Review Article

CMJ

www.cmj.ac.kr

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

Abu Fahad Abbasi[1], Aleksandra Marinkovic[2], Stephanie Prakash[2], Adekunle Sanyaolu[3,*], and Stella Smith[4]

[1]Loyola University Medical Center, Maywood, IL, USA, [2]Saint James School of Medicine, Anguilla, British West Indies, [3]Federal Ministry of Health, Abuja, [4]Nigerian Institute of Medical Research, Lagos, Nigeria

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*

Article History:
Received June 30, 2022
Revised July 28, 2022
Accepted August 2, 2022

Corresponding Author:
Adekunle Sanyaolu
Federal Ministry of Health, New Federal Secretariat Complex, Phase III, Ahmadu Bello Way, Central Business District, Abuja, Nigeria
Tel: +234-18134036073
Fax: +234-18134036073
E-mail: sanyakunle@hotmail.com

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

https://doi.org/10.4068/cmj.2022.58.3.96

pharyngitis, cephalgia, myalgia and pains, diarrhea, skin rash with or without discoloration of fingers or toes, and irritated red eyes.[3] Severe symptoms consist of difficulties in breathing, loss of physical mobility or mental confusion or speech impairment, and chest pain.[3]

Human microbiotas are symbiotic microbial communities that coexist with humans.[4] These microbiotas are crucial in the host's immunological response to viral infections.[4] Research linking the human microbiota to COVID-19 is still lacking,[4] even though gut microbiota has been associated with the development and/or maintenance of GI disorders.[5] In a variety of ways, the gut microbiota can influence viral transmission and illness progression.[5] *Clostridium hathewayi* and *Clostridium ramosum*, as well as lower levels of *Alistipes* spp. and *Faecalibacterium prausnitzii*, were connected to the severity of COVID-19 symptoms in a study.[5] Furthermore, microbial sequencing demonstrated increased quantities of *Coprobacillus* species (spp.) in the microbiome of seven antibiotic-naive COVID-19 patients on admission to the hospital.[5] Similarly, in other research, a higher abundance of several bacteria species (i.g., *Burkholderia contaminans*, *Bifidobacterium longum*, and *Blautia* sp. CAG 257) have been connected to severe sickness.[6]

Other studies found a correlation with *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis*, and *Bacteroides ovatus*, which inhibit ACE2 production in the mouse gut, linked negatively with SARS-CoV-2 burden in fecal samples from patients throughout hospitalization.[7] The microbiome composition changes significantly as the severity of COVID-19 grows.[8] The microbiome may be used to predict which patients are more likely to develop severe disease or to modify treatment to reduce severity.[8] Disease severity alters microbiota and the occurrence of complications in COVID-19 positive patients is correlated with low-risk or a reduction in *Faecalibacterium prausznitzii* and potentially an abundance or high-risk with *Parabacteroides* ssp.[9] In addition, a favorable disease progression has been linked to a steady gut bacterial makeup.[9] The purpose of this paper is to discuss the association between COVID-19-positive patients and their gut microbiome alterations.

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.

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 microbiota of patients with COVID-19 infections.[10]

Respiratory virus infections have been reported to manifest with gastrointestinal issues caused by gut dysbiosis.[11,12] This relationship has been historically viewed on a larger scale during outbreaks.[13] 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 microbiota.[14]

Additionally, Deriu et al.[15] 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.[16] linked an influenza infection with indirect intestinal inflammation via microbiota-mediated Th17 cell-dependent inflammation. Furthermore, Groves et al.[17] 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.[18] 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.[19] 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 underrepresentation remained low in stool samples, even 30 days post-recovery.[20]

The data suggests that there is a significant association between COVID-19-positive patients and their gut microbiomes' dysbiosis.[21] Analysis across multiple studies identified key pathogens as opportunistic and having been re-

corded in abundance, during the time of infection.[22] The *Coprobacillus* 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.[23] 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 multisystem 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*, *Ruminoccocus obeum*, *Coprococcus comes*, *Dorea longicatena*, and *Forea 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 bodies' 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.[34] 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;[35-37] as well as pulmonological malfunctions and cardiac abnormalities.[25] 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, nonalcoholic 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-

tension.[42] The impact of gut dysbiosis coupled with COVID-19 causes health instability across multiple systems.[9]

Issues regarding gut microbiome health early on in life have also been exceedingly recognized and linked as risk factors to short and long-term diseases.[43] The formation of the microbiome begins at birth and has been linked to prenatal variables as well as incidental life events such as gestational age at birth, delivery route, formula or breastfeeding, and antibiotic exposure.[44,45] COVID-19 has been linked to an increased risk of dysbiosis, and because pregnancy and early infant life are key times for microbiome development, newborns and expectant mothers are at a higher risk for difficulties caused by dysbiosis of the gut microbiota.[46,47] However, the contemporary nature of the virus, its long-term effects, and its impact on children born during the COVID-19 pandemic are unknown. Future prospective studies are required for evaluation.[47]

Given the link between gut dysbiosis and COVID-19 infections, the notion of modifying the gut microbiome to reduce the impact of the infection is a very real possibility shortly.[47] Research has shown that plant-based fibers assist the growth of beneficial gut microbiota such as *Bifidobacterium* and *Lactobacillus* spp, while at the same time reducing harmful microorganisms such as Clostridia.[48] Additionally, through the fermentation of specific dietary fibers via bacteria, helpful metabolites and SCFAs emerge. These metabolites regulate the mucosal integrity of the colon, as well as regulate the immune system.[49] SCFAs help through their anti-inflammatory function in the circulatory system and their presence has also been proven in mouse models to prevent allergic inflammation in the lungs while having the reverse effect when SCFA amount is reduced.[50] Further research is required to assess if the beneficial impacts of dietary fibers expand to affect the COVID-19 illness.

Oral probiotics are live bacteria that when ingested, change the composition of the gut microbiomes.[48] When the shift in the microbiome holds a higher number of beneficial bacteria, the result is a greater balanced inflammatory response as well as positive influences upon respiratory infections and other intestinal issues. In mouse models, the probiotic bacterium *Lactobacillus gasseri* prevented the contraction of the syncytial virus, which is a respiratory virus.[51] Ingesting *Bifidobacterium lactis* enhanced cellular immunity in an elderly cohort study.[52] The probiotics *Lactobacillus rhamnosus GG*, *Bacillus subtilis*, and *Enterococcus faecalis* were shown to assist ventilated pneumonia patients in clinical trials.[53] These positive influences show that if dysbiosis is a causing factor in disease exacerbation, then treating the dysbiosis through convenient probiotics should beneficially impact the disease severity. The National Health Commission of China reported it, that gut dysbiosis in patients with severe COVID-19 infections, were allegedly treated with probiotics to reset their gut microbiomes to normal homeostatic levels and avoid additional infections.[54] Although there is no straightforward evidence linking probiotics to COVID-19 protection, given the virus's spread and the relative safety and simplicity of probiotic therapy, examining these possibilities seems like a plausible approach even before the results of clinical studies are known.

Fecal Microbiota Transplantation (FMT) is the active process of transferring fecal bacterial colonies from a healthy individual to the GIT of an afflicted individual. The idea suggests that this transfer will facilitate the restoration of the microbiome's homeostasis. This therapy has been proven to work for refractory *C. difficile* enterocolitis.[55] Further research is required to link any FMT therapies and COVID-19 infections. Hypotheses surrounding the management of the microbiota, to influence COVID-19 in patients make compelling arguments, and clinical studies are set to begin. However, further study and testing are needed 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 at this time; however, there is the potential for long-term repercussions. It has been suggested that disease severity, age, and the management of the gut microbiome are some factors that determine either the abundance or reduction of certain microbes. As more information about the virus becomes available, it will be critical to comprehend the pandemic's effects on the gut microbiota, as well as the possible long-term consequences.

ACKNOWLEDGEMENTS

A. F. A.: conceptualization and design. A. M.: drafting of the article and project administration. S. P.: drafting of the article. A. S.: review, editing and approval of the final version; responsibility for the accuracy and integrity of all the aspects of the research. S. S.: supervision and revision of the article for intellectual content and editing.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2021;19:141-54. Erratum in: Nat Rev Microbiol 2022;20:315.
2. Larsen JR, Martin MR, Martin JD, Kuhn P, Hicks JB. Modeling the onset of symptoms of COVID-19. Front Public Health

2020;8:473.
3. WHO. Coronavirus disease (COVID-19). Geneva:World Health Organization,2022.
4. Yamamoto S, Saito M, Tamura A, Prawisuda D, Mizutani T, Yotsuyanagi H. The human microbiome and COVID-19: a systematic review. PLoS One 2021;16:e0253293.
5. Walton GE, Gibson GR, Hunter KA. Mechanisms linking the human gut microbiome to prophylactic and treatment strategies for COVID-19. Br J Nutr 2021;126:219-27.
6. Sun Z, Song ZG, Liu C, Tan S, Lin S, Zhu J, et al. Gut microbiome alterations and gut barrier dysfunction are associated with host immune homeostasis in COVID-19 patients. BMC Med 2022; 20:24.
7. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 2020;159:944-55.e8.
8. Shilts MH, Rosas-Salazar C, Strickland BA, Kimura KS, Asad M, Sehanobish E, et al. Severe COVID-19 is associated with an altered upper respiratory tract microbiome. Front Cell Infect Microbiol 2022;11:781968.
9. Schult D, Reitmeier S, Koyumdzhieva P, Lahmer T, Middelhoff M, Erber J, et al. Gut bacterial dysbiosis and instability is associated with the onset of complications and mortality in COVID-19. Gut Microbes 2022;14:2031840.
10. Hussain I, Cher GLY, Abid MA, Abid MB. Role of gut microbiome in COVID-19: an insight into pathogenesis and therapeutic potential. Front Immunol 2021;12:765965.
11. Bartley JM, Zhou X, Kuchel GA, Weinstock GM, Haynes L. Impact of age, caloric restriction, and influenza infection on mouse gut microbiome: an exploratory study of the role of age-related microbiome changes on influenza responses. Front Immunol 2017;8: 1164.
12. Yildiz S, Mazel-Sanchez B, Kandasamy M, Manicassamy B, Schmolke M. Influenza A virus infection impacts systemic microbiota dynamics and causes quantitative enteric dysbiosis. Microbiome 2018;6:9.
13. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202:415-24.
14. Dickson RP, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, et al. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol 2016;1:16113.
15. Deriu E, Boxx GM, He X, Pan C, Benavidez SD, Cen L, et al. Influenza virus affects intestinal microbiota and secondary Salmonella infection in the gut through type I interferons. PLoS Pathog 2016;12:e1005572.
16. Wang J, Li F, Wei H, Lian ZX, Sun R, Tian Z. Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. J Exp Med 2014;211:2397-410. Erratum in: J Exp Med 2014;211:2683. Erratum in: J Exp Med 2014;211:2396-7.
17. Groves HT, Cuthbertson L, James P, Moffatt MF, Cox MJ, Tregoning JS. Respiratory disease following viral lung infection alters the murine gut microbiota. Front Immunol 2018;9:182.
18. Molyneaux PL, Mallia P, Cox MJ, Footitt J, Willis-Owen SA, Homola D, et al. Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;188:1224-31.
19. Gu L, Deng H, Ren Z, Zhao Y, Yu S, Guo Y, et al. Dynamic changes in the microbiome and mucosal immune microenvironment of the lower respiratory tract by influenza virus infection. Front Microbiol 2019;10:2491.
20. Yeoh YK, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 2021;70:698-706.
21. Littlejohn P, Finlay BB. When a pandemic and an epidemic collide: COVID-19, gut microbiota, and the double burden of malnutrition. BMC Med 2021;19:31.
22. Wallen ZD, Appah M, Dean MN, Sesler CL, Factor SA, Molho E, et al. Characterizing dysbiosis of gut microbiome in PD: evidence for overabundance of opportunistic pathogens. NPJ Parkinsons Dis 2020;6:11.
23. Wang H, Wang H, Sun Y, Ren Z, Zhu W, Li A, et al. Potential associations between microbiome and COVID-19. Front Med (Lausanne) 2021;8:785496.
24. Liu Q, Mak JWY, Su Q, Yeoh YK, Lui GC, Ng SSS, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. Gut 2022;71:544-52.
25. Chen Y, Gu S, Chen Y, Lu H, Shi D, Guo J, et al. Six-month follow-up of gut microbiota richness in patients with COVID-19. Gut 2022;71:222-5.
26. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20:363-74.
27. Albrich WC, Ghosh TS, Ahearn-Ford S, Mikaeloff F, Lunjani N, Forde B, et al. Excessive inflammatory and metabolic responses to acute SARS-CoV-2 infection are associated with a distinct gut microbiota composition. BioRxiv. 465865 [Preprint]. 2021. Available from: https://doi.org/10.1101/2021.10.26.465865.
28. Shen B, Yi X, Sun Y, Bi X, Du J, Zhang C, et al. Proteomic and metabolomic characterization of COVID-19 patient sera. Cell 2020;182:59-72.e15.
29. Gao L, Jiang D, Wen XS, Cheng XC, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res 2020;21:83.
30. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. Am J Emerg Med 2020;38:1722-6.
31. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 2008;105:16731-6.
32. van den Munckhof ICL, Kurilshikov A, Ter Horst R, Riksen NP, Joosten LAB, Zhernakova A, et al. Role of gut microbiota in chronic low-grade inflammation as potential driver for atherosclerotic cardiovascular disease: a systematic review of human studies. Obes Rev 2018;19:1719-34.
33. Parada Venegas D, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol 2019;10:277.

Erratum in: Front Immunol 2019;10:1486.
34. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: current state of the science. Immunity 2020;52:910-41.
35. Tai N, Wong FS, Wen L. The role of gut microbiota in the development of type 1, type 2 diabetes mellitus and obesity. Rev Endocr Metab Disord 2015;16:55-65.
36. Aleman FDD, Valenzano DR. Microbiome evolution during host aging. PLoS Pathog 2019;15:e1007727.
37. Hufnagl K, Pali-Schöll I, Roth-Walter F, Jensen-Jarolim E. Dysbiosis of the gut and lung microbiome has a role in asthma. Semin Immunopathol 2020;42:75-93.
38. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913-6.e7. Erratum in: Gastroenterology 2013;144:250.
39. Shen TD. Diet and gut microbiota in health and disease. Nestle Nutr Inst Workshop Ser 2017;88:117-26.
40. Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. Environ Res 2020;188:109890.
41. Aktas B, Aslim B. Gut-lung axis and dysbiosis in COVID-19. Turk J Biol 2020;44:265-72.
42. Avery EG, Bartolomaeus H, Maifeld A, Marko L, Wiig H, Wilck N, et al. The gut microbiome in hypertension: recent advances and future perspectives. Circ Res 2021;128:934-50.
43. Sarkar A, Yoo JY, Valeria Ozorio Dutra S, Morgan KH, Groer M. The association between early-life gut microbiota and long-term health and diseases. J Clin Med 2021;10:459.
44. Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 2014;158:705-21.
45. Gur TL, Shay L, Palkar AV, Fisher S, Varaljay VA, Dowd S, et al. Prenatal stress affects placental cytokines and neurotrophins, commensal microbes, and anxiety-like behavior in adult female offspring. Brain Behav Immun 2017;64:50-8.
46. Ebrahimi S, Khatami S, Mesdaghi M. The effect of COVID-19 pandemic on the infants' microbiota and the probability of development of allergic and autoimmune diseases. Int Arch Allergy Immunol 2022;183:435-42.
47. Segal JP, Mak JWY, Mullish BH, Alexander JL, Ng SC, Marchesi JR. The gut microbiome: an under-recognised contributor to the COVID-19 pandemic? Therap Adv Gastroenterol 2020;13:17562 84820974914.
48. Abid MB, Koh CJ. Probiotics in health and disease: fooling Mother Nature? Infection 2019;47:911-7.
49. Ratajczak W, Rył A, Mizerski A, Walczakiewicz K, Sipak O, Laszczyńska M. Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). Acta Biochim Pol 2019;66:1-12.
50. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med 2014;20:159-66.
51. Eguchi K, Fujitani N, Nakagawa H, Miyazaki T. Prevention of respiratory syncytial virus infection with probiotic lactic acid bacterium Lactobacillus gasseri SBT2055. Sci Rep 2019;9:4812.
52. Gill HS, Rutherfurd KJ, Cross ML, Gopal PK. Enhancement of immunity in the elderly by dietary supplementation with the probiotic Bifidobacterium lactis HN019. Am J Clin Nutr 2001;74: 833-9.
53. Zeng J, Wang CT, Zhang FS, Qi F, Wang SF, Ma S, et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. Intensive Care Med 2016;42:1018-28.
54. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med 2010;182:1058-64.
55. Liu X, Li Y, Wu K, Shi Y, Chen M. Fecal microbiota transplantation as therapy for treatment of active ulcerative colitis: a systematic review and meta-analysis. Gastroenterol Res Pract 2021;2021:6612970.