THE ROLE OF PHYSICAL MEDICINE AND REHABILITATION IN LONG COVID-19 MANAGEMENT

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Introduction

SARS-CoV-2 initially surfaced in December 2019 and triggered a pandemic. A substantial portion of the patients recover from the disease without the need for hospitalization. However, it is severe enough to require clinical hospitalization in about 15% of patients, and it is estimated that about 5% of patients are critically ill [1]. Almost three-quarters of survivors of COVID-19 infection described deterioration in organ systems 4 months after the first clinical appearance [2]. These prolonged effects are expressed in the literature with different terminologies such as 'long haulers', 'long COVID-19', 'post COVID syndrome', 'chronic COVID syndrome' and 'post-acute COVID syndrome' [3-7].

Long COVID-19 Syndrome is a generic-inclusive term that involves post-acute COVID-19 and postCOVID-19 syndrome, based on the time from the acute onset of the disease clinic (Figure 1).
UK NICE guidelines define these terms as follows: Post-acute COVID-19 includes individuals whose symptoms persist between 4 and 12 weeks from the start of the clinic, while post-COVID-19 syndrome covers individuals who report symptoms for more than 12 weeks [8]. Patients with long COVID-19 report a wide variety of symptoms. The frequency of symptoms varies between studies. Aiyegbui et al. [9] evaluated 27 articles on long COVID-19 in their review article and presented the symptoms as in Table 1.

Table 1. Symptoms and findings in Long COVID-19 patients

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Hearing disorders</th>
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</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Diarrhea</td>
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<tr>
<td>Palpitation</td>
<td>Nausea</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Difficulty in concentrating</td>
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<td>Taste disorder</td>
<td>Depression</td>
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<tr>
<td>Olfactory disorder</td>
<td>Anxiety</td>
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<td>Cough</td>
<td>Mood disorder</td>
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<td>Myalgia</td>
<td>Neuropathy-polyneuropathy</td>
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<td>Arthralgia</td>
<td>Seizures</td>
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<td>Memory loss</td>
<td>Visual disorder</td>
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<td>Cognitive dysfunction</td>
<td>Vertigo</td>
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<td>Tinnitus</td>
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<td>Rhinitis</td>
<td>Skin lesions</td>
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<td>Congestion</td>
<td>Bladder disorders</td>
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<tr>
<td>Deconditioning</td>
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<td>Sarcopenia-atrophy</td>
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This situation mediates the multi-organ effects and damages in COVID-19 [10].

Despite significant efforts in the global COVID-19 vaccination procedure, the number of individuals affected by the disease is growing. Therefore, understanding the consequences of COVID-19 on organ systems and managing long COVID-19 patients is critical. Given the long-term impacts of COVID-19. It is clear that healthcare systems will struggle with the disorders of long COVID-19 patients.

There are several reviews presenting rehabilitation approaches for long COVID-19 and COVID-19 survivors [11, 12, 13]. In these reviews, topics covering telehabilitation, rehabilitation settings during and after COVID-19 and rehabilitation approaches are emphasized. This review presents the long-term consequences of COVID-19 on the respiratory, cardiovascular, musculoskeletal, and neurological systems, as well as to provide recommendations on the rehabilitation of long COVID-19.

Search strategy

The search strategy was determined in line with the recommendations reported by Gasparyan et al. [14]. The terms 'long COVID-19 physical therapy,' 'long COVID-19 physiotherapy,' and 'long COVID-19 rehabilitation' were searched on the Web of Science, and MEDLINE/Pubmed databases. The titles and abstracts of all articles listed on the databases were reviewed, and papers relevant to the subject were identified. Following that, the full texts were reviewed. Articles directly related to the subject were evaluated.

Respiratory system

Following the discovery of COVID-19's affinity for the lung, various questions arose regarding the recovery of lung function and capacity in COVID-19 survivors. The clinical spectrum can present a picture that can range from mild upper respiratory disease to acute respiratory distress syndrome [15, 16]. According to studies on discharged individuals, the most common respiratory system abnormalities are diffusion disorder and restrictive alterations [17]. A one-year follow-up study after COVID-19 hospitalization demonstrated that chest computer tomography abnormalities persisted, along with diffusion abnormality [18]. These data conform to the 1-year SARS follow-up study, which found diffusion disorders in nearly a quarter of patients [19].
As the number of treatment days in the intensive care unit increases, the lesion area width in high-resolution computed tomography grows and it has been discovered that intubated patients are more exposed to lung fibrosis findings in the follow-up [20]. Furthermore, dyspnea and venous thromboembolism were stated as the primary sequelae in a study of 8983 COVID-19 individuals with milder clinical symptoms [21]. Despite normal physical findings and pulse oximetry measurements, persistent dyspnea is a typical long COVID-19 observation. The reason is most likely multi-faceted and the experiences, psychological state and feelings of the person during the COVID-19 period can lead to this situation [22]. This should be taken into account when evaluating persistent pulmonary symptoms.

Pulmonary fibrosis is tightly linked with the long COVID-19 syndrome that can be verified radiologically and histologically. The permanent deterioration in pulmonary parameters can be detected in a group of patients despite viral clearance [23].

**Cardiovascular System**

COVID-19 has substantially unfavorable effects on microcirculation. These effects are mediated by endothelial dysfunction, capillary damage and microthrombus formation. Thus, the barrier function in the microcirculation is impaired. It has been determined that vascular involvement is associated with the cytokine storm clinic and leads to functional disorders in the endothelial structure [24, 25]. It has been suggested that vascular inflammation may be responsible for the inexplicable symptoms after COVID-19.

There is a relationship between COVID-19 and myocardial involvement. According to the results of the examination with cardiac magnetic resonance imaging, myocarditis was detected between 12 and 53 days after COVID-19 infection in approximately half of the athletes without a history of hospitalization; the vast majority of participants either had mild symptoms or were asymptomatic [26]. In a study in which participants were evaluated with cardiac magnetic resonance imaging between 2 and 3 months after COVID-19, atypical findings were detected at the level of 78%, and no link could be established between the severity of COVID-19 and myocardial inflammation in almost two-thirds of the participants [27]. The clinical course of myocarditis after COVID-19 is mild and mortality rates are low. However, subclinical myocardial inflammation may persist in long COVID-19 patients, resulting in myocardial dysfunction and cardiac death. Therefore, long COVID-19 individuals can be screened for myocardial involvement and cardiac rhythm disorders [23, 28].

Transthoracic echocardiography is the imaging modality of the first choice in patients with suspected myocarditis, and one of its most important advantages is that it can be performed on the bedside in unstable patients. However, this method has certain limitations [29]. The possibility of a pre-COVID-19 ventricular dysfunction and rhythm abnormality should always be kept in mind. Particularly if the patient has defined risk factors and cardiovascular system examinations have not been performed recently, the COVID-19 link should be considered suspicious.

**Musculoskeletal System**

Myalgia, fatigue, and weakness are frequently reported symptoms in long COVID-19 patients regardless of disease severity [30]. In a cross-sectional research, post-COVID-19 muscle weakness and impaired physical competence were found in participants without musculoskeletal disorders before COVID-19 infection [31]. In severe cases of COVID-19, autopsy findings demonstrate immune-mediated localized myofibril necrosis and atrophy. Additionally, it has been demonstrated that virus-related myopathic alterations and critical illness myopathy exist in COVID-19 survivors [32, 33]. Musculoskeletal disorders may be associated with systemic inflammation, prolonged mobilization deficit, mechanical ventilation requirement, and sedation in patients who need intensive care treatment [34]. Zampogna et al. [35] reported that long COVID-19 participants may experience functional impairment and decrease in muscle performance, worsening in dyspnea scores, and deterioration in perceived health status.

Musculoskeletal pathologies are not only valid for patients who require hospitalization or who need treatment in intensive care units. The strict quarantine cautions implemented due to the pandemic have pushed the society into inactivity. Immobilization, weight gain and decrease in exercise frequency will increase the musculoskeletal system disorders of community [36]. Another condition that may be associated
with musculoskeletal complaints is deterioration in psychological state. Epidemiological studies reveal that the prevalence of psychological disorders increases during the pandemic period [37, 38]. Consistent with this view, a relationship between depressive symptoms and musculoskeletal pain has been demonstrated during the quarantine period [39].

**Neurologic System**

The most common symptoms of long COVID-19 associated with the neurological system are headache, dizziness, impaired cognitive functions, brain fog, smell and taste disorders [40]. The virus's invasion of the central nervous system and olfactory bulb has been linked to olfactory abnormalities. Imaging studies conducted on this patient group revealed radiological abnormalities, degeneration and atrophy in the olfactory bulb [41]. Evidence confirming the findings of hypometabolism in several regions of the central nervous system of long COVID-19 patients was obtained in a study comparing long COVID-19 and healthy controls with positron emission tomography. Regions of reduced metabolism and activity in the central nervous system may explain the neurological symptoms associated with long COVID-19 [42]. Patients who were hospitalized due to COVID-19 were radiologically examined, and structural alterations in the patients' central nervous systems were detected. As a result, SARS-CoV-2 has a neuro-invasive effect [43].

A considerable proportion of long COVID-19 patients report long-term memory loss. Memory problems and cognitive dysfunction can be explained by disease-related ischemic lesions developing in the central nervous System [44]. The mechanisms underlyng the neurological disorders in long COVID-19 patients can be vascular damage, impaired oxygenation, neuro-invasive character of the virus, and cellular damage caused by systemic inflammation [45]. One of the central nervous system regions that should be emphasized is the brain stem. The brain stem involves various nuclei and divisions that regulate different physiological functions. Prolonged persistence of brainstem dysfunction following COVID-19 may contribute to the long COVID-19 syndrome [46]. Furthermore, COVID-19 has been linked to disorders such as stroke, demyelinating diseases, and Guillain-Barre Syndrome that will require rehabilitation programs in their follow-up [47, 48].

**Role of Physical Medicine and Rehabilitation**

Long COVID-19 rehabilitation should be designed to include individuals with different system involvements and symptoms, regardless of the severity of the acute stage, with or without hospitalization. If these facilities are not available, existing rehabilitation centers should be organized and developed in accordance with the clinical conditions of long COVID-19 patients. Another point to be emphasized is that undefended groups such as people in nursing homes and elderly care centers, refugees and asylum seekers should be included in this service [49]. Since COVID-19 can influence numerous systems, it is recommended to establish teams that include multiple medical disciplines under the leadership of rehabilitation specialists [50]. Patients with a history of long-term hospitalization, those with severe pulmonary diffusion capacity impairment, and those with radiologically confirmed extensive lung involvement should be prioritized for long-term rehabilitation programs.

Another issue to focus on is the timing of rehabilitation and early rehabilitation. Belli et al. [51] reported that a considerable portion of the participants had a high level of disability and addiction at discharge (Barthel index ≤ 60) and required early rehabilitation. General rehabilitation principles are also valid for long COVID-19 patients, and early rehabilitation will benefit more to this patient group. Since the affected organ systems can differ in long COVID-19, an issue that should be emphasized is the individualization of rehabilitation programs.

Muscle weakness, loss of condition, sarcopenia, atrophy, myopathies and polynuropathies can occur in COVID-19 patients with a history of hospitalization in intensive care units. This clinical scenario addresses the critical parameters of long COVID-19. To prevent or alleviate this clinical spectrum that will impair the quality of life and cause disability in COVID-19 survivors, preventive rehabilitation programs should be implemented in the intensive care unit as soon as the clinical situation allows [52].

Education is regarded as the cornerstone of all rehabilitation programs. Since COVID-19 is an unique disease, patients should be educated about the impacts and possible consequences of the disease, and answers to the patients' queries
should be found as much as possible. This approach will increase the adaptation of individuals to rehabilitation programs [53].

Pulmonary rehabilitation has long been recommended as a method for ensuring comprehensive care, improving the quality of life and daily living activities of patients with disorders involving the respiratory system [54]. Even in individuals with irreversible damage and changes in the lung structure, pulmonary rehabilitation reduces the severity of symptoms, improves the functional status, and quality of life, even if it does not provide a cure. Pulmonary rehabilitation programs can be provided in a healthcare center as inpatient, outpatient, home exercise recommendations, and telemedicine techniques [55]. Pulmonary rehabilitation programs include optimization of medical care, exercise recommendations, education sessions, psychological, social and occupational assistance, and behavior modification suggestions [56] (Figure 2). Exercise training is the main component of pulmonary rehabilitation programs and is the most extensively suggested technique in the programs implemented by numerous rehabilitation centers [57]. It has been noted that early pulmonary rehabilitation is not well tolerated in the acute disease phase and can induce a rapid decrease in oxygen saturation [58]. Liu et al. [59] reported that 6 weeks respiratory rehabilitation program involved respiratory muscle training, controlled cough exercises, diaphragm training, stretching exercise and home exercise program significantly improved respiratory function, quality of life, and anxiety in elderly long COVID-19 patients.

The administration of pulmonary rehabilitation has various purposes. Reducing airway resistance and regulating ventilation is one of them. Positioning, mobilization, effective coughing and secretion drainage strategies are used for this aim. The position and function of the diaphragm and other accessory respiratory muscles are restored. The respiratory rate is reduced. Efforts are made to reduce workload and energy consumption by providing correct respiratory training. Chest mobility increases with appropriate exercises. Endurance and exercise capacity are increased. As a result, the quality of life improves [60].

It is recommended to organize neuromotor rehabilitation programs as early as possible to improve neuromuscular functions [61]. This patient group needs comprehensive rehabilitation practices to reduce pain, improve sarcopenia, prevent atrophy, provide mobilization and ameliorate balance-coordination. Oxygenation and fatigue should be constantly monitored during the rehabilitation program in high-risk patients, and the intensity of exercise should be gradually increased as the patient's capacity improves, starting with low-intensity physical exercises. Stretching and low-intensity strengthening exercises can be recommended before structured aerobic exercise sessions [62]. Progressive resistance exercises should be recommended to counteract the negative effects of atrophy and sarcopenia and to increase muscle mass.

**Age-related Strategies for Long COVID-19 Rehabilitation**

Aging is one of the major risk factors for many chronic and life-threatening disorders, such as cancer and cardiovascular disease. This is also accepted for COVID-19 [63]. Increasing age, male sex and deterioration in cognitive and physical activity have been demonstrated to be independent predictors of mortality in COVID-19 patients [64]. Therefore, the importance of timely diagnosis and individualized restorative management for elderly patients is emphasized [65]. Positive potential effects of systemic steroids on the management of COVID-19 have been demonstrated [66]. However, the geriatric patient group is more likely to experience steroid adverse effects. Long COVID-19 patients may face hypocalcemia, vitamin D deficiency, bone demineralization and osteoporosis, and this whole process is triggered by the immobilization period.
due to the disease [67]. Moreover, elderly long COVID-19 patients will struggle with arthralgia, myalgia and sarcopenia. From this perspective, elderly long COVID-19 patients should be prioritized for rehabilitation programs. Fall risk, osteosarcopenia status, frailty and pain level should be considered in this patient group. The immobilization period should be kept as short as possible.

Conclusion

Considering the long-term immobilization, musculoskeletal system disorders, respiratory-cardiovascular system related clinical conditions and other multi-system involvements, long COVID-19 patients need comprehensive rehabilitation practices. In particular, patients with considerable respiratory or neuro-motor dysfunction should continue their rehabilitation programs in structured rehabilitation units with multidisciplinary approach. Home, outpatient, or telemedicine rehabilitation approaches are more appropriate for patients with mild symptoms or those with near-normal functional capacity. It is obvious that healthcare systems will struggle with the problems of long COVID-19 patients for a long time. Therefore, there is a need for specialized teams in long COVID-19 rehabilitation interventions like neuro-orthopedic rehabilitation. Rehabilitation approaches will reduce hospital admissions with the management of long-term symptoms and the prevention of complications.

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AUTHOR CONTRIBUTIONS

BFK designed the study. BFK reviewed the literature and generated data. BFK drafted the initial draft. BFK revised the initial manuscript. BFK prepared the tables and figures. BFK substantively contributed to the drafting of the initial and revised versions of this review. BFK takes full responsibility for the integrity of all aspects of the work.

CONFLICTS OF INTERESTS

Author has completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/; available on request from the corresponding author). Author declares that there are no potential conflicts of interest.

DISCLAIMER

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