Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Nov 25; 9(F):676-682.
https://doi.org/10.3889/oamjms.2021.7470
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Narrative Review Article*

OPEN ACCESS

Digestive System and Severe Acute Respiratory Syndrome Coronavirus 2: New Era of Microbiome Study and Gastrointestinal Tract Manifestations during the Coronavirus Disease-19 Pandemic

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Edited by: Slavica Hristomanova-Mitkovska
Citation: Kossumov A, Mussabay K, Pepoyan A, Tsaturyan V, Sidamonidze K, Tsereteli D, Supiyev A, Kozhakhmetov S, Chulenbayeva L, Dusmagambetov M, Pignatelli M, Zhumadilov Z, Marotta F, Kushugulova A. Digestive System and Severe Acute Respiratory Syndrome Coronavirus 2: New Era of Microbiome Study and Gastrointestinal Tract Manifestations during the Coronavirus Disease-19 Pandemic. Open-Access Maced J Med Sci. 2021 Nov 25; 9(F):676-682. https://doi.org/10.3889/oamjms.2021.7470
Keywords: Severe acute respiratory syndrome coronavirus 2; Virus-host interaction; Angiotensin-converting enzyme 2 receptor; Gut microbiome; Gastrointestinal tract; Probiotic
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Received: 28-Sep-2021
Revised: 13-Oct-2021
Accepted: 15-Nov-2021

Funding: This work was supported by the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan under Grant number AP09563198.
Competing Interest: The authors have declared that no competing interest exists

Abstract

The main topic of this review article is the study of gastrointestinal disorders that were accompanying the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although SARS-CoV-2 primarily causes lung infection through binding to angiotensin-converting enzyme 2 (ACE2) receptors, intestinal epithelial cells, especially enterocytes of the small intestine, also express ACE2 receptors. Viral RNA and viral particles can be observed in feces for more than 30 days. It is also known that a respiratory viral infection causes disturbances in the gut microbiota. Diets, environmental factors, and genetics play an important role in the formation of the gut microbiota, which can affect the immune system. The diversity of the gut microbiota diminishes with age, which means that the fact that coronavirus disease (COVID-19) has proved to be mostly fatal in older patients further indicates the role that gut microbiota may play in this disease. It is, therefore, plausible that the gut microbiota could be a new therapeutic target and that probiotics could also have a role in the management of the patients affected by COVID-19.

Introduction

Studies of the human microbiome have shown that, on average, each person is the host of hundreds of different types of microbes, with each person having a unique microbial composition. Modern science has studied the microbiomes of thousands of people in different parts of the world, established certain patterns specific for a geographic location, type of nutrition, background diseases, and other external and internal factors [1]. The microbiome is responsible for a wide range of metabolic and developmental processes, from food digestion to vitamin synthesis, and even brain function. The gut microbiota affects the function of the human gut by promoting intestinal tissue regeneration, motility, and decreased permeability of intestinal epithelial cells [2]. Changes in microbiota composition affect host metabolism, behavior, and stress responses. In addition, the microbiota can also affect the vascular

system and the nervous system of the host, suppressing synaptic connections, and promoting anxiety-like behavior [3], [4].

Altered Gastrointestinal (GI) Tract MAY Lead to Severe Coronavirus Disease (COVID-19) Symptoms

COVID-19 is a new public health crisis threatening humanity. From December 31, 2019 to current 2021, cases of COVID-19 infections in the world have passed 200 million marks and have only continued to accelerate in number [5].

A recent study reports evidence that the gut microbiome may play a role in severe COVID-19 infection cases [4], [6], [7]. The GI epithelium is a potential target for this virus. Xiao *et al*. demonstrated the idea of angiotensin-converting enzyme 2 (ACE2), which is the primary receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and virus nucleocapsid in biopsy samples of gastric, duodenal, and rectal mucosa from infected patients [8].

It is important to note that the bacterial strains differed between people who showed severe SARS-CoV-2 infection signs and those with lighter symptoms.

The overwhelming majority of the adverse course for COVID-19 with fatal outcomes or serious consequences with multi-organ damage occurs in patients with certain risk factors, and age is a significant one among them [9]. It is necessary to remember that the biological age of the intestine is associated with a degradation of the functions of the immune system, chronic inflammation, long-term adverse effects of various drugs such as antibiotics, hormones, non-steroidal anti-inflammatory drugs, and so on [10]. It is known that destabilization of the microbiome composition leads to disruption of important functions of the microbiota, such as its trophic potential, provision of short-chain fatty acids (SCFA) to colonocytes, or participation in bile acid metabolism [11], [12]. In turn, metabolites of intestinal bacteria are a key link in the interaction of the microbiome with the mucous membrane and the systemic immune system [13].

Based on the available data from retrospective clinical studies conducted during the first wave of COVID-19 in hospitals of Wuhan (Hubei Province, Central China), it is known that the majority of patients diagnosed with COVID-19, along with other respiratory diseases, had symptoms such as fever, cough, and a shortness of breath [14], [15], [16], [17]. Extrapulmonary symptoms also spread into the GI tract (GIT). In some cases, patients initially developed signs of a digestive disorder, such as diarrhea, anorexia, nausea, and vomiting, rather than respiratory symptoms. A study of 138 confirmed patients diagnosed with COVID-19 showed that the main symptoms of COVID-19 included fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%), and dyspnea (31.2%), GI symptoms included abdominal pain (3.6%), diarrhea (10.1%), and vomiting (3.6%). It is worth noting that in 14 cases (10.1%) patients have experienced diarrhea and nausea first, then preceding with fever [18], [19], [20], [21].

Another retrospective analysis of 1099 patient with COVID-19 showed that the main symptoms of COVID-19 were fever (87.9%) and cough (67.7%), whereas diarrhea (3.7%) and vomiting (5.0%) were less frequent. Among GI symptoms, the incidence of diarrhea and abdominal pain in patients with severe COVID-19 symptoms was higher than that in patients with mild symptoms of COVID-19 [8], [18], [19], [22], [23]. In a recent systematic review and meta-analysis of 35 studies, comprising 6686 patients on GI manifestations of SARS-CoV-2 infection, the pooled prevalence of all GI symptoms was 15%, with nausea and/or vomiting, diarrhea, and loss of appetite being the three most common [18], [19].

Recently, several reports on the clinical features of COVID-19 outside of Wuhan have been published. Wan *et al*. reported that diarrhea occurred in 21% of the patients [24]. In another large cohort of 651 patients infected with SARS-CoV-2 from the Zhejiang Province, 11.4% presented with at least 1 digestive symptom, including nausea, vomiting, and diarrhea [25]. Moreover, in a systematic review and meta-analysis of 60 studies, including 4243 patients, the pooled prevalence of digestive manifestations in COVID-19 was 18%. Loss of appetite was the most frequent one, followed by diarrhea, nausea or vomiting, and abdominal pain and/or discomfort [26], [27].

Recently, Nobel *et al*. published the first case–control study on the GI symptoms in COVID-19 in a large cohort from the United States. In a multivariable analysis, they showed that digestive symptoms were associated with patients that showed a 70% risk of testing positive for SARS-CoV-2 [28]. They discovered that 35% of patients had GI manifestations, and they were related to longer disease duration in a short-term follow-up. According to Poland research, GI symptoms were diagnosed as a first clinical presentation of SARS-CoV-2 infection [29], [30].

At the initial stages, the presence of concomitant symptoms of disorders of the digestive system often interfered with the diagnosis of coronavirus infection, since typical respiratory symptoms were not initially predominant, which also lengthened the time of manifestation of the main symptoms of the disease [31], [32].

Interaction of gut and lung microbiome in SARS-CoV-2 infection

The gut microbiota has proved itself to affect pulmonary health through a vital cross-talk

between the gut microbiota and the lungs which is referred to as the “gut-lung axis” [33]. The gut-lung axis is supposed to be bidirectional, meaning the endotoxins, or, alternatively, microbial metabolites, can impact the lung through blood and when inflammation occurs in the lung, it can affect the gut microbiota as well [34]. This raises an interesting possibility that novel SARS-Cov2 might also have an impact on the gut microbiota. In fact, several studies have demonstrated that respiratory infections are associated with a change in the composition of the gut microbiota [35]. One of the serious clinical manifestations of COVID-19 is pneumonia and progression of acute respiratory distress syndrome (ARDS), especially in elderly, immune-compromised patients [36]. Numerous experimental and clinical observations have suggested that the alteration of Proteobacteria phylum, which contains many clinically familiar gram-negative rods, such as *Pseudomonas aeruginosa, Escherichia coli,* and some members of the Firmicutes phylum, such as *Staphylococcus aureus* and *Enterococcus* in gut microbiota play a key role in the pathogenesis of sepsis and ARDS [37].

It is important to note that an active and long-term infection of the SARS-CoV-2 virus was discovered in the GIT of people with a confirmed diagnosis of COVID-19 for the first time. Stool tests were positive in people without GI symptoms, and in some cases negative results were obtained within 6 days of nasopharyngeal swabs. That is, even after recovery, the pathogens of the coronavirus infection remained active in the intestines of the patients [19], [20], [24], [26], [38]. Similar to that, SAR-SCoV-2 was initially reported in stool samples of the first case in the United States [7], [27], [28], [31] where the discovery that the stool specimens of three out of seven patients remained positive after a negative throat swab test was made [33], [34], [39].

A small pilot study in Hong Kong found asymptomatic but active coronavirus gut infection. Stool testing revealed genomic evidence of active infection in seven of the 15 participants tested [26].

According to the published work witch showed that in patients with COVID-19, agents of *Bacteroidetes* were twice more numerous (23.9% versus 12.8%) compared to patients not infected with COVID-19 [40]. The changes were caused by the enrichment of the following taxa: *Ruminococcus gnavus, Ruminococcus torques* and *Bacteroides dorei*, and the depletion of *Bifidobacterium adolescentis, Faecalibacterium prausnitzii,* and *Eubacterium rectale*.

SARS-CoV-2 RNA was initially detected in a stool specimen from the first reported COVID-19 case in the United States. In another subsequent Chinese cohort with 73 SARS-CoV-2-infected hospitalized patients, viral RNA was detected in the stools of 53.42% (39/73) of patients. Viral RNA remained positive in 17 patients (23.29%), even after the levels becoming undetectable in the respiratory tract. Meanwhile, SARS-CoV-2 has also been detected in stool samples from patients without GI symptoms [41], [42], [43].

Probiotics, a Possible Solution to Treat COVID-19

It is necessary to study therapeutic approaches, issues of recovery and rehabilitation after the transferred COVID-19, including neutralizing the activity of the SARS-CoV-2 virus in the intestine and changing the composition and functions of the intestinal microbiome. The composition of the microbiome of each patient changed during the courses of both primary and concomitant diseases [44], [45].

The question of whether the microbiome influences the course of COVID-19 or COVID-19 influences the composition of the microbiome requires more research. Further studies are needed to identify infection and pathogenesis of SARS-CoV-2 in the GIT. It is also worth investigating the significance of altering the human gut microbiome in the patient population. In China, some patients with COVID-19 showed a change in the microbiome composition. Specifically, there was a detection of the decrease in the number of Lactobacillus and Bifidobacterium *in the composition* [46].

To date, there are no approved guidelines for the management of patients with GI disorders that are associated with coronavirus infection.

Thus, there is an urgent need to study the role of the intestinal microbiome in patients, within the framework of the existing national health system, based on the experience gained during the global pandemic, the outbreak of COVID-19, with systemic damage to the respiratory, cardiovascular, digestive, and excretory systems. It needs to be done to improve the outcomes of the course of the disease itself, as well as early rehabilitation processes and the improvement of the health of the patients [38].

Improving the profile of the gut microbiota through personalized nutrition and supplements known to improve immunity may be one preventive way to minimize the impact of this disease on older patients and immunocompromised patients [47], [48].

At present, there is no specific treatment for COVID-19 and its management is mainly based on supportive care. No evidence on the efficacy of antidiarrheal drugs is available, but an adequate rehydration and potassium monitoring should be performed the same way it is performed with all patients with diarrhea [49]. It is important to underline that antibiotics and antivirals are often used for COVID-19 treatment, involving a likely alteration of the gut microbiota and causing diarrhea [40], [50], [51]. It is, therefore, plausible that the gut microbiota could be a

new therapeutic target and that probiotics could have a role in the management of these patients [22], [52]. Clinical trials and experimental studies have shown that probiotics as well as probiotics' different components or their sterilized variants (paraprobiotics) may be successfully used as biotherapeutic agents for the prevention/treatment of GI diseases [53], [54], [55] and for resistance enhancement in cases of intestinal viral infections [56], [57]. Furthermore, some authors suggest probiotics as agents against viral infections of the respiratory tract [58]. According to Lehtoranta *et al*., this most likely associates with modulation of the innate immune system and enhancement of acquired immune responses [59].

Immunomodulation by Probiotics

Host immune protection is provided by the mucous membrane's immunity, in which probiotics promote the stimulation and modulation of immune responses, contributing to the development of the immunological barrier. The immunomodulatory effect of probiotics is provided by the release of cytokines and chemokines from immune cells that regulate the innate and adaptive immunity, which has strain-specific effect. Probiotics and paraprobiotics, depending on their composition, may increase the level of interferon (IFN) I, simultaneously increasing the number and functions of antigen-presenting cells, NK cells, and T cells, as well as increasing the level of secretory antibodies in all organs that have a mucous membrane [60].

Probiotics have also been shown to affect the pro-inflammatory and immunoregulatory cytokines, for example IFN-α, tumor necrosis factor (TNF-α), interleukin (IL-1), and IL-6 that participate in non-specific and specific antiviral immune responses. Suppression of pro-inflammatory cytokines in plasma, such as IFN-γ and TNF-α, when using *Lactobacillus* DR7I was indicated in randomized controlled trials involving adolescent children, while enhancing anti-inflammatory cytokines IL-4 and IL-10 were found in young adults [61]. Based on this information, it is possible to use pro and paraprobiotics to prevent ARDS, which is one of the most dangerous complications of COVID-19.

The role of the cytokine storm has already been taken into account in many studies, as the leading link in the pathogenesis of the manifestation of COVID-19. It is likely that the cytokine storm as a pathological process involves the immune system of the whole organism. At this point, it is very important to emphasize the importance of using probiotics, considering that they are consumed orally, and that they will contribute to the reshaping process of the immune response of the intestine, which is a critical point in protection of the macroorganism. In addition, probiotic strains improve colonocyte function, hence reducing SARS-CoV-2 invasion by increasing butyrate levels. These experimental clinical studies also show that probiotic strains have antiviral activity [62]. Other studies have shown that probiotics help maintain the levels of intestinal secretory immunoglobulin A (IgA), and, in turn, the antigen-specific antibodies IgA suppress viruses and prevent pathogens from adhering to or penetrating the mucosal epithelial barrier. The probiotic supplements with a variety of lactic acid bacteria (*Lactobacillus* and *Bifidobacterium*) recommended for formula-fed babies, maintained a higher level of secretory IgA (SigA) in feces at the end of the 4-week treatment period, indicating a positive effect of SIgA production on probiotic production. This study demonstrates the safety of this probiotic formulation for babies. Bottle-fed babies with confirmed COVID-19 may benefit from probiotic supplementation to support mucosal immunity [63]. Considering that COVID-19 is more common in people with comorbid conditions, an effort should be made to study the effect of probiotics on the clinical course of these conditions. To cite a few examples, in a previous randomized, double-blind, and placebo-controlled study in peritoneal dialysis patients who also had decreased residual renal function, episodes of peritonitis, and cardiovascular events, oral probiotics were found to have a positive effect on endotoxemia and cytokines levels. Long-term receiving probiotics serum TNF-α, IL-5, IL-6, and endotoxin levels decreased significantly, while serum IL-10 levels increased noticeably [64].

Moreover, nowadays, patients with severe viral infections are likely to develop secondary bacterial infections. Previous studies showed that mice with *P. aeruginosa* and Staphylococcus aureus pulmonary infection, when administered orally with probiotic *Lactobacillus* acidophilus strains, showed a decrease in bacterial load in the lungs and a decrease in the probability of lung damage and systemic infection.

China's National Health Commission recommended the use of probiotics also for the treatment of patients with severe COVID-19 to preserve intestinal balance and to prevent secondary bacterial infections. Among several proposed mechanisms by which probiotic-immunobiotics mediate their effects is modulation of the innate immune response, having both anti-inflammatory [65], [66] and pro-inflammatory nature [67]. However, the research data on the recommendations of probiotics for the COVID-19 are still insufficient. Additional trials could be initiated to see the effect of co-ingesting personalized functional foods, including prebiotics/probiotics, with existing therapies. The importance of the gut in the interaction between the body and the vast world of pathogenic and symbiotic microbes is beyond question. Doctors and scientists show serious concerns about the consequences of the coronavirus infection, the so-called post-COVID syndrome.

Conclusion

GI symptoms were present in 35% of patients diagnosed with COVID-19. The duration of positive viral signals was significantly longer in stool samples than in respiratory samples. And as the available data show, they are manifested in a delayed effect of recovery and in the severity of the course of rehabilitation processes, manifested in the form of a post-COVID syndrome.

Intestinal microbiota play an important role in maintaining human health and prescribing probiotics to maintain the intestinal micro-ecological balance and prevent secondary bacterial infection in COVID-19 patients requires further investigation and solid evidence of the effectiveness. It is, therefore, plausible that the gut microbiota could be a new therapeutic target and that probiotics could also have a role in the management of the patients affected by COVID-19.

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