot be explained by other diseases, comorbidities, hospitalization, or aging [1,3]. The pathophysiology of long COVID is currently unknown, but deconditioning [4,5], viral persistence [6], dysregulated immune system [7], localized hypoxia, and/or endothelial dysfunction [8], as well as autoimmunity [2], have been predominantly suggested as potential determinants (Figure 1).

The most prevalent long COVID symptoms are fatigue, brain fog, cognitive impairments, muscle pain (myalgia), and post-exertional malaise (PEM) (Figure 1); PEM is the worsening of symptoms or onset of new symptoms up to 48 h following physical or cognitive exertion above a patient- and time-specific threshold, and can last for days to weeks or even months [9–11]. Typically, exercise reduces mortality and improves treatment outcomes in almost all chronic diseases [12], but the occurrence of PEM prevents patients with long COVID from engaging in regular exercise.

PEM is also a hallmark diagnostic symptom for patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [13]; many cases of ME/CFS are known to occur following either bacterial or viral infections, typically not requiring hospitalization [14,15]. Patients with ME/CFS exhibit symptoms similar to those of patients with long COVID, and many patients with long COVID tend to meet the Canadian Consensus Criteria for ME/CFS diagnosis [13]. Similarly to long COVID [16], a large proportion of patients with ME/CFS are female and middle-aged [14,15]. While long COVID research is in its infancy, ME/CFS research can help in our better understanding of long COVID.

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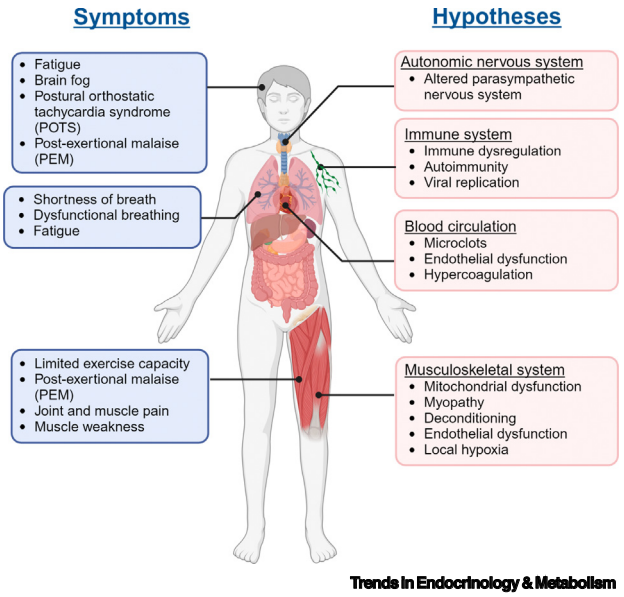

Figure 1. Common long coronavirus disease 2019 (COVID) symptoms (blue boxes) and pathophysiological hypotheses on the mechanisms underlying tissue alterations (red boxes). Figure generated with BioRender.

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Given the increasing recognition of long COVID, understanding muscle-specific alterations is essential for developing targeted therapeutic strategies. Here we provide a comprehensive overview of current evidence and highlight knowledge gaps with respect to the current understanding of skeletal muscle adaptations occurring in long COVID, and how this differs from or resembles other post-acute infectious diseases (e.g., ME/CFS); we also briefly outline potential therapies for patients with long COVID. Due to the high prevalence of patients exhibiting PEM and fatigue [11], the skeletal muscle abnormalities outlined here will reflect these specific phenotypes; however, it is unknown whether other phenotypes (i.e., those with smell/taste difficulties [11]) observe similar alterations.

Whole-body exercise and skeletal muscle adaptations in long COVID

Reduced aerobic capacity

The ability to perform aerobic exercise is a key determinant of quality of life [17]. Patients with long COVID exhibit a reduced aerobic capacity [18,19] and earlier onset of lactate accumulation during exercise [20,21]. The reduced exercise capacity in patients with long COVID has most often been attributed to alterations in skeletal muscle, with minor contributing impairments of the pulmonary and cardiac systems [22]. Dysregulated breathing and improper heart rate responses indicate that a dysfunctional autonomic nervous system might be a contributor. Alterations in skeletal muscle structure and function in long COVID – such as mitochondrial function and content, capillarization, and muscle fiber size and type – are likely to contribute to the reduced exercise capacity of patients [18,21]. Figure 2 outlines skeletal muscle alterations in patients with long COVID. While evidence for impaired aerobic capacities in long COVID continues to grow, the similarities to aerobic deficits observed in ME/CFS are becoming more apparent [23,24].

Skeletal muscle mitochondria and metabolism

Aerobic capacity is partly dictated by mitochondrial content and function [19–22], but fragmentation and spatial distribution of the mitochondrial reticulum also play important roles [25,26]. Markers for skeletal muscle mitochondrial content in patients with long COVID have yielded inconsistent results, with some studies reporting lower mitochondrial content [18], while others

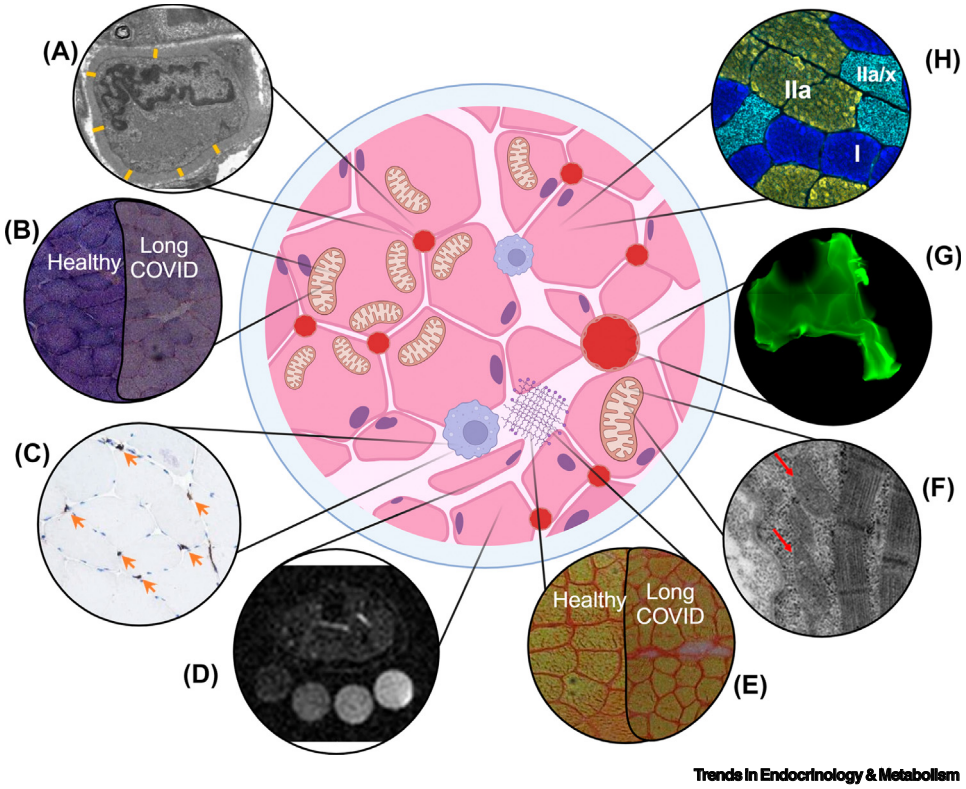

Figure 2. Contribution of skeletal muscle cell types in long coronavirus disease 2019 (COVID). (A) Capillary basal lamina thickening observed in patients with long COVID (from Aschman *et al*., 2023 [28]). (B) Lower succinate dehydrogenase activity in patients with long COVID compared with healthy controls (from Colosio *et al*., 2023 [18]). (C) CD68+ macrophage infiltration between muscle fibers (from Aschman *et al*., 2023 [28]). (D) High skeletal muscle sodium content, as viewed using 3T magnetic resonance imaging (from Petter *et al*., 2022 [70]). (E) Connective tissue content was similar in long COVID as in healthy controls (from Colosio *et al.* 2023 [18]). (F) Patients with long COVID have abnormal mitochondria imaged using electron microscopy (from Bizjak *et al.,* 2023 [19]). (G) Amyloid-containing deposits can be found in skeletal muscle and blood of patients with long COVID (unpublished data). (H) Patients with long COVID have more glycolytic, type II muscle fibers. Dark blue represents type I fibers, yellow represents type IIa fibers, turquoise represents type IIa/IIx fibers (Appelman *et al*., 2024 [21]). Figure created with BioRender.

showed no differences compared with individuals who have recovered from acute COVID [21]. Nonetheless, skeletal muscle mitochondrial respiration in patients with long COVID is consistently impaired compared with that observed in healthy/recovered individuals [18,21], highlighting a contributing role for a lower intrinsic mitochondrial function in a lower exercise capacity. Recently, evidence of lower mitochondrial complex I activity in long COVID might indicate direct virus-induced alterations [19]. Some abnormalities in mitochondrial ultrastructure (i.e., size, density) in patients with long COVID have been described, some of which are worsened in patients with ME/CFS [19,27]. An increased expression of mitochondrial fission proteins and decreased expression of mitochondrial fusion proteins [18] suggest altered mitochondrial fission/fusion regulation in patients with long COVID. It remains unknown whether mitochondrial distribution or mitophagy are also affected, and how this relates to disease severity and progression.

Capillary density and endothelial function

An optimal muscle capillary network and intact vascular function are needed to provide sufficient oxygen and substrates to skeletal muscle fibers. Skeletal muscle capillary-to-fiber ratios are either not altered [21] or lower [28] in patients with long COVID. Alterations in endothelial cells, such as

vasodilatory dysfunction [29], endothelial basal laminae thickening [28,30], or endothelial barrier damage [31], have been described in these patients. This could cause capillary hypoperfusion, reduced oxygen and substrate diffusion, or an increase in the resistance for diffusion of oxygen and oxidative metabolic substrates [22,32]; however, experimental data are lacking. Under normal physiological conditions, skeletal muscle fatigue is related to the accumulation of fatigue-inducing metabolites [33]; however, it is unknown whether hypoperfusion, capillary thickening, or endothelial dysfunction may contribute to earlier fatigue in long COVID.

Muscle fiber type, size, and distribution

Composition of muscle fiber type shapes the functional and metabolic alterations in skeletal muscle during exercise. Oxidative (type I) fibers typically have high mitochondrial densities, providing resistance to fatigue. Glycolytic (type IIa or IIa/x) fibers produce more power, but have lower mitochondrial densities [34]. Patients with long COVID have more glycolytic muscle fibers [18], similar to patients with other chronic diseases [35,36]. However, no longitudinal data exist to conclude whether those with higher glycolytic fiber proportions are more prone to developing long COVID, or whether the disease progression induces a shift in composition of muscle fiber type.

Limited evidence suggests a sex-specific type I fiber atrophy in long COVID [21]. Whether muscle atrophy occurs in long COVID is currently unclear, as many studies also included patients that had been hospitalized or presented with other comorbidities, which may confound the results [3]. Patients with long COVID exhibiting small-fiber neuropathy [37,38] also present more frequently with very small, atrophic muscle fibers [21,30]. The relationship between small-fiber neuropathy, prevalence of small, atrophic muscle fibers, and possible type I specific or general atrophy warrants further investigation.

PEM

Currently, diagnosis of PEM is strictly clinical, wherein patients must fulfill criteria for the DePaul Symptom Questionnaire – Post-Exertional Malaise (DSQ-PEM) questionnaire [39]. Two-day exercise tests and handgrip strength tests can help to confirm PEM diagnosis [40], but patient burden for a 2-day exercise test is substantial. Future research should focus on biomedical biomarkers to complement the DSQ-PEM. The underlying mechanism for PEM is currently unknown; however, PEM can also occur after cognitive exertion, suggesting a neurological or circulating contributor to the onset of PEM. Skeletal muscle adaptations are poorly understood in the context of PEM, but a 2-day muscle biopsy protocol after PEM induction suggested that skeletal muscle abnormalities worsen upon PEM onset [21]. Mitochondrial respiration and markers for mitochondrial density and metabolism decreased 1 day after maximal, PEM-inducing exercise in patients with long COVID [21]. Maximal exercise resulted in more severe skeletal muscle damage and enhanced immune cell infiltration [21]. Whether a similar process occurs in patients with ME/CFS or other post-acute infectious diseases is unknown. While long COVID and ME/CFS are the most prevalent diseases exhibiting PEM, subsets of patients with multiple sclerosis also experience PEM [41]. Future studies should include other populations to fully understand the underlying pathology of PEM.

Proposed pathological mechanisms for PEM

The underlying mechanisms for the skeletal muscle adaptations, and their time course of disease progression in patients with long COVID, are unknown. Further, it is not understood how these structural alterations relate to rapid changes underlying PEM. Multiple hypotheses exist that may explain skeletal muscle abnormalities in these patients (Figure 3). Here, we discuss the most likely candidates of these abnormalities, namely deconditioning, local hypoxia, autoimmunity, electrophysiological alterations, and central fatigue, according to the most recent literature.

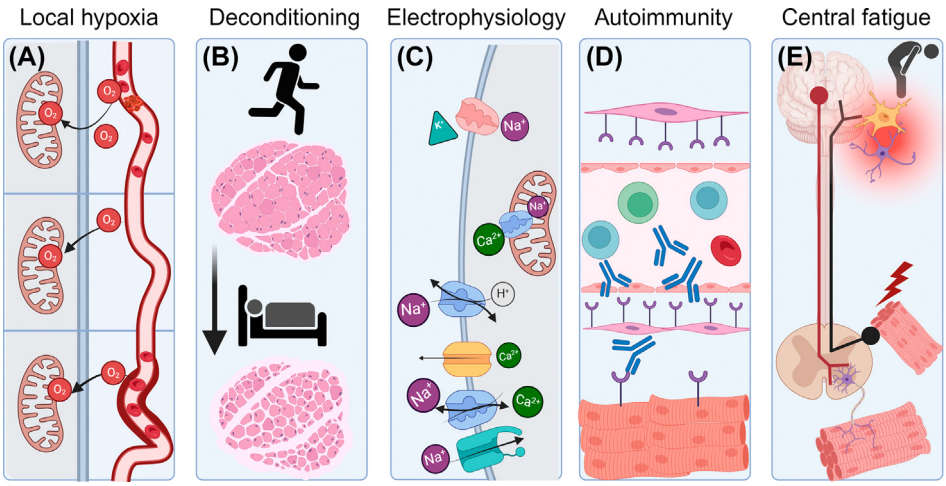

Figure 3. Schematic illustration of the five predominant mechanisms underlying long COVID skeletal muscle symptoms: local hypoxia, deconditioning, electrophysiological alterations, autoimmunity, and central fatigue. (A) Local hypoxia may be due to amyloid-containing clots (top panel), endothelial dysfunction (middle panel), or capillary thickening increasing oxygen diffusion distances (bottom panel). (B) Deconditioning results in muscle fiber atrophy, a loss of mitochondria, and capillary rarefaction, reducing aerobic capacity. (C) Electrophysiology may be altered by changes in ion distributions or effects on specific ion channels. (D) Generation of autoantibodies may target tissue receptors, including skeletal muscle. (E) Central fatigue may be caused by abnormal neurological processes, irregular responses to exercise, and feelings of myalgia and pain. Figure created with BioRender.

Deconditioning. Due to the development of PEM, several research groups have proposed that the skeletal muscle alterations in long COVID are simply due to deconditioning or physical inactivity [4,5]. Although patients with long COVID tend to be less active than healthy individuals [21], many still maintain physical activity levels that are similar to the average US citizen [42] who does not suffer from PEM. Physically inactive people do not suffer from PEM, and the skeletal muscle alterations in long COVID are distinct from those resulting from strict bed rest. Strict bed rest or limb immobilization induces muscle atrophy, capillary rarefaction (already present within 6 days of bed rest), insulin insensitivity, and an altered mitochondrial substrate utilization [43–45], conditions that are not predominantly observed in patients with long COVID. It should be noted that, as with any chronic disease, the increase in sedentary activity will have long-term impacts on health outcomes [46]. While the consequences of deconditioning could have long-term impacts on severely affected patients with long COVID in particular, the observed skeletal muscle adaptations in long COVID are distinct from those occurring after deconditioning.

Local tissue hypoxia. Some of the skeletal muscle adaptations in patients with long COVID resemble those occurring following chronic hypoxia exposure, which have led to the suggestion that patients may experience hypoxia. In hypoxic conditions (e.g., at high altitude), perceived exertion during exercise increases and exercise performance decreases [47]. Skeletal muscle metabolism shifts to non-oxidative glucose oxidation [48], which increases blood lactate during submaximal exercise [49]. Chronic hypoxia results in higher hematocrit values [50], lower mitochondrial content and function, and increases in glycolytic enzymes [51]. Whether the capillary-to-fiber ratio and capillary density change in long COVID is not clear, but hypoxia-induced muscle atrophy results in higher capillary densities [50,52,53].

Patients with long COVID, however, do not exhibit reduced arterial oxygen pressures and saturation during exercise, but oxygen extraction [22] and muscle oxygen diffusing capacity [54] may be

impaired. A lower mitochondrial function, independent of tissue oxygenation [18,19,21], also results in increased lactate production during exercise [55]. Such phenomena can be misinterpreted as simply caused by local hypoxia. However, the contribution of local hypoxia deserves further study. Local tissue hypoxia in patients with long COVID may be induced by capillary blockage and/or endothelial dysfunction, preventing oxygen and substrate delivery. Evidence of thickening of the capillary basal lamina has been observed in patients with long COVID [28], suggesting an impaired muscle oxygen diffusing capacity. Amyloid-containing clots (so-called microclots) [8] in venous blood from patients with long COVID may be big enough to block capillaries [56], causing a local hypoperfusion. However, these amyloid-containing clots were not found inside capillaries, but rather in the extracellular matrix, suggesting an alternative role [21]. Amyloid-containing clots may exert local cytotoxic effects resulting in endothelial dysfunction [8,56,57], similar to that observed in Alzheimer's disease [58]. The potential link between amyloid-containing clots, endothelial dysfunction, hypoperfusion, and local hypoxia is currently unclear.

Autoimmunity. There is substantial evidence indicating that autoimmunity may be implicated in long COVID pathophysiology [2]. However, how autoimmune antibodies found in patients with long COVID may affect skeletal muscle, either acutely or chronically, is poorly understood. There is some evidence of autoantibodies for β-adrenergic receptors (β_2-ARs) in patients with long COVID [59–61], which are implicated in a variety of exercise-related responses. Specifically, β_2-AR signaling is implicated in mitochondrial biogenesis, and in substrate oxidation and blood flow regulation [62,63]. Autoantibodies in myasthenia gravis and myositis – two well-studied autoimmune diseases which also exhibit muscle fatigue and worsening of symptoms with exercise [64,65] – are known to be associated with muscle weakness and muscle fatigue [66,67]. However, the mechanistic role of autoantibodies in the development of skeletal muscle adaptations in long COVID and the development of PEM is unknown.

Electrophysiological alterations. Several recent studies indicate that some patients with long COVID exhibit signs of myopathies [68,69] with myopathic histopathology [30,68]. Small-fiber neuropathy is common in patients with long COVID [37,38]. A recent study in patients with ME/CFS indicated higher tissue sodium levels [70], although it is unclear whether this is an intracellular or extracellular sodium accumulation. Sodium affects multiple channels, including the mitochondrial sodium–calcium exchanger, which is critical in mitochondrial function. It has been hypothesized that disturbances in muscle sodium homeostasis make mitochondria and muscle fibers susceptible to damage [71], which is linked to an early fatigue development [72] and altered ion channel function. More studies are necessary to fully understand the electrophysiological changes apparent in long COVID.

Central fatigue. Various research groups have suggested that central fatigue and neurological alterations contribute to long COVID symptoms [73–75], including brain fog, sleep difficulties, anxiety, depression, headaches, and somatic pain [76]. Neurophysiological alterations, such as neuroinflammation and small-fiber neuropathy, likely modulate long COVID symptoms. Central fatigue, defined as a reduction in the central nervous system's capacity to drive skeletal muscle contractions, could play a role in limiting exercise tolerance, though the necessary studies involving voluntary activation assessment, transcranial magnetic stimulation, and peripheral nerve stimulation have not yet been performed. It is also possible that a heightened interleukin (IL)-6-induced perception of effort leads patients to terminate exercise earlier [77]. However, patients with long COVID often exhibit earlier lactate accumulation onset during moderate exercise [20,21,78], independently of physical effort and psychological state [23]. Future studies should include interpolated twitch techniques to fully investigate central fatigue in long COVID [79]. Non-invasive methods to assess neurological alterations, using (functional) magnetic resonance imaging (MRI), are warranted to further understand the neurological consequences of PEM, as cognitive and mental exertion can also trigger PEM.

Therapeutic treatments in long COVID

There are currently no therapies for long COVID; however ongoing clinical trials are promising. Recently, immunoadsorption therapy temporarily alleviated long COVID symptoms [61]; however, further investigations are required. Other recent trials (found on ClinicalTrials.gov) include dietary supplementation (mitoquinone, vitamin K2, vitamin D3, and N-acetylcysteine), anti-inflammatory or immune regulatory drugs (i.e., lithium, naltrexone, and rintatolimod), and some antiviral drugs (e.g., Paxlovid) [80]. The majority of trials are ongoing, and we eagerly await new results.

Concluding remarks and future perspectives

Most research on long COVID has focused on immune function, but skeletal muscle adaptations in these patients are gaining more attention. There is clear evidence of skeletal muscle alterations, including mitochondrial and endothelial abnormalities in patients with long COVID that may underly whole-body exercise responses. The heterogeneity and the duration of the disease result in different skeletal muscle phenotypes, and these deserve further study. Future research should also investigate endothelial function, the possible implications of amyloid-containing deposits in skeletal muscle, and the underlying pathophysiology of PEM and how it contributes to long COVID disease progression (see Outstanding questions). We applaud new studies that investigate the factors contributing towards skeletal muscle adaptations, including deconditioning, hyperbaric oxygen therapy, novel medications targeting autoimmunity, and the neurological component of PEM. As many new groups worldwide are now studying the fundamental pathophysiology of long COVID and testing potential new therapies to relieve patient symptoms and the disease burden, we await exciting times in this research field.

Outstanding questions

What triggers post-exertional malaise (PEM) in patients with long COVID?

What is the relative contribution of a sedentary lifestyle to the skeletal muscle alterations seen in patients?

To what extent is endothelial function impaired in patients with long COVID, and does this contribute to exercise limitation and PEM?

How does long COVID induce small-fiber neuropathy and muscle atrophy, and what are the long-term consequences?

Could autoimmunity or amyloid-containing clots be central to the muscle and vascular dysfunction in long COVID?

Are non-invasive techniques – such as qualitative electromyography, near-infrared spectroscopy, or functional magnetic resonance imaging – viable alternatives for patient diagnosis and monitoring patient progression?

What non-invasive alternatives are available to assess neurophysiological and skeletal muscle function in patients with long COVID?

Which medications can increase the threshold for post-exertional malaise, and how do these treatments alter long COVID disease progression?

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Declaration of interests

The authors declare no conflicts of interest.

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