COVID-19 and the Human Gut Microbiome: An Under-Recognized Association

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Coronavirus disease 2019 (COVID-19) is an infectious disease with a wide range of respiratory and extrapulmonary symptoms, as well as gastrointestinal symptoms. Despite recent research linking gut microbiota to infectious diseases like influenza, minimal information is known about the gut microbiota’s function in COVID-19 pathogenesis. Studies suggest that dysbiosis of the gut microbiota and gut barrier dysfunction may play a role in COVID-19 pathogenesis by disrupting host immune homeostasis. Regardless of whether patients had taken medication or disease severity, the gut microbiota composition was significantly altered in COVID-19 patients compared to non-COVID-19 individuals. Several gut commensals with recognized immunomodulatory potential, such as Faecalibacterium prausnitzii, Eubacterium rectale, and bifidobacteria, were underrepresented in patients and remained low in samples taken several weeks after disease resolution. Furthermore, even with disease resolution, dysbiosis in the gut microbiota may contribute to chronic symptoms, underscoring the need to learn more about how gut microbes play a role in inflammation and COVID-19.

Key Words: Microbiota; Gastrointestinal Disease; COVID-19; SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a highly transmissible and pathogenic infection that first appeared in late 2019 and has since created a pandemic, which poses a threat to public safety and human health.1 Those infected are extremely contagious and can spread the disease even if they are asymptomatic, which emphasizes the importance of isolating and testing frequently.2 COVID-19 is also two to three times as infectious as influenza and therefore, outbreaks develop in clusters due to these characteristics.2 Early detection of COVID-19 could lessen the burden; however, initial signs remain unclear.2 As of April 8, 2022, 494,587,638 cases have been confirmed and 6,170,283 deaths have been reported globally, with the United States of America (USA) leading in the sheer number of confirmed cases (79,544,396), according to the World Health Organization (WHO).3

According to single-cell ribonucleic acid (RNA) sequencing data, transmembrane protease serine protease 2 (TMPRSS2) is strongly expressed in various tissues and body regions and is co-expressed with the receptor, angiotensin-converting enzyme 2 (ACE2), in nasal epithelial cells, lungs, and bronchial branches, which explains some of the SARS-tissue coronaviruses (CoV-2) tropism.1 Therefore, COVID-19 has a variety of effects on different people.3 The majority of those infected will have mild to moderate respiratory symptoms; in addition, most will recover without the need for medical attention.3 Patients with SARS-CoV-2 have fever first, then upper respiratory symptoms, and eventually upper and lower gastrointestinal (GI) symptoms.2 The following are the most common symptoms: fever, cough, tiredness, and loss of gustatory or olfactory senses.3 Less common symptoms include
pharyngitis, cephalgia, myalgia and pains, diarrhea, skin rash with or without discoloration of fingers or toes, and irritated red eyes. Severely symptomatic patients with COVID-19 are more likely to develop severe disease or to modify treatment to reduce severity. Disease severity alters microbiota and the occurrence of complications in COVID-19 positive patients is correlated with low-risk or a reduction in Faecalibacterium prausnitzii and potentially an abundance or high-risk with Parabacteroides spp. In addition, a favorable disease progression has been linked to a steady gut bacterial makeup. The purpose of this paper is to discuss the association between COVID-19-positive patients and their gut microbiome alterations.

**HUMAN MICROBIOTA AND COVID-19**

There is much to learn regarding the human gastrointestinal microbiome concerning its immune responses and microbiological interactions. Through examining the microbiome of patients with respiratory virus infections, notional concepts can be derived regarding the gut microbiome of patients with COVID-19 infections.

Respiratory virus infections have been reported to manifest with gastrointestinal issues caused by gut dysbiosis. This relationship has been historically viewed on a larger scale during outbreaks. One example from 2002, is severe acute respiratory syndrome (SARS) which was commonly accompanied by diarrhea in up to 73% of patients. Severe acute respiratory syndrome coronavirus (SARS-CoV-1) was met with such a strong immunological response of elevated T helper 2 (Th2) cytokines, that the result was a “leaky” gut due to the altered state of the gut microbiome.

Additionally, Deriu et al. demonstrated how influenza in mouse models resulted in gut dysbiosis causing a predisposition to secondary Salmonella infection via circulatory type I interferons. Wang et al. linked an influenza infection with indirect intestinal inflammation via microbiota-mediated Th17 cell-dependent inflammation. Furthermore, Groves et al. observed gut dysbiosis in mice models with respiratory syncytial and influenza virus infections, with an increase in Bacteroidetes and a decrease in Firmicutes phyla abundance, but not in vaccinated mice. An elevation of colonic Mucin 5AC (Muc5ac) and fecal lipocalin-2 was observed during respiratory virus infection, in the pathogenic infection group suggesting the presence of low-grade gut inflammation. Molyneaux et al. found rhinovirus-infected patients with chronic obstructive pulmonary disease (COPD) to have an increased amount of Proteobacteria and Haemophilus influenzae in their lower respiratory tract microbiota. Gu et al. inoculated mice with the H1N1 influenza virus and proved a bacterial class shift in the lung microbiota, which persisted post-recovery. Evaluating the results of these limited studies, a clear association can be discerned between respiratory virus infections and altered gut and respiratory tract microbiota, along with gastrointestinal tract (GIT) inflammation.

In a two-hospital cohort study, following 100 patients with lab-confirmed SARS-CoV-2 infections, stool samples were tested and showed that COVID-19-positive patients’ gut microbiomes were modified in comparison to patients who were negative for COVID-19 infection. Microorganisms, known for their potential to alter individuals’ immunologic responses, such as Faecalibacterium prausnitzii, Eubacterium rectale, and bifidobacteria were marginalized in patients confirmed to have the virus. This under-representation remained low in stool samples, even 30 days post-recovery.

The data suggests that there is a significant association between COVID-19-positive patients and their gut microbiomes’ dysbiosis. Analysis across multiple studies identified key pathogens as opportunistic and having been re-

**METHODOLOGY**

PubMed, Google Scholar, EBSCOhost, Mendeley, and MedLine Plus were used to conduct the electronic literature search. The search was confined to relevant publications and articles published through April 8, 2022. If a manuscript was relevant to the issue of gut microbiome influences and the severity of COVID-19, it was chosen. To narrow and guide the search process, the listed keywords were sought: COVID-19, SARS-CoV-2, gastrointestinal disease, and human microbiota are among them.
corded in abundance, during the time of infection.22 The Coprococcus family, Clostridium family, Candida family, Streptococcus infantis, Acinetobacter, and Chryseobacterium, amongst others, were all documented as abundant in association with COVID-19 severity. An inverse correlation was observed between the abundance of Faecalibacterium prausnitzii and disease severity.23 Although a reduction in beneficial commensals such as Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdinkii, and the Lachnospiraceae bacterium was observed, it was not done solely in the absence of a COVID-19 infection.24 Patients who tested positive, yet the infection was declining, also reported lower levels of these commensal bacteria, indicating that disease severity impacts the range of dysbiosis within the gut microbiome.23 Gut dysbiosis was prevalent in patients who had cleared COVID-19 and were still reporting at least one symptom four weeks after; Faecalibacterium prausnitzii, Eubacterium rectale, and bifidobacteria were underrepresented in this group and remained low for up to 30 days following.24 Furthermore, Chen et al.25 deduced that patients’ gut microbiomes were not restored to pre-infection states after six months of recovery.

An immune response is triggered when the SARS-CoV-2 virus is detected, and respiratory tissues have been destroyed. Macrophages and monocytes rush to release cytokines and prime adaptive T and B-cells as the body’s immune response. Usually, this process is effective at neutralizing the infection. Occasionally, an improper immune response may occur causing substantial lung or multi-system failure.26 Cytokines and inflammation markers were measured at admission in a study using principal component analysis (PCA) to visualize sample clustering; it was observed that C-X-C motif ligand 10 (CXCL10), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), C-reactive protein (CRP), lactate dehydrogenase (LDH), N-terminal pro-b-type natriuretic peptide (NT-proBNP), and erythrocyte sedimentation rate (ESR) were strongly associated with microbiota composition.20,27 Since CXCL10, IL-10, TNF-α, AST, GGT, CRP, LDH, and NT-proBNP are usually found in abundance with severe COVID-19,28-30 these findings indicate that gut microbiota composition is correlated with the level of immune response to COVID-19 and subsequent tissue damage; thus, they could play a significant role in controlling the severity of the disease.

Six main species of microbiota were greatly diminished in individuals that had COVID-19 with a negative correlation to CXCL10 (i.e., Bifidobacterium adolescentis, Faecalibacterium prausnitzii, Eubacterium rectale, Collinsella aerofaciens, Dorea longicatena, and Coprococcus comes); five species with IL-10 (i.e., Collinsella aerofaciens, Ruminococcus obeum, Coprococcus comes, Dorea longicatena, and Fora formicigenerans); two species from TNF-α (i.e., Collinsella aerofaciens and Coprococcus comes); and two more species with C-C motif ligand 2 (CCL2) (i.e., Eubacterium rectale and Coprococcus comes).20 The depleted microbiota included B. adolescentis, E. rectale, and F. prausnitzii which are known to modify the body's gastrointestinal immune response. Reciprocally, two species of microbiota were heightened in individuals within the COVID-19-positive cohort. B. dorei and Akkermansia muciniphila had a positive correlation with IL-1α, IL-6, and C-X-C motif ligand 8.31-33 Additionally, gut microbiomes for COVID-19-positive patients who were hospitalized were shown to correlate with plasma concentrations of many different cytokines, chemokines, and inflammatory markers, indicating that the gut microbiota is impacting the body’s immune response. This perceived influence on the hosts’ immune response has the potential to alter the impact of the disease.34 The multiplication of TNF-α, CXCL10, CCL2, and IL-10 was observed in patients with COVID-19 who had a reduction in their bacterial species. Since the reduction of these species triggered an increase in cytokines, the connection can be made that the reduced commensals mitigate the hosts’ inflammatory response.35 Further supporting evidence has shown that the reduction of gut microbiota such as B. adolescentis, F. prausnitzii, E. rectale, R. (Blautia) obeum, and D. formicigenerans has been linked to a lessened inflammatory response from the host.31

Gut dysbiosis indicates an imbalance within the microbiome and has been linked to various chronic ailments such as asthma, arthritis, obesity, and type 2 diabetes;36-37 as well as pulmonaryological malfunctions and cardiac abnormalities.38 Acute lung injury was attributed to gut dysbiosis and the microbiome’s involvement via several potential mechanisms, such as the direct translocation of bacterial pathogens from the gut to the lung and the direct immunomodulation effects of microbe-related metabolites.25 Gut microbes also influence energy metabolism by regulating glucose metabolism and fat stores. Unfavorable changes in the gut microbiota may also contribute to the evolution of metabolic disorders such as obesity, diabetes, non-alcoholic fatty liver disease, and liver cirrhosis, which in turn worsen secondary chronic illnesses.38

Research shows that diet directly affects the health of the microbiome via impacting microbial metabolite production. A dysbiotic gut microbiome associated with disease shows alteration in its make-up. The alteration is usually seen as a loss of diversity among the contributing microbial species and the proliferation of pathogenic bacterial taxa.39 Age factors should also be considered when assessing the impact of dysbiosis in COVID-19-positive patients. Individuals 65 and older have a higher mortality rate attributed to COVID-19 than those 65 years or younger.40 The incidence of diarrhea in COVID-19-positive patients when analyzed alongside the high mortality rate in patients greater than 65 years of age, signals involvement from the gut-lung axis in COVID-19-associated gut dysbiosis.41 Hypertensive individuals would also benefit from maintaining a healthy gut microbiome since linkage has shown that by consuming dietary fibers, the body produces short-chain fatty acids (SCFAs) that assist in the expansion of anti-inflammatory immune cells, thus protecting them from further hyper-
The gut microbiome plays a significant role in human health and disease, and it may also play a part in the COVID-19 infection's interaction with the host. Microbiome research could aid in the understanding of the pandemic and provide insight into prevention and treatment options. The long-term effects of COVID-19 infection on a variety of organs are unknown. Future prospective studies are required to determine the precise biological pathways and magnitude of impact that gut dysbiosis has on COVID-19 patients before it can be deemed a viable therapy option.

CONCLUSIONS

The gut microbiome plays a significant role in human health and disease, and it may also play a part in the COVID-19 infection's interaction with the host. Microbiome research could aid in the understanding of the pandemic and provide insight into prevention and treatment options. The long-term effects of COVID-19 infection on a variety of organs are unknown. Future prospective studies are required to determine the precise biological pathways and magnitude of impact that gut dysbiosis has on COVID-19 patients before it can be deemed a viable therapy option.

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CONFLICT OF INTEREST STATEMENT

None declared.

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