Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Long COVID: systemic inflammation and obesity as therapeutic targets

Fanatic Studio/Gary Waters/Science Photo Library

Published Online
April 23, 2022
https://doi.org/10.1016/S2213-2600(22)00159-X

See Articles page 761

Management of the post-COVID-19 condition—often referred to as long COVID—is a challenge for health-care professionals because of the heterogeneity and complexity of its clinical manifestations and the probable need for multidisciplinary management approaches.[1] Identification and understanding of modifiable determinants associated with manifestations of long COVID would help in the adaptation of treatment pathways for particular phenotypes.[1] In *The Lancet Respiratory Medicine*, the PHOSP-COVID Collaborative Group[2] report the latest results from the UK-based, multicentre, prospective Post-hospitalisation COVID-19 (PHOSP-COVID) study, in which the investigators identified systemic inflammation and obesity as factors that might be associated with long COVID, representing potentially treatable traits in people with more severe post-COVID-19 symptoms. In the current report, the PHOSP-COVID Collaborative Group found increased levels of several biomarkers related to systemic inflammation and lung damage in individuals with more severe physical and mental health impairments 1 year after hospital discharge. The presence of increased levels of systemic inflammatory biomarkers (eg, cytokines) in individuals with severe acute COVID-19 has been reported previously.[3] Moreover, the use of anti-inflammatory agents such as corticosteroids[4] or interleukin-6 (IL-6)-blocking agents[5] has been found to be associated with positive outcomes in patients hospitalised with acute COVID-19. The PHOSP-COVID Collaborative Group found that long-lasting systemic inflammation was present in people with more severe symptoms of long COVID, which could provide biological plausibility for the presence of severe impairments in people with persistent symptoms after acute COVID-19—sometimes referred to as long haulers—and allow new therapeutic strategies to be applied in these patients via a personalised medicine approach. The presence of long-lasting systemic inflammation in some patients with long COVID would suggest that anti-inflammatory agents might have potential not only during the acute phase of infection,[4,5] but also during the post-acute phase. However, no clinical trial has yet investigated the effects of anti-inflammatory agents in patients with long COVID. Accordingly, a pharmacological treatment strategy based on anti-inflammatory agents for individuals with severe symptoms of long COVID, combined with other therapeutic or rehabilitative approaches that might be considered for specific symptoms (eg, pain or cognitive blurring), should be considered in future research. However, several questions need to be addressed about the potential use of such agents. For example, should individuals with less severe long COVID receive anti-inflammatory agents? The current study confirmed the presence of four clusters of symptoms with different severities of mental and physical health impairment—very severe, severe, moderate–cognitive, and mild—and found that inflammatory mediators of tissue damage and repair, including IL-6, were elevated in both the very severe and the moderate–cognitive clusters compared with the mild cluster; identifying individuals who might benefit from an anti-inflammatory approach will be an important aim of future studies. Because extended use of anti-inflammatory agents often leads to side-effects, when should these agents be given after the acute phase of infection and for how long? Should anti-inflammatory agents be given when symptoms are severe, or could a preventive therapeutic approach be implemented? The results of the PHOSP-COVID study open up highly relevant questions from a clinical viewpoint.

The PHOSP-COVID Collaborative Group[2] also found that female sex and obesity are factors associated with more severe physical and mental health impairments 1 year after hospital discharge. These results are consistent with previous reports in the medical literature that obesity and female sex are risk factors for long COVID.[6–8] However, The PHOSP-COVID Collaborative Group's findings add to the evidence base by confirming these associations in a large cohort with long-term follow-up.[2] The association between obesity and severe long COVID might be expected because the multisystemic changes (ie, hormonal, metabolic, and a pro-inflammatory state) associated with obesity[9] could promote the maintenance of a systemic inflammation. Therefore, management of patients with long COVID should include the promotion of healthy lifestyle habits (eg, nutrition habits and exercise) to reduce the impact of obesity. Additionally,

exercise is proposed as a therapeutic strategy to be applied in patients with long COVID because it has anti-inflammatory and proimmune effects[10] and it could lead to reduced bodyweight. Nevertheless, considering that patients with obesity are at increased risk of developing severe long COVID symptomatology, exercise and physical activity should be carefully monitored by health-care professionals.

All these therapeutic considerations should be applied from a sex-based perspective, since female sex is a non-modifiable risk factor associated with severe long COVID.[2] For example, the use of anti-inflammatory agents and exercise programmes might be applied differently in males and females. Biological (eg, hormones, sex differences in ACE2 and transmembrane protease serine 2 receptors), social (different health-care requirements and treatment perceptions), and emotional (beliefs, previous experience, and fear) differences according to sex and gender must be considered in future studies investigating the management of long COVID.

In addition to pharmacological treatment, other therapeutic approaches could help to control specific symptoms of long COVID. For instance, graduated exercise could help in the management of fatigue, respiratory programmes could help with symptoms such as breathlessness, and pain neuroscience education could help in the management of pain symptoms.

In summary, we propose that long COVID is a multifactorial condition, in which determinants related to the pathogen (SARS-CoV-2-associated factors) intersect with the host response (within-individual factors) and with external (hospitalisation-related) and emotional (COVID-19 outbreak-associated) factors. The latest report from the PHOSP-COVID Collaborative Group provides evidence about the first two factors, wherein elevated inflammatory mediators—comprising the so-called cytokine storm—induced by the SARS-CoV-2 virus (pathogen) during the acute phase could induce a sustained and long-lasting systemic inflammatory response (host response) perpetuated and promoted by within-individual factors such as obesity. This model implies that multidisciplinary treatment of patients with long COVID should include both pharmacological and rehabilitation approaches, but also social and welfare support for promoting healthy lifestyle habits.

We declare no competing interests.

*Lidiane L Florencio, César Fernández-de-las-Peñas
lidiane.florencio@urjc.es

Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), 28922 Madrid, Spain

1 Parker AM, Brigham E, Connolly B, et al. Addressing the post-acute sequelae of SARS-CoV-2 infection: a multidisciplinary model of care. *Lancet Respir Med* 2021; **9:** 1328–41.
2 The PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med* 2022; published online April 23. https://doi.org/10.1016/S2213-2600(22)00127-8.
3 Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020; **8:** 1233–44.
4 Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: a systematic review and network meta-analysis. *PLoS Med* 2020; **17:** e1003501.
5 Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. *Cochrane Database Syst Rev* 2021; **3:** CD013881.
6 Fernández-de-Las-Peñas C, Torres-Macho J, Elvira-Martínez CM, Molina-Trigueros LJ, Sebastián-Viana T, Hernández-Barrera V. Obesity is associated with a greater number of long-term post-COVID symptoms and poor sleep quality: a multicentre case-control study. *Int J Clin Pract* 2021; **75:** e14917.
7 Maglietta G, Diodati F, Puntoni M, et al. Prognostic factors for post-COVID-19 syndrome: a systematic review and meta-analysis. *J Clin Med* 2022; **11:** 1541.
8 Fernández-de-Las-Peñas C, Martín-Guerrero JD, Pellicer-Valero ÓJ, et al. Female sex is a risk factor associated with long-term post-COVID related-symptoms but not with COVID-19 symptoms: the LONG-COVID-EXP-CM Multicenter Study. *J Clin Med* 2022; **11:** 413.
9 O'Rourke RW, Lumeng CN. Pathways to severe COVID-19 for people with obesity. *Obesity (Silver Spring)* 2021; **29:** 645–53.
10 Nieman DC. Exercise is medicine for immune function: implication for COVID-19. *Curr Sports Med Rep* 2021; **20:** 395–401.

COMBATing airway inflammation in infants with cystic fibrosis

Published **Online**
June 2, 2022
https://doi.org/10.1016/S2213-2600(22)00216-8

See **Articles** page 776

Cystic fibrosis lung disease is characterised by a progressive cycle of mucus obstruction, airway infection, and inflammation. The Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF)[1] intensive surveillance programme has provided strong evidence that this process starts early in infancy, before respiratory symptoms. In a landmark study, the team reported that free neutrophil elastase in bronchoalveolar lavage done in infancy predicts the subsequent development of bronchiectasis by age 3 years, rendering