

COVID-19 and its Multiple Long Term Neuromuscular Features and Implications

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Abstract

Since the emergence of the novel virus later termed COVID-19, its rate of infection and its widespread impact remains an immense public health concern and challenge. But how specifically can orthopaedic problems such as hip fractures and falls injuries, plus painful arthritis become specifically impacted? This mini review updates what is known about the recently observed long COVID syndrome neuromuscular challenges not apparently associated with their health history profile in all cases. A second was to establish if any health associated preventive and intervention can be recommended especially for the older adult with long COVID-19 manifestations, who may still be very vulnerable to falling, and fracturing a bone, plus varying degrees of joint pain. Although long COVID symptoms have been attributed to psychosocial factors, it appears that more attention to how COVID-19 can induce neuromuscular disability through biological mechanisms is indicated.

Keywords: COVID -19; Long-COVID-19; Myalgia; Older Adults; Prevention

Abbreviations

SARS-COV-2 2019: Severe Acute Respiratory Syndrome-Coronavirus-2 Infection

Introduction

As of January 2023, endless reports pertaining to the outcomes of a lethal and novel corona virus later termed COVID-19 that emerged in Wuhan, China in December 2019 prevail. A pandemic of immense proportion [1], now, over three years since its onset, COVID-19 disease and its variants not only remain a serious global health concern, but a subgroup of older as well as younger post-acute COVID-19 survivors are now found to manifest a wide array of persistent physical, neurological, functional, and mental health complaints deemed attributable to COVID-19 and variably termed 'long or post-acute COVID-19' syndrome [2,3-5]. As per current data, this complex non uniform health condition, which can manifest for up to one year, and possibly longer, is especially common in older COVID-19 survivors, who often have underlying multiple health conditions impacting multiple body systems including the neurological and musculoskeletal systems [5,6].

This mini review sought specific details on what is known about those multiple debilitating symptoms that include, but are not

limited to: fatigue, shortness of breath, persistent coughing, joint and chest pain, muscle aches, muscle mass losses, headaches, and a cognitive condition situation known as 'brain fog' [1,3,6-8] that all have ramifications for the pursuit of optimal functional wellbeing among the older population. At present however, although the organ specific COVID-19 disease targets are quite well established [7], the emergent long COVID musculoskeletal and neurological disturbances observed in a sizeable percentage of COVID-19 survivors and how these interact at the physical, mental, and emotional health levels in older adults are less well charted, defined, differentiated, and understood, albeit clearly of high clinical as well as fiscal significance [9-15].

However, rather than examining all topical long COVID discussion papers and clinical reports, this present report elected to focus primarily on what is known about long COVID-19 health attributes in the context of aging and more specifically from the perspective of the symptoms of muscle pain, muscle mass declines, neurological observations, falls injuries, and their overlapping features with many age associated musculoskeletal health challenges. Drawn largely from the PUBMED database, the world's largest research data base, it was hoped the overview might provide the interested reader with a general perspective of current observations and

trends in this regard, plus data and proposals worthy of further consideration and study in the pursuit of cost effective and timely solutions [16,17] for examining what is known about the impact of COVID-19 on musculoskeletal and neuromuscular outcomes of wellbeing in more depth. Directives or indicators of how to possibly mitigate any emergent orthopaedic attribute and avert any preventable functional decline among vulnerable COVID-19 older adult survivors were also sought.

Materials and Methods

To obtain the desired data for review, the electronic data source PUBMED was carefully searched, and the selected articles were confirmed as those of key import after conducting a scan of PubMed Central, GOOGLE Scholar and Science Direct data bases. The key time period of interest searched ranged from January 1 2022- January 30, 2023. Applied were the key words, *COVID -19 [syndrome, symptoms, review], long COVID and its management, corona virus, myalgia, neuromuscular complications, older adults, and post-acute COVID-19 syndrome*. All forms of study or analysis were deemed acceptable. However, because this is an emerging topic with few clinically sound prospective analyses, and random samples, most reports were considered as being of medium to moderate in terms of providing solid generalizable evidence. As well, most articles retrieved were either review articles of available data including all forms of research design, or case reports, or proposals for future study. Since this topic is clearly in its infancy, only a brief overview of these current observations is provided and the article focuses instead on those most salient facts relevant to long COVID-19 complications, and if possible those among the older adult, rather than children or adolescents. Papers on muscle and neural dimensions of the long COVID syndrome were specifically sought. Excluded were articles that did not focus specifically on this set of issues, proposals for future study, and non-English based articles.

Results

Although many articles currently categorized as being reflective of one or more long lasting COVID health issues prevail in general, only very few focus on one or more of the well documented post COVID-19 neuromuscular symptoms specifically. However, as per a sizeable volume of current reports that do detail aspects of the emergent long or post-acute COVID-19 syndrome, a complicated array of diverse symptoms appears to clearly show that COVID-19 infections, which may occur independently or in conjunction with one or more chronic health conditions, may go unnoticed and untreated in the older population or where symptoms are confused with either aging or pre existing health states. In addition, the possible impact of persistent neuromuscular attributes, such as poor physical endurance and limited mobility as observed in long COVID older adult survivors, and the fact that their persistence could possibly raise the risk

for second or subsequent COVID-19 or variant viral infections and a higher than necessary disabling low quality of life is not well articulated in most current articles as of January 2023, in general, or with reference to any neuromuscular attribute, that may determine immunity and viral resistance status.

It is also consistently reported that long COVID complications may persist to varying degrees for up to one year beyond the acute COVID-19 phase of recovery, but the fact that very few long term studies prevail does not exclude any possible long term chronic evidence of one or more long COVID manifestations. Among these may be symptoms of excess muscle weakness [7], as well as persistent fatigue and/or cognitive impairments that may prove debilitating [3,18-20] with far reaching health consequences. For example, the persistence of poor mental health may impact self-management ability, attention to dietary recommendations, or contribute to dizziness that leads to falls, or fears that increase sedentary behaviors. In addition, as in the case of acute COVID-19, long COVID-19 complications may involve multiple organs and body systems including those that may extend beyond the respiratory, cardiovascular, neurological, and gastrointestinal systems, and may closely mimic various autoimmune diseases, an array of chronic musculoskeletal conditions, sarcopenia, declines in physical activity, and type 2 diabetes.

Zeng, *et al.* [3] who examined 36,625 records, plus a total of 151 studies involving 1,285,407 participants from 32 countries noted that at least one post acute COVID-19 symptom occurred in 50.1% of COVID-19 survivors for up to 12 months post infection. The most common abnormalities were those involving respiratory tissues, followed by generalized symptoms, such as fatigue, and psychiatric symptoms of depression and neurological symptoms as well as cognitive deficits and memory impairment. Those at highest risk were older, mostly male, living in a high-income country, with more severe status when initially infected. Although they concluded that their findings were of high clinical importance and warrant attention, very little precise data on the topic of muscle mass declines, and muscle weakness, despite evidence of a possible state of acute sarcopenia developed during COVID-illness that may well persist [7], have been put forth.

Astin, *et al.* [19] support the idea that it is hence imperative to uncover the origins and predictors and intervention approaches that can minimize COVID-19 debilitating outcomes among many survivors because in the case of long COVID, the prolonged illness and fatigue suffered by a small proportion of those infected with SARS-CoV-2, is placing an increasing burden on both the individual as well as society. There is no surprise therefore that a Physiological Society virtual meeting held in February 2022 that brought

clinicians and researchers together to discuss the current understanding of long COVID mechanisms, risk factors and recovery, to exploring its links with other post-viral illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome highlighted a need for long COVID research to better support those suffering from this syndrome and other comparable post-viral syndromes.

It was further mentioned that the success in recovering from COVID-19 in active populations may yet be very challenging among debilitated older adults living in the community who may have cardiopulmonary problems as well as cognitive challenges including emergent or ongoing alterations in peripheral muscle function, breathing problems and autonomic dysfunction. Other issues recognized as being salient to examine and act upon were signs of postural orthostatic tachycardia syndrome, fatigue and bone mass losses, and possible sympathetic over activation and an impaired oxygen delivery system due to micro-clotting and disruption of cellular energy metabolism.

Work by Graham, *et al.* [6] support a very clear case for comprehensive timely research in this new health domain to better address findings of depression/anxiety, autoimmune responses, neurologic manifestations, and myalgias. Moreover, 85% of the cohort examined expressed the fact they also experienced fatigue, despite the fact no correlation between time from disease onset and any subjective impression of recovery was evidenced. Both groups exhibited impaired quality of life in cognitive and fatigue domains, and those who had been SARS-CoV-2 positive patients performed worse in attention and working memory cognitive tasks compared to a demographic-matched US population.

Another report that showed post-COVID conditions continue to afflict patients long after acute severe acute respiratory syndrome-coronavirus-2 infection stated that over 50 symptoms across multiple organ systems have been reported, especially pulmonary, cardiovascular, and neuropsychiatric symptoms. However, standardized assessments and treatment algorithms for patients have generally been lacking and are derived from a multitude of observational studies that may not be designed to reveal musculoskeletal complications per se [21]. As well, very few reports commented on whether a possible role for vitamin D insufficiency was worthy of consideration as far as mediating COVID risk and its severity [22] even though this along with a calcium deficit might explain some degree of pain and muscle weakness and depression described by COVID survivors, plus a possible bone loss [23]. Also observed has been a high prevalence of skeletal complications, such as vertebral fractures, poor nutritional status and bone mass declines [24] that could stem from deficits in both calcium and vitamin D, plus poorly managed post acute COVID-19 complications. Muscle based com-

plications have appeared to emerge following a COVID-19 infection and that can lead to or account for symptoms of fatigue, lower mobility, weakness, and declines in function [25], along with an array of cognitive and physical ability deficits [26,27]. Symptoms of arthritis, lupus-like disease, muscle and vascular inflammation [28] plus cardiovascular disease complications [4] may also greatly limit daily functioning even after experiencing only mild COVID-19 [29]. Additionally, alterations in immune functioning, oxidative stress processes, a decline in lung capacity and bone health are consistently noteworthy attributes of many COVID-19 'long haulers' [30-31]. Those most vulnerable include adults deemed obese, those with a smoking history, those who are female, belong to an ethnic minority, and have one or more pre existing chronic health condition [32] and a severe COVID-19 diagnosis [33-35].

Also of concern are complaints of 'brain fog', along with various muscular and neurological associated symptoms and muscle mass declines that may wax or wane or reoccur after they appear to have resolved [36]. The role of immune system alterations that are prolonged, rather than attenuated over time has also been discussed in cases of severe neuro-associated COVID diagnoses [37].

At the same time, cases complaining of musculoskeletal pain are said to have no radiographic signs to match these [38]. It also appears that the terminology used such as long COVID, COVID-19 syndrome, post-acute COVID-19 and others in efforts to report study findings adds some confusion to attempts to understand this overall syndrome [39,40], as do the numerous forms of cognitive dysfunction that may increase significantly in prevalence over time, but have no distinct link to any validated laboratory test, and especially in the absence of any carefully tailored evidence based intervention approaches [41].

As well, traditional self management practices may not be viable for those who claim to have persistent feelings of 'brain fog', and excess fatigue, dizziness, muscle pain, memory impairment; reduced strength, and their functional consequences [42] and may be neglected or even unattainable if health services resources remain low and need to focus on acute health concerns. There is also a need to unify the emergent body of knowledge and apply this to those subgroups found most vulnerable and to have preexisting health conditions as well as new onset neurological, neuromuscular, and/or psychological complaints [20,43,44] as noted among a high percentage of COVID-19 survivors [45,46]. The severity of the COVID-19 illness, an independent predictor of long COVID neurological manifestations and other negative health correlates such as breathlessness, anxiety and fatigue, poor sleep [47-49] may further impact possible secondary COVID-19 infection risk as well as adverse cardiovascular events, plus a high risk of excess sedentary

rather than active health practices if this remains unaddressed and of marginal concern. Moreover, if unaddressed or unresolved, it can be predicted that even if the older COVID-19 survivor was previously healthy, if they face extended periods of excess pain, mood and cognitive alterations, sleep quality disruptions, plus complaints of muscle pain, muscle and bone attrition with increases in fatigue and a declining ability to function physically they will probably experience an excess degree of negative health outcomes in the future even if their symptoms wane [45,48-50], including sensory and/or sub-acute diverse musculoskeletal complications or symptoms found to be more prevalent with age [50-52] and among those older adults with preexisting chronic health disorders [53], and those categorized as being obese [54]. Although Pavli, *et al.* [53] imply long COVID-is largely a manageable syndrome of modest concern, those COVID-19 survivors prone to worse than desired mental health outcomes [55], and who appear to experience a reduced sense of wellbeing, plus bouts of chronic pain, fatigue, multiple musculoskeletal challenges, and possible frailty, may also be expected to fail to demonstrate a timely recovery and sufficient resilience to offset future infections, fall injuries, and bone fractures [56-60]. The symptoms which can arise soon after recovery from an acute COVID bout of infection are also symptoms similar to those seen in myalgic encephalomyelitis/chronic fatigue syndrome, a chronic multi-system illness characterized by profound fatigue, sleep disturbances, neurocognitive changes, orthostatic intolerance, and post-exertional malaise in the absence of any significant clinical or laboratory findings [56], but yet findings that should be examined rather than overlooked. Also associated somewhat with osteoarthritis manifestations [60], long COVID must clearly be a major concern to those in the geriatric field where care and resources must surely be needed now more than ever. The extent of musculoskeletal suffering may also be overlooked due to reporting bias and limitations in interpreting the diverse reports. The inability to interview all older surviving adults post COVID-19 infection, an inability to accurately assess the trajectory of non hospitalized recovering older adults, and samples from diverse countries, service delivery approaches, social and community settings [59] may further hamper definitive conclusions and the ability to act proactively and optimally, rather than reactively and with uncertainty [59].

Another recent observation is that this long term syndrome of COVID-19 associated medical symptoms is not only non uniform, but there now appears to be at least three distinctive long COVID sub or phenotypes of this syndrome. Yet, even here, challenges in establishing their severity and mortality risk persist [61-65], as well what its rheumatologic disease features denote [63,66], what variations in neurological symptoms from mild to severe in the central as well as the peripheral nervous system imply, if one or

more of these emergent sequels to COVID-19 recovery are found to have little correlation with any objective pathology or established pathophysiological mechanisms [67,68]. The role of muscle mass losses and strength capacity, and an hypothesis that at least some long COVID cases may have brainstem dysfunction or subnormal impacts' that account for their diverse complications, and possible decreases in cortical grey matter volume also adds another challenge to deciphering the approach needed to limit a possible bout of secondary infections, as well as declines in health and how to assess these and intervene effectively [69-71]. As well, multiple post-acute neurophenotypes of long COVID, with different etiological pathways and recovery trajectories may prevail that will require phenotype-specific approaches to treatment, once identified [72]. Moreover, muscle management protocols are needed to address the varied skeletal muscle forms of dysfunction observed in post acute COVID cases that are emergent or ongoing [73]. At the same time whether any of these observed long term post COVID disturbances including fatigue, muscle weakness, myalgia, and a decline in physical and functional performance, evidenced as long as 4 or more weeks after the onset of acute COVID-19 symptoms, plus muscle injury biomarkers that may be altered during the acute phase of the disease [73] exposes the older adult to a more vulnerable health profile than not, and in what way, especially in those with pre existing health conditions is not addressed to any degree in any sphere, for example in the sphere of possible involvement of the peripheral neural pathways and persistence of chronic bouts of intractable inflammatory pain and long COVID associated muscle injury, weakness, exercise intolerance, and muscle wasting [73-75].

Discussion and Concluding Remarks.

After appearing quite suddenly in December 2019, and despite over three subsequent years of intense endeavors to mitigate COVID-19 and its variants, even more challenging is the increasing evidence that recovery from acute COVID-19 disease is often attenuated and associated with multiple symptoms of ill health that may preside for up to one year or longer after the initial infection. In addition, second or third infections are found to occur, as well as the onset of one or more chronic health conditions [53], along with challenges in returning to pre COVID clinical status among those who were not in optimal health or were in the higher age ranges [59]. At the same time, there is consistent agreement that no matter where the long COVID patient may reside, its incomplete picture hampers any consensus on the best means of ameliorating one or more signs of long COVID-19 distress such as bone loss, muscle wasting, inflammation, and pain among the older adult population [60,73,74].

In addition, most reports were summaries of research published in the early post COVID period, that relied on retrospective

analyses, and involved multiple cross sectional observation from diverse but not all clinical records collected in some spheres. The short term nature of the follow up studies in this regard, even when patients themselves were surveyed, often limited an understanding of the older adults' challenges, in particular. Sampling only those who could respond to electronic surveys at one point in time may also have the effect of underestimating the persistence of current or additional emergent health challenges that may unfold over time in the future and only become evident later on. The reliance of researchers on subjective reports of limited survey items, further weakens any definitive perspective at this point in time.

As a consequence, the prevailing data while in agreement that there is a risk of prolonged ill health that can follow an acute COVID-illness, does not explain who is likely to recover, who is likely to sustain severe functional limitations, who is likely to acquire myalgia for example [59] or why some may develop 'brain fog' or excess fatigue, joint pain, adiposity, or poor endurance or none of these states, but rather, frailty and vulnerability to recurrent falls [57,59].

Whether older community dwelling adults who were previously able to live independently should be encouraged to be more proactive towards their own health and become educated about how they can help to minimize their health risks and COVID complications and foster their health and possible independence rather than dependence, is unclear, for example if they suffer bouts of dizziness and tingling [60]. Alternately, should policy makers and others advance the idea of fostering a careful transitioning of an older COVID-19 survivor to the community, or assume the syndrome will wane on its own, an idea not discussed at any length in the current literature. In addition, while the obese older adult survivor is unlikely to benefit from interventions that address the frail survivor, should more sub group recommendations be forthcoming to avert the onset and worsening of post-acute COVID 19 frailty states. Moreover, if those older adults suffering from cognitive disturbances may not be deemed acutely ill, or have any tangible clinically objective test findings, may they not still suffer from multiple musculoskeletal health challenges that include frailty, fatigue, and sleep disturbances, and as a result of social isolation factors, and being anxious, excessively stressed or more physically challenged than desirable in the face of respiratory challenges and others become depressed or inactive without assisted living mechanisms.

In short, while the outcomes of COVID-19 among older adults remain to be explored, it appears much work is needed in the realm of caring for the older adult at risk for COVID disease, and its possible adverse repercussions that threaten life quality and the limits of social resources that drive health care practices and resources and the data show this situation cannot be ignored without immense negative consequences.

Indeed, until more concerted evidence based clinical directives emerge, and while this brief scoping review is not all encompassing, nor without limitations, it appears safe to conclude that there is compelling evidence that

- Many older adults, even those who are vaccinated, may experience long COVID-19 complications if they survive an incident infection that can predictably jeopardize their life quality, body composition, muscle and bone mass, cognitive, neurological, and functional abilities and health outlook.
- Efforts that are not timely and carefully tailored and isolate rather than support the older COVID-19 adult survivor will fail to both attain the public health goals of many nations that seek to extend the years of an optimally healthy life for all and will also fail to adequately mitigate long COVID syndrome manifestations optimally.
- Attention to the neurological features of long COVID and addressing one or more of these possible remediable attributes is strongly indicated.
- Indicated in particular are gentle breathing exercises, nutrients that sustain muscle mass, function as well as bone mass, non toxic pain relief approaches, meditation approaches, counseling, and carefully structured non impactful movement activities.
- Frail and weak COVID-19 survivors suffering from long COVID should be assessed periodically for falls risk and directives should be forthcoming as indicated.
- Older COVID-19 survivors who are overweight with cardiovascular challenges need to be carefully monitored and directed as well.
- More efforts are needed to establish whether long COVID is in fact a limited syndrome temporally, as well as whether it is not a predictor of future chronic health complaints or increases in pre-existing disabling health conditions such as chronic arthritis and osteoporosis.
- To more clearly discern the range and magnitude of health care needs for those considerable number of older COVID-19 survivors living in the community at the time of their acquiring an acute COVID-19 infection a role for both participatory qualitative as well as quantitative research is strongly indicated.

In sum, simply believing the COVID-19 pandemic is 'over' or warrants downgrading, and that public health imperatives to wear a mask and be vaccinated can eliminate the post COVID misery of many must be carefully considered to ensure dignity and a high quality life course for all in years to come. The specific lack of attention to the multiple musculoskeletal consequences currently reported alone indicates more substantive insightful holistic and carefully construed value and humane driven comprehensive clinical and research practices with a focus on the most vulnerable are imperative.

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Conflicts of Interest

None.

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