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Review Article

Advance in the mechanism and clinical research of myalgia in long COVID

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Abstract: As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve, mortality rates of coronavirus disease 2019 (COVID-19) have significantly decreased. However, a variable proportion of patients exhibit persistent prolonged symptoms of COVID-19 infection (long COVID). This virus primarily attacks respiratory system, but numerous individuals complain persistent skeletal muscle pain or worsening pre-existing muscle pain post COVID-19, which severely affects the quality of life and recovery. Currently, there is limited research on the skeletal muscle pain in long COVID. In this brief review, we review potential pathological mechanisms of skeletal muscle pain in long COVID, and summarize the various auxiliary examinations and treatments for skeletal muscle pain in long COVID. We consider abnormal activation of inflammatory response, myopathy, and neurological damages as pivotal pathological mechanisms of skeletal muscle pain in long COVID. A comprehensive examination is significantly important in order to work out effective treatment plans and relieve skeletal muscle pain. So far, rehabilitation interventions for myalgia in long COVID contain but are not limited to drug, nutraceutical therapy, gut microbiome-targeted therapy, interventional therapy and strength training. Our study provides a potential mechanism reference for clinical researches, highlighting the importance of comprehensive approach and management of skeletal muscle pain in long COVID. The relief of skeletal muscle pain will accelerate rehabilitation process, improve activities of daily living and enhance the quality of life, promoting individuals return to society with profound significance.

Keywords: SARS-CoV-2, COVID-19, long COVID, skeletal muscle pain, myalgia

Introduction

COVID-19, a disease widely spread and regarded as a public health emergency, is caused by SARS-CoV-2. COVID-19 has severely threatened people's normal life and contributed massive damage to global health and economy. In addition to respiratory system, SARS-CoV-2 causes multiorgan dysfunctions including damages to neurological [1, 2], musculoskeletal, cardiovascular [3], gastrointestinal, skin, and other systems [4, 5]. COVID-19 has been demonstrated to manifest as a broad clinical spectrum, ranging from asymptomatic to severe or fatal, with up to 15%-20% of patients requiring hospitalization [6, 7]. Independent studies suggest that 35.8% to 62.5% of SARS-CoV-2 patients during acute phase experience skeletal muscle pain, indicating skeletal muscle injury occurs during the acute phase of the infection [8-12].

To our knowledge, persistent symptoms may exist after infection with many viruses and bacteria [13-15]. COVID-19 is no exception. A significant number of COVID-19 patients experience long-term symptoms, known as long COVID [16-18]. There is no unified definition for long COVID by far, but we have compiled several literature sources to define it as symptoms and signs that persist for more than four weeks after acute COVID-19 in order to early identification. With the long-term prevalence of COVID-19, global scholars have conducted several prospective follow-up studies on long COVID and found that persistent symptoms after COVID-19 include cough, dyspnea, chest/throat pain,

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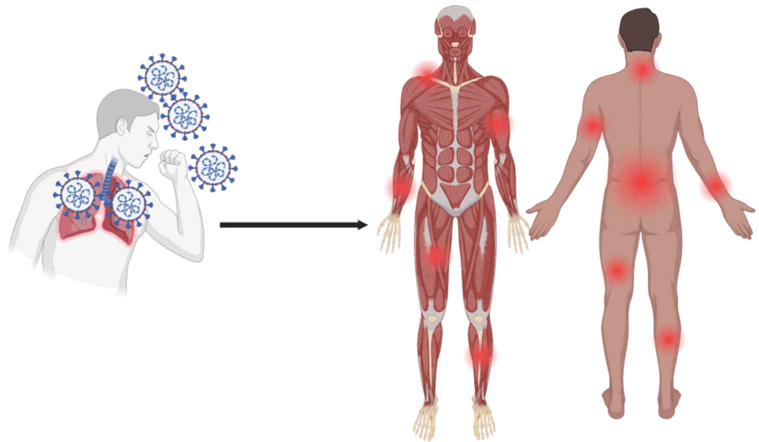

Figure 1. Common locations of skeletal muscle pain in long COVID. Common locations of chronic skeletal muscle pain include the spine, shoulders, and limbs. Spinal pain is more common, with the highest incidence of skeletal muscle pain occurring in the lumbar muscles of the spine. Created with BioRender.com.

headache, musculoskeletal symptoms (myalgia, arthralgias, fatigue), abdominal symptoms, cognitive symptom, olfactory or gustatory dysfunction, sleep disorders, anxiety or depression [19-21]. The majority of these symptoms extend from the acute phase of COVID-19.

Constituting 40% of body weight, the skeletal muscle composed of myofibers is a indispensable part of human body and plays a prominent role in energy metabolism, mechanical movement [22] and respiratory ventilation [23, 24]. Therefore, our attention has been drawn to persistent skeletal muscle pain. Studies indicated that 42%-65%, 21%, 15%, 5%-41%, 6%, 15-43% and 6%-38% of COVID-19 patients still had skeletal muscle pain at post discharge [25-28], five [29], eight weeks [26], three [27, 30-33], six months [32, 34-37] and one year [37-42] after discharge, respectively. The follow-up population was mainly hospitalized patients, but there are still a few follow-up data of non-hospitalized COVID-19 patients with mild symptoms. Myalgia was one of the main symptoms during 1.5 to 6 months of follow-up in 451 non-hospitalized COVID-19 patients [6]. 55% of 100 non-hospitalized patients with neurological symptoms still complained skeletal muscle pain at 5 months of follow-up [43]. Furthermore, premorbid skeletal muscle pain has been shown to confer an increased susceptibility to long-COVID, with a prevalence of 38% at 7 months after COVID-19 infection [44]. We consider that the heterogeneity of populations, preexisting comorbidities, history of skeletal muscle pain, disease severity and treatment regimens are meaningful interpretations of discrepancy in the prevalence of skeletal muscle pain in long COVID.

With respect to sex predisposition to myalgia in long COVID, there is no consensus. Albeit musculoskeletal pain exhibits a female predominance after 6 months, 8 months and 1 or 2 years following acute SARS-CoV-2 infection [28, 32, 37, 45, 46], some studies have reported opposite results that suggest no associations with sex 5 months post infection while female is susceptible to skeletal muscle pain during acute COVID-19 [47].

Locations where chronic skeletal muscle pain appear include spine, shoulders, and limbs. The spine is not only the most prevalent musculoskeletal pain position experienced by patients before COVID-19 but also the persistent pain region complained by patients infected with COVID-19 (**Figure 1**) [44]. The most common region of spine pain in post-acute COVID-19 patients was the back (30.4%) [48]. This phenomenon may be due to widespread expression of coronavirus-related factors and receptors in human dorsal root ganglia (DRG) at lumbar and thoracic levels [49]. In an extension cohort study of hospitalized COVID-19 survivors at 6 months, regional muscle pain was distributed in the lower leg, arm, and shoulder girdle [32].

Based on a review of current researches, we believe that myalgia in long COVID may be primarily associated with abnormal activation of inflammatory response, myopathy, and neurological damages (**Figure 2**). Persistent pain after COVID-19 has demonstrated to decrease the quality of life, ultimately resulting in psychological disorders such as anxiety and depression [31, 50-53]. Chronic pain is a complex and distressing issue, and patients must receive comprehensive examizations and effective and

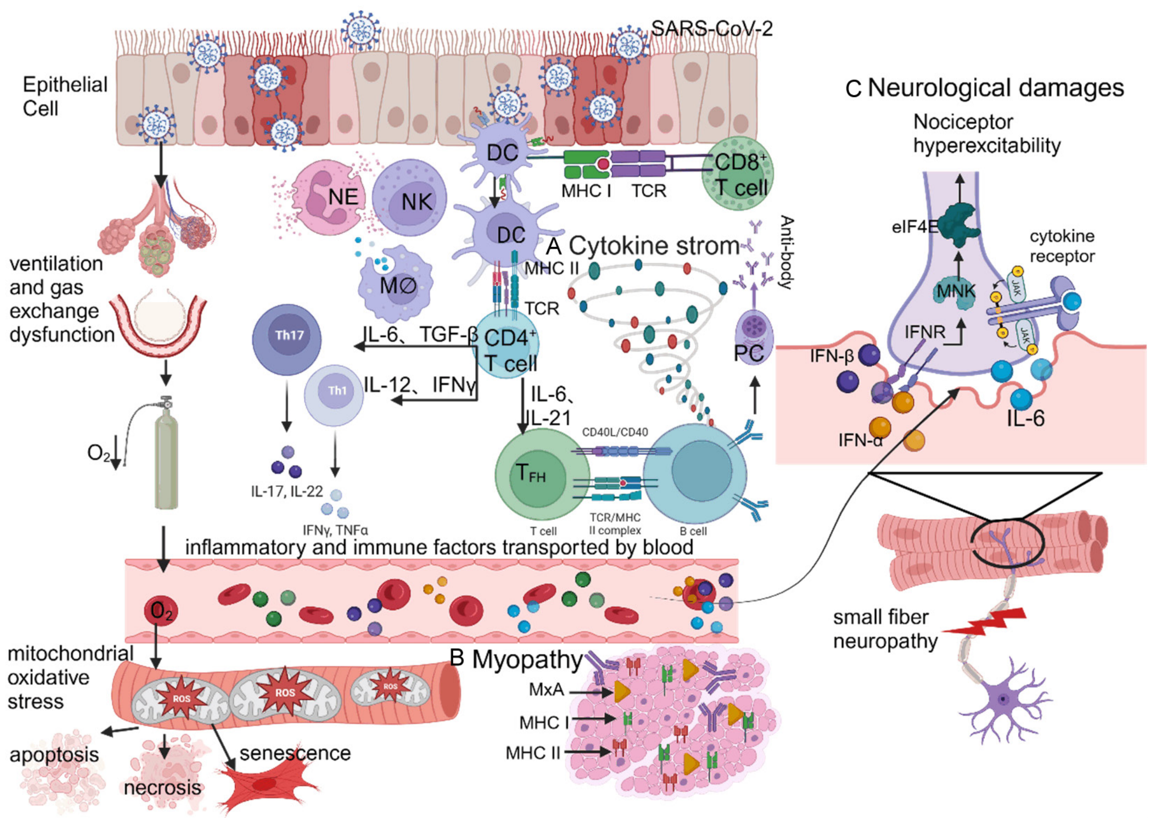

Figure 2. Schematic illustration of the main underlying pathophysiological mechanisms of skeletal muscle pain in long COVID. A. Upon entry into the body through the respiratory tract, SARS-CoV-2 can activate the innate and adaptive immune responses of the organism, with excessive activation of the inflammatory system leading to a cytokine storm. After SARS-CoV-2 infection, respiratory ventilation and gas exchange dysfunction can lead to hyoxemia, inducing skeletal muscle mitochondrial oxidative stress. If the damaged mtDNA is not repaired in time, the skeletal muscle may ultimately face outcomes such as apoptosis, necrosis, and aging, further promoting the progression of inflammation. B. Cross-reactivity between SARS-CoV-2 and muscle antigens induce myopathy. C. Inflammatory cytokines such as IL-6 and immune-active substances such as IFN-α, IFN-β contribute to nociceptor hyperexcitability in muscle injury. Besides, SARS-CoV-2-induced small fiber neuropathy participate in persistent skeletal muscle pain. Created with BioRender.com.

sustained treatments to control their long-term pain to an acceptable level [54].

Literature search methods

Curiously, research on skeletal muscle pain in long COVID mainly focuses on the description of incidence and clinical characteristics, with limited studies on its pathogenesis. We conducted a comprehensive literature search using three electronic databases including Web of Science, PubMed, and Google Scholar, without a date limit. The last literature search was performed on 20th December 2023. The search terms were set to [("Post-acute COVID-19 syndrome" OR "Post-Acute COVID-19 Syndromes" OR "Long-COVID" OR "Long-COVID syndrome" OR "Long-COVID-19" OR "Long-haul" OR "Long-hauls" OR "Long-haul COVID" OR "Long Haul COVID-19" OR "Post-Acute Sequelae of SARS-CoV-2 Infection" OR "Post-acute sequelae of SARS-CoV-2" OR "Long Post-COVID symptoms" OR "persistent Post-COVID symptoms" OR "Post-COVID-19 syndrome" OR "Post-COVID Conditions" OR "Post-COVID Condition" OR "post COVID" OR "post COVID-19" OR "chronic COVID" OR "PASC" OR "PACS" OR "persisting COVID" OR "COVID complications" OR "SARS-CoV-2 complications") AND ("myalgia" OR "myositis" OR "myopathy" OR "Muscle Pain" OR "Muscle Soreness" OR "Muscle Tenderness")]. The search results were screened by title, abstract and full text, and reference lists were checked for further articles meeting the search criteria. The types of literature obtained included original research articles, case reports, case series, reviews, comments and letters to the editor. We excluded studies in non-English language and literatures that were not associated with or did not mention myalgia in long COVID, finally 211 articles were included in this review. Due to the limited number of studies, clinical heterogeneity and methodologic diversity on myalgias in long COVID, we did not make a meta-analysis. Therefore, we have integrated this information and present it in a narrative form in each section of this review for comprehensive discussion, looking forward to providing a reference for clinical work.

Potential pathological mechanisms of myalgia in long COVID

The relationship between SARS-CoV-2 infection and skeletal muscle pain in long COVID

Skeletal muscle pain is a common and non-specific symptom in long COVID and its diagnosis in terms of etiology is a particularly challenging job in clinical practice. The relationship between SARS-CoV-2 infection and myalgia remains a comparatively under-researched field. However, it is a generally acknowledged fact that the pathogenesis of SARS-CoV-2 involves binding to angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface, resulting in the proteolysis of transmembrane protease serine 2 (TMPRSS2) protein and the activation of coronavirus S protein fusion signal peptide (S2 subunit), which facilitates the fusion between SARS-CoV-2 and cell membranes [55, 56]. Hence, viral RNA replicates in human cytoplasm [57-59]. Since ACE2 receptors express in various tissues including human skeletal muscles, it is postulated that SARS-CoV-2 may directly infect skeletal muscle cells via ACE2 [11, 60, 61], activate immune cells and cause direct and immune-mediated indirect muscle impairment.

Diaphragm is the main skeletal muscle of respiration. SARS-CoV-2 viral RNA were found in the autopsy diaphragm specimens of 4 patients (15.4%) who had been critically ill with COVID-19 [62]. However, Aschman discovered that inflammation was more pronounced in subacute and chronic stages, and while some muscle specimens showed SARS-CoV-2 RNA, it could be attributed to viral RNA in circulation rather than true myocyte infection. Moreover, upregulation of major histocompatibility-complex (MHC) class I and II antigens on the muscle membrane indicates that skeletal muscle is involved in the immune response against SARS-CoV-2 [3]. Evidence of inflammation or immune-mediated myopathy was revealed in skeletal muscle autopsies of 35 patients who died due to SARS-CoV-2 infection, but no direct invasion of SARS-CoV-2 into skeletal muscle was observed, suggesting that skeletal muscle damage was secondary to inflammatory or immune response [63]. The above findings were based on deceased COVID-19 patients, and extrapolation to mild disease course is likely to provoke debates. Fortunately, although muscle biopsies are rarely performed, there are a few case reports. For instance, Manzano performed a biopsy of the left deltoid muscle of a patient with COVID-19 infection and myopathy. They reported that no SARS-CoV-2 virus in the muscle and no membrane attack complex deposition, but abnormal expression of MHC class I antigens and myxovirus resistance protein A (MxA) on muscle fibers and capillaries, indicating that his SARS-CoV-2 myopathy may have been due to type I interferonopathy [64]. Type I interferons activate the MNK-eIF4E signaling pathway through DRG-specific receptors (IFNR) and drive the plasticity of nociceptors, promoting pain and worsening existing pain status [65]. In conclusion, we speculate that persistent skeletal muscle pain in long COVID may be associated with inflammation, myopathy, and neurological damages rather than direct viral infection of skeletal muscle. Of course, we sincerely appeal to long COVID patients with persistent skeletal muscle pain to engage in muscle biopsy to further validate this hypothesis.

Abnormal activation of inflammatory response

Skeletal muscle, with abundant content of mitochondria, occupies an important position in energy metabolism. There are two populations of mitochondria in skeletal muscle, subsarcolemmal mitochondria (SSM) and interfibrillar mitochondria (IFM), respectively. The former one generates greater amounts of reactive oxygen species (ROS). Mitochondrial stress still exists in asymptomatic or mild COVID-19 patients 40 days after infection, with an increase in peroxiredoxin 3 (PRDX3) and a decrease in carbamoyl phosphate synthase 1 (CPS1), indicating a long-term disruption of anti-inflammatory and stress response [66].

Table 1. Common hematological indicators of myalgia in long COVID

Characteristic	Indicators
Blood Routine	WBC, Lymphocytes, Neutrophil, Platelet count, Hemoglobin
Inflammation marker	CRP, ESR, PCT
Cytokines	IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, IL-17, TNF-α, IFN-γ
Muscle Metabolism	LDH, CK, CK-MB, hs-Troponin-T
Autoantibodies	Anti-PM/Scl, anti-Jo1, anti-Mi-2, anti-TIF1-γ, anti-MDA5
Blood gas analysis	PH, PO2, $HCO3^{-}$
Coagulation	INR, Fibrinogen, D-dimer, aPTT, PT, TT
Clinical Chemistry	Albumin, ALP, ALT, AST, Creatinine, Taurine, electrolyte

Abbreviations: WBC = White Blood Cells; CRP = C-Reactive Protein; ESR = Erythrocyte Sedimentation Rate; PCT = Procalcitonin; IL = interleukin; TNF-α = Tumor Necrosis Factor-alpha; IFN-γ = interferon-gamma; LDH = Lactate Dehydrogenase; CK = Creatine Kinase; CK-MB = Creatine Kinase Myocardial Band; hs-Troponin-T = high sensitive Troponin-T; PM/Scl = Polymyositis Scleroderma; TIF1-γ = Transcription Intermediary Factor 1-gamma; MDA5 = Melanoma Differentiation Associated Gene 5; INR = International Normalized Ratio; aPTT = activated Partial Thromboplastin Time; PT = Prothrombin Time; TT = Thrombin Time; ALP = Alkaline Phosphatase; ALT = Alanine Transaminase; AST = Aspartate Transaminase.

Compared with twelve patients without long-term symptoms, citrate synthase, peroxisome proliferator-activated receptor-γ coactivator (PGC)1α in vastus lateralis biopsies and JO2 for mitochondrial complex II were significantly lower in eleven patients with PASC. This study indicates impaired mitochondrial biogenesis and reduced mitochondrial function in myalgia patients. What's more, pro-fusion protein levels (OPA1) were lower while proteins involved in fission [pDRP1 (Ser616), and FIS1] were higher in myalgia patients. The pro-fission shift in mitochondrial dynamics activated mitophagy to optimizes the function of mitochondria and muscles [67]. However, this conclusion will be more convincing if enlarging number of patients and excluding mood disorders and nervous system diseases [68]. Pulmonary function still reduced in 6 months after hospital discharge due to SARS-CoV-2 infection [69]. Moreover, patients who had recovered from COVID-19 for 11 months without cardiopulmonary disease exhibited impaired oxygen extraction and ventilation inefficiency during exercise, suggesting that skeletal muscle pain in long COVID may be associated with mitochondrial dysfunction due to low oxygen supply [70, 71]. Mitochondrial oxidative stress can also lead to an increase in mitochondrial DNA (mtDNA) damage. If the limited efficiency of the mtDNA repair mechanisms cannot ensure the integrity of mtDNA, it will bring about adverse outcomes such as apoptosis, pyroptosis, necrosis, or senescence of skeletal muscle cell, further aggravating the body's inflammatory response [72-74]. In summary, it is highly likely that inflammation triggered by SARS-CoV-2 infection is related to skeletal muscle pain in long COVID.

Immunological dysfunction was reported in mild-to-moderate SARS-CoV-2 infection individuals at 8 months. It mainly manifested as highly activated innate immune cells such as cytotoxic $CD8^{+}$ T cells, lacked naive T and B cells and elevated expression of inflammatory mediators such as type I IFN (IFN-β), type III IFN (IFN-λ1) [75]. A cross-sectional study following mild COVID-19 cases for 3 months found the values of serum CRP, fibrinogen and neutrophil count were slightly but significantly higher in patients with Post-COVID syndrome (PCS). This study demonstrated that SARS-CoV-2 not only trigger elevated cytokines but also cause the release of damage-associated molecular patterns (DAMPs) to contribute to low-grade inflammation (LGI) in long COVID. Myalgia is one of the most reported symptoms of LGI and can be interpreted by higher fibrinogen levels [76, 77].

The uncontrolled replication of viruses and systematic inflammatory responses, typically referred to cytokine storms, are caused by hyperactivation of numerous cells, including T cells, B cells, dendritic cells, nature killer (NK) cells, macrophages, neutrophils, monocytes, and tissue cells such as epithelial and endothelial cells, which release large amounts of pro-inflammatory cytokines and soluble inflammatory markers (**Table 1**), hence furtherly sustaining abnormal systemic inflammation [78]. Among molecules increased in cytokine storm serum, interleukin-1β (IL-1β), IL-6, IL-12, IL-17, tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) are crucial [79, 80]. $CD4^+$ T cells differentiate into various T helper cells after being activated by antigen presenting cells (APCs) [81, 82]. Cytokines secreted by Th1 and Th17 cells can mediate muscle damage by directly inducing muscle fiber proteolysis and reducing protein synthesis [83-88]. On the other hand, cytokines can directly act on muscle fibers to promote the synthesis of soluble pro-inflammatory mediators, thus contributing to the sustained presence of the inflammatory response [89, 90]. Besides, long COVID may be associated with mast cell activation syndrome (MCAS) [91]. MACS is characteristic of hyperactivation of mast cells and increase in mast cell mediator levels [92]. The markers of mast cell activation mainly include tryptase, histamine metabolites, prostaglandin D2 or metabolites, leukotriene E4 and chemokines such as IL-1β and IL-6 [93, 94]. However, the relationship between myalgia in the long COVID and MACS are scarcely reported.

Myalgia is usually due to generalized inflammation and cytokine response, with IL-6 playing a predominant role. IL-6 not only provokes acute muscle hyperalgesia but also results in chronic latent hyperalgesia [95]. Specifically, IL-6 activates peripheral nociceptors by upregulating TNFα and IL-1β expression, promoting immune cell infiltration, activating multiple signaling pathways [96]. There are reports of applying tocilizumab to critically ill COVID-19 patients in clinical practice. Tocilizumab is a humanised anti-IL-6 receptor monoclonal antibody of the IgG1 subtype that has been recommended to treat rheumatoid arthritis and other chronic inflammatory diseases, effectively inhibiting signal transduction pathway by blocking IL-6 receptor interactions [97]. Considering that the cytokine storm induced by COVID-19 manifests as an increase in cytokines such as IL-6, TNF-α and IL-1β, the pathophysiology of skeletal muscle pain also involve these cytokines. Therefore, it seems reasonable to link SARS-CoV-2 infection with muscle pain through the inflammatory response. Moreover, MicroRNAs, small noncoding RNAs that regulate genes, are reported to invovle in pathogenic mechanisms of chronic pain in the long COVID population. Differentially expressed miRNAs which included miR-21-5p, miR-29a, b, c-3p miR-92a, b-3p, miR-92b-5p, miR-126-3p, miR-150-5p, miR-155-5p, miR-200a, c-3p, miR-320a, b, c, d, e-3p, and miR-451a were associated with IL-6/STAT3 proinflammatory axis [98].

The literature has well documented that sustained presence of hyperinflammatory state in long COVID contributes to the reduction in muscle protein synthesis and increased protein degradation [99]. In addition, the decreased physical function and lack of enough physical activity, as well as inadequate nutrient intake because of olfactory or gustatory dysfunction, are beneficial to the development of sarcopenia [22]. Therefore, we should be alert to sarcopenia when individuals complain sustained skeletal muscle pain after acute COVID-19 infection. Low muscle strength, evaluated using grip strength, is considered the main parameter of sarcopenia. According to the latest EWGSOP2 consensus definition, male subjects aged 65 or above with handgrip strength < 27 kg and female subjects < 16 kg are considered to suffer from sarcopenia. Cut-off values for subjects in the lower age groups are identified by age- and sex-matched healthy controls from the community (Lookup 7+ sample) [100, 101]. A prospective observational study indicated that COVID-19 survivors experiencing high muscle mass loss during actue infection can not fully recover muscle health 6 months post discharge, whereas the low muscle loss group did. High and low muscle loss group were stratified according to the magnitude of loss in vastus lateralis muscle by B-mode ultrasound. Furthermore, high muscle loss group showed greater prevalence of myalgia at 6 months after discharge [102].

Myopathy

Agergaard conducted neurophysiological examinations on 20 patients who were suspected of neurological disorders and infected with COVID-19 8 months ago, but found no signs of neurological pathology. However, quantitative electromyography suggested myopathy in 11 cases, with 8 of these myopathy patients experiencing muscle pain [103]. This discovery provides a strong support for the hypothesis that myopathy may be a significant cause of skeletal muscle pain in long COVID. Terms commonly used to describe myopathy events include muscle pain, virus-induced muscle damage, myopathy, myositis, and rhabdomyolysis. To date, there is no consensus on the nomenclature of myopathies, therefore the confusion of terminology may lead to inadequate attention and delayed diagnosis of muscle injury events [104].

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous autoimmune muscle diseases, which have been classified into the following main types based on their unique clinical and pathological features and potential immunopathogenic mechanisms: polymyositis (PM) [105, 106], dermatomyositis (DM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (IMNM). A recent cross-sectional study studies have documented 24% patients experienced myopathy post-COVID-19 infection while the prevalence of myopathy is 7.8% in control group [107].

Common autoantibodies of myopathy are listed in **Table 1**. The relationship between COVID-19 infection and IIMs has remained elusive. Megremis identified six antigenic epitopes highly homologous to human SARS-CoV-2 in the serum of 20 patients with TIF1-γ (TRIM33)-positive dermatomyositis, three of which were highly specific to SARS-CoV-2, suggesting that immune system abnormalities after COVID-19 infection may contribute to the development of IIMs [108]. Muscle biopsy from a 51-year-old Chilean-American man suggested acute necrotizing myositis 3 months after COVID-19 infection and his symptoms was alleviated when treated with Prednisolone and Azathioprine [109]. Muscle biopsies of 16 long COVID patients who complained of fatigue, muscle pain, or weakness lasting for up to 14 months, among whom 44% had persistent muscle pain, 75% had myopathy on electromyography, revealed that all patients had histological changes and 62% patients had mitochondrial changes comprising cytochrome c oxidase deficiency, subsarcolemmal accumulation, and/or abnormal cristae [110], implying that persistent skeletal muscle pain is not ascribed to a single factor and the possibility of COVID-19-related myopathy caused by hyperinflammation cannot be ruled out. Myalgia is not only a common symptom in patients with long COVID, but also may be associated with systemic autoimmune rheumatic diseases (SARDs) and fibromyalgia (FM). The key point to distinguish them lies in history inquiry, clinical and hematological examination. Patients suffered from SARD always exhibit strongly positive disease-specific autoantibodies [111] and skin rashes while FM is not accompanied with muscle weakness and increase of CK [112].

Although rare, SARS-CoV-2-related rhabdomyolysis is a serious complication of myositis that should be taken into account [113-116]. The characteristic features of rhabdomyolysis are elevation of CK (typically > 10 times the upper limit of normal), creatinine elevation, and usually brown urine or myoglobinuria. The primary causes are myotoxic anti-COVID-19 drugs, severe electrolyte imbalances, ischemia, prolonged bed rest, and immune-mediated injury [117, 118]. Myotoxic drugs that rhabdomyolysis patients take include azithromycin, hydroxychloroquine, paclitaxel, propofol, imatinib, piperacillin, meropenem, hydrochlorothiazide, and acetaminophen. 74% of patients with COVID-19 and coexisting rhabdomyolysis during the acute phase reported muscle pain. Diagnosis of rhabdomyolysis during the COVID-19 pandemic has been challenging because fatigue, muscle pain, elevated liver enzymes and lactate dehydrogenase levels are common manifestations in COVID-19 and rhabdomyolysis. Hence, we should keep rhabdomyolysis in mind when encounter with skeletal muscle pain during the acute phase of COVID-19 [104, 119]. Importantly, after recovery from rhabdomyolysis, patients are supposed to experience all-round neurological examinations, electromyography, and even muscle biopsy or genetic testing in case of overlooking persistent muscle damage. Patient with carnitine palmitoyltransferase II (CPT II) deficiency suffered from rhabdomyolysis after administering COVID-19 vaccine [120]. Besides, COVID-19 infection was regarded as a fatal triggering factor for patient affected with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency [121]. Therefore, proper caution should be exercised when delivering vaccinations (including the COVID-19 vaccination) or infecting with SARS-CoV-2 in population with an underlying neuromuscular disorder.

Neurological damages

COVID-19 is primarily a respiratory disease, but it can affect multisystem including the nervous system, with nearly 34% of SARS-CoV-2 infected individuals diagnosed with neurological or psychiatric illnesses 6 months after acute COVID-19 [122]. Neurological manifestations in long COVID can be classified into two categories: central nervous system (fatigue, headache, sleep disorders, cognitive impairment, emotional/mood disorders, dizziness, dysautonomia), peripheral nervous system manifestations (muscle weakness, myalgias, hyposmia, hypogeusia, hearing loss, sensorimotor deficits) [2, 123-130].

It is still unclear whether the virus can directly infect the nervous system. No virus invasion is supported by many observations [131-133]. For example, Suh did not detect direct viral invasion of psoas muscle or femoral nerve of deceased COVID-19 patients, suggesting that the damages to these tissues may be mediated by inflammatory or immune response [63]. On the other hand, many studies found direct SARS-CoV-2 viral invasion of cerebrospinal fluid and frontal lobe tissue [134-137]. Matschke reported detecting SARS-CoV-2 viral proteins in the IX and X cranial nerves of the medulla oblongata during autopsy, suggesting that the persistent taste impairment commonly seen in COVID-19 may be related to SARS-CoV-2's tropism for gustatory neurons, which provide a pathway to brainstem. This study also found the presence of SARS-CoV-2 RNA and protein in the brain of COVID-19 patients, indicating that SARS-CoV-2 could invade the central nervous system, but its presence does not correlate with the severity of neurological pathology [133]. Therefore, it is interpreted that SARS-CoV-2 invasion of brain can take place but not in every case. Besides, central nervous system damage and neurological symptoms may be caused by other factors such as cytokine storms, neuroimmune activation, rather than the virus directly infecting the central nervous system. This point of view is consistent with the mechanisms underlying COVID-related headaches. Tolebeyan proposes that COVID-related headaches which resemble migraines and other types of headaches primarily caused by inflammation, which activate nociceptive neurons via cytokines and chemokines [138]. Sun also suggests that in addition to systemic inflammation, changes in the immune system play a role in the development of chronic pain following COVID-19 [54].

Skeletal muscles connected to bones not only produce movement through contraction under the control of motor neurons in the central and peripheral nervous system [139], but also transmit signals to the central nervous system via receptors. Myalgia, a nonspecific descriptor, encompasses a series of abnormal muscle sensations such as cramping, stiffness, and tenderness. However, the common feature of all these sensations is the activation of pain receptors in skeletal muscle. Hyperexcitability and hyperactivity of nociceptive neurons are the basis for pain [140]. Type I IFNs promote nociceptor sensitization by activating mitogen-activated protein kinase interacting kinase (MNK) eukaryotic initiation factor (eIF) 4E signaling axis in DRG neurons when viral infection [65, 141]. Furtherly, eIF4E phosphorylation contribute to elevated interleukin (IL)-1β and tumor necrosis factor (TNF)-α [142] and translational control of brain-derived neurotrophic factor (BDNF) expression [143]. The nature of pain turns to chronic muscle pain when structural changes generate.

Bocci firstly combined neurophysiological assessments, quantitative electromyography (qEMG), and sympathetic skin response (SSR) to investigate myalgia and fatigue symptoms in long COVID patients. Surprisingly, these symptoms are not related to myopathy, but to the autonomic nervous system [144]. Besides, a retrospective study reported that the skin biopsy results of 13 patients who suffered from new-onset painful paresthesias within 2 months after acute SARS-CoV-2 infection. Six out of 13 patients were diagnosed as small fiber neuropathy (SFN) on skin biopsy, including two patients exhibited autonomic dysfunction by autonomic function testing (AFT). This finding suggests that SFN may underlie pain in long COVID [145]. Additionlly, a considerable amount of COVID-19 patients complained of paroxysmal diffuse burning and itching sensation in the skin. After excluding drugs, diabetes, neurological diseases, or autoimmune diseases, skin biopsies were performed in a few patients, revealing small nerve hypertrophy in sensory C fibers [146], indicating that skin pain in long COVID-19 may ascribe to dermal neural hyperexcitability. Small fiber neuropathy is a structural abnormality at the distal termination of small fibers (thin myelinated and unmyelinated fibers of the sensory input and autonomic neurons), which typically presents as progressive and chronic pain. Abbott described three cases of acute persisted skin pain after receiving the Oxford-AstraZeneca ChAdOx1-S vaccine, eventually diagnosed as small fiber neuropathy. Skin biopsy demonstrated that protein gene product 9.5-immunoreactive fibers and single intraepidermal nerve fiber cross the basement membrane of the epidermis [147]. Taken together, we propose nociceptor hyperexcitability and small fiber neuropathy play a crucial role in skeletal muscle pain in long COVID. Local anesthetics (LA) with injections of 0.5% procaine 3 times over 3 months to action site of the autonomic nervous system (ANS) progressively improved a 54-year-old man with post COVID-19 symptoms lasting 14 weeks including muscle pain. These studies strongly supported that the autonomic nervous system (ANS) dysfunction was a contributor to myalgia in long COVID [148].

Other conditions

In addition to the aforementioned factors, other conditions are also associated with skeletal muscle pain in long COVID. The dysregulation of the renin-angiotensin system (RAS) after COVID-19 infection contributes to the occurrence of sustained skeletal muscle pain. When SARS-CoV-2 makes contact with host cells, the expression of ACE2 on membrane of susceptible cells downregulates, leading to deactivation of the alternative ACE2-Ang-(1-7)-Mas pathway which is against fibrosis and atrophy of skeletal muscles. Conversely, overactivation of the classical ACE-Ang II-AT1R pathway which can lead to oxidative stress, neuroinflammation, vasodilation, and thrombosis [149, 150]. Detailed history inquiry and clinical examination are necessary, as skeletal muscle pain in long COVID is also associated with pre-existing skeletal muscle pain history, inappropriate physical exercise [151], harmful effects of hospitalization such as the use of myotoxic drugs, immobility, ventilation was also a risk factor for persisting fatigue and myalgia [152]. Age < 30 years was also found to be an independent risk factor for myalgia post mild and moderate SARS-CoV-2 infection in Jordan [153]. Interestingly, a population-based prospective cohort study in Spain reported that there is a higher incidence of post-COVID-19 myalgia in B group among ABO Blood Groups [154]. Besides, patients infected with Omicron variant were susceptible to myalgia in the long COVID, compared with those infected with the Alpha variant, Delta variant and wild-type strain [155]. Luckily, the risk of muscle pain in patients who had a filled nirmatrelvir or molnupiravir prescription within 5 days of SARS-CoV-2 positive test result decreased at 180 days when compared with control group [156, 157]. Interestingly, there is a significant change in the composition of gut microbiota 1 year post COVID-19 infection [158].

Evaluation

The long COVID has multifaceted influences on the body. To distinguish the etiology of myalgia in long COVID and provide guideline for treatment, multisystem and interdisciplinary evaluations to cover all aspects is necessary. Taken together, we advocate that a comprehensive range of ancillary examination methods, as shown in **Figure 3**.

Pain scales such as the Visual Analog Scale (VAS), Numeric Rating Scale (NRS) [51] assess the nature and intensity of skeletal muscle pain and its impact on daily life. Long COVID contains complex multi-organ disorder, therefore the COVID-19 Yorkshire Rehabilitation Scale (C19-YRS) [159, 160] and the Post-COVID-19 Functional Status scale (PCFS) [161] are recommended to be applied to measure functional outcomes in patients with SARS-CoV-2 infection. Besides, health-related quality of life (HRQoL) can also be measured by the EQ-5D-5L questionnaire before and during the infection [162].

Common hematological indicators of myalgia in long COVID are listed in **Table 1**. They reflect inflammatory state and muscle condition. Blood routine mainly include WBC, lymphocytes and neutrophil count. WBC count > 11 × 10^9/L was a risk factor associated with persistent myalgia after COVID-19 infection [152].

Inflammation markers have C-reactive protein (CRP), ESR, PCT and serum ferritin. A prospective, longitudinal study revealed that there was no statistical significance differences in blood CRP and D-dimer of hospitalized COVID-19 patients followed-up for 12 months. However, these indicators were higher in long-term symptomatic patients than non-long-term symptomatic patients [163]. CRP was positively corre-

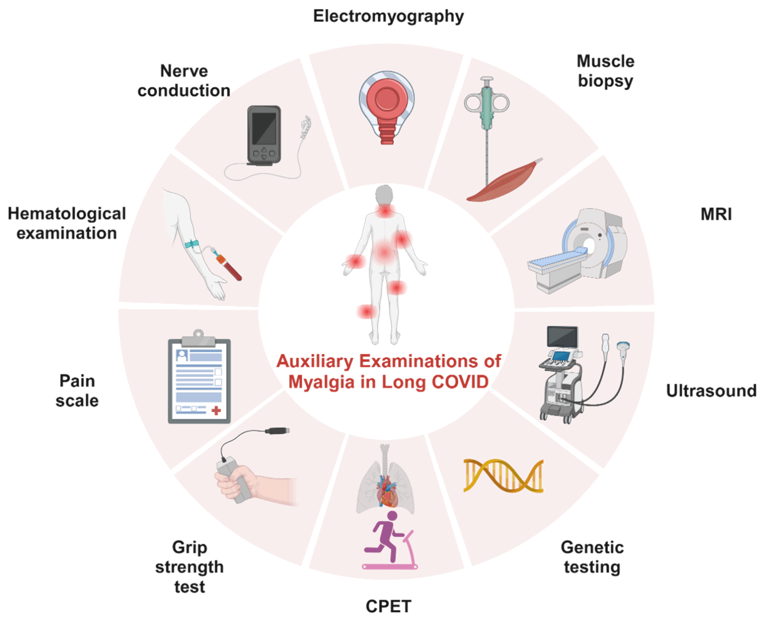

Figure 3. Auxiliary examinations for skeletal muscle pain in long COVID. Muscle biopsy is the gold standard for identifying the cause of skeletal muscle pain. Pain scales are applied to evaluate the nature and intensity of pain while hematological examinations reflect the degree of inflammation and muscle condition. Nerve conduction tests and electromyography help to confirm muscle disease while non-invasive MRI and ultrasound examinations observe histological changes in the affected muscle. Besides, genetic testing help to identify individuals susceptible to myopathy. CPET evaluate oxygen supply condition in the body. Grip strength test is a tool for screening sarcopenia. Created with BioRender.com.

lated with long COVID-19 myalgia at one year after discharge [164]. Besides, common cytokines are IL-1β, IL-6, TNF-α, and INF-γ. It is necessary to check muscle metabolism when patients complain of myalgia. LDH, CK, CK-MB, hs-Troponin-T are widely applied. To diagnose or exclude coexisting rheumatic immune diseases, rheumatoid factor, antinuclear antibody, anticyclic citrullinated peptide, anticardiolipin, and creatine phosphokinase tests are advised [165]. In addition, blood gas analysis reflect the oxygen supply of the body [166]. Certainly, it is recommended that blood oxygen levels can be monitored using a pulse oximeter. At the third month follow-up visit, oxygen saturations at rest and after 6-min walk test of patients with prior intensive care hospitalization were lower than those without [167]. INR, fibrinogen, D-dimer [168-170], aPTT, PT, and TT represent coagulation function. A cross-sectional study following mild COVID-19 cases for 3 months found that patients with persistent myalgia were always along with higher fibrinogen levels [76]. Moreover, plasma proteome profile of patients with fibromyalgia exhibited increased fibrinogen [171]. It is well-known that fibrin engage in inflammation, tissue injury, remodeling, and repair by multiple cellular receptors and mechanisms [172]. Hence, fibrinogen may be a sensitive biological marker of myalgia in long COVID.

Nutritional status is provided by hemoglobin and albumin. Although SARS-CoV-2 can precipitate multisystem disorder and other organ systems can contribute to secondary persistent myalgia, hematological indicators such as ALP, ALT, AST, Creatinine are beneficial to exclude potential involvement of other organ systems [168]. Elevated plasma taurine concentrations were reported in the 3-month COVID-19 follow-up patients with respect to controls. Taurine is not a specific marker but indicative of possible skeletal muscles damage [173]. Last but not least, serum electrolyte mainly potassium and sodium play an important role in skeletal muscle electrophysiology.

Electromyography (EMG) and nerve conduction tests are beneficial to confirm muscle disease and exclude alternative diagnoses such as motor neuron disease [174]. Muscle biopsy is considered as the gold standard for diagnosing muscle diseases, but data on skeletal muscle biopsies in patients with COVID-19 are scarce [175-177]. Sepsis and coagulation dysfunction such as prolonged bleeding and recovery time result in a low muscle biopsy rate. In contrast, non-invasive imaging examinations are more popular. They can support diagnosis and describe histological changes in the affected tissues, with MRI being the preferred method [178-181] and ultrasound being the second one. Mehan described a cohort study of 9 post-COVID-19 patients who underwent spinal MRI, among whom 7 had back pain or bilateral leg pain, and MRI showed paraspinal muscle inflammation in 7 cases, predominantly characterized by intramuscular edema or enhancement, offering a radiological evidence for myositis as a potential mechanism for long COVID-associated myalgia [182]. A small-scale prospective study has indicated attenuation of most plasma skeletal muscle injury indicators such as cardiac troponin Ic and CRP, despite the persistence of extracellular volume (ECV) abnormalities at 3 months after acute COVID-19. In this study, the researchers measured extracellular volume (ECV) in the shoulder skeletal muscle using cardiac magnetic resonance (CMR) in 19 patients without any prior history of cardiac disease but with a peak troponin-Ic > 50 ng/ml at the time of the first COVID-wave. 74% of patients had extracellular volume (ECV) abnormalities in the shoulder skeletal muscle at the first CMR examination (median of 3 months), with most plasma indicators having essentially returned to normal levels. At the second CMR (median of 11 months), ECV in the skeletal muscle had significantly decreased or returned to normal ranges in 13 patients. This study also provides insights into the course of skeletal muscle edema and method of examination after COVID-19 infection [183].

Besides, genetic testing can help to identify individuals susceptible to myopathy. Antioxidant Genetic Profile studies suggested that individuals carrying GSTP1ABIleIle/GSTO1AlaAla/GPX1LeuLeu/GPX3CC genotype were more susceptible with long-COVID myalgia when compared with GSTP1ABValVal/GSTO1AspAsp/GPX1ProPro/GPX3TT genotype, indicating the involvement of genetic susceptibility in long-COVID myalgia [184].

Cardiopulmonary exercise testing (CPET) is a mature test which can be applied to reflect the oxygen supply of patients with persistent skeletal muscle pain after COVID-19. TLC% pred was negatively correlated with long COVID-19 myalgia at one year after discharge [164]. Besides, a portable spirometer (Conter® SP10) is recommended to evaluate respiratory function. Moreover, Grip strength test is an available tool for screening of sarcopenia.

Treatments

Treatment of people with myalgia post acute COVID-19 infection requires a multi-disciplinary approach. Since it is an emerging disease, the knowledge regarding treatment is still evolving. So far, there is no specific pharmacological or surgical treatment for myalgia in long COVID. However, we found that rehabilitation interventions for myalgia in long COVID contain but are not limited to management of pain, strength training [185]. Drug, nutraceutical therapy, gut microbiome-targeted therapy, interventional therapy are beneficial for pain relief in specific circumstance.

Management of pain

Drug: The most common analgesics drugs taken by post-acute COVID-19 outpatient service with persistent myalgia in Italy were acetaminophen (31%), ibuprofen (31%) and other non-steroidal anti-inflammatory drug (NSAID) (29.5%). Analgesic therapy relieved pain in 84% subjects [186]. Besides, immunomodulators such as glucocorticoids play an important role in anti-inflammation [181, 187].

Gabapentinoids (pregabalin) are recommended to be the first-line drug for treatment of fibromyalgia [188]. So far, pregabalin has been proved to relieve pain symptoms [189] and reduce anxiety [190], and chronic cough [191] in patients during and after COVID-19. Gabapentin, another drug which has a similar pharmacokinetic profile but more slowly and variably absorbed than pregabalin, has been reported to effectivly reduce the pain symptom of a 40-year-old woman diagnosed with COVID-19 with acute symptoms while acetaminophen, NSAIDs, and opioids can not alleviate this patient's pain [192]. Therefore, pregabalin and Gabapentin may be promising drugs to treat myalgia in long COVID.

Nutraceutical therapy: Nutraceutical therapy includes polydatin, zinc, melatonin, vitamin D3 [187] and creatine. Polydatin is demonstrated to decrease the production of IL-17 and oxygen free radicals based on peripheral blood mononuclear cells study. This drug is approved by Food and Drug Administration (FDA) from May 2020 to treat COVID-19. Zinc supplementation inhibits gene expression of IL-1β and TNF-α to downregulate inflammatory cytokines [8, 193].

The cytokine storm in long COVID can partly ascribe to the conversion of macrophages from anti-inflammatory M2 to proinflammatory M1, which can be reversed by Melatonin [194]. Besides, melatonin can neutralize cytokines such as TNF-α, IL-1β, IL-6, IL-8 and IL-10 [195]. Therefore, Melatonin plays a role in antioxidation, anti-inflammation, and immuno-modulation.

Vitamin D as an immunomodulator is able to enhance the development of Th2 cells and suppress Th17 [196, 197]. Since vitamin D reduces renin generation and activates the pro-renin receptor, it has a negative regulatory effect on the RAS [150].

The creatine levels in vastus medialis muscle can be assessed by proton magnetic resonance spectroscopy (MRS), a gold standard noninvasive technique. The creatine concentration of long COVID patients was significantly lower compared with general population. Besides, long COVID patients whose muscle creatine levels were lower were susceptible with more severe myalgia. Exogenous administration of creatine is a possible strategy to correct the deficit and help relieve myalgia in this specific clinical population [198].

Gut microbiome-targeted therapy: Gut microbiome-targeted therapy for the myalgia of PACS exhibit huge potential. The features of gut microbiomes in patients with PACS were decreased microbial diversity and richness, reduced abundance of short-chain fatty-acid producing bacteria after SARS-CoV-2 clearance [164, 199] and increased of pathogenic bacteria such as Klebsiella genus. A micro-encapsulated lyophilised powder, called SIM01, contains 20 billion colonyforming units of three bacterial strains and three prebiotic compounds. The bacterial strains are B adolescentis, Bifidobacterium bifidum and Bifidobacterium longum and the prebiotic compounds are galactooligosaccharides, xylo-oligosaccharides, and resistant dextrin [200]. In a randomised, doubleblind, placebo-controlled trial, more PACS patients in the SIM01 group achieved relieved muscle pain after 6 months of treatment compared with placebo vitamin C group. Increased bacterial diversity and short-chain acid-producing bacteria A and decreased pathogenic bacteria associated with PACS such as Klebsiella genus in the gut microbiota of SIM01 group provide plausible mechanisms to explain the clinical benefits observed for SIM01 in relieving myalgia in long COVID [201].

Interventional therapy: Interestingly, myalgia in long COVID may be a new-onset myofascial pain. Trigger point injections and dry needling achieved effective outcome in relieving short- and long-term pain. However, we need to expand study population to further verify the conclusion [202].

Rehabilitation

The rehabilitation of myalgia in long COVID should be conducted under the guidance of the framework of the International Classification of Functioning, Disability, and Health. It is no doubt that rehabilitation start as early as possible to reduce the harmful effects of the disease such as sarcopenia, thrombosis. Inadequate physical activity was associated with a higher prevalence of myalgia in COVID-19 Survivors with Post-Acute Symptoms [203]. What's more, the type, intensity, frequency, and duration of exercise are supposed to be personalized, incremental and adjustable according to patients' specific goals, demands and priorities [88].

Currently, whole-body cryostimulation (WBC) is being applied for relieving symptoms in fibromyalgia, muscle soreness after strenuous physical exercise [204], post-Covid syndrome [205]. This new physical therapy can train the autonomic nervous system [206] and decrease the production of pro-inflammatory and oxidative substances [207]. Unfortunately, evidence of the clinical benefits of WBC remains preliminary stage because of limited sample sizes and methodological issues. However, we believe that it is a matter of time for the medical use of WBC to be popular in the field of rehabilitation.

Besides, studies revealed that patients suffering from myalgia due to long COVID can benefit from eccentric training (ECC). This is a novel alternative to conventional concentric (CONC) exercise. ECC not only reduces cardiopulmonary stress, inflammatory and oxidative stress (OS), but also improves muscle mass. Consequently, ECC improves cardiopulmonary capacity and mitigates dyspnoea and fatigue. However, ECC can induce muscle injury at the onset of exercise and aged patients are prone to muscle damage. Luckily, muscle damages attenuate when ECC exercises persist [208]. Therefore, it is necessary to monitor the side effect of ECC in order to achieve maximum benefit.

Conclusion

The persistent skeletal muscle pain in long COVID is due to abnormal activation of inflammatory response, myopathy, and neurological damage. In addition, dysregulation of the renin-angiotensin system, history of musculoskeletal pain, myotoxic drugs, immobility, age, blood group, virus strain, anti-virus drugs and gut microbiome contribute to the development of myalgia in Long COVID. We believe that in the future, a comprehensive approach that integrates pain scales, hematological tests, nerve conduction tests, electromyography, muscle biopsy, imaging tests such as MRI and musculoskeletal ultrasound, genetic testing, cardiopulmonary exercise testing, grip strength testing, and other examinations will provide a more detailed comprehension of the pathological and physiological mechanisms of post-COVID-19 persistent musculoskeletal pain. So far, the rate of muscle biopsy in patients with persistent musculoskeletal pain post-COVID-19 is low. Therefore, we call on patients with unrelieved skeletal muscle pain post-COVID-19 to complete this examination as much as possible. Rehabilitation interventions for myalgia in long COVID are limited. So far, interventions are drug, nutraceutical therapy, gut microbiome-targeted therapy, interventional therapy and strength training. The relief of skeletal muscle pain will accelerate rehabilitation process, improve activities of daily living, and enhance the quality of life, promoting individuals return to society with profound significance.

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Disclosure of conflict of interest

None.

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