Effect of physical activity on long COVID fatigue: an unsolved enigma

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Abstract

COVID-19 disease is well documented and often the most common symptoms include myalgia and muscle fatigue. Approximately 10% of those infected complain of persistent fatigue even many months after the end of the acute phase of the disease. This gives rise to a condition different from the previous one and commonly known as 'post-acute COVID-19 syndrome' or simply Long-COVID. Although the origin of muscle fatigue is multifactorial, the state of prolonged fatigue observed in the Long-COVID syndrome suggests the existence of a possible state of atrophy or rather acute sarcopenia. Under these conditions, the use of physical activity programs can effectively counteract the state of atrophy underlying the fatigue phenomena observed. If this is also the situation during the Long-COVID, the muscular symptom should be positively influenced by the administration of programmed physical activity cycles. In fact, in patients with Long-COVID, the few published papers seem to indicate that patients who are physically active and who make an effort to engage in physical activity even during the illness have decreased duration and intensity of the illness. However, analysis of the studies in the literature also suggests that a small percentage of people with Long-COVID do not appear to benefit from the application of physical activity programs, so further studies on homogeneous samples are needed to provide a firm answer to the question: can planned physical activity help patients during the pathological course of Long-COVID?

Key Words: SARS-CoV-2; muscle fatigue; Long-COVID syndrome; physical activity; skeletal muscle.

Eur J Transl Myol 33 (3) 11639, 2023 doi: 10.4081/ejtm.2023.11639

Today we live in a time when the COVID-19 pandemic seems to be loosening its grip, but as if to remind us of its existence, it is leaving behind a significant group of acute infection survivors who have not returned to pre-COVID normality, but who show symptoms of functional impairment from which they continue to suffer for weeks or months. This condition, known generically as Long-COVID, leaves those affected in a state of prostration and difficulty in carrying out normal daily activities and a return to the state that existed before the SARS-CoV-2 (severe acute respiratory syndrome by Corona virus 2) infection.[1,2] Further confusion arises from the different names used to define the condition. According to the UK's National Institute for Health and Care Excellence (NICE), 'post-acute COVID-19 syndrome' (PACS) can be further subdivided into a subacute phase, in which the changes associated with the disease persist for at least 4-12 weeks, and a chronic phase, in which symptoms persist for more than 12 weeks after the onset of the disease, as reported by National Institute for Health and Care Excellence (UK). COVID-19 rapid guideline: managing the long-term effects of COVID-19, available from: https://www.nice.org.uk/guidance/ng188. The World Health Organisation (WHO) defines Long-COVID as a condition of persistent, debilitating psychophysical alteration that is present at least 3 months after the onset of acute COVID-19 symptoms and persists for at least 2 months without

being associated with another diagnosis (World Health Organization: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1). In addition, the variety and severity of the functional changes that occur during this period are not well understood, nor are specific intervention plans, including pharmacological approaches, able to significantly influence the intensity and duration of the changes identified. However, this does not mean that there are no specific molecular and/or clinical markers to define the onset of the disease.[3,4,5]

Aim of the review

The most common symptom in patient with Long COVID diagnosis from the Long-COVID syndrome is fatigue, which makes daily activities difficult and as in people suffering from Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS), can lead to changes in the psycho-affective state.[6] Although the origin of muscular fatigue is multifactorial, the state of prolonged fatigue seen in the Long-COVID may be linked to the establishment of cellular atrophy with consequent loss of muscle mass.[7] As reported in Figure 1, the steps of the mechanism leading to this situation may be schematized as follows: the virus induces molecular changes in the muscle cells (stress), followed by the activation of atrophic processes that lead to prolonged fatigue.[8] Although the mechanisms are not yet fully understood, muscular atrophy, which results in the loss of the muscle's ability to produce force, is directly linked to the likelihood of death of muscle cells.[9] This makes the loss of muscle strength a marker of the severity of the subject's functional situation.[10] If a state of muscle atrophy is established in Long-COVID, the loss of fibrillar organization, the establishment of autophagic processes and mitochondrial dysfunction may lead to a decrease in anabolism and an increase in catabolism, with a consequent acceleration of muscle fatigue.[11] Physical activity is considered to be one of the most important measures that can be taken to effectively counteract the muscular dysfunction (including fatigue) typical of sarcopenia, and change. Exercise is a powerful and therapy capable of reducing both chronic inflammation and oxidative damage. Exercise programs can be both endurance and aerobic, and can regulate balance and movement.[12] Each type of prescribed exercise improves established components of the body's functioning and therefore should be combined according to the particular situation and the resulting responses.[13] The aim of this review is to highlight the attempts that are being made to minimize the negative effects of the presence of the symptom of protracted fatigue in those subjects who are recovering from acute COVID-19. In the absence of a therapeutic intervention scheme capable of pharmacologically reversing this state,[13] we will focus on the results obtained with physical activity programs, as this approach can counteract the state of muscle fiber atrophy.[14] The study for this review was conducted using as data sources (January 2023) both the COVID-19 section of the WHO internal clinical trials registry

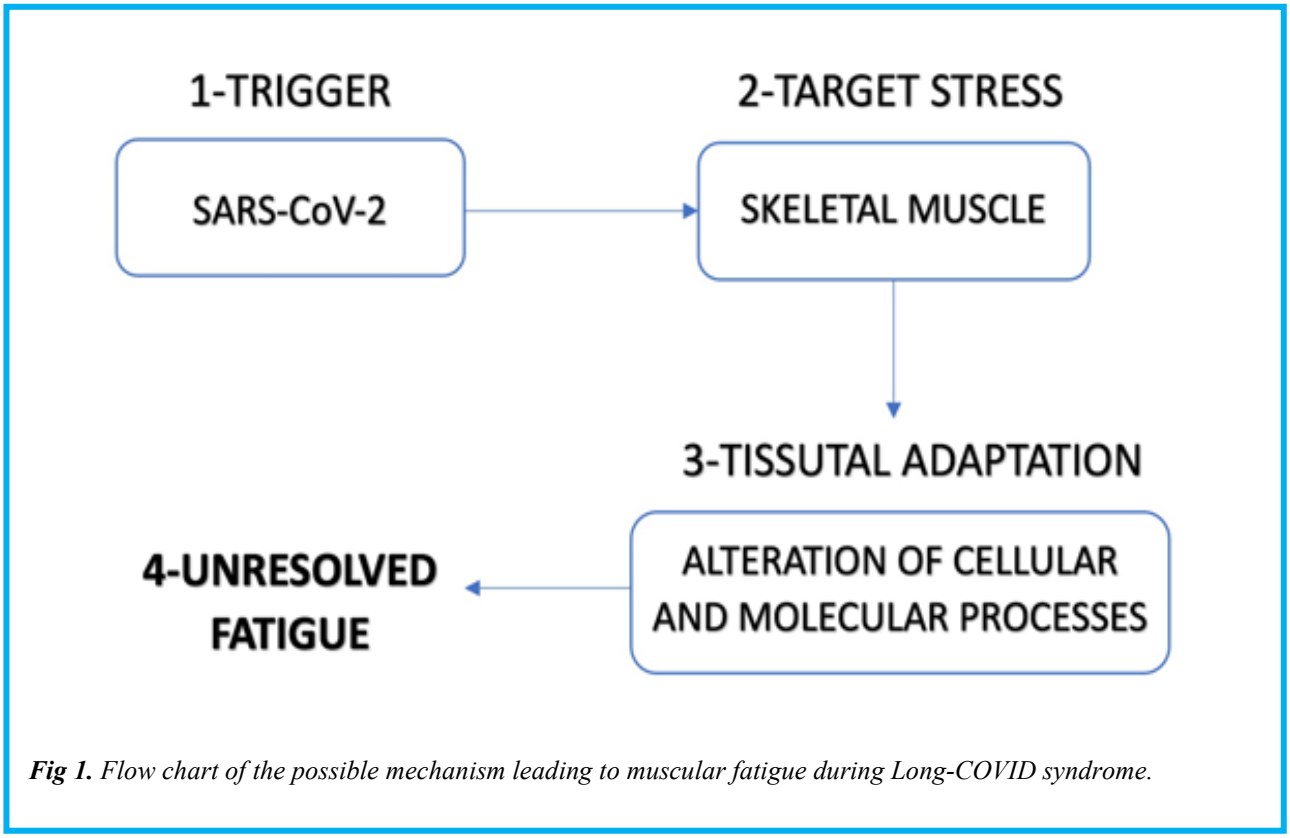

Fig 1. *Flow chart of the possible mechanism leading to muscular fatigue during Long-COVID syndrome.*

platform and, most prominently, the PubMed registry using Boolean operators: AND, OR, NOT. The keywords used were SARS-CoV-2; muscle fatigue; Long-COVID syndrome; physical activity; skeletal muscle.

Difficulties, limitations and bias of Long-COVID studies

Diagnosis of Long-COVID based on symptoms is difficult because most of them, such as fatigue, sleep disturbance, cognitive difficulties, musculoskeletal pain, shortness of breath, etc., are also common in the general population.[15] This situation has been made more complex by the more or less long periods of shut down, which have caused widespread stress among the population, as they have restricted social relations by altering daily routines, with a reduction in travel and physical activity, often in the context of increased social and economic insecurity.[16] This has led to an increase in physical symptoms, independent of COVID infection.[17] Given that in many cases baseline data on pre-morbid symptoms were not available, the effect of COVID-19 on pre-existing symptoms cannot be assessed. Furthermore, there is no universally accepted definition of symptom duration of Long-COVID.[18] Further complications are the variability in vaccine status of those infected and the predominant COVID-19 variant that led to their Long-COVID.[19]

The data reported in Table 1 derived from a very recent systemic review of published data registered on the World Health Organization's International Clinical Trials Platform, published in January 2023 by Fawzy et al.,[20] 388 studies were consistent with the definition of Long-COVID syndrome, but only 45 of them were included in the systematic analysis of the highlighted symptoms for a total of 9751 subjects. Unfortunately, the studies varied considerably, which makes it difficult to interpret the results clearly and to compare them with each other.[20,21] Many studies have pointed out that there is a wide variation in the incidence of Long-COVID syndrome in the different countries studied, ranging from 3.3% in the UK to 39% in Denmark.[22,23] In other words, at least 65 million people worldwide suffer from Long-COVID today, but this number is set to increase.[24] It is known that the severity and death caused by acute SARS-CoV-2 infection is also a direct consequence of the presence of co-morbidities such as cardiovascular disease, renal disease, diabetes, obesity, cancer and organ transplantation, but the relationship between these co-morbidities and the occurrence of Long-COVID remains to be assessed.[25,26] In addition, there is still a significant lack of knowledge about the molecular mechanisms involved in the cellular changes resulting from SARS-CoV-2 infection, not only in muscle but also in other organs or tissues. It is therefore necessary to try to understand whether there are one or more cellular targets of the virus that lead to Long-COVID. One hypothesis is based on the observation of the deleterious effects of this infection on the central nervous system, especially in subjects already suffering from other debilitating conditions such as neurodegenerative diseases.[27] In particular, it has recently been hypothesised that neuronal damage could be due to a dysregulation of mitochondrial function, which is not only an early marker of neurodegenerative processes but also, more generally, a specific sign of general ageing,[28] also because mitochondria are involved in the activation of the inflammatory response.[28] Given that mitochondria must be involved in the phenomenon of muscle fatigue, this organelle becomes a potential target for understanding at least some of the molecular mechanisms underlying the cellular changes induced by the binding of Spike protein of SARS-CoV-2 to angiotensin I converting enzyme 2 (ACE-2). The Physiological Society (UK) organised a virtual meeting in February 2022, the results of which were published in January 2023. The meeting brought together clinical and basic researchers to review risk factors, treatments, and management of Long-COVID patients. One of the main outcomes of this meeting was to highlight how research on Long-COVID has produced more homogeneous results in those populations that can be followed with constant monitoring of their own physical performance, such as military personnel and elite athletes.[20] However, the available data do not provide a firm answer to the question: can exercise reduce recovery times and the severity of Long-COVID?[29,30] On the contrary, some epidemiological studies have shown that physical inactivity is associated with a significantly higher risk of hospitalization.[31] During the period when Long-COVID is present, there is an increase in the sarcopenic state, mainly due to the generalized inflammation induced by SARS-CoV-2 and

Table 1. *Syndrome of Long-COVID-19: incidence of major characteristics registered on WHO International Clinical Trials Platform*

Long-COVID/Total acute COVID	10.0-30.0 % non-hospitalized; 50-70% hospitalized
Presence of fatigue or tiredness	40.0 %
Shortness of breath or dyspnoea	36.0 %
Sleep disturbance or insomnia	29.4 %

the reduction in physical activity. Therefore, the use of specific light physical activity programs (from simple walking to low-intensity endurance exercises) may interrupt this harmful situation and favour the establishment of less intense inflammatory states with a reduction in the sarcopenic state.[32] However, even world-class athletes can develop Long-COVID with severe effects on the athlete's activity.[33] In support of that, there is also a paper.[34] This observational study by our research group was carried out on athletes and/or ski instructors (n=506, including 138 women) from a population (n=6000) who were first infected with SARS-2-CoV-2 and subsequently manifested typical symptoms of Long-COVID and were followed up for one year. The study of this homogeneous population, which was very effectively and continuously followed up by the Sports Medicine Service of two Italian hospitals (Inniken and Brunek, Bolzano), has shown that good fitness, both before and during the illness, combined with strong motivation, can restore the pre-COVID state in about 92% of the subjects within one year, with very little statistical variation within the various groups.[34] In the UK, approximately 10% of elite athletes experienced symptoms of Long-COVID, similar to the general population for more than one month.[35] However, some data from US college athletes showed a much lower prevalence of Long-COVID than in the general population (0.8% at one month).[36] Military personnel tested also showed a similar reduction. As these drastic reductions occurred after the introduction of the vaccines, it is thought that the discrepancy is due to due to prior immunization.[29]

Oxidative stress and polysymptomatology in Long-COVID

In severe and Long-COVID-19 syndrome, the presence of a state of oxidative stress resulting from an imbalance between Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) and antioxidant defence mechanism has been highlighted.[37] Thus, oxidative and nitrosative stress are bidirectionally linked. Given that both nitric oxide (NO) and ROS mediate cellular signalling and activation of defence against pathogens, if there is an imbalance and/or alteration of the oxidant/antioxidant system, cellular components, including proteins, lipids and DNA, will be damaged.[38] This also explains why various organs and systems other than the respiratory epithelium are adversely affected by the presence of SARS-CoV-2.[3,39] An important finding relates to the effect of the syndrome on altered oxygen delivery due to microcoagulation, resulting in altered cellular energy metabolism, mitochondrial uncoupling and the creation of an intracellular oxidative stress status of relevant intensity.[40,41] Within this possibility, the link between oxidative stress in COVID-19 patients, involved in the amplification and perpetuation of the cytokine storm, and cellular hypoxia, leading to the death of infected cells, has also been proposed.[42] The high neutrophil to lymphocyte ratio observed in critically ill COVID-19 patients is also associated with excessive levels of ROS, which induce tissue damage, thrombosis and red blood cell dysfunction, contributing to the severity of the disease.[43] Oxidative stress may be therefore fundamental to the pathophysiology of both COVID-19 and Long-COVID. Indeed, inflammation and oxidative stress are mutually reinforcing, leading to a systemic hyperinflammatory state that is the keystone of the most severe stages of the disease.[37,44] In addition, this possibility has also been shown in a recent paper suggesting the existence of an at least partial correlation between the presence and level of oxidative stress (measured by monitoring several plasma markers) and the occurrence of affective-cognitive deficits mediated by neuro-immune and neuro-oxidative pathways.[45] One of the possibilities as to why a state of generalized oxidative stress develops and then consolidates in subjects with COVID is related to the reduced capacity of antioxidant systems in the presence of SARS-2-Cov-2. Reduced glutathione (GSH), a tripeptide consisting of glutamate, glycine and cysteine, is located in the nuclei and mitochondria of tissues and is the body's most efficient endogenous antioxidant system.[46] GSH is crucial in reducing oxidative stress-induced damage such as inflammation; oxidative stress and inflammation interact with multiplier effect.[47] The levels of total glutathione and the ratio to its oxidised form (GSSG) influence the redox capacity of the GSH/GSSG system. In the case of patients with SARS-CoV-2 infection, experimental studies have shown that hypoxia, when associated with bed rest, directly reduces the total glutathione concentration in whole blood.[48] Figure 2 schematizes the effects of Long-COVID on active and inactive people of both Long-COVID parameters and muscle functional capacity.

Oxidative stress in skeletal muscle of Long-COVID patients

Fatigue is a complex and not fully understood phenomenon that usually occurs after intense and prolonged activity and consists of a deterioration in the functional capacity of a single organ or apparatus (local fatigue) or of the whole organism (general fatigue). Local fatigue, particularly muscular fatigue, is due to a decrease in the high-energy compounds required for contraction (ATP, phosphocreatine) or to an accumulation of the end products of muscle metabolism (lactic acid). Usually of short duration, it is reversible and is perceived as a feeling of tiredness or lack of energy.[49] There is also another type of muscular fatigue that lasts longer, does not disappear with rest and is due to exposure to certain toxic compounds (or drugs) or associated with pathological conditions. The main cause of this second type of fatigue is related to the loss of skeletal muscle mass and consequent atrophy due to negative nitrogen balance, an increase in skeletal muscle protein degradation.[50] The induction of this functional muscle debacle is evident in

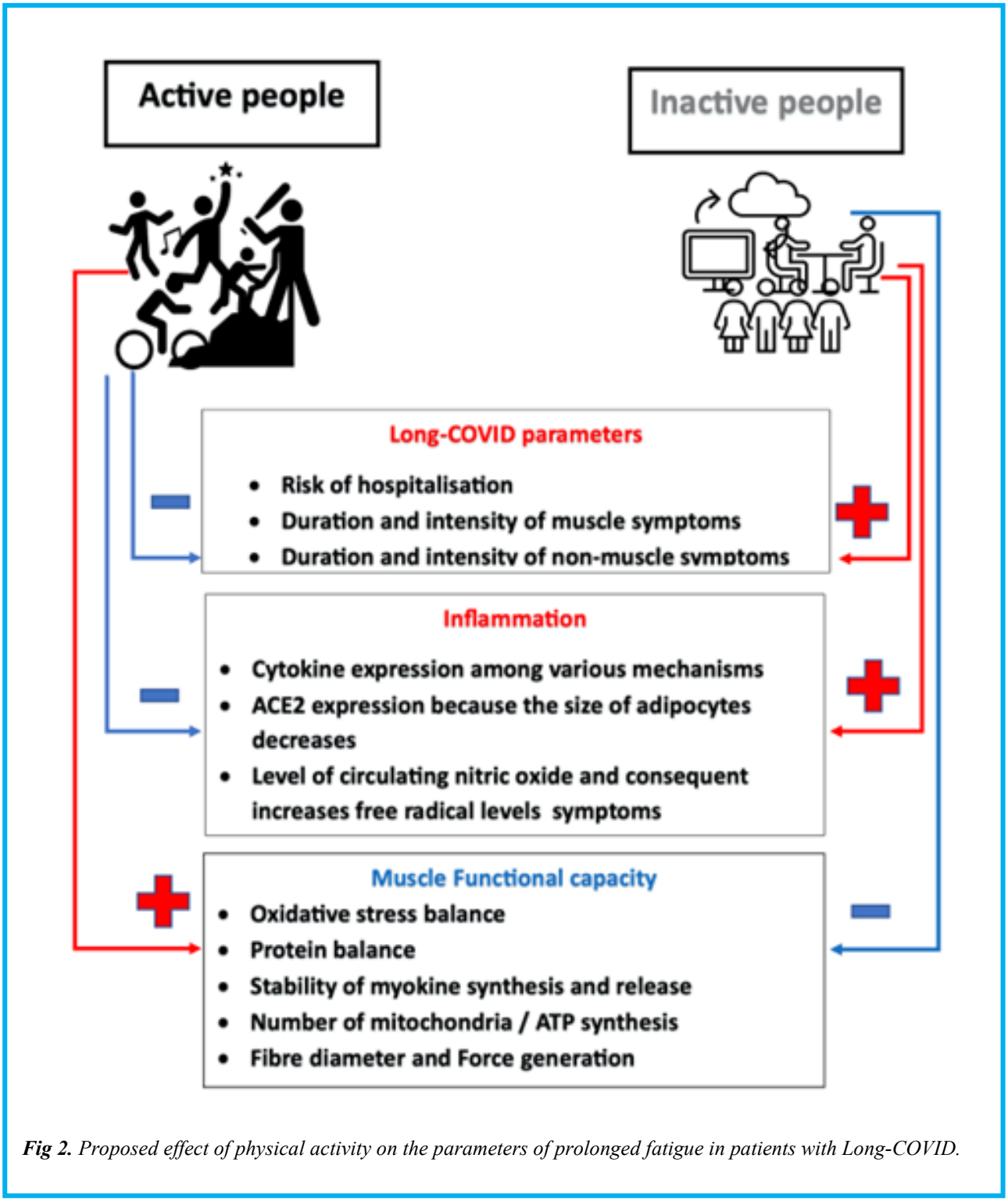

Fig 2. *Proposed effect of physical activity on the parameters of prolonged fatigue in patients with Long-COVID.*

pathophysiological conditions such as ageing, immobility, insulin resistance and diseases associated with systemic inflammation such as arthritis, cardiovascular and respiratory diseases. One of the most noticeable changes that occurs in the majority of people with is the onset of a state of muscular fatigue that preventsong-COVID is the onset of a state of muscular fatigue that prevents the patient from performing their daily activities properly and that is not alleviated by rest,[48] a situation that is ultimately very similar to the musculoskeletal manifestations of ME/CFS.[51] The characteristics that link ME/CFS to Long-COVID are essentially two: the post-viral origin of the functional state and the presence in both categories of a state of a profound prostration that sleep cannot resolve.[52] As in the case of COVID-19, the exact aetiopathogenesis of the

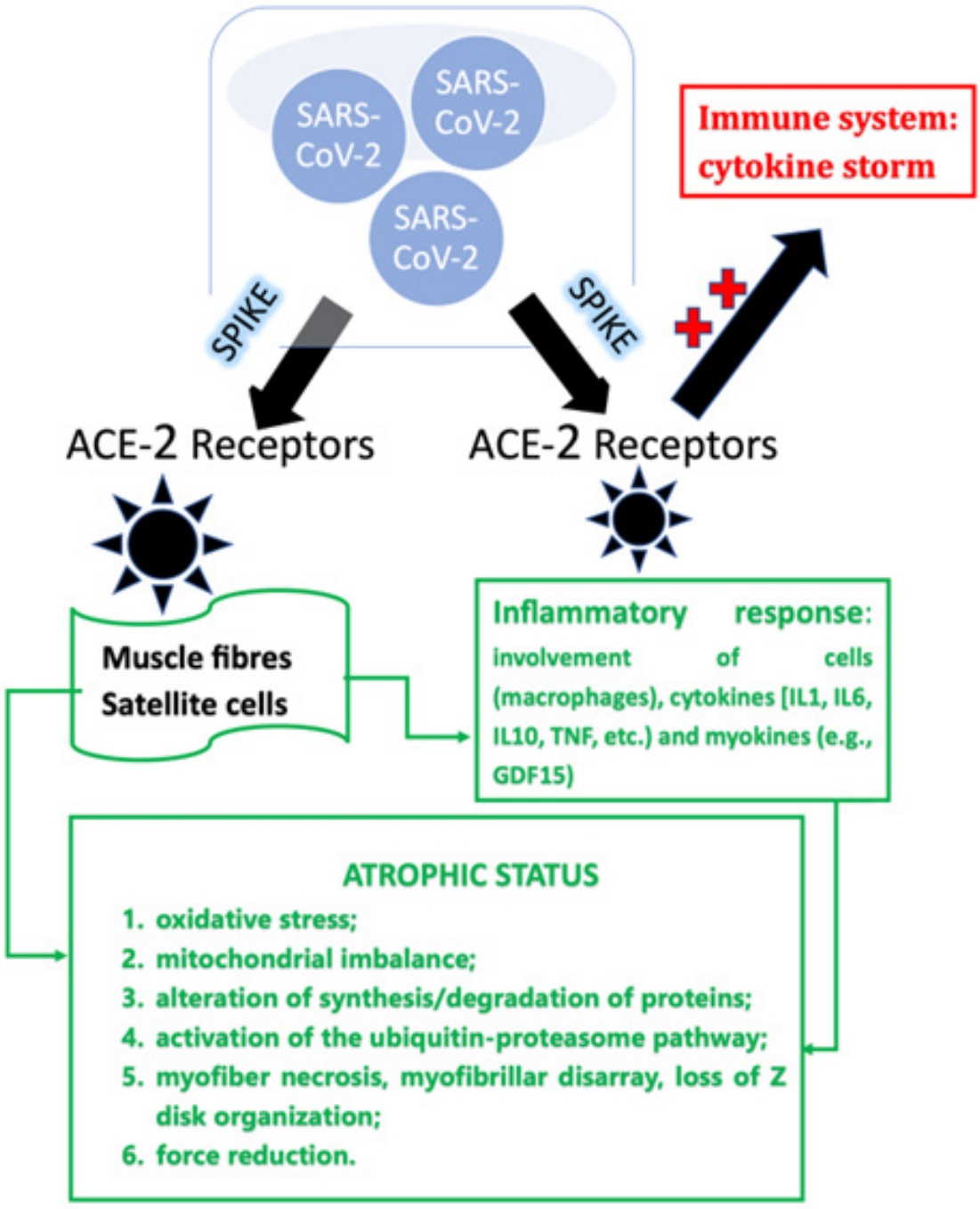

Fig 3. *Mechanisms involved in skeletal muscle of Long-COVID patients.*

pathology of ME/CFS is not known, but certain dysmetabolisms of the neuromuscular system are known that could at least justify the onset of the fatigue phenomenon in both situations.[53] High levels of ROS have been linked to changes in mitochondrial function in ME/CFS muscles, resulting in a reduced rate of ATP synthesis and impaired cellular control.[53,54] The molecular cause of this event is likely to be related to the oxidation of at least two substrates: membrane lipids and DNA, also due to an established inefficiency of scavenging and/or repair in the mitochondria.[55] It is well known that mitochondrial respiration produces ATP, which covers all the chemical reactions required in the body through oxidative phosphorylation or glycolysis. Mitochondrial production capacity increases with stress and fitness when ATP consumption can reach values two

orders of magnitude higher than at absolute rest. However, in doing so, mitochondria produce free radicals that are potentially capable of altering the cellular redox state.[56] It is therefore clear that mitochondrial activity must be involved in both the deficit in energy production and the increase in ROS in muscle fibres; an alteration in this delicate system could account for the state of fatigue seen in both ME/CFS and long-term COVID.[54] In addition, muscle mitochondria are a major source of ROS generation in cells and are therefore highly sensitive to oxidative damage. It has previously been shown that the age-dependent increase in oxidative damage in muscle of healthy subjects may reflect either increased free radical production or insufficient activity of scavenger/repair systems.[57] Histological and molecular data on skeletal muscle from Long-COVID patients are currently very limited. They are mainly based on case reports and are insufficient to define an established hypothesis. Obvious signs of atrophy and regeneration of muscle fibres, the presence of disruption of sarcomeric ultrastructure and loss of myosin are some of the main features derived from observations made on a biopsy sample of vastus lateralis muscle from a middle-aged Long-COVID patient.[44] Studies on the mitochondrial capacity (number and function) of muscles from patients with Long-COVID are also very few and always case reports. A lower capacity to produce energy stimulated by ADP, as well as a lower sensitivity to ADP, was also observed in a young patient who later developed Covid-19. This suggests that there may be early changes in skeletal muscle mitochondrial function before the symptoms of Covid-19 become manifest.[58] In skeletal muscle, metabolic activity and therefore functional capacity (included mitochondrial regulation), is also controlled by a complex system of regulatory factors secreted by the tissue itself called myokines.[59] In many patients with acute Covid-19 indirect evidence supports the presence of mitochondrial stress mediated by a myokine (GDF15) that is released from skeletal muscle, on which it has an autocrine effect. The control of its release is a direct consequence of mitochondrial proteotoxic stress.[60] In conclusion, both in ME/CFS and in Long-COVID (with less evidence), mitochondrial capacity dysfunction and metabolic alterations have been found that may explain at least some aspects of the post-exercise fatigue present in these two pathologies. However, given the paucity and partial inconsistencies of the published studies,[61] it will be necessary to improve the experimental design in future studies, focusing on the homogeneity of the sample and the accuracy of the diagnosis made on the subjects involved.[54]

Can physical activity counteract Long-COVID muscle fatigue?

SARS-CoV-2 infects human cells through its surface glycoprotein, called Spike, which binds with ACE-2 to initiate clinical manifestations in patients with COVID-19 (Figure 3). In skeletal muscle cells, both fibres and satellite cells, ACE-2 is widely expressed.[62] Given that skeletal muscle tissue accounts for approximately 40% of body weight, it is highly likely that the effect of SARS-Cov-2 infection is significantly mediated through its association with this tissue.[63] Regardless of the tissue in which the virus replicates, it causes a massive attack on the immune system, generating a cytokine storm of impressive proportions.[64] But in skeletal muscle cells, the binding of the virus to its receptors alters some cycles related to protein metabolism,[65] leading to the formation of a sarcopenic-like state with activation of atrophic pathways and mitochondrial imbalance with severe alteration of the cellular oxidative state.[66,67] Moreover, considering that another consequence of the disease is the alteration in the synthesis and release of some of the myokines that regulate protein synthesis, it is not surprising that one of the consequences of Covid-19 is a decrease in muscle mass and consequently in developed strength.[11] For these reasons, understanding the effect of COVID-19 on muscle strength may help to clarify the structures and mechanisms, such as ATP synthesis and availability, electromechanical coupling, fibre composition and type, trophic state of the muscle fibre and the muscle regeneration system, that contribute to the onset of the symptom of muscle fatigue.[68] In a paper published this year, the authors showed, without hypothesising a cause-and-effect relationship, that the muscles of the Long-COVID subjects showed a reduction in strength of around 30% in the limb muscles, compatible with a state of muscular atrophy.[69]

Similar results, albeit obtained under different conditions in both hospitalised and non-hospitalised subjects, confirmed the impairment of musculoskeletal structures, but were unable to identify the cause: was the observed atrophy caused by immobility or by the virus?[70]

If SARS-2 were the cause, the viral agent, directly or via the cytokine storm, could lead to pathological changes in skeletal muscle tissue.[71] In an observational study recently published in Diagnostics,[34] we observed in a population of professional and amateur skiers that a habit of constant exercise can alleviate the effects of Long-COVID. When compared with a sample of sedentary people but from the same geographical area (mid-mountain), the intensity and duration of the symptom associated with prolonged fatigue was significantly halved.[34] Indeed, the use of exercise as a means of alleviating the effects of fatigue in patients with Long-COVID has been called into question by the apparent similarity of this symptom to that of patients with ME/CFS.[53] In these patients, the presence of physical (but also emotional or cognitive) stress, many of the symptoms of the disease get worse. This condition has been termed post-stress malaise, and its presence makes it difficult to perform even light physical activity. The use of continuous exercise therapy has been attempted in the past to alleviate, if not solve, this problem[72]. Unfortunately, different attempts at exercise-based rehabilitation programmes have led some authors to

conclude, although not in an unequivocal way, that the use of exercise may even be harmful and that it should be avoided.[73] On the contrary, a Cochrane review, of 8 randomized trials,[74,75]show benefit of graded exercise in ME/CFS. However, in our opinion, these doubts do not seem to be there in people with Long-COVID, at least according to the limited data currently available. In senescence and in the presence of sarcopenic states or in post-infectious phases, the continued practice of physical activity is an integral part of disease state management programmes.[76]

Therefore, in the case of their applicability to patients with post-Covid, an attempt has been made to apply exercise regimens that have already been used in other similar situations.[77] In fact, only a few studies have evaluated exercise regimens in detail, so the final suggestions are very general.[78,79] In a recent systematic review of functional changes after exercise training in post-COVID-19 patients, the authors describe how training programmes consisting of aerobic and resistance exercise can improve functional capacity and quality of life; however, the studies showed methodological heterogeneity and did not compare the results with a control group.[80] At least two studies have been proposed that provide a precise scheme for rehabilitation treatment during and after Long-COVID.[81,82] In the proposal by Cattadori et al.,[81] a multiple exercise programme consisting of aerobic exercise (200-400 minutes per week, 5-7 days per week) and resistance training (two sessions per week). The proposed exercise protocol lasts 12 weeks and, for safety reasons, should be carried out in a rehabilitation centre under the supervision of a specialist for at least 2 weeks; at the end of the 2 weeks, patients can carry it out independently. However, the authors admit that further studies are needed. In the second paper,[82] the authors highlight not so much the results obtained by applying the proposed programmes, but some recommendations for their use, such as the caution that should be exercised when using training protocols that have not been scientifically validated: as

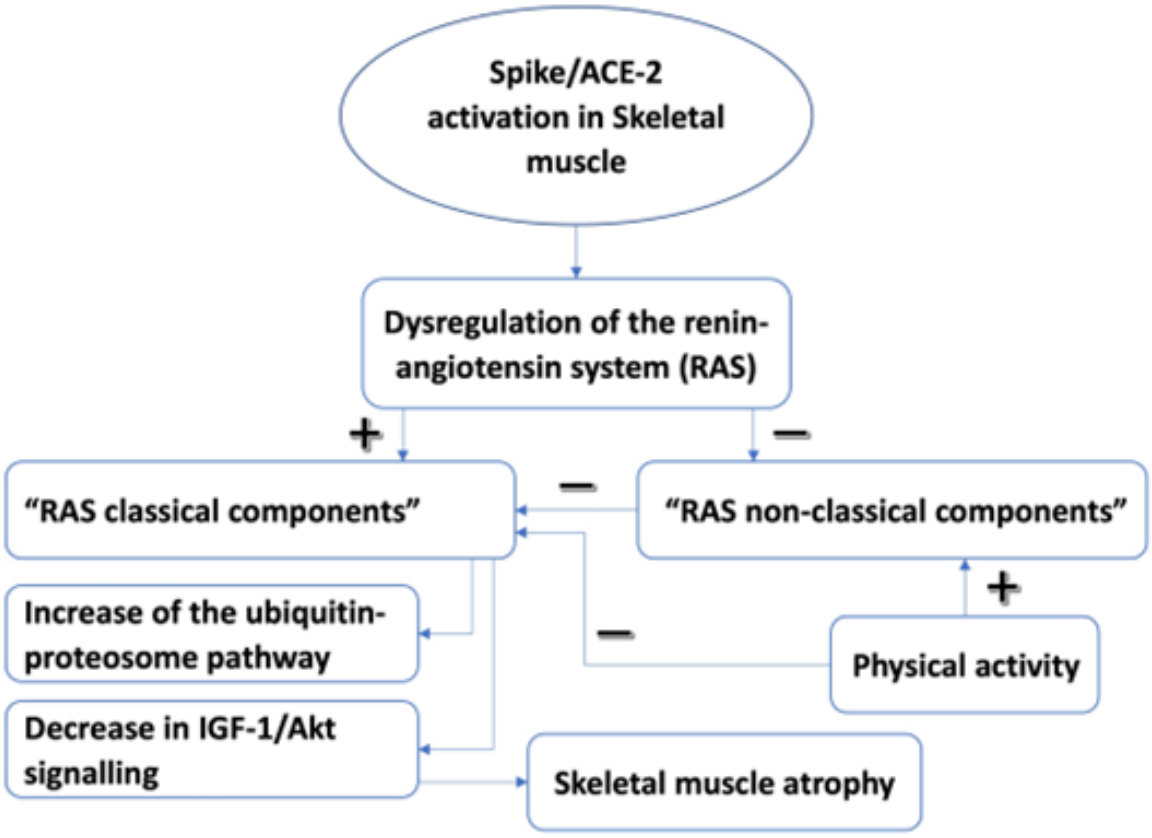

Fig 4. *Possible genesis of Long-COVID derived muscle atrophy. SARS-CoV-2 infection leads to the establishment of a state of atrophy due to the decrease in IGF-1/Akt signalling and the increase in the activity of the ubiquitin-proteosome pathway. This process may be triggered by dysregulation of the renin-angiotensin system (RAS) Hyperactivity of the classical pathway in skeletal muscle has been associated with the state of atrophy; in contrast, activation of the non-classical RAS would have protective effects (see text for more details).*

with all drugs, exercise may not be the right solution for all patients. In addition, continuous monitoring of patients during exercise should be mandatory to avoid post-exercise discomfort and overexertion. The World Health Organisation provides some guidelines for the rehabilitation of CAPS patients to enable them to resume activities of daily living at an appropriate pace that is safe and compatible with the patient's energy capacity. According to the WHO indications, physical activity and exercise programmers should be used with caution, especially in the presence of dyspnoea disproportionate to exertion, inappropriately increased heart rate (tachycardia) and/or chest pain. Even gradual exercise therapy should never be used in the presence of worsening post-exertional symptoms as indicated in the World PT Day |World Physiotherapy (https://hhphysio.com/blog/physiotherapy /world-physioterapy). Reduced physical activity during SARS-CoV-2 infection leads to a state of atrophy with loss of strength and muscle mass.[69] The main players in this situation are the decrease in IGF-1/Akt signalling and the increase in activity of the ubiquitin-proteosome pathway, leading to increased degradation of myofibrillar proteins, activation of autophagic processes and a decrease in mitochondrial number and capacity.[83] Dysregulation of the renin-angiotensin system (RAS) is known to have deleterious effects in skeletal muscle, inducing an atrophic state leading to muscle wasting. This system can be functionally divided into a classical component whose main components are angiotensin converting enzyme (ACE), angiotensin II (Ang-II) and Ang-II receptors (AT). There is another component of the RAS called the non-classical axis, which consists of ACE2, angiotensin 1-7 [Ang (1-7)] and the Mas receptor.[84] Hyperactivity of the classical pathway in skeletal muscle is associated with atrophy, whereas activation of the non-classical RAS would be beneficial. In addition, it is known, at least in animal models, that exercise can stimulate the ACE2-Ang-(1-7)-Mas receptor axis in parallel with inhibition of the ACE-Ang II-AT1 receptor pathway.[85] On the basis of these considerations and the studies reported, it can therefore be assumed that during SARS-2 infection, Spike binding to the ACE-2 receptor is capable of altering the classical RAS pathway, leading to the atrophy phenomena that can lead to the onset of fatigue. In this situation, if the non-classical RAS pathway is also activated by an appropriate exercise programme, the muscular symptomatology of long-COVID could benefit (see Figure 4).

Conclusions

Exercise has an important functional role as a key determinant of health status and as a preventive and therapeutic agent in various diseases. The levels at which the correct use of physical activity acts are diverse, and its effects determine the maintenance of homeostasis throughout the organism, acting through tissue, cellular and molecular mechanisms, as well as endocrine and immune modalities. In summary, literature derived from the observation of subjects suffering from Long-COVID-19 but engaged in continuous motor activity, both competitive and non-competitive, seem to show a better prognosis in terms of both the duration and intensity of fatigue-related symptoms. In fact, fatigue was less of a problem for these patients, both in terms of duration and intensity, than for sedentary people. However, in a small but significant percentage of the population (8%) using physical activity as a treatment for Long-COVID, exercise provides no benefit.[23] Unfortunately, the data available today do not allow us to answer this question. For example, we do not know whether there are gender differences in the effects of physical activity programmes, nor do we know whether modulating activity between the strength and endurance components during training leads to significant differences in the results obtained. In conclusion, further studies in homogeneous samples are needed to optimize the care of patients suffering from Long-COVID via exercise regimens and other modalities.

List of acronyms

ACE-2 angiotensin-converting enzyme 2
COVID-19 - Corona virus 2, 2019
GSH- Reduced glutathione
GSSG- Oxidised form of glutathione
Long-COVID - post-acute COVID-19 syndrome
ME/CFS-Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
NICE - National Institute for Health and Care Excellence
PACS - post-acute COVID-19 syndrome
RAS- Renin Angiotensin System
RNS- Reactive Nitrogen Species
ROS- Reactive Oxygen Species
SARS-CoV-2 - Severe Acute Respiratory Syndrome by Corona virus 2
WHO - World Health Organisation

Contributions of Authors

Conceptualization, FC, PVG and GF-I; methodology, ESD; data curation, FC and ESD; writing—original draft preparation, GF-. and ESD, review and editing, ESD, GF-I, PVG. All authors have read and agreed to the final edited version of the manuscript.

Acknowledgments None.

Funding

This research received no external funding.

Conflict of Interest

The authors declare they have no fconflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Submission: August 4, 2023
Revision received: August 19, 2023
Accepted for publication: August 19, 2023