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The Impact of Long COVID-19 on Muscle Health

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KEYWORDS

• COVID-19 • Postacute COVID-19 syndrome • Muscle mass • Aging
• Body composition • Muscle strength • Muscle function • Quality of life

KEY POINTS

- Long COVID negatively impacts muscle mass, function, and quality of life.
- Longitudinal studies, including long-term assessment of muscle mass and function, can help identify the impact of long COVID on muscle health.
- Respiratory muscle dysfunction may be a marker of muscle wasting and recovery outcome during long COVID.
- Age differences should be explored in future studies to better understand how long COVID affects muscle health across the life course.

INTRODUCTION

The World Health Organization (WHO) has recently created a clinical case definition to frame a condition of symptom persistence following a coronavirus disease 2019 (COVID-19).[1] The condition, known as post-COVID-19, postacute sequelae of COVID-19, or long COVID, develops in individuals with a history of probable or

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confirmed SARS-CoV-2 infection in the past 3 months and encompasses a wide range of signs and symptoms that persists for weeks or months and cannot be explained by an alternative diagnosis. Long COVID symptoms can develop de novo after acute COVID-19 or persist from the initial illness. Common symptoms include, but are not limited to shortness of breath, fatigue, weakness, cognitive dysfunction, body aches, sore throat, cough, diarrhea, anosmia, and dysgeusia.[2,3] It has been estimated that up to 80% of people who recovered from a COVID-19 episode experience at least one long-term symptom.[4,5]

Long COVID has been shown to negatively impact several organs and body systems, including skeletal muscle.[6] This organ is essential for movement, balance, posture, daily activities, and a variety of metabolic functions.[7] Indeed, more than 60% of individuals presenting with long COVID have reported fatigue, lower mobility, and weakness.[8,9] Interestingly, a high prevalence of skeletal muscle weakness and low physical performance has been reported in COVID-19 survivors without prior musculoskeletal problems.[10] Older adults are at increased risk of developing musculoskeletal symptoms during long COVID,[11,12] possibly because of the combined effect of viral infection and preexisting age-related declines in muscle mass and function.

The purpose of this narrative review is to describe the potential long-term effects of COVID-19 on muscle health in adults. We used the term muscle health to describe muscle mass and function (ie, strength and performance). Here, we describe muscle health outcomes in people with long COVID presenting with different degrees of disease severity and assessed by different body composition and physical function methods. In addition, we report the impact of long COVID on quality of life (QoL) related to muscle health.

MECHANISMS OF MUSCLE DAMAGE IN LONG COVID

After entering the human body, the spike protein of SARS-CoV-2 binds to the cell membrane receptor angiotensin converter enzyme 2 (ACE2) using the transmembrane protease, serine 2 (TMPRSS2) to deliver its genetic material.[13,14] Upon cellular entry, the virus replicates and causes disruption of cellular functions, leading to cell death and tissue dysfunction.[15] Because ACE2 and TMPRSS2 are expressed in most tissues and organs, SARS-CoV-2 can invade and cause damage to almost all body systems, including the skeletal muscle.[16] In addition to direct virus-mediated injury, other factors contributing to muscle damage during a COVID-19 episode include systemic inflammation, electrolyte disturbances, critical ill myopathy, drugs (eg, corticosteroids), and hypoxia.[16] Some of these mechanisms and factors are likely to play a role in musculoskeletal damage and its related outcomes in long COVID.

Inflammation is advocated as one of the primary factors associated with muscle catabolism in patients with long COVID.[10] Systemic inflammation sustained by increased blood levels of interferon gamma, C-reactive protein, interleukin (IL) 6, IL-2, IL-10, and tumor necrosis factor α has been described in people with long COVID.[17,18] These proinflammatory cytokines are well known for their ability to negatively impact muscle protein metabolism through triggering catabolic pathways and suppressing anabolism.[19] The mechanisms underlying the transition from acute to chronic inflammation after a COVID-19 episode are largely unknown. Anomalous microclots enriched in acute-phase inflammatory molecules and resistant to fibrinolysis have been found in blood samples of individuals with long COVID.[20] Hence, it is plausible that inflammatory cytokines trapped within microclots may leak into the circulation, thereby maintaining a state of chronic inflammation. SARS-CoV-2 infection was also shown to cause long-term proinflammatory reprogramming of

macrophages, possibly via epigenetic modifications.[21] In older COVID-19 survivors, SARS-CoV-2–induced long-term inflammation may superimpose to the age-dependent chronic inflammation (inflamm-aging), leading to more severe disruption of muscle metabolic homeostasis.[5] Over time, proinflammatory cytokines lead to muscle fiber proteolysis, decreased protein synthesis, hindered capacity of satellite cells to proliferate and differentiate, and eventually fibrosis.[15]

Muscular issues in long COVID are more likely to occur in patients with more severe diseases who had been admitted to the intensive care unit (ICU).[22,23] However, Doykov and colleagues[24] observed an increase in proinflammatory biomarkers and disruption of muscle metabolic homeostasis 40 to 60 days after initial diagnosis in individuals who had mild and asymptomatic COVID-19.

Physical inactivity potentially exacerbated by quarantine and hospitalization has also a major impact on muscle mass and function.[6] Lastly, inadequate dietary intake and poor nutritional status, which are common during a COVID-19 episode, negatively impact skeletal muscle during recovery.[25,26] Bedock and colleagues[27] observed that ~42% of hospitalized patients with COVID-19 were malnourished and the prevalence increased to ~67% in those admitted to ICU. It has been hypothesized that reduced food intake caused by COVID-19 symptoms (ie, anorexia, diarrhea, vomiting, nausea, abdominal pain, anosmia, and dysgeusia) and increased nutritional needs are main factors leading to malnutrition.[25,27,28] **Fig. 1** illustrates some of the mechanisms associated with muscle damage in individuals with long COVID.

CURRENT EVIDENCE

A summary of findings specifically related to body composition, muscle function, and QoL related to muscle health is shown in **Table 1**.

Muscle Mass and Other Body Composition Compartments

Body composition was assessed in 4 studies investigating long-term health sequelae of COVID-19 infection[29–32] using the following techniques: bioelectrical impedance analysis (BIA),[29,32] computed tomography (CT),[30] and ultrasound (US).[31]

After 4 to 5 weeks of COVID-19 infection, Tanriverdi and colleagues[32] assessed fat mass and fat-free mass (FFM) using BIA in people who recovered from mild (n = 25) and moderate (n = 23) disease severity. The 2 body compartments were not different between individuals who suffered mild or moderate disease, although a sex-specific comparison was not presented.[32] Another study assessed the body composition of patients discharged after COVID-19 using BIA.[29] Patients were classified according to disease severity (mild: n = 27; moderate: n = 51; severe: n = 26; critical: n = 20).[29] Fat-free mass index (FFMI) was calculated as FFM/height^2 and classified as low in 19% of the patients (7/27; 5/51; 7/26; 4/20).[29] No differences in FFMI or in the number of patients with low FFMI were observed among the 4 groups.[29]

In a prospective cohort study, 46 patients who were admitted to the ICU and received mechanical ventilation were assessed 3 months after hospital discharge.[30] Thoracic CT scans at the 12th vertebra were used to quantify skeletal muscle area, skeletal muscle radiation attenuation (an index of muscle quality), and intermuscular adipose tissue (IMAT).[30] Patients were categorized based on their performance on the 6-min walk distance (6MWD) test as having normal (n = 24) or low physical performance (<80% of predicted, n = 22).[30] Both skeletal muscle area and skeletal muscle radiation did not differ between patient subgroups; however, IMAT was higher in those with low physical performance.[30] Physical performance remained significantly

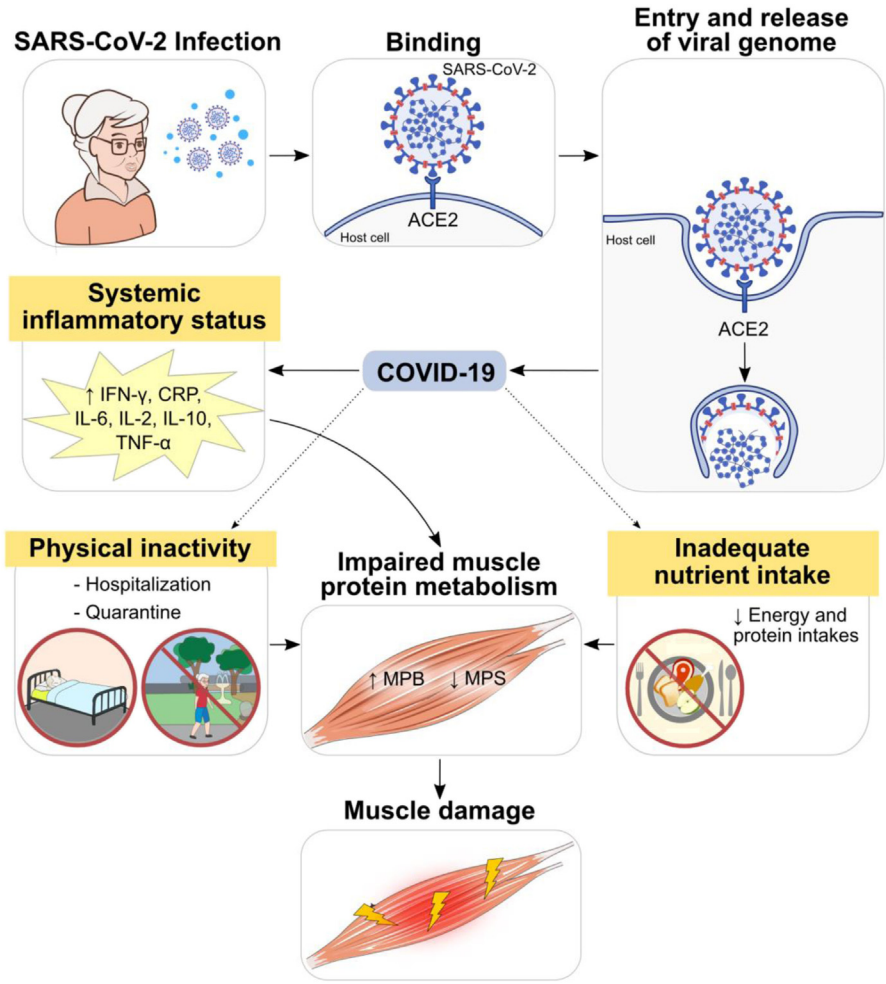

Fig. 1. Potential mechanisms of muscle damage in patients with long COVID-19. Systemic inflammatory state during the acute phase results in chronic release of proinflammatory cytokines, contributing to imbalances in muscle protein metabolism and impaired muscle health. In addition, physical inactivity due to hospitalization and quarantine as well as inadequate nutrition intake may also negatively impact muscle mass, quality, and function. (*From* Servier Medical Art. Servier. Available at https://smart.servier.com/; under Creative Commons Attribution 3.0 Unported License)

associated with IMAT after adjusting for age, sex, handgrip strength, and diffusing capacity for carbon monoxide.[30]

US images of the diaphragm muscle were assessed in 21 patients admitted to rehabilitation after severe COVID-19 and compared with 11 non–COVID-19 controls who needed ventilator support during hospitalization.[31] Diaphragm muscle thickness was not different between cases and controls, but the thickening ratio (ie, maximal inspiration/end-expiration) was reduced in patients who had been diagnosed with COVID-19, suggesting reduced diaphragm function.[31]

Table 1
Summary of findings related to body composition, muscle function, and quality of life related to muscle health in individuals with long COVID

Body Composition

Reference	Body Compartment	Technique	Timeline	Selected Main Findings
Tanriverdi et al,[32] 2021	FM and FFM	BIA	>3 mo after COVID-19	• No differences in FM and FFM by disease severity.
van den Borst et al,[29] 2021	FFMI	BIA	3 mo after COVID-19	• 19% had low FFMI, prevalence not different by disease severity.
van Gassel et al,[30] 2021	SMA, SMD, and IMAT	CT	3 mo after hospital discharge	• No differences in SMA and SMD between groups of physical performance. • IMAT was higher in patients with impaired physical performance.
Farr et al,[31] 2021	Diaphragm muscle thickness and thickening ratio	Ultrasound	Admitted to a rehabilitation after COVID-19	• Muscle thickness was not different between cases and controls. • Thickening ratio was reduced in patients with COVID-19.

Muscle Function

Reference	Muscle Function Evaluation	Assessment Test	Timeline	Selected Main Findings
van Gassel et al,[30] 2021	Muscle strength and physical performance	Handgrip strength	3 mo after COVID-19	• Trend for lower relative handgrip strength (no statistical difference in patients with impaired physical function).
Tanriverdi et al,[32] 2021	Muscle strength and physical performance	Handgrip and quadriceps muscle strength, and 4-m gait speed	>3 mo after COVID-19	• Disease severity did not relate to muscle weakness and function.
van den Borst et al,[29] 2021	Physical performance	6MWD	3 mo after COVID-19	• Greater impairment in individuals with moderate and severe disease.
Mittal et al,[33] 2021	Muscle strength	Handgrip strength	Not specified. Average: 3 mo	• Handgrip strength was significantly reduced in patients with COVID-19 with high fatigue scores.

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Table 1
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Muscle Function

Reference	Muscle Function Evaluation	Assessment Test	Timeline	Selected Main Findings
Bellan et al,[34] 2021	Physical performance	SPPB and 2MWT	4- and 12-mo postdischarge	• 31.5% and 7.1% of patients had poor physical function at 4- and 12-mo follow-up. • Decrease in the prevalence of impaired physical performance at 12 mo.

Quality of Life

Reference	QOL Test	Timeline	Selected Main Findings
van den Borst et al,[29] 2021	Nijmegen Clinical Screening Instrument	3 mo after COVID-19	• High prevalence of functional impairment, fatigue, and low QoL
van Gassel et al,[30] 2021	EQ-5D	3 mo after COVID-19	• Lower QoL in patients with impaired physical performance.
Cuerda et al,[35] 2021	EQ-5D-5 L	Ongoing study: patients are being followed for 12 mo	• 71.2% unable to move or with moderate impairment. • 75.5% with problems to perform daily activities.
Vaes et al,[36] 2021	EQ-5D-5 L	3 and 6 mo after COVID-19	• 62% with moderate-to-extreme problems performing daily activities.

Abbreviations: 6MWD, 6-minute walking distance; 2MWT, 2-minute walk test; BIA, bioelectrical impedance analysis; COVID-19, coronavirus disease, 2019; CT, computerized tomography; EQ-5D, European Quality of Life Five Dimension; EQ-5D-5L, 5-level European Quality of Life Five Dimension; FFMI, fat-free mass index; FFM, fat-free mass; FM, fat mass; IMAT, intermuscular adipose tissue; QoL, quality of life; SMA, skeletal muscle area; SMD, skeletal muscle radiodensity; SPPB, short physical performance battery.

Muscle Function

Muscle strength

Muscle strength was evaluated by handgrip strength testing in 3 studies assessing the health impact in individuals diagnosed with long COVID.[30,32,33] In a prospective cohort study, handgrip strength was assessed in 46 COVID-19 survivors 3 months after ICU discharge.[30] Individuals who tested lower than predicted on the 6MWD test showed a trend for lower handgrip strength than those with a normal 6MWD test result.[30]

Mittal and colleagues[33] compared handgrip strength of 52 patients with type 2 diabetes (T2D) who had mild to moderate COVID-19 and T2D patients who did not have COVID-19 (n = 56). Although no difference in strength was found between groups, handgrip strength was significantly reduced when patients with COVID-19 were categorized into high and low fatigue scores.[33] These findings indicate that neither patient group had significant dynapenia, but patients with T2D who had COVID-19 had higher fatigue and lower muscle strength than those who did not have COVID-19.

Handgrip strength and quadriceps muscle strength were assessed in a cross-sectional study including patients recovering from mild (n = 25) and moderate (n = 23) interstitial pneumonia after at least 12 weeks from COVID-19 diagnosis.[32] The prevalence of quadriceps and handgrip weakness was not different between groups (mild: 35%; moderate: 43.5%; $P = .597$).[32]

Physical performance

The prevalence of impaired physical performance in long COVID was evaluated in 4 studies including participants with different degrees of disease severity.[29,30,32,34] Direct measures of physical performance included walking tests (ie, 6MWD, 4-m gait speed test, and 2-min walk test)[29,30,32] and the short physical performance battery (SPPB).[34]

In a prospective observational study of mild to critical COVID-19 cases (n = 124), 22% of patients presented with low performance on the 6MWD test (ie, <80% of predicted) at 10 weeks after hospital discharge.[29] Although the prevalence of low 6MWD performance was numerically greater in individuals with moderate (28%) and severe (32%) compared with mild (12%) and critical (5%) disease, no statistical difference was found among groups, possibly due to the small sample size.[29] Using the same criteria to define impaired physical performance, another study observed that 48% of patients who survived critical COVID-19 had low performance on the 6MWD test at 3 months after hospital discharge.[30] Notably, the greater proportion of functional impairment observed in the latter study was likely driven by patients who required mechanical ventilation during ICU stay. Tanrivedi and colleagues[32] compared physical performance between groups of disease severity, and found that survivors of mild (n = 25) and moderate (n = 23) COVID-19 had similar 4-m gait speed.

The longest study evaluating physical performance in long COVID assessed 238 and 198 individuals after 4 and 12 months postdischarge, respectively.[34] Using a cut-off of 10 on the SPPB, low physical performance was found in 22.3% and 18.7% of patients at 4 and 12 months of follow-up, respectively. Highly functioning individuals (ie, those who scored 10 or more on the SPPB) also performed a 2-min walk test at both time points; 31.5% and 7.1% of patients had a poor physical function at 4 months and 12 months follow-up, respectively. Furthermore, the proportion of patients with low performance on either the SPPB or the 2-min walk test) was smaller at 12 months (25.8%) than at 4 months (52.8%).[34] This finding suggests that although some patients improved their physical function as they recovered, a significant proportion of individuals was still experiencing detrimental effects of COVID-19 after 12 months of hospital discharge.

Quality of Life Related to Muscle Health

QoL is related to several factors, and not only muscle health or physical performance. However, in this article, we focused only on studies assessing QoL related to muscle health. QoL of patients diagnosed with long COVID has been reported in 4 studies that assessed muscle function.[29,30,35,36] Two studies used the Euro-QoL-5D (EQ-5D) questionnaire.[30,36] This instrument evaluates 5 dimensions of a person's QoL (ie, mobility, self-care, daily activities, pain, and anxiety/depression).[30,35] Van Gassel and colleagues[30] assessed the QoL of 46 patients 3 months after hospital discharge using the EQ-5D. Health-related QoL was lower in people with low performance on the 6MWD test (n = 22) compared with those presenting with a normal test result (n = 24). The second study is an ongoing multicenter observational study including 176 COVID-19 survivors.[35] Preliminary results showed that 71.2% of participants were unable to move or presented with moderate impairment and 75.5% reported problems to perform daily activities.[35]

QoL of 239 patients with long COVID was assessed 3 and 6 months after the onset of COVID-19-related symptoms using the 5-level EuroQol-5 Dimensions version (EQ-5D-5 L).[36] This questionnaire is similar to the EQ-5D but with higher sensitivity[36]; 61.9% of the patients reported they were receiving physiotherapy and 11.7% rehabilitation between 3 and 6 months of follow-up. However, 62% of the patients still presented with moderate-to-extreme problems performing daily activities, and 49% experienced moderate-to-severe pain/discomfort.[36]

Lastly, QoL was assessed using the Nijmegen Clinical Screening Instrument in 124 patients with symptoms persisting for more than 6 weeks who attended a COVID-19 aftercare facility.[29] Patients were divided into 4 groups (mild: n = 27; moderate: n = 51; severe: n = 26; and critical: n = 20). Functional impairment was observed in 64% of the patients, fatigue in 69%, and reduced QoL in 72%.[29]

DISCUSSION

Long COVID has recently only been recognized; therefore, available evidence on the impact of this condition on muscle health is limited. Overall, studies suggest that long COVID negatively impacts body composition, muscle function, and QoL.

Body composition in individuals with long COVID was not found to differ based on disease severity.[29,30,32] However, this finding may be attributed to limitations of the body composition techniques used and small sample size, among others. Furthermore, the lack of body composition assessments during the acute phase and at hospital discharge hinders our understanding of whether people did experience changes in body composition, and at which disease phase. In one study, IMAT was found to be greater in patients with low physical performance.[30] This measurement is an estimate of skeletal muscle "quality" and has been associated with COVID-19 severity[37] and physical function after recovery.[38] Notably, long COVID was associated with a reduction of the thickening ratio of the diaphragm muscle, which can be related to diaphragm dysfunction.[31] This is an interesting marker in COVID-19 survivors, as it relates to fatigue after the acute phase.[39] In fact, 4 ongoing clinical trials are investigating how abnormal diaphragm muscle thickening ratio, which is related to muscle contractility, can impact QoL of individuals with long COVID.[40–43]

Muscle function of people with long COVID was shown to improve over 12 months.[34] The negative effects of long COVID on muscle function were obvious after 4 months and 12 months posthospital discharge,[32,34] although one study showed improvements at 1-year follow-up.[34] Inconsistency between the studies might be related to the degree of disease severity, age, and the presence of comorbidities.[44,45] Similarly

to the findings observed by Huan and colleagues,[9] some studies hereby included reported worse physical performance in patients who recovered from severe COVID-19, when compared with those who had suffered a mild or moderate disease.[30,32,33] Notably, the presence of comorbidities also plays a critical role in long COVID. Cox and colleagues[46] observed that critically ill patients with low muscle mass who were recovering from sepsis experienced worse physical function 6 months after hospital discharge, when compared with critically ill patients with normal muscle mass. The presence of other comorbidities, such as obesity and pulmonary disease, has also been associated with symptoms of long COVID, including poor muscle function,[47] and is therefore an important variable to assess in future studies investigating long COVID.

Long COVID negatively affects QoL,[29,30,35,36] especially in individuals with impaired physical performance.[30] Some individuals still reported fatigue and difficulties in performing daily activities 6 months after hospital discharge and rehabilitation.[29,36] According to Rios and colleagues[48] and Rives-Lange,[49] malnutrition is a possible contributor to low QoL during long COVID. The relationship between QoL and nutritional status has been previously investigated in other conditions and is associated with impaired functional status and delayed recovery.[50] However, reduced QoL is not entirely explained by reduced physical performance, QoL also depends on mental and cognitive factors.[51]

Although older adults are at greater risk for the detrimental effects of long COVID on muscle health, little is known regarding age-related differences, and whether the sequelae are worse in older compared with younger adults. Age differences should be explored in future studies to better understand how long COVID affects muscle health across the lifespan.

Finally, despite the limited literature, long COVID directly or indirectly impacts muscle health. Muscle mass and function assessments can contribute toward the identification, diagnosis, and management of poor muscle health resulting from long COVID, consequently informing the design of targeted interventions.[52] Early approaches to optimize muscle health throughout disease trajectory and the recovery period are essential and should involve a multidisciplinary team of health professionals.

SUMMARY

Despite the relatively low number of studies and the presence of methodological limitations, available evidence suggests long COVID negatively impacts muscle health and QoL. These sequelae may be amplified in older adults due to preexisting age-related declines in muscle health. Acute and long-term assessments of these parameters are needed to optimize patient care. The mechanisms by which long COVID impacts muscle health are multifactorial and involve a combination of systemic inflammation, physical inactivity, poor nutritional status, and inadequate dietary intake. Other factors such as age, comorbidities, and degree of disease severity may also contribute to negative musculoskeletal outcomes during long COVID.

Overall, the evidence to date suggests long COVID negatively impacts body composition, muscle function, and QoL. Recovery and rehabilitation services with adequate nutrition, mental and social support should be explored as potential multimodal interventions to improve muscle health of these patients.

CLINICS CARE POINTS

- Clinicians should be aware of the prevalence and deleterious impact of poor muscle health in individuals with long COVID.

- People with long COVID can present with skeletal muscle symptoms 1 year after diagnosis.
- Muscle health in long COVID is related to low quality of life

DISCLOSURE

The authors have nothing to disclose.

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