Editorial Commentary

Chicken, meet, egg: long COVID and the intestinal microbiome

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One of the many sequalae of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been the identification of post-acute COVID syndrome (PACS); defined as the presence of prolonged symptoms beyond 4 weeks from the time of initial coronavirus disease (COVID-19) symptom onset (1). Multiple studies from across the globe have reported persistent symptoms post COVID up to 6 months after the acute infection (2-5). This multiorgan disease has been found to have long term sequelae involving the pulmonary, cardiovascular, renal, hematologic and gastrointestinal systems. Fatigue, joint pain, dyspnea, cough, sleep disturbances, anxiety, chest pain, loss of smell/taste, diarrhea being the most commonly reported symptoms (2,6-8). The mechanisms that underlie this phenomenon remain of interest to clinical practice.

The recently published study titled "Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome" examined the relationship between gut microbiota composition and the development of PACS (9). In this prospective observational study in Hong Kong, the gut microbiome of 106 COVID patients were compared to those of 68 non-COVID controls by serially analyzing a total of 258 samples for up to 9 months. A majority of the patients with COVID developed PACS (76%), which manifested most commonly as fatigue, poor memory and hair loss. There were no significant differences in age, gender, comorbidities, use of antibiotics, use of anti-viral drugs and severity of COVID-19 in patients who did, or did not, develop PACS at 6 months.

At baseline (COVID admission), the patients who later developed PACS had significantly lower bacterial diversity compared with patients who would not develop PACS, their samples being relatively deficient in Bifidobacterium, Blautia and Bacteroides. During the follow-up period, gut microbiota composition in patients without PACS recovered to a level similar to non-COVID-19 controls. In contrast, bacterial diversity and richness in patients with PACS were significantly lower than in those without PACS (and controls) at 6 months post-COVID. The authors also correlated PACS symptom categories (neuropsychiatric, gastrointestinal, respiratory, dermatological, and musculoskeletal) with bacterial taxa. Poor lung function, fatigue and hair loss were all associated with specific bacterial species in this analysis. Butyrate-producing bacteria, like *Bifidobacterium pseudocatenulatum* and *Faecalibacterium prausnitzii* were found to have a negative correlation to the development of poor lung function and hair loss in this study. The study concluded that altered gut microbiome composition is strongly associated with PACS, up to 6 months after clearance of SARS-CoV-2 virus.

What constitutes 'long COVID', or PACS, remains an area of mixed data and conflicting opinions (1). How do we attribute persistent symptoms after SARS-CoV-2 infection to differences in gut microbial composition? Similar to this study, Haran *et al.* reported similar findings of dysbiosis in the oral microbial environment in their study of 84 COVID-19 patients, including 14 with prolonged COVID symptoms for up to 10 weeks. These patients were noted to have higher levels of pro-inflammatory oral flora (10). Yeoh *et al.* in their study of 100 patients also reported patients with severe COVID-19 had lower levels of favorable gut bacteria (known to have immunomodulatory effects) (11). These studies raise the question if SARS-CoV-2 infection outcomes are influenced by underlying physiology

(microbiome impacts outcomes), or do persistent symptoms after COVID-19 alter patient behaviors (outcomes impact microbiome)?

The results of this study certainly associate baseline and subsequent gut microbial ecology with PACS patterns, suggesting a pathogenic process in the PACS group (9). It is possible that underlying microbial metabolic processes influence PACS syndromes. A wide range of disorders including autoimmune (rheumatoid arthritis, atopic eczema, asthma), gut inflammatory conditions [inflammatory bowel disease (IBD), irritable bowel syndrome], metabolic disorders (diabetes mellitus, obesity, non-alcoholic fatty liver disease), chronic kidney disease, mental health conditions (schizophrenia, depression, anxiety and dementia) and more recently PACS have been linked to the derangement of gut microbiota (9,12). A healthy and favorable gut microbiome has been proposed to act through metabolites which alter the immune mechanisms and help maintain host-microbe homeostasis. Disruption in normal bacterial homeostasis, such as after a viral infection, can result in altered intestinal barrier function, modulation of intestinal macrophages, regulation of colonic T cells, insulin sensitivity, antioxidants and neuroprotectants, and IL-22 and IgA production (13-19). Zollner *et al.* have reported that most patients with PACS in their Austrian cohort had SARS-CoV-2 viral antigen persistence in gut biopsies from patients with IBD (20). Thus, prolonged viral components at the tissue level, could influence intestinal ecology long after the initial infection has resolved systemically.

There are a few caveats from this study to note. This is an observational study of a small population and does not establish cause and effect relationship. About 80% of the patients only had mild to moderate disease symptoms. The most commonly reported PACS symptoms in the study like fatigue, anxiety and sleep disturbances; these were not recorded in the control population to determine their prevalence and association with microbial alterations in the non-COVID controls. Gut microbiome can be influenced by many factors like genetics, physical activity and diet, so patients who exercise less or change their diet post-COVID may alter their microbial composition (21). It would be helpful to compare microbial composition in PACS patients and controls with and without these symptoms.

Nonetheless, the authors are to be commended for providing data from comparable populations for several months post-COVID illness. It is insufficient at this stage to recommend prophylactic strategies for preventing PACS by microbial manipulation in clinical practice. These interventions have been promising in animal models but for successful clinical translation of gut microbiota modulation in humans, we must first understand the complete natural history of the composition of our microbiome. The appropriate microbe selection and the right timing/duration of treatment still remain unknown. The restoration of a microbial balance in the human gut to achieve favorable outcomes for disease management and prevention remains a daunting challenge, yet many microbial therapeutics for intestinal disease are in the pipeline.

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Footnote

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References

1. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27:601-15.
2. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397:220-32.

3. Carfì A, Bernabei R, Landi F, et al. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020;324:603-5.
4. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine 2020;25:100463.
5. Xiong Q, Xu M, Li J, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin Microbiol Infect 2021;27:89-95.
6. Moreno-Pérez O, Merino E, Leon-Ramirez JM, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. J Infect 2021;82:378-83.
7. Chopra V, Flanders SA, O'Malley M, et al. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Ann Intern Med 2021;174:576-8.
8. Arnold DT, Hamilton FW, Milne A, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax 2021;76:399-401.
9. Liu Q, Mak JWY, Su Q, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. Gut 2022;71:544-52.
10. Haran JP, Bradley E, Zeamer AL, et al. Inflammation-type dysbiosis of the oral microbiome associates with the duration of COVID-19 symptoms and long COVID. JCI Insight 2021;6:152346.
11. Yeoh YK, Zuo T, Lui GC, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 2021;70:698-706.
12. Vijay A, Valdes AM. Role of the gut microbiome in chronic diseases: a narrative review. Eur J Clin Nutr 2022;76:489-501.
13. Kelly CJ, Zheng L, Campbell EL, et al. Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. Cell Host Microbe 2015;17:662-71.
14. Chang PV, Hao L, Offermanns S, et al. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc Natl Acad Sci U S A 2014;111:2247-52.
15. Simeoli R, Mattace Raso G, Pirozzi C, et al. An orally administered butyrate-releasing derivative reduces neutrophil recruitment and inflammation in dextran sulphate sodium-induced murine colitis. Br J Pharmacol 2017;174:1484-96.
16. Zelante T, Iannitti RG, Cunha C, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 2013;39:372-85.
17. Kaikiri H, Miyamoto J, Kawakami T, et al. Supplemental feeding of a gut microbial metabolite of linoleic acid, 10-hydroxy-cis-12-octadecenoic acid, alleviates spontaneous atopic dermatitis and modulates intestinal microbiota in NC/nga mice. Int J Food Sci Nutr 2017;68:941-51.
18. Hwang IK, Yoo KY, Li H, et al. Indole-3-propionic acid attenuates neuronal damage and oxidative stress in the ischemic hippocampus. J Neurosci Res 2009;87:2126-37.
19. Garibay-Nieto N, Queipo-García G, Alvarez F, et al. Effects of Conjugated Linoleic Acid and Metformin on Insulin Sensitivity in Obese Children: Randomized Clinical Trial. J Clin Endocrinol Metab 2017;102:132-40.
20. Zollner A, Koch R, Jukic A, et al. Postacute COVID-19 is Characterized by Gut Viral Antigen Persistence in Inflammatory Bowel Diseases. Gastroenterology 2022;163:495-506.e8.
21. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. PeerJ 2019;7:e7502.

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