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COVID-19 and the long-term cardio-respiratory and metabolic health complications

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Abstract

SARS-CoV-2 (COVID-19) transmission continues to impact people globally. Whilst the acute symptoms and management strategies are well documented, millions of people globally are experiencing a prolonged and debilitating symptom profile that is reported to last months and even years. COVID-19 is a multi-system disease however the magnitude of the effects and its associated legacy is presently not well understood. Early reports indicate that multidisciplinary approaches between clinical and non-clinical entities are needed to provide effective and rehabilitative patient support pathways and restore pre-COVID-19 quality of life and functional status. Accordingly, this review provides a summary of the impact on cardiovascular, inflammatory, respiratory, and musculoskeletal function following an acute COVID-19 infection along with the prolonged effects of long-COVID.

Key words: COVID-19, long-COVID, cardiorespiratory, cardiometabolic, recovery, rehabilitation

Introduction

Severe Acute Respiratory Syndrome coronavirus type-2 (SARS-CoV-2) is a novel coronavirus that surfaced in late 2019. The virus resulted in a worldwide pandemic of a disease named by the World Health Organisation (WHO) as COVID-19. The COVID-19 pandemic continues to infect many people worldwide with extreme symptoms now being well documented [1-4]. However, the long-term effects on those infected by the virus remain largely unknown. Whilst a series of longitudinal investigations are underway to increase the knowledge and understanding, reports highlight that sustained transmission and emerging variants continue to cause global challenges to healthcare providers. Currently, it is estimated that of those infected with COVID-19 in the UK, one in ten people will experience prolonged symptoms lasting months to years including fatigue, breathlessness, neurological deconditioning [5]. These effects are referred to as Post-Acute Sequelae of SARS-CoV-2 infection colloquially termed 'long-COVID' with the magnitude and the associated legacy impacts and the burden to population health and wellbeing being presently not understood in its entirety. Whilst the authors acknowledge the evident and documented favourable female sex bias in COVID-19 infection and severity, the need to understand the mechanisms and causal relationships (e.g., comorbidities and underlying health status) requires further investigation [6] and is outside of the scope of this current review.

Cardiovascular Function

Initially, COVID-19 was thought to primarily be an acute respiratory distress syndrome (ARDS) however, it has since become clear that COVID-19 is in fact a multiple organ disease. Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality globally [7] and medication prescribed to reduce the risk of CVD could increase the susceptibility to or the severity of a COVID-19 infection [8]. It also appears that COVID-19 infection can promote cardiovascular disorders. The virus enters host cells through the binding of the spike protein to Angiotensin converting enzyme 2 (ACE-2) on pulmonary epithelial cells causing damage to the lungs (6, 7) as well as directly binding to vascular endothelial cells of other organs, such as the kidneys and heart [9, 10].It is possible that, due to the mediating effects of ACE-2 on blood pressure, those with hypertension could have some dysregulation of ACE-2 function therefore predisposing individuals to severe conditions and mortality [11]. It has also been suggested that the occurrence of cardiovascular events in those with COVID-19

is caused by inflammation and vascular remodelling brought about by endothelial dysfunction [9, 12]. Such dysfunction is due to ‘cytokine and coagulation storms’ that can compromise the integrity and physiological anti-thrombotic and anti-inflammatory properties of the endothelium within vessels [13].

Data suggests an increased risk of severe complications and mortality in those who contract COVID-19 with pre-existing CVD or who present with one or more risk factors such as hypertension, diabetes mellitus, hypercholesterolaemia, or obesity [14-16]. For example, a meta-analysis performed in China suggested that mortality in those with pre-existing CVD and infected with COVID-19 was around 11%[17]. In addition, a report of 393 patients hospitalised with COVID-19 in the USA demonstrated that ~50% of patients had underlying hypertension (54% of ventilated patients), 36% were obese (43% of ventilated patients), 25% had diabetes mellitus (28% of ventilated patients) and 14% were diagnosed with coronary artery disease (19% of ventilated patients) [18]. The high prevalence of obesity amongst those hospitalised with COVID-19 reported here was also deemed to be a considerable risk factor for respiratory failure, prompting the need for mechanical ventilation.

It appears that a COVID-19 infection promotes the development of cardiovascular disorders including myocardial injury, myocarditis, arrhythmias, acute coronary syndrome, and venous thromboembolism [8, 13, 14, 19]. Elevated cardiac troponin (cTn) levels are evident in 8-62% of hospitalised patients with COVID-19 and are suggestive of myocardial injury alongside being associated with greater disease severity, need for mechanical ventilation, and mortality [19-22]. Along with biomarker evidence, echocardiographic abnormalities are also commonly reported. Such abnormalities include right ventricular dysfunction (26.3%), left ventricular wall motion abnormalities (23.7%), global left ventricular dysfunction (18.4%), diastolic dysfunction (13.2%), and pericardial effusion (7.2%) [21]. In addition, it appears that coronary artery calcium and total thoracic calcium obtained via chest computed tomography (CT) on admission of COVID-19 patients in hospital, could be used to help with risk stratification and help assess patients’ mortality risk [23]. It has been suggested that drugs such as canakinumab, previously used as an interleukin-1β blocking agent in cancer patients, can significantly reduce mortality rate and CVD in patients deemed to be at a higher risk of mortality [24].

The severity, extent, and long-term cardiovascular effects of COVID-19 and its treatments are yet to be understood entirely. However, there is evidence of cardiovascular involvement post-COVID-19 infection. Puntmann et al [25] reported cardiac involvement in 78%, and ongoing inflammation in 60% of patients (n=100) in the months following COVID-19 infection. It was also evident that various cardiac symptoms were common with atypical chest pain (17%), palpitations (20%), and dyspnoea and exhaustion (36%) all being reported [25]. For those with CVD, long-COVID is of concern due to its association with high morbidity and exacerbation of underlying cardiovascular disorders. Studies examining patients with long-COVID have reported dyspnoea, joint pain and muscle weakness, chest pain, sleep difficulties and reduced quality of life [26, 27]. What remains unclear, is the link between cardiac involvement and insult as a result of a COVID-19 infection and the symptoms evident in those with long COVID.

Blood Biomarkers

The clustering of cardiovascular risk factors (hyperglycaemia, obesity, dyslipidaemia, and hypertension) is termed metabolic syndrome [28]. Although the presence of these components is associated with adverse outcomes of COVID-19 [29-36], there is limited evidence on the risk of long-term complications, with most finding no increased risk of long-covid [37-39]. Conversely, infection with COVID-19 does appear to increase the risk of future development of cardio-metabolic issues such as myocardial inflammation and substantial impairment within multiple organs (e.g., lungs, liver, pancreas) [25, 40-42].

The components of metabolic syndrome can stimulate the dysregulation of the Renin-Angiotensin-Aldosterone System, modulated by ACE-2, leading to an increased presence of Angiotensin II. The binding of Angiotensin II to Angiotensin II type I receptors can be a stimulus for cardiovascular insult, such as endothelial dysfunction, thrombosis, chronic inflammation [19, 43]. COVID-19 binds to ACE-2 [44] and enters cells via ACE-2 receptors present on the cells of multiple organs [45]. The cardioprotective role of ACE-2, and the binding of COVID-19 to ACE-2, has created uncertainties in the susceptibility to COVID-19 in patients prescribed ACE inhibitors, [46] whilst suggestions of pharmaceutical discontinuation should not be made without evidence of an increased risk of infection in this population [47]. That being said, a study by Wang and colleagues suggests that ACE inhibitors are safe for COVID-19

patients and can also help in the treatment of COVID-19 induced pneumonia and can be used in line with relevant guidance [48]. The influence of Angiotensin II on COVID-19 severity has been demonstrated in a cross-sectional study that evidenced higher concentrations of Angiotensin II in critically-ill COVID-19 patients, in comparison to mildly-ill and controls [49]. In populations with components of metabolic syndrome, the concentration of Angiotensin II is elevated and the subsequent elevation of Angiotensin II due to COVID-19 infection will likely exacerbate cardiovascular, respiratory, and metabolic complications [50].

COVID-19 stimulates an inflammatory response with interleukin-6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor-alpha (TNF-α) [51-54]. The chronic presence of IL-6 and TNF-α within the endothelium stimulates vascular smooth muscle cell migration from the Media to the Intima [55, 56], contributing to arterial wall thickening and atherosclerotic plaque formation. Furthermore, the maximum value of IL-6 and CRP have predicted respiratory failure [57]. On 6th July 2021, the World Health Organisation updated its patient care guideline to include IL-6 receptor blockers for severely or critically ill COVID-19 patients [58] as administration of these drugs reduces the need for mechanical ventilation (30 fewer per 1000 patients), length of hospital stay (4.3 days fewer), but the association with mortality was less clear (15 fewer per 1000 patients) [59].

It appears that pre-existing metabolic syndrome components do not appear to be predictors of long-COVID, but the SARS-CoV-2 infection does appear to increase the risk of future cardiometabolic complications. It seems that part of the pathophysiology surrounding this increased risk of future cardiometabolic issues could to due to the disruption in the Renin-Angiotensin-Aldosterone System and systemic inflammatory responses. Further longitudinal research will be required to determine the need and efficacy of (non)pharmaceutical intervention to manage cardiometabolic implications of COVID-19 infection [60].

Respiratory Function

The respiratory system is the front-line of the COVID-19 infection, with the respiratory tract epithelium the key entry point upon inhalation [61]. The respiratory symptoms and outcomes of COVID-19 are diverse, with many displaying mild upper respiratory tract symptoms, however, some patients develop more severe illness, commonly viral

pneumonia, leading to ARDS relating to poor health outcomes and/or mortality [62]. Data on the short-term respiratory sequelae is still emerging, and longer-term follow-up studies remain scarce. However, from the limited available data, 188 patients (from 1370 pulmonary CT scans) identified the presence of pleural effusion which was linked to increased risk of cardio-respiratory complications and in hospital mortality [63]. Whilst more detailed investigations and cohort analysis are needed, the presence of pulmonary effusion in hospitalized patients, might serve as an clinical indicator to COVID-19 severity and post-COVID-19 outcomes. Early data, and that from previous coronavirus outbreaks, indicates that long-term respiratory complications and a profound and complex symptomology are likely to persist in some patients [64].

Current evidence on the acute effects of COVID-19 shows reduced pulmonary diffusing capacity (DLco) as the key impairment following infection. This is largely associated with disease severity, with abnormally low DLco (<80% predicted) reported in approximately 60% of patients with severe disease, 32% in moderate disease and 20% in mild disease [65]. COVID-19 appears to have little impact on spirometry measures, with lung volumes close to normative values, particularly in those with milder disease [66]. At 3 months post-infection, chronic dyspnoea is reported in approximately half of the patients and is associated with greater restriction on spirometry, lower DLco, reduced functional capacity and greater desaturation during exertion, compared to those without persistent dyspnoea [67], suggestive of an underlying physiological mechanism that is responsible for this.

As the pandemic ensues, studies looking at the longer-term (>3 months) implications of COVID-19 are beginning to emerge [26, 68, 69]. The UK-based multi-centre PHOSP-COVID study [60, 69] concluded that 5-months post-hospitalisation, recovery was only 29%, with 94% of patients experiencing prolonged symptom profiles. At 6 months, studies have shown that impaired DLco (<80%) persists, with low DLco present in 30-55% of patients [26, 68, 69]. However, significant improvements in DLco have been shown 6-12 months post-hospitalisation, with evidence that women are at higher risk of persistent lung diffusion impairment [68]. In this 12-month follow-up study, exercise capacity improved significantly over time, however persistent physiological and CT scan abnormalities were evident in a sub-group of patients. Persistent radiological abnormalities included interstitial thickening and reticular opacity, suggestive of evolving fibrosis [68]. Experience from MERS and SARS-CoV-

1 indicates that fibrotic disease may be an outcome of concern from COVID-19 [70]. Evidence from SARS-CoV-1 showed that 4.6% of patients had interstitial lung abnormalities at 15 years, with the greatest recovery from interstitial lung damage occurring within the first two years following infection [71].

The extent of pulmonary function and physical impairment following COVID-19 remains unclear. In addition to the paucity of long-term follow-up data following COVID-19 infection, most data report the health consequences of hospitalised individuals, thus more research on long-COVID and in non-hospitalised individuals is crucial [72] to inform and meet the broad needs of patients and to mitigate against the impending impact upon healthcare systems, the economy and society.

Skeletal Muscle

It is important to recognise the integrative pathophysiological processes following COVID-19 infection and subsequent long-COVID. Cardiorespiratory fitness is a key predictor of functional capacity, quality of life, and a strong predictor of mortality [73, 74]. Aerobic capacity, quantified by maximal oxygen consumption (VO_{2peak}), and ventilatory efficiency, is quantified by the minute ventilation/carbon dioxide production (VE/VCO_2) slope, are two established measures obtained through cardio-pulmonary exercise testing and several initial studies to date have reported the impact of COVID-19 on both [75]. Indeed, at discharge from hospitalisation, VO_{2peak} is impaired in COVID patients, which has been attributed to a peripheral oxygen extraction limitation, rather than central impairment [76]. Similarly, investigations at 3 months [77] and 11 months post-hospitalisation [78] have shown impaired VO_{2peak} and early attainment of ventilatory threshold alongside ‘normal’ pulmonary function. It is well-established that VO_{2peak} is determined by the delivery and utilisation of oxygen [79]. The latter depends on factors within the periphery that mediate the pathway of oxygen from haemoglobin to mitochondria, as well as mitochondrial function itself [80]. Long-COVID symptoms could be underpinned by dysfunction in the pathway of oxygen from the blood to mitochondria [75]. Strategies are needed to augment impaired physiological processes and also require detailed investigation. Cardiovascular exercise is known to be a potent stimulus for mitochondrial biogenesis and improving mitochondrial function [81]. The optimal prescription and inclusion of exercise in long-COVID patients must be considered with the balance of factors such as reduced exercise

capacity and tolerance as well as post-exertional malaise [82]. As highlighted by Twomey et al.,[82] and enforced here, exercise is not the route to recovery for all patients in other diseases, such as cancer or chronic fatigue syndrome; therefore, careful consideration and appropriate measures should be taken when prescribing exercise as a rehabilitative tool in long-COVID patients.

The hyperinflammatory state and altered cardio-respiratory function result in excessive fatigue or post-exertional malaise that is being reported in patients with long-COVID. In conditions where post-exertional malaise and excessive fatigue are characteristics such as myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), there is a demonstrable reduction in VO_{2peak} in the days following testing with an altered metabolic [83] and inflammatory response to exercise observed [84, 85]. There is a strong link between ME/CFS and autonomic nervous system abnormalities. The autonomic nervous system plays a vital role in the regulation of the whole-body homeostasis and so any disruption can have a significant effect on multiple bodily systems[86]. There is some evidence to suggest that long-COVID may also include autonomic dysfunction therefore aggravating some cardio-respiratory and metabolic complications therefore supporting the multi-system nature of COVID-19 [86, 87].A shift in energy system contribution to ATP resynthesis is common in viral infections [88], with an increased rate of glycolysis and downregulation of oxidative phosphorylation typically observed [89]. Impaired oxidative phosphorylation likely occurs during the acute COVID-19 infection period. During exercise, this can lead to the accumulation of deleterious metabolites which impair the contractile function of skeletal muscle, but additionally, a shift in the inflammatory status of muscle. There is a need to increase mechanistic insight into mitochondrial (dys)function in long COVID to test this hypothesis although, it does seem to be the case in other diseases with similar symptomatology such as ME [83].

COVID-19 induces a systemic hyperinflammatory state causing multi-organ damage via the ‘cytokine storm’ [90, 91]. In addition, viral infections increase mitochondrial production of reactive oxygen species and suppress endogenous anti-oxidant systems [92]. Combined, this hyperinflammatory state leads to cachexia and sarcopenia [93, 94]. The resulting loss of muscle tissue alongside disuse atrophy results in premature loss of muscle strength impeding physical function and potentially future independence of patients with long-COVID. Taking approaches from combating age-

related and disease-related muscle atrophy (e.g., nutrition and exercise) could provide beneficial adaptations in preventing neuromuscular decline. The National Institute for Health Care and Excellence (NICE) recommends that following COVID-19 infection, initiating progressive rehabilitation programmes within the 30 days will lead to optimal impacts and enhancement of recovery [95]. These programmes should be multidisciplinary and holistic, but with respect to enhancing musculoskeletal health, should primarily focus on rectifying any muscle atrophy that has occurred with consideration to excessive fatigue or post-exertional malaise [45, 74].

Conclusion

The results of observational studies highlight that long-COVID patients report persistent and debilitating symptoms that impact recovery, quality of life and broader economic and social activities [96]. A recent scoping review reports that patients highlighted >100 different symptoms with varying severity [97] broadly defined in the areas of cardiovascular [98], pulmonary [99] and respiratory [26], pain [100], fatigue [101], psychological and cognitive disorders [102], sensory impairment [103], functional impairment [104] alongside general infection symptoms (e.g. nausea and fever). Whilst these studies have identified commonly reported symptoms, it is clear that patient experiences are broad and there is a need for longitudinal approaches to determine the prevalence and fluctuation of symptom exacerbation. The information obtained from such approaches should be used in conjunction with the lived experiences of patients in the design and development of COVID-19 specific support pathways that are developed using a non-pharmacological and rehabilitative basis that can be used to restore pre-COVID-19 functional status.

What is increasingly apparent is that multiple agencies will need to come together in interdisciplinary approaches to support long-COVID patients. To be effective the patient support pathways will undoubtedly be as complex as the symptomology, creating a unique challenge for clinical (e.g., primary care) and non-clinical entities (e.g., community health services and academic research institutions) to work collaboratively in the interest of improved patient outcomes. With long-COVID affecting ~57% of confirmed cases in the 6-months post-infection [105], pressure on clinical services will continue to grow with a broad impact upon all clinical areas. In a previous paper, the role and importance of utilising complementary expertise, knowledge and

resource from sports medicine and the exercise sciences were highlighted [106, 107]. As the prevalence of long-COVID increases globally and the need for complex and multi-faceted support pathways is apparent. There is undoubtedly a need to look at broader opportunities to facilitate service delivery and address existing and longstanding issues with morbidity and functional capacity.

Author Contributions

All authors contributed to the writing and editorial changes in the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

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