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Gut microbial signature and gut-lung axis: A possible role in the therapy of COVID-19

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Abstract

The impact of gut as the origin of different disorders has led to the "gut-origin concept" of diseases. The gut microbiome regulates host defenses against viral infections, thus dysbiosis can play a major role in triggering the cascade of inflammation and causing immune imbalances in COVID-19 patients. It appears that gut microbial signature in COVID-19 patients can be used as a potential diagnostic, therapeutic, and even a prognostic marker. Personalized nutrition therapy can be used by profiling the gut microbiota of individual patients and specialized probiotics/synbiotics to modify gut dysbiosis. Hence, improving overall immune responses can be recommended in these patients.

Keywords: Gut microbiota, Probiotics, Gut lung axis, COVID-19

Dear Editor,

COVID-19 is pushing the whole world to a new situation which the faster we understand the different pathophysiological aspects of this disease, the better we can manage the war against this disease. Recently, many studies have shown the impact of gut as the origin of different disorders as well as its important effect on the pathophysiology of diseases. This has resulted in the new perception of "gut-origin concept" of diseases, which was introduced for the first time by Deitch EA in 2012.[1] SARS-CoV-2 primarily induces pulmonary infection through binding to angiotensin-converting enzyme 2 (ACE2) receptors presented in alveolar epithelial cells leading to COVID-19-associated acute respiratory distress syndrome with a high mortality rate. It has been shown that the virus has been detected in feces of involved patients as the virus binds to the ACE2 receptors presented on the enterocytes of small intestine.[2] Gu et al evaluated the gut microbiota of patients with influenza and COVID-19 and found a significant change in the structure and the composition of gut microbiome compared to normal population and even between the two diseases. They identified specific signatures of the fecal microbiota in COVID-19 patients, H1N1 influenza patients, and healthy controls in Chinese population by high-throughput 16S rRNA gene sequencing. They suggested the potential value of the gut microbiota as a diagnostic biomarker and therapeutic target for COVID-19 which needs more future trials.[3] As a patient gets infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus mostly aggregates in the airways and the gastrointestinal (GI) tract, and then binds to ACE2 receptors presented on the surface of the epithelial cells. The gut microbiome regulates intestinal defense mechanisms against pathogens such as viruses as the intestine is one of the main routes of viral invasions. Consequently, dysbiosis can play a major role in starting the cascade of inflammation and causing immune imbalances in COVID-19 patients. One of the involved mechanisms in the gut-lung axis theory (the bi-directional cross-talk between gut and lung) of COVID-19 is the fact that dietary fibers can increase the production of short-chain fatty acids, improve antiviral CD8+ T-cell immune response during infection, and decrease neutrophil-mediated lung injury, which are all linked to better outcomes.[4] Moreover, prebiotics such as wheat bran, fructooligosaccharides, and galactooligosaccharides

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are known to increase butyrate levels, thereby reducing inflammation and improving lung immunity as a link between gut and lung.[5] Tang et al showed that dysbiosis in COVID-19 patients was associated with disease severity. They showed that the change in the number of butyrate-producing bacteria, such as *Faecalibacterium prausnitzii*, *Clostridium leptum*, *Clostridium butyricum*, and *Eubacterium rectale* may help differentiate critical patients from general patients.[6] Zuo et al found similar results in their study on 15 patients with COVID-19 and concluded that persistent alterations were observed in the fecal microbiome of these patients during the time of hospitalization compared to healthy controls. They also showed that fecal microbiota changes were associated with fecal levels of SARS-CoV-2 and COVID-19 severity.[7] Gut-lung axis consists of host-microbe and microbe-microbe interactions which can have a role in human immune system (immunomodulation). This microbial inter-compartmental crosstalk can be performed through bacteriobiota, mycobiota, and virobiota affecting T-helper response pathway which results in acute and chronic respiratory disease.[8] Thus, modulation of this axis (using specific diet, probiotics, etc.) can be an option for the management of respiratory disease.

The prevention protocols are utilized all over the society, as hands are frequently washed; sanitizers, bleaches, and detergents are over-used; surfaces are over-sanitized; and the food consumed is made sure to be perfectly microbe-free; thus, the daily intake of commensal bacteria and probiotics is intensely limited. These nutritional and habitual changes can change gut microbiome and deprive the intestine of the beneficial bacteria, predisposing the body to GI disturbances. Based on the "Hygiene Hypothesis", sanitization reduces our exposure to non-pathogenic commensal strains which may lead to the increased prevalence of allergic disorders in urban areas.[9] This hypothesis might apply to COVID-19 susceptibility as the emphasis on personal hygiene can lead to dysbiosis and its consequent results.[10] Studies have shown that patients presenting GI symptoms through the course of COVID-19 infection, are more likely to require hospitalization and further medical assistance. Specifically, patients with diarrhea have more hospital stays, develop more complications, and have higher mortality rates.[11] This significant change of morbidity and mortality is attributed to the increased cytokine levels, neutrophilia, and lymphopenia.[12] Although these findings are still debatable, enhancing gut microbiota profile by targeted and personalized pharmaconutrition can improve immunity, and is one of the prophylactic and therapeutic ways by which the destructive impact of this disease can be minimized in different populations. Finally, it seems that microbial signature in COVID-19 patients should be further recognized and investigated in larger cohorts, including subgroups at different stages of the disease to be used as a diagnostic, therapeutic, and even a prognostic marker.

Personalized nutrition therapy can be used by profiling the gut microbiota of the individual patients and recommendation of specialized probiotics/synbiotics to improve gut dysbiosis, thereby improving overall immune responses in these patients. These data can be used for prescribing an optimal diet to help in the management of patients with COVID-19. In the complicated COVID-19 patients with organ dysfunction, foodomics, alongside the pharmacotherapy, is the most essential part of any therapeutic intervention that should be carefully considered.[13] This also can be performed as a prophylactic strategy in high risk populations which can result in a better control of the disease. Hence, considering the gut microbial signature and modifying its function might serve as important strategies regarding COVID-19 prevention and treatment.

Report Highlights

What is the current knowledge?

√ Based on the "Hygiene Hypothesis", the emphasis on personal hygiene during the COVID-19 pandemic can lead to dysbiosis and its consequent results.

What is new here?

√ The impact of gut as the origin of different disorders has resulted in the "gut-origin concept" of diseases, and gut-lung axis plays a role in COVID-19 pathogenesis.

√ Gut microbial signature in COVID-19 patients might be used as a potential diagnostic, therapeutic, and even prognostic marker.

√ Personalized nutrition therapy by profiling the gut microbiota of individual patients and use of probiotics/synbiotics can be recommended for the improvement of gut dysbiosis and overall immune responses in these patients.

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Competing interests
The authors declare no competing interests.

Authors' contribution
AS and SS equally contributed to the conception and design of this letter; SS and AM drafted the manuscript; AS and AM critically revised the manuscript. All authors read and approved the final manuscript.

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