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Development of Rehabilitation Measures for Post-Covid Syndrome

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Annotation: The article provides an overview of research into post-COVID syndrome. Post-COVID conditions have been shown to have a significant negative impact on people's daily functioning and quality of life. It presents with a wide variety of clinical symptoms in the cardiopulmonary and neurocognitive domains. Therefore, a multidisciplinary approach to the treatment of post-COVID syndrome is necessary. The development of rehabilitation measures based on physical exercise can play an important role in treatment and is relevant.

Key words: post Covid-19 syndrome, rehabilitation, physical exercises.

COVID-19 has affected more than 676 million people worldwide and caused more than 6.8 million deaths (https://coronavirus.jhu.edu/map.html, accessed August 31, 2023). Depending on age, comorbidities, and severity of symptoms, recovery from COVID-19 usually takes 2 to 4 weeks (Wang et al., 2020). However, it is estimated that between 30 and 80% of patients experience one or more long-term symptoms (Nalbandian et al., 2021). A condition in which symptoms are still present 3 months after initial SARS-CoV-2 infection or new symptoms appear is called post-COVID condition (PCC) or long COVID. These symptoms cannot be explained by an alternative diagnosis and persist for at least 2 months. PCC does not appear to be related to the severity of the initial infection, as it can be observed in patients with mild, even asymptomatic, COVID-19, in patients with more severe cases, and in patients who have been hospitalized (Rolin et al., 2022) . It occurs in people of all ages and has a significant negative impact on quality of life. Moreover, due to persistent symptoms, 45.2% of RCC patients require workload reduction and 22.3% are not even able to work (Varatharaj et al., 2020).

Introduction. COVID-19 has affected more than 676 million people globally and caused more than 6.8 million deaths (https://coronavirus.jhu.edu/map.html accessed on 31 August 2023). Depending on age, comorbidities, and severity of symptoms, recovery from COVID-19 takes usually 2 to 4 weeks (Wang et al., 2020). However, it has been estimated that from 30 to 80% of patients experience one or more long-term symptoms (Nalbandian et al., 2021). A condition in which symptoms are still present after 3 months from the initial SARS-CoV-2 infection or new symptoms appear has been called the post-COVID condition (PCC) or long COVID. These symptoms cannot be explained by an alternative diagnosis and last for at least 2 months. The PCC does not seem to be related to the severity of the initial infection because it can be observed in patients who have had mild, even asymptomatic COVID-19, patients with more severe cases, and patients who had been hospitalized (Rolin et al., 2022). It occurs in people of all ages and has a significant negative impact on the quality of life. Moreover, due to persisting symptoms, 45.2% of PCC patients require a reduced workload and 22.3% are even unable to work (Varatharaj et al., 2020).

Symptoms of PCC. Evidence from nine longitudinal studies suggests that the most prevalent symptoms of PCC are fatigue, breathlessness, chest tightness, muscle pain, difficulty concentrating, impaired memory, loss of smell and taste (Bowyer et al., 2023). Other studies have reported similar symptoms. For example, a review by Crook and colleagues showed that long COVID is characterized mainly by fatigue, shortness of breath, chest pain, and impaired cognition (Crook et al., 2021). A meta-analysis performed by Martimbianco et al. identified chest pain, fatigue, shortness of breath, and cough as the main symptoms of PCC (Cabrera Martimbianco et al., 2021). Caspersen et al. analyzed data

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from 73,727 adults followed throughout the pandemic and suggested that long COVID symptoms can be divided into two categories - 'cardiorespiratory' and 'neurocognitive' (Caspersen et al., 2022). Subjective cognitive complaints (often described as 'brain fog') are associated with objective cognitive deficits in domains of attention, verbal memory, long-term verbal memory, working memory, executive function, praxis, and verbal fluency (Dacosta-Aguayo et al., 2022). There is also accumulating evidence of psychiatric complications. One recent systematic review found that patients with long COVID very often suffer from post-traumatic stress disorder (PTSD), irritability, anxiety, insomnia, depression, obsessive-compulsive disorder (OCD), and paranoia (Rogers et al., 2020). Such variety of PCC symptoms suggests that SARS-CoV-2 infection is not only a respiratory disease, but rather a multisystem illness with complex and multifaceted pathogenesis.

Possible mechanisms of PCC. Although exact mechanisms of PCC are still poorly understood, several hypotheses have been proposed so far:

Persistent viral infection theory. SARS-CoV-2 usually disappears from circulating blood in 1 week; however, there is evidence indicating that it may persist in various tissues for a longer period. For example, Zollner et al. (2022) found that patients with long-COVID continue to shed SARS-CoV-2 antigens with their gut mucosa for up to 7 months, even after mild COVID-19 infection. In contrast, viral antigens could not be identified in patients without PCC, suggesting that long-COVID may be caused by persistence of the virus in the gastrointestinal tract (Zollner et al., 2022), or other organs, such as the lungs, eyes, liver, blood, kidneys, or brain (Kalkeri et al., 2020). How exactly the virus evades immunity is currently unclear. It has been suggested that superantigens expressed by the SARS-CoV-2 might play a role. Superantigens are known for their ability to activate polyclonal T cells that induces a very strong, but non-specific immune response and massive release of inflammatory cytokines ("cytokine storm"). In turn, such a strong immune response may prematurely activate immunological feedback loops that down-regulate immune reactions too early allowing viruses to survive, especially in the tissues where immunity is weak or exhausted (Jacobs, 2021). However, this proposed mechanism does not fully explain cases of viral persistence after mild and asymptomatic initial infection without a "cytokine storm". Therefore, future investigations of viral persistence mechanisms are needed.

Neurodegenerative theory. As described above, neurocognitive complaints, such as headaches, difficulties with concentration, memory, and objective deficits in cognitive functions are frequently reported in patients with PCC. It has been suggested that these symptoms may result from direct and indirect damage caused by the virus to the CNS (Mukaetova-Ladinska et al., 2021). Neuropathological studies in dead patients have revealed edema, partial neuronal death and inflammatory changes in the white matter (Zanin et al., 2020). The virus enters host cells through the angiotensin 2-converting enzyme (ACE-2) receptors on cell surfaces. These receptors are mainly expressed by respiratory and gastrointestinal epithelial cells, but can also be found on neurons and microglia, although in lesser density (Gupta et al., 2020). Thus, SARS-CoV-2 viruses are able to invade neurons too, causing direct damage to the neural tissue. Initially, viruses may infect sensory or motor nerve endings and migrate retrogradely using neuronal inner transport system (Mukaetova-Ladinska et al., 2021). Supporting this idea, anosmia is one of the first clinical symptoms of COVID-19 infection (Yan et al., 2020). Although the neuroimaging reports are not conclusive, anosmia has been linked to the atrophy and transient morphological changes in the olfactory bulb (Chiu et al., 2021). Thus, olfactory tract may be one of the main gateways through which SARS-CoV-2 may enter the brain in the early stages of infection and spread throughout the brain later (Mori, 2015).

Besides neurons, in the CNS SARS-CoV-2 can also infect macrophages, microglia, and astrocytes. By activating these cells, the virus may cause a hyperinflammatory state with excessive production of such cytokines as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF), chemokines (CCL-2, CCL-3 and CCL-5), and many other inflammatory substances. Hyperinflammation may lead to vascular leakage, vasculopathy, and coagulation cascade reactions resulting in secondary hypoxic damage to the nervous tissue. Laboratory experiments have confirmed that primary glial cells cultured *in vitro* and infected with SARS-CoV-2 secrete a large amount of inflammatory factors such as IL-6, IL-12, IL-15

and TNF-α (Mukaetova-Ladinska et al., 2021). Combined with viral persistence, chronic inflammation in the nervous system may cause structural and functional changes that mediate occurrence of neurocognitive and neuropsychiatric symptoms of PCC. Supporting this view, elevation of proinflammatory cytokines, including IL-1, IL-6 and TNF-alpha, has been associated with fatigue, depression and anxiety, as well as with hostility and irritability (also referred as sickness behaviours), irrespective of whether the increase was triggered by infection or prolong and repetitive stress. Similarly, elevation of the wide spectrum of cytokines has been described in PTSD (Zhang et al., 2020). Altered immune response and increased plasma levels of IL-1β, IL-6 and TNF-α were also found in patients with OCD (Karagüzel et al., 2019). Collectively, all these findings suggest that neurocognitive and neuropsychiatric symptoms of PCC may be triggered by a combination of direct damage to the neural tissue and secondary effects of hyperinflammation induced by the virus.

Autoimmune theory. Numerous studies have found increased levels of autoantibodies in patients with SARS-CoV-2, including antinuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) (Gazzaruso et al., 2020). For example, Chang et al. found that approximately one half of the subjects hospitalized with SARS-CoV-2 infection had autoantibodies associated with various rheumatic disorders such as myositis or systemic sclerosis (Chang et al., 2021). Results of another study by Zhou et al. (2020) show that 50% of hospitalized patients have increased levels of antinuclear antibodies, suggesting activation of autoimmunity (Zhou et al., 2020). One proposed mechanism of autoimmunity is molecular mimicry (Gasparotto et al., 2021). Parts of coronavirus antigens (e.g., spike glycoprotein S) are similar to human antigens. This mimicry plays an important role in the processes of host cell invasion, escapement from immune response, and viral persistence. Similar antigens (epitopes) are expressed in several tissues of the human body. Thus, a diverse array of organ-specific and systemic lesions observed in patients with PCC to some extent may be explained by autoimmune reactions (Chang et al., 2023).

Autonomic nervous system imbalance theory. Interestingly, autoimmune mechanisms have also been linked to dysfunction of the autonomic nervous system. It has been suggested that autoantibodies to α-/β-adrenoceptors and muscarinic receptors may cause such PCC symptoms as fatigue, breathlessness, chest pain, dizziness, panic attacks, and anxiety (Dani et al., 2021).

As one can see, all 4 proposed mechanisms are not mutually exclusive, but rather complementary to each other. Apart from its direct damaging effect on various tissues and organs, persistence of SARS-CoV-2 in the body may cause chronic inflammation that, in turn may contribute to neurodegeneration, trigger autoimmune reactions and disturbances in the autonomic nervous system.

Significant negative impact of long-COVID on functional outcomes, quality of life, and productivity indicates a need for early rehabilitation intervention to reduce or prevent debilitating symptoms (Rolin et al., 2022). Success of rehabilitation depends on how efficiently it targets central links of the pathogenesis. Below, we discuss benefits of exercise-based rehabilitation in the light of possible mechanisms of long COVID outlined above.

Implications for rehabilitation. One common component of all suggested theories of PCC is hyperinflammation resulting from altered immune response. There is a compelling evidence suggesting that physical exercise can induce positive changes in the immune system. For example, it has been shown that short-term (e.g., 20-30 min) moderate intensity (e.g., 50-70% VO2 max) exercise 3 times per week enhances activity of tissue macrophages, increases the number of neutrophils, NK cells, T- and B-lymphocytes and immunoglobulins. Thus, enhancement of immune functions through physical exercise may help patients with PCC to eliminate remaining viruses (Thirupathi et al., 2023).

Moreover, exercise-based rehabilitation may also help to normalize patients' cytokine imbalance and reduce inflammation. Skeletal muscle is now considered as a 'secretory organ' that may act in an endocrine fashion by communicating with and influencing other tissues and organs (Schnyder & Handschin, 2015). In response to contraction, it produces over 3000 of cytokines, including IL-6, IL-7, IL-15, myostatin, and others (Docherty et al., 2022). For example, it is well documented that levels of IL-6 increase after physical exercise (Keller et al., 2001; Pedersen et al., 2003). Although it is mainly

recognized as a pro-inflammatory cytokine, in the context of physical exercise IL-6 exerts an anti-inflammatory effect (Benatti & Pedersen, 2015). During infection, IL-6 is produced by the monocytes along with other inflammatory cytokines, such as TNF-α and IL-1β. In contrast, during moderate physical exercise IL-6 is produced by the muscle tissue itself and levels of TNF-α and IL-1β decrease. Muscle-derived IL-6 inhibits production of pro-inflammatory TNF-α by the monocytes (Docherty et al., 2022). It has been suggested that anti-inflammatory effects of muscle-derived IL-6 are mediated by the induction of other anti-inflammatory cytokines, namely IL-10 and IL-1Ra (Pedersen & Febbraio, 2008). IL-10 is considered a classic anti-inflammatory cytokine, which suppresses inflammation through direct inhibition of the action of pro-inflammatory cytokines and through inhibition of their synthesis (Driessler et al., 2004; Ostrowski et al., 1999). IL-10 produced after physical exercise inhibits a number of pro-inflammatory cytokines, including TNF-α and IL-1β (Rehman et al., 1997). In contrast to IL-10, which influences several pro-inflammatory cytokines, IL-1Ra mediates its anti-inflammatory effects only on IL-1. IL-1Ra released after physical exercise inhibits inflammatory actions of IL-1α and IL-1β by competitively binding to IL-1 receptor complex (Dobbs et al., 1999) [39]. IL-1Ra is a potent anti-inflammatory agent used, for example, in the treatment of rheumatoid arthritis (Dayer et al., 2017). Interestingly, it has also been shown to be effective in the treatment of COVID-19 patients. Results of the recent systematic review and meta-analysis demonstrate that IL-1Ra reduces the need for invasive mechanical ventilation and mortality risk of hospitalized non-intubated patients (Barkas et al., 2021).

Overall, the evidence described above suggests that moderate physical exercise may play a crucial role in the management of long-COVID as it is beneficial for patients' immune system and cytokine profile. Exercise-based rehabilitation has been shown to improve breathlessness, fatigue, functional capacity, strength, quality of life, and psychiatric symptoms in COVID-19 patients (Compagno et al., 2022; Jimeno-Almazán et al., 2022; Nopp et al., 2022). For example, a randomized controlled trial performed by Jimeno-Almazan et al. (2022) showed that 8-week supervised aerobic and resistance exercise program at low to moderate intensity has significant positive effects on exercise capacity, strength, quality of life, breathlessness, fatigue, and depression symptoms in patients with long COVID. Importantly, compared to the control group, a greater proportion of participants in the intervention group were reported symptom-free after the intervention (42.1% vs. 16.7%, $p = 0.091$) (Jimeno-Almazán et al., 2022).

Moreover, physical exercise has been found to improve neurocognitive functions such as attention, processing speed, executive functioning, and memory (Rolin et al., 2022). A meta-analysis of studies investigating the effects of exercise on cognitive functions have found cognitive improvements even in patients with mild cognitive impairment (Smith et al., 2010). Regular exercise is also beneficial for psychological well-being of PCC patients (Compagno et al., 2022; Jimeno-Almazan et al., 2022). It has been shown that exercise is associated with increased feeling of control (Weinberg & Gould, 2023), competency, self-efficacy (Craft, 2005; Rodgers et al., 2014), and self-esteem (Zamani Sani et al., 2016). Individuals who exercise regularly are less depressed or anxious than those who do not (De Moor et al., 2006), suggesting the use of physical exercise as a treatment (Carek et al., 2011). For example, it has been demonstrated that aerobic (Craft & Perna, 2004) and anaerobic (Martinsen, 1990) exercise programs can significantly reduce severity of depressive symptoms in patients with major depressive disorder (MDD) and anxiety in anxiety disorders (Scully et al., 1998). Numerous studies have demonstrated that in adults, physical exercise is associated with increased gray matter volume, for example, in the frontal lobes, hippocampus, cerebellum, and motor cortex (Chaddock-Heyman et al., 2014; Colcombe et al., 2006; Erickson et al., 2011). Such positive changes in the nervous system associated with regular physical exercise have been linked to increased blood-flow (Ainslie et al., 2008; Brown et al., 2010), increased cerebral angiogenesis (Isaacs et al., 1992), improved plasticity of neurotransmitter systems (Praag et al., 2005) (39), better glucose and lipid metabolism, and release of neurotrophic factors such as BDNF (Mandolesi et al., 2018). Thus, exercise-based rehabilitation may also help to restore structural and functional changes in the CNS caused by the SARS-CoV-2 infection.

Considering all of the above, a growing body of evidence suggests that exercise-based rehabilitation is a key component of the management of PCC. Considering that long COVID may manifest with a wide

range of cardiorespiratory, neurological and psychiatric symptoms, rehabilitation should be individually-tailored and carried out by a multidisciplinary team (Chuang et al., 2023). Comparisons of the effectiveness of different types of rehabilitation on long COVID have not yet been provided by randomized controlled trials. However, several recommendations based on expert opinion or evidence from other diseases have been made (DeMars et al., 2023). Prior to rehabilitation, patients should be thoroughly evaluated to rule out contraindications. Chest X-ray, spirometry, 1-min sit-to-stand test or 6-min walking test, or cardiopulmonary exercise testing (CPET) can be used to assess cardiopulmonary functions, exercise capacity, and oxygen saturation change. Presence of such cardiopulmonary symptoms as chest pain, dyspnea, palpitation, or syncope requires further cardiac testing with electrocardiography (ECG), cardiac sonography, troponin, N-terminal pro-BNP to evaluate the severity of cardiac impairment (Bhave et al., 2022). The underlying pathology should be managed before the commence of rehabilitation (WHO, 2022). Patients should also be screened for post-exertional symptom exacerbation (PESE) which is defined as worsening of symptoms, such as fatigue, pain, dyspnea, cognitive impairment, and other symptoms after physical, mental, or emotional exertion. The worsening of symptoms may occur immediately or 12–72 h after exertion and last from several hours to weeks (Stussman et al., 2020). Elevating the intensity of rehabilitation without considering PESE should be avoided. Precautions should also be taken in patients with orthostatic intolerance - dizziness, breathlessness, presyncope, or syncope after a prolonged period in an upright position. For such patients, rehabilitation programs should mainly consist of exercises performed in a non-upright position, such as recumbent ergometer and resistance training (Chuang et al., 2023).

Long-term symptoms of COVID-19 infection might require long-term rehabilitation and follow-ups. In order to reduce costs and risks of re-infection follow-up visits or entire rehabilitation programmes may be performed in the form of telerehabilitation, which refers to home-based exercise under the supervision of a clinician via web (i.e., mobile phone with specific health apps or PC-based exercises) (Maggio et al., 2020). When developing such remote rehabilitation programmes clinicians should include the possibility to adjust the level of difficulty of the exercises to the patient's performance and the possibility to choose different kinds of exercises based on prevailing symptoms of PCC. Telerehabilitaiton provides the opportunity to deliver rehabilitation in a safe and convenient manner and also to improve social functioning and psychological well-being of patients by avoiding isolation (Pistarini et al., 2021) (37).

Conclusions. Post-COVID condition has a significant negative impact on individuals' daily functioning and quality of life. It presents with a large variety of clinical symptoms in cardiopulmonary and neurocognitive domains. Therefore, a multidisciplinary approach for management of PCC is essential. Although mechanisms of long-COVID are poorly understood, there is evidence indicating an important role of viral persistence, altered immune response and chronic inflammation. Exercise-based rehabilitation might play an essential role in the management of PCC as multiple lines of evidence suggest that it may enhance immune system and reduce inflammation. However, precautions should be taken in patients with severe cardiac dysfunction and orthostatic intolerance. Also, the optimal timing, dosage, and modules of rehabilitation are yet to be established.

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