European Review for Medical and Pharmacological Sciences 2020; 24: 10853-10859

COVID-19 – gastrointestinal and gut microbiota-related aspects

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Abstract. – OBJECTIVE: The aim of this review paper was to discuss the gut microbiota-related aspects of COVID-19 patients. We presented the faecal-oral transmission of SARS-CoV-2, gut microbiota imbalance, and fecal microbiota transplantation as a hidden source of this virus.

MATERIALS AND METHODS: We analyzed the available literature (PubMed, Embase, Google Scholar databases) regarding COVID-19 and gut microbiota related aspects.

RESULTS: The gastrointestinal symptoms, such as nausea, vomiting, diarrhea, abdominal discomfort/pain, may occur in these patients. Notably, these symptoms may contribute to the severity of COVID-19. Recent several studies have revealed a new SARS-CoV-2 transmission possibility, opening a fresh view on COVID-19. It is observed the possibility of SARS-CoV-2 transmission via faecal-oral route. Fecal microbiota transplantation may be a hidden source of SARS-CoV-2. Additionally, the pharmacological treatment of COVID-19 and other factors may significantly alter the composition of gut microbiota. Among others, loss of bacterial diversity, the decrease of commensal microbes as well as the increase of opportunistic pathogens are observed.

CONCLUSIONS: The alterations of gut microbiota in COVID-19 patients consequently may lead to the development of gut dysbiosis-related diseases even after recovery from COVID-19. Therefore, it is recommended to screen stool samples taken from recovered patients at least 35 days after clearance of virus from respiratory tract. Before 35 days period, SARS-CoV-2 may still be detected in feces. It is also recommended to screen the composition as well as the activity of gut microbiota to assess its balance. In the case of gut dysbiosis, there should be introduced an appropriate method of its modulation. Additionally, all the fecal samples which are prepared for fecal microbiota transplantation should be tested for SARS-CoV-2 to provide protection for its recipients.

Key Words:
COVID-19, SARS-CoV-2, Gut microbiota imbalance, Faecal microbiota transplantation.

Introduction

On March 11, 2020 the World Health Organization (WHO) declares the outbreak of coronavirus disease (COVID-19) a pandemic. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belonging to the β-coronavirus cluster[1,2]. SARS-CoV-2 appeared in December 2019 in the Wuhan, Hubei province and has been rapidly spreading from China to other countries[3,4]. According to the most recent WHO report (August 22nd, 2020, 10 CET), 22,812,491 individuals are infected, and 795,132 deaths registered globally[5]. Huang et al[6] (2020) have shown the clinical features of patients with COVID-19 in Wuhan. In this cohort, 49 years was the median age of patients, and most of the infected individuals were men (73%). The most common symptoms were fever (98%), cough (76%), dyspnoea (55%), myalgia or fatigue (44%). There were also observed sputum production (28%), headache (8%), and diarrhoea (~2.44%, 1 patient)[6]. Nevertheless, further studies have shown that gastrointestinal symptoms may occur definitely more often than it was observed previously. Moreover, they may have an impact on the clinical outcome of these patients[7]. Furthermore, the presence of viral RNA in feces of patients with COVID-19 showed a new possibility of SARS-CoV-2 transmission[8].

Therefore, this review paper is mainly focused on the current knowledge regarding the gut microbiota-related aspects in COVID-19 patients. Firstly, we presented non-classic gastrointestinal symptoms of COVID-19 and discussed the possibility of fecal-oral transmission of SARS-CoV-2.

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Secondly, we briefly described the link between angiotensin-converting enzyme II (ACE2), digestive system, and inflammatory bowel diseases (IBDs) in the context of SARS-CoV-2. In the next part of this paper, we concentrated on fecal microbiota transplantation (FMT) to present it as a potential hidden source of this virus. Moreover, we discussed the possibility of gut microbiota imbalance in COVID-19 patients, which consequently may lead to the development of gut dysbiosis-related diseases in recovered individuals in the future.

Gastrointestinal Symptoms of COVID-19 and Possibility of Faecal-Oral SARS-CoV-2 Transmission

COVID-19 is typically manifested by fever, dry cough, fatigue, dyspnoea, myalgia, and headache. However, some patients may develop less common non-classic symptoms, *i.e.,* gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, and diarrhea[1]. In Chen et al[9] retrospective, single-centre study, 99 patients with COVID-19 in Wuhan Jinyintan Hospital from 1 to January 20th, 2020 were included. It was noted that only 3% of patients had gastrointestinal symptoms, such as diarrhoea (2%) as well as nausea and vomiting (1%)[9]. However, the recent report from Wuhan has shown that even 79.1% of patients with COVID-19 experienced gastrointestinal symptoms[10]. Additionally, in a systematic review and meta-analysis Cheung et al[8] have presented the gastrointestinal manifestations of COVID-19. The authors collected the data from the cohort of patients with COVID-19 in Hong Kong (n=59) and searched the papers (60 studies, n=4243 patients) of gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal pain/discomfort) and detection of the virus in stool. Among the 59 patients in Hong Kong, the gastrointestinal symptoms and viral RNA in stool (positive tested) were observed in 25.4% and 15.3%, respectively. Moreover, stool viral RNA was more often detected in patients with diarrhoea compared to those without this symptom (38.5% *vs.* 8.7%, respectively; p=0.02). In 17.6% of patients, all gastrointestinal symptoms were noted. Moreover, 11.8% of patients with non-severe COVID-19 and 17.1% of subjects with severe COVID-19 had gastrointestinal symptoms. Notably, 48.1% of stool samples were positive for RNA. Interestingly, 70.3% of these samples were collected after loss of virus from respiratory specimens[8].

Overall, these results proved that the faecal samples should be collected carefully to prevent the development of COVID-19 in also medical staff. Additionally, it should be emphasized that endoscopic procedures in patients with COVID-19, as well as in recovered individuals, need special caution[10]. Notably, Xiao et al[11] have also reported that more than 20% of patients with COVID-19 had positive viral RNA in faeces even after negative result from respiratory specimens. Therefore, the viral gastrointestinal infection and potential faecal-oral transmission after clearance of virus in the respiratory tract may occur. It is strongly needed to perform rRT-PCR testing SARS-CoV-2 routinely from feces in patients with COVID-19, even if the patients are assessed as recovery. If SARS-CoV-2 is still detected, the precautions should be introduced for hospitalized patients with this virus[11]. Moreover, in Chen et al[12] (2020) study, the presence of SARS-CoV-2 in fecal was detected in 66.67% patients with COVID-19. Furthermore, among these patients, 64.29% of individuals remained positive for viral RNA in fecal, even after negative results from respiratory tract. Indeed, these results also confirm the possibility of SARS-CoV-2 transmission *via* the faecal-oral route[12]. Additionally, Wu et al[13] (2020) have shown that SARS-CoV-2 viral RNA may be present in fecal samples for nearly 5 weeks after the patients' respiratory samples tested negative for this virus.

To conclude, the gastrointestinal symptoms in patients with COVID-19 occur commonly. They may significantly contribute to the intensification of other classic COVID-19 symptoms. Therefore, there is a need to pay more attention to non-classic symptoms, which was shown in Jin et al[7] study. They have presented the characteristics of 74 patients with COVID-19 who had gastrointestinal symptoms. The significantly higher rate of >38.5°C fever and increased complication acute respiratory distress syndrome (ARDS) were noted in patients with gastrointestinal symptoms in comparison to those without these symptoms. It can be the result of electrolyte imbalance (*i.e.,* significantly decreased level of serum sodium, p=0.016)[7]. These results indicated that gastrointestinal symptoms may significantly contribute to the severity of COVID-19.

The Link Between Digestive System, ACE2, IBDs, and SARS-CoV-2

The role of ACE2 has been observed as an entry mechanism for SARS-CoV-2[14-16]. Interestingly, Zhang et al[17] (2020) bioinformatics analysis based on single-cell transcriptomes has shown

that the digestive system is a potential route of COVID-19 infection. It is associated with the high expression of cell receptor invaded ACE2 in esophagous upper and stratified epithelial cells and absorptive enterocytes from ileum and colon. Additionally, the authors supposed that the enteric symptom of diarrhoea may be linked to the ACE2-expressing enterocytes. Overall, this study provided bioinformatics evidence of the potential route for COVID-19 infection in the digestive system contributing to the prevention and treatment of this disease[17].

Interestingly, Monteleone et al[18] have reported that there is no evidence suggesting that in patients with IBD there is a higher risk of COVID-19 compared to healthy individuals (based on PubMed search on March 17th, 2020). Additionally, they emphasized that no IBD patients with COVID-19 was noted in the tertiary IBD centres in Wuhan. It is noteworthy that the increased expression of the above-mentioned ACE2 is increased in the inflamed gut of IBD patients. The significantly higher ACE2 expression is noted in Crohn's disease compared to ulcerative colitis. Therefore, the risk of COVID-19 in these patients is expected to be higher than in those without IBD. Nevertheless, IBD patients are taking immunosuppressors to induce or maintain remission. It consequently prevents IBD-related complications development. These compounds block intracellular signals needed to act against pathogens, thus, increase the risk of infections. On the contrary, suppression of the effector cytokine driven-inflammatory response in IBD could potentially prevent COVID-19-driven pneumonia[18]. Notwithstanding, Mazza et al[19] (April 3rd, 2020) have presented the first fatal case of COVID-19 pneumonia, which occurs in elderly patients (80 years old female) with severe acute ulcerative colitis treated with corticosteroid. On admission, fever up to 38.5°C, severe anaemia, and increased CRP were noted. The patient was started to be treated with corticosteroid – methylprednisolone in dose 40 mg/day. During the next 3 days, the fever was resolved, and CRP was normal. Nevertheless, on the fourth day, fever went up to 39°C and dry cough was observed. The patient suffered from COVID-19 and was treated with non-invasive ventilation, a combination of lopinavir/ritonavir as well as hydroxychloroquine, and prednisolone instead of corticosteroid. The patient died after 14 days of hospitalization. The authors suggested that the patient was potentially protected before COVID-19 by initial corticosteroid administration. Fiorino et al[20] have been reported that the use of steroids during COVID-19 is controversial. However, it seems that low-dose and short-term administration of steroids are not associated with worse prognosis even in patients with critical COVID-19 pneumonia. They can be used to treat IBD flares rather in case of need. It is not suggested to discontinue therapy despite the absence of precise data[20]. However, further studies are necessary to establish the most appropriate therapeutic strategy for IBD patients in this pandemic period[20].

Faecal Microbiota Transplantation – A Hidden Source of SARS-CoV-2?

Gut microbiota is a complex ecosystem that consists of bacteria, viruses, fungi, and *Archeae*. The most innovative method used to alter the composition and activity of gut microbiota is FMT. It is defined as transplantation of gut microbiota from healthy donors to ill patients *via* upper or lower gastrointestinal tract. FMT is mainly administered *via* gastroscopy, colonoscopy or is given as an oral capsule[21,22]. FMT has been approved as a clinical method to treat recurrent CDI by 2013 guidelines[23,24]. Nowadays, the clinical use of FMT is more common and not only restricted to CDI. However, the safety of FMT is still controversial and is associated with the risk of adverse events from mild (for instance, abdominal discomfort/pain, sore throat) to severe, such as bacterial infections and death[25].

FMT may be strongly associated with the risk of SARS-CoV-2 transmission[3]. The most recent recommendations regarding screening of faecal microbiota transplant donors were published in 2019[13]. Recently (in 2020), the international group of experts in FMT and stool banking has been proposed the update of these recommendations due to the risk of transmitting SARS-CoV-2 by FMT[3]. These recommendations have been published in *Lancet Gastroenterology & Hepatology*. These authors noted that the risk of SARS-CoV-2 transmission *via* FMT may be higher than by other tissue transplants. The occurrence of gastrointestinal symptoms, in particular diarrhoea, in COVID-19 positive subjects can contribute to the spread of the virus. Interestingly, Ianiro et al[3] emphasized the severe problem regarding the uncontrolled practice of FMT due to the lack of its common classification. For instance, FMT is considered a drug in USA, UK, and France. However, its'

form is unregulated in some countries. These dysregulations may contribute to hidden and uncontrolled transmission of SARS-CoV-2. Nevertheless, Green et al[26] (in the correspondence published in the *Lancet Gastroenterology & Hepatology*) have been reported that the updated recommendations proposed previously by Ianiro et al[3] should be extended. These recommendations should include screening for the presence of typical COVID-19 symptoms within the previous 30 days and the donor's history of travel. It is also recommended to store and quarantine stool samples for 30 days before use. Notwithstanding, after taking into consideration Wu et al[13] most recent data, it is recommended to prolong this period to at least 35 days. Additionally, stool banks should retrospectively check the health status of the donor before using stool samples[3]. Green et al[26] have also reported that the updating recommendations in this current form is insufficient and potentially unsafe due to pandemic not epidemic anymore. According to these authors, the asymptomatic carries should also be taken into consideration. They could potentially spread the virus in the stool for an undefined time and that during this period they should be ineligible as donors. The University of Birmingham Treatment Centre, which is the second largest provider of FMT for the treatment globally, currently is not processing any new donors hoping that this situation is temporary[26].

Summarizing, nowadays, if stool samples are taken from donors, they should be screened carefully regarding the possibility of SARS-CoV-2 occurrence in feces to provide the highest protection for FMT recipients. It should also be noted that FMT may be considered as a method used to modulate gut microbiota in COVID-19 patients. However, there is a lack of data, which is mentioned in the next part of this paper.

The Possible Alterations in Gut Microbiota in SARS-CoV-2 Infected Patients

The quantitative and qualitative changes in the composition of gut microbiota are described as gut microbiota imbalance or dysbiosis[27]. It should be noted that the development of gut microbiota imbalance is multifactorial and include, among others, the pharmacotherapy of COVID-19. Moreover, the gastrointestinal symptoms of COVID-19, such as vomiting and diarrhea may contribute to gut microbiota alterations[28]. Xu et al[28] have reported that some patients with COVID-19 had an imbalance in gut microbiota homeostasis observed as a decrease of beneficial genera, such as *Lactobacillus* and *Bifidobacterium*. Recently, Zuo et al[29] have been investigated the alterations in the gut microbiota of SARS-CoV-2 infected patients (n=15) hospitalized in Hong Kong. The fecal samples were taken 2-3 times during hospital stay. The amount of commensal microbes, *i.e., Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Roseburia,* as well as *Rachnospiraceae* taxa, was reduced. At the same time, the increased amount of opportunistic pathogens, such as *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii* was observed. Moreover, it was noted that the abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* was associated with the severity of COVID-19. The alterations of gut microbiota in SARS-CoV-2 infected patients were also investigated in Gu et al[30] trial. This cross-sectional study included 30 patients with COVID-19, 30 matched healthy controls, and 24 influenza A subjects. It was noted that COVID-19 patients had a significantly reduced microbial diversity, a higher abundance of opportunistic bacteria (*Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces*) as well as an increased amount of beneficial microbes. Additionally, it was shown that microbial signature in these patients was different than in those with influenza A and healthy controls[30].

The summary of possible alterations of gut microbiota observed in SARS-CoV-2 infected patients is presented in Figure 1.

The drugs used to treat COVID-19 are, among others, chloroquine phosphate, lopinavir, ritonavir, and remdesivir. Moreover, in the case of pneumonia broad-spectrum antibiotics can also be administered[31]. It is well known that antibiotics, even short-term administered, alter gut microbiota and may lead to its dysbiosis[32]. The administration of antibiotics causes a reduction of microbial diversity and loss of key taxa[32]. Moreover, other pharmacological therapy used to treat COVID-19 also contributes to changes of gut microbiota.

Chloroquine is recommended to prevent and treat malaria. Moreover, it is used to treat rheumatoid arthritis and lupus erythematosus due to its anti-inflammatory effects[33]. Chloroquine may cause changes of gut microbiota. Angelakis et al[34] have shown the gut microbiota modifications associated with long-term doxycycline and hydroxychloroquine usage. The significantly decreased amounts of *Bacteroidetes* (p=0.002),

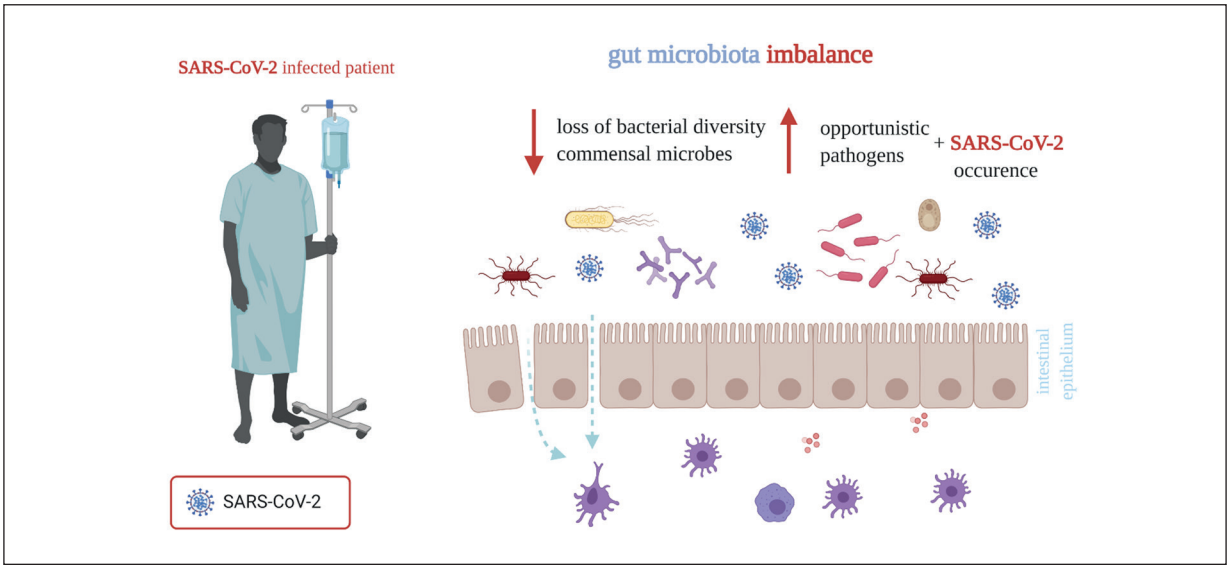

Figure 1. The possible alteration OF gut microbiota in SARS-CoV-2 infected patients. Own elaboration based on literature[28-30].

Firmicutes (p=0.01), and *Lactobacillus* (p=0.02) were noted in patients treated with these drugs. These and other changes may similarly occur in COVID-19 patients leading to gut dysbiosis. Consequently, they may cause the development of gut dysbiosis-related diseases even after recovery from COVID-19. Therefore, it is recommended to screen stool samples taken from recovered patients at least 35 days after clearance of virus from respiratory tract. Before 35 days period, SARS-CoV-2 may be still detected in faeces[24]. It is also recommended to screen the composition as well as the activity of gut microbiota to describe its balance. In case of gut dysbiosis, there should be introduced the appropriate methods of its modulation.

Overall, the modifications of gut microbiota in COVID-19 patients seems to be useful to reduce the disease severity[29]. Nowadays, however, there is a lack of well-established data regarding which methods altering gut microbiota may be introduced to these patients. For instance, in *ClinicalTrials.gov* system, there is a registered study (*ClinicalTrials.gov* Identifier: NCT04517422) assessing the efficiency of a combination of *Lactobacillus plantarum* CECT7481, *Lactobacillus plantarum* CECT 7484, *Lactobacillus plantarum* CECT 7485, and *P. acidilactici* CECT 7483 in adults COVID-19 patients. Nevertheless, the current status of this study is "not recruiting yet". There is also a registered study (*ClinicalTrials.gov* Identifier: NCT04251767) regarding washed microbiota transplantation for COVID-19 patients. However, its current status is "withdrawn".

Conclusions

The non-classic symptoms of COVID-19, such as gastrointestinal-related symptoms, occur often, and they may contribute to the severity of COVID-19. The knowledge about the viability of SARS-CoV-2 is still limited. Therefore, it is recommended to screen stool samples carefully regarding the possibility of SARS-CoV-2 occurrence in faeces to provide the highest protection for FMT recipients. Moreover, in COVID-19 patients, gut microbiota imbalance may be observed, which among others, is the result of pharmacotherapy. Consequently, it may contribute to the development of gut microbiota-related diseases in the future. Therefore, it is strongly needed to screen stool samples taken from recovered patients after 35 days to detect not only the possibility of SARS-CoV-2 occurrence but also to assess the profile of gut microbiota. In the case of gut dysbiosis, the appropriate methods used to modulate its composition and activity should be introduced (Figure 2).

Conflict of Interest

The Authors declare that they have no conflict of interests.

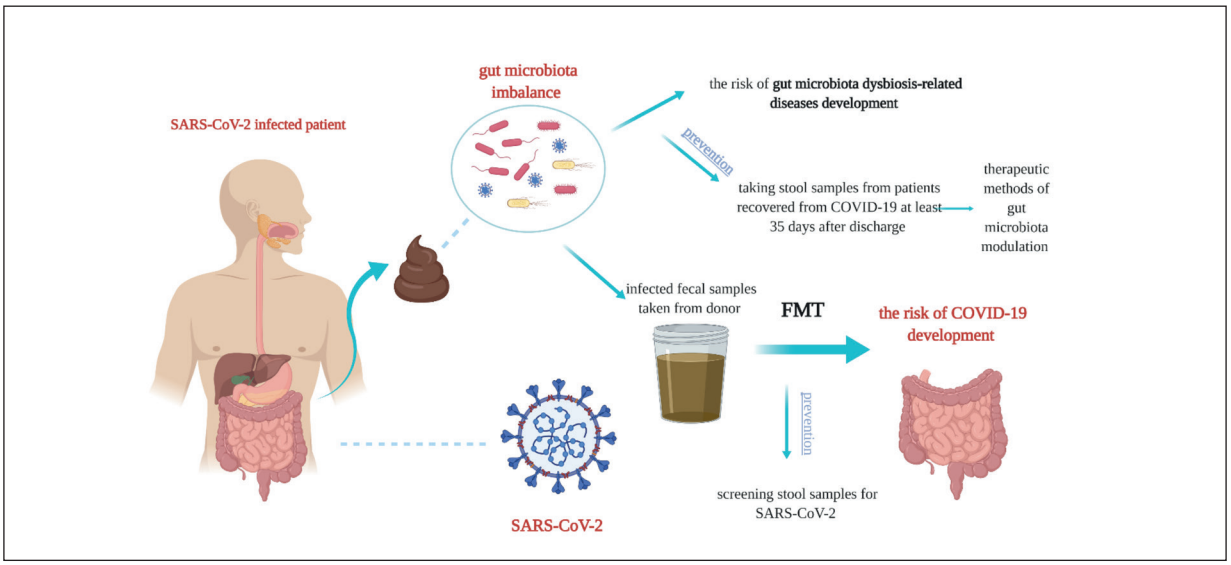

Figure 2. COVID-19 and gut microbiota-related aspects. Own elaboration based on literature[3,25,26]. FMT – fecal microbiota transplantation; COVID-19 – coronavirus disease; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2.

Statement

All the authors have been accepted the current form of this paper.

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