Gastrointestinal Involvement in Long COVID and Potential Pathogenic Mechanisms

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Long COVID-19 refers to a collection of symptoms in COVID-19 patients which continue for at least 12 weeks after disease onset.[1] The clinical manifestations are numerous and can affect nearly any organ of the body. Disease symptoms can be new or similar to that reported for acute COVID-19 and can occur in patients who had differing degrees of initial disease severity during acute infection.[2]

33%-98% of COVID-19 survival suffer from long COVID-19 and factors such as female sex, older age, racial/ethnic minorities, and comorbidities can increase the risk of disease.[3]

The incidence of gastrointestinal (GI) symptoms in patients with long COVID-19 vary between 3%-79% and can appear in different parts of digestive system. Loss of appetite, nausea, acid reflux, diarrhea, abdominal pain, and bloody stools are relatively common complications. Nonetheless, there have been some reports of rare but more serious complications like post–COVID-19 cholangiopathy.[4]

COVID-19-related GI involvement is clinically important for many reasons: (a) GI system works in conjunction with other body systems and any derangement in its functions can cause derangements in many other systems; (b) serves as a portal of the SARS-CoV-2 entry and act as a potential route of virus transmission; (c) is a leading cause of morbidity and can be life-threatening if not treated on time. Therefore, various investigations have been focused on identifying the gastrointestinal aspects of COVID-19 and their root causes.

To date, the pathogenic mechanisms of gastrointestinal injury in long COVID-19 have not been clearly elucidated. However, several theories have been put forward to explain the pathophysiological mechanisms of these complications.

Direct viral invasion to GI epithelial cells provide a plausible mechanism for the presence of GI symptoms, because of the high expression of the entry receptor of SARS-CoV-2[angiotensin-converting enzyme 2 (ACE2)] in the digestive system organs.[5]

The interaction of receptor-ligand (SARS-CoV-2 spike protein) leads to the reduced protective activity of the ACE2/Ang-(1–7)/Mas axis, and

elevated activity of ACE/Ang II/AT1R axis. Under this circumstance, elevated activity of nicotinamide adenine dinucleotide phosphate oxidases and increased oxidative activity can occur which in turn can cause chronic inflammation. Immune cells migration to the site of infection and massive production of proinflammatory cytokines play a major role in intestinal inflammation. The uncontrolled inflammation may contribute to gut microbiota disruption and can also lead to diarrhea. Dysfunctionalities in ACE2 can also alter the blood levels of molecules (such as tryptophan) that are essential for brain functions.[6] Moreover, reduced intestinal absorption of tryptophan, resulting in dysregulated expression of anti-microbial peptides and changes in intestinal microbial contents. Disturbance in the commensal gut microbiota have a profound impact on intestinal disease, because these organisms can contribute to different aspects of health including, participating in immunomodulatory processes including (a) inhibition of pro-inflammatory cytokines or promotion of anti-inflammatory cytokines, (b) regulating intestinal epithelial barrier integrity and (c) maintenance of its homeostasis via upregulation of tight junction proteins and stimulation of mucus secretion.

Gut flora are also capable of maintaining the oxygen level in the gut. On the other hand, hypoxia is an important consequence of COVID-19 which is also linked with changes of gut microbiota. These bidirectional relations appears to be important in increasing the risk of gut complications of infected patients.

Digestive post-COVID symptoms may be secondary and appear after infection in other organs. This might occur due to the interrelationship of the digestive and other systems. Some previous observation have indicated the lack of SARS-CoV-2 in the feces of COVID-19 patients who are also exhibiting digestive symptoms. Therefore, it has been speculated that GI system may be invaded indirectly by SARS-CoV-2. It has been indicated that gut microbiota dysbiosis can affect the natural lung microbiota and vice versa. The level of lung-derived C-C chemokine receptor type 9 (CCR9), that controls the migration of CD4+T cells to the intestine increases during the infection with respiratory viruses like influenza. Furthermore, the chemokine CCL25 is expressed in the small intestinal epithelium which is important in recruiting of CCR9+CD4+T cells into the small intestine. These changes may have a detrimental effect on immune system's performance and may destroy the intestinal flora homeostasis.[7]

Some studies have also confirmed that anti-COVID-19 agents have adverse effects on the GI tract. For instance remdesivir may cause some unwanted effects such as nausea.

Altogether, characterization of long COVID-19 complications is an important aspect for the management and eradication of disease. It is now obvious that GI manifestations are common in long COVID-19, but its underlying mechanism is unclear. Therefore, understanding the disease mechanisms will allow recognition of targets for better management and assessment of GI abnormalities.

Ethical Approval

Not applicable.

Conflict of Interest

The authors declare no conflict of interest related to this work.

References

1. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of COVID-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ* 2021;372:n136. doi: 10.1136/bmj.n136
2. Amenta EM, Spallone A, Rodriguez-Barradas MC, El Sahly HM, Atmar RL, Kulkarni PA. Postacute COVID-19: an overview and approach to classification. *Open Forum Infect Dis* 2020;7(12):ofaa509. doi: 10.1093/ofid/ofaa509
3. Jiang DH, Roy DJ, Gu BJ, Hassett LC, McCoy RG. Postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection: a state-of-the-art review. *JACC Basic Transl Sci* 2021;6(9):796-811. doi: 10.1016/j.jacbts.2021.07.002
4. Roth NC, Kim A, Vitkovski T, Xia J, Ramirez G, Bernstein D, et al. Post-COVID-19 cholangiopathy: a novel entity. *Am J Gastroenterol* 2021;116(5):1077-82. doi: 10.14309/ajg.0000000000001154
5. Zhang H, Li HB, Lyu JR, Lei XM, Li W, Wu G, et al. Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-nCoV infection. *Int J Infect Dis* 2020;96:19-24. doi: 10.1016/j.ijid.2020.04.027
6. Nataf S, Pays L. Molecular insights into SARS-CoV2-induced alterations of the gut/brain axis. *Int J Mol Sci* 2021;22(19):10440. doi: 10.3390/ijms221910440
7. Ye Q, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. *Am J Physiol Gastrointest Liver Physiol* 2020;319(2):G245-G52. doi: 10.1152/ajpgi.00148.2020