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This study supports the premise that microbiota gut bacteria transplanted into someone with COVID-19 or Long Covid (called FMT) will experienced improvements in immune function and reduced autoimmunity.

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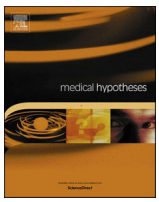

Fecal microbiota transplantation for COVID-19; a potential emerging treatment strategy

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ABSTRACT

At the end of 2019, an emerging outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that first reported from Wuhan, China. The first manifestations of patients infected with SARS-CoV-2 was flu-like symptoms, while other type of manifestations, especially gastrointestinal manifestations were discovered recently. As of June 2020, there is no specific drug or treatment strategy for COVID-19, a disease caused by SARS-CoV-2, so different combination of antiviral drugs is currently being used. Gut microbiota mostly consists of four phyla, including Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. The interaction between gut microbiota and immune system through releasing some cytokines such as IL-1β, IL-2, IL-10, TNF-α, and IFN-γ that play roles in the severity of COVID-19. In this article, a new potential treatment for COVID-19 by fecal microbiota transplantation (FMT) is described. FMT revealed promising results in different diseases, especially recurrent clostridium difficile infection, and it might reduce length of hospital admission and severity of the disease by modification of gut microbiota composition.

Introduction

Current burden of COVID-19

In late December 2019, a new spices of coronaviruses called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing COVID-19 disease, initially caused a large scale outbreak in Wuhan City, Hubei Province, China [1]. It rapidly spread to almost all countries and territories worldwide and the severe cases increased. As a result, the World Health Organization (WHO) declared the COVID-19 as a pandemic on March 11, 2020 [2]. As of late July 2020, it caused more than 16 million and 650,000 prevalent cases and deaths, respectively [3].

Treatment approaches for COVID-19

Since the beginning of the COVID-19 epidemic, lots of efforts have been done to find a specific treatment for SARS-CoV-2, whereas the evidence on efficacy of current drugs used for SARS-CoV-2 is not sufficient [4]. Currently, two major groups of drugs are used for SARS-CoV-2 treatment. One, repurposed and investigational drugs, which target different levels in viral entry and replication system like inhibition of glycosylation of host cell receptors (chloroquine), inhibition of viral RNA polymerase (ribavirin), and inhibition of protease (lopinavir, ritonavir). Two, adjunctive therapies such as monoclonal antibodies, especially against interleukin (IL)-6, and convalescent plasma therapy [5]. Results of a systematic review and meta-analysis revealed that anti-coronary virus drugs have higher rate of adverse events (AEs) (relative risk (RR): 1.74, 95% confidence interval (CI): 0.72, 4.18), including transaminitis, bradycardia, and diarrhea in interventional arms compared with controls despite of better efficacy of these drugs [6]. Although there is not enough literature and well-established clinical trials on the safety and efficacy of convalescent plasma therapy, enrolled participants of a clinical trial showed improved efficacy, including

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decreasing of sequential organ failure assessment score and no AEs were reported [7].

Effects of gut microbiota on human health

The gut microbiota is considered as a major part of the health because it plays roles in different aspects of human health [8]. For example, it can modulate different functions such as gut development [9], protecting from pathogens [10], preparing the energy and nutrients of nondigestible foods [8], and physiologic cerebral function [11]. The human gut microbiota mostly consists of bacteria, fungus, yeasts, viruses, and archaea [12]. The bacterial component of human gut microbiota mostly include Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Verrucomicrobia of phyla which the first two ones have the highest frequency [8,13]. Eukaryotic viruses such as rotavirus, astrovirus, and norovirus in addition to adenoviridae are some examples of human gut virome composition that are associated with diseases like gastroenteritis [14]. The fungal and yeasts components of human gut microbiota known as "gut mycome", including Candida, Aspergilli, Cryptococci, and Trichospora genera can play roles in natural history of hepatitis B virus infection and some other gastrointestinal disorders [15]. However, we mostly concentrate on the roles of bacterial component of human gut microbiota because bacteria is the dominant part of human gut microbiota and the roles of other components of human gut microbiota have not been described explicitly yet [16]. The gut microbiota imbalance has a potential link with some diseases such as pancreatic diseases [17], irritable bowel syndrome (IBS) [18], ulcerative colitis (UC) [19], obesity [20], bipolar disorder [21], Parkinson's disease and amyotrophic lateral sclerosis (ALS) [22].

History and clinical applications of fecal microbiota transplantation (FMT)

To our knowledge, the earliest utilizing of FMT was at least in the fourth century in China [23]. The donor stool is suspended through some solutions, homogenized, filtered or strained, and finally, it is administered through lower and/or upper gastrointestinal (GI) tract or as gelatin capsules after centrifuging [24]. The fecal compositions that can be transferred by FMT include bacteria (*Escherichia coli*, *Bifidobacterium*, *Lactobacilli*, and *Faecalibacterium prausnitzii*), viruses (anelloviruses, *Microviridae*, and *Siphoviridae*), archaea and fungi (*Candida albicans*), human colonocytes, and metabolites [25–27].

FMT is an approved therapy for recurrent clostridium difficile infection (rCDI), and Quraishi et al. showed that it is more effective than vancomycin for rCDI (RR = 0.23, 95% CI = 0.07–0.80) [28]. In addition to rCDI, FMT has been evaluated for some other diseases or disorders like metabolic disorders [29] and hepatic encephalopathy [30]. Also, a case report reported the efficacy of FMT for a rare primary immunodeficiency disease called Good's syndrome [31]. FMT has some short- and long-treatment-related AEs, which has a range from minor to serious AEs, including abdominal discomfort, bloating, transmission of enteric pathogens, and induction of chronic diseases due to the imbalance the gut microbiome [32]. The dysbiosis in the function and structure of gut flora is a precipitating factor for *C. difficile* or other bacteria like Adherent-invasive Escherichia coli [33], Helicobacter sp. [34], and Campylobacter sp. [35] that are potential pathogens causing IBD to be colonized in the intestine and develop these diseases [36]. FMT help imbalanced intestinal microbiome to be reconstruction, so that it might prevent from or treat CDI or IBD [36]. Also, FMT for patients with viral infections like human immunodeficiency virus (HIV) and patients receiving antiretroviral therapy (ART) is under explored and it was well-tolerated in these individuals [37].

Up to July 2020, there is not definite treatment or vaccines for COVID-19. Here, we will describe a new potential treatment strategy for patients infected with severe SARS-CoV-2 infection who have presented with GI manifestations.

The hypothesis

Immune system, gut microbiota, and COVID-19

Some cytokines and chemokines, including IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factor (FGF), granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-γ), IP-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), MIP-1B, platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF) were higher in patients with COVID-19 than healthy controls [38]. Also, some cytokines such as IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α might contribute to the severity of COVID-19 because these cytokines were higher in patients in intensive care units (ICU) than non-ICU patients [38]. The balance between pro-inflammatory cells (T-helper 17) and inflammatory regulatory cells (T-reg) in the gut lead to homeostasis and health, which can be resulted by two pathways regulated by microorganisms, including microorganism-associated molecular patterns (MAMPs), and pathogen-associated molecular patterns (PAMPs) [39]. Toll-like receptors (TLRs) have a major role in evocation of immunologic reactions, so altering the expression of TLRs might cause intestinal diseases [39].

In a cross-sectional multicenter study on 204 patients, about half of them presented with GI clinical manifestation, including lack of appetite, diarrhea, vomiting, and abdominal pain [40]. Meta-analysis of 2,477 patients showed that diarrhea and nausea/vomiting are the most common GI manifestations with 7.8% and 5.5% incidence rate, respectively [41]. Wanglong et al. revealed that *Ruminococcus*, *Blautia*, and *Lactobacillus* genera have a positive relationship with some host inflammatory cytokines, including IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, and IFN-γ [42]. The same study revealed that *Bacteroides*, *Streptococcus* genera, as well as *Clostridiales* order have a negative association with aforementioned inflammatory cytokines [42]. Other viruses like influenza virus and SARS can also cause damage in regulation of pro-inflammatory and anti-inflammatory responses, a phenomenon which is called "cytokine storm" [43,44]. Moreover, some other species like Alistipes spp., Bilophila spp., and Clostridium spp. except for *Clostridium hathewayi* represented negative associations with cytokine responses which is beneficial for treatment of COVID-19 and can promote potential therapeutic methods based on microbiome alterations [45]. *Lactobacillus* genus have revealed potential efficacy in bacterial and viral infectious diseases such as infections due to Epstein–Barr virus (EBV), Cytomegalovirus (CMV), hepatitis C virus, and Cryptosporidium [46].

The microbiota in different sites of the human body can play antiviral roles against murine norovirus, rotavirus, influenza virus, and Respiratory Syncitial Virus (RSV) [47]. Expression of angiotensin-converting enzyme 2 (ACE2) on GI cells and the relationship between GI and respiratory systems through gut-lung axis might be a reason for GI manifestations of COVID-19, and explain how the gut microbiota can effect on respiratory viral infection [47,48]. The most prevalent commensals in healthy population with median age of 48 years old are *Eubacterium*, *Faecalibacterium prausnitzii*, *Roseburia*, and *Lachnospiraceae taxa*, while in COVID-19 patients, including both antibiotic naïve and those received empirical antibiotics with median age of 55 years old, those commensals will drop and opportunistic pathogens like *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii* will be increased [49]. Another study introduced two other probiotics, *Lactobacillus* and *Bifidobacterium*, which were decreased in COVID-19 patients [50].

Lung microbiota and COVID-19

The effects of lung microbiota can also be remarkable. Although the diversity and population of lung microbiota is much less than gut, it has been found that in acute respiratory distress syndrome (ARDS) the

number of microbes in the lung increases and the composition tend to be like the gut. For instance, the number of *Bacteroidetes* phylum and *Enterobacteriaceae* family increases in acute lung diseases [51]. Also, gut microbiota can contribute to pulmonary microbiota in some respiratory diseases like asthma or chronic obstructive pulmonary disease (COPD) [52]. Hilty et al showed that *Haemophilus* spp. and *Prevotella* spp. are higher in patients with asthma/COPD and controls, respectively [53]. As a result, the higher numbers of *Haemophilus* spp. can contribute to the severity and ICU admission of COVID-19 patients, according to findings of a systematic review and meta-analysis revealed that *Haemophilus influenza* were detected in 12% of patient with COVID-19 [54]. A pilot study on 15 patients with COVID-19 revealed that antibiotics-naïve COVID-19 patients had reduced numbers of some bacteria species, inclucidng *Fecalibacterium prausnitzii*, *Eubacterium rectale*, *Ruminococcus obeum*, and *Dorea formicigenerans* in comparison with patients received empirical therapy that were associated with severity of COVID-19 and fecal levels of SARS-CoV-2 [49]. Furthermore, *Firmicutes* phylum has the highest correlation with the severity of COVID-19, which seems to be as a result of effects of bacteria of this phylum on alterations in ACE2 expression [49].

As a result of mentioned effects of gut-lung axis and associations between gut microbiota and pulmonary diseases, FMT might also be effective in COVID-19 patients with pulmonary presentations.

As there is no specific drugs or treatment strategy for COVID-19 and based on the above data, fecal/gut microbiota transplantation of asymptomatic or COVID-19 cases with mild symptoms could be used as an adjuvant therapy in combination with local treatment guidelines, especially in severe or critically ill patients, and patients with digestive manifestations who do not response to other treatments.

Evaluation of the hypothesis

Current evidence on FMT for COVID-19

To our knowledge, there has not any completed clinical trial on the safety or efficacy of fecal/gut microbiota transplantation in patients with COVID-19 as of July 2020. Zhang et al. conducted a randomized-controlled trial (RCT) on patients infected with SARS-CoV-2 to discover the efficacy of washed microbiota transplantation on improving the severity of the disease [55]. This study had two arms which both arms received standard therapy, as well as washed microbiota suspension or placebo through nasogastric/nasojejunal tube or orally [55]. NCT04251767 was withdrawn in order to follow new disciplines of the government [55]. Some other ongoing clinical trials aim to evaluate the relationship between fecal microbiota composition and severity, mortality, and quality of life of patients with COVID-19 [56,57].

Cost-effectiveness of FMT

Compared to vancomycin, fidaxomicin, or vancomycin plus bezlotoxumab, FMT is the best treatment approach in case of cost-effectiveness for rCDI [58]. In fact, there is no evidence to compare the cost-effectiveness of FMT with other potential therapeutic approaches for COVID-19, but it seems that costs of admission to ICU in addition to combination therapy with different antiretroviral drugs might be more than FMT, especially in critically ill patients [59].

Safety of FMT

Results of a systematic review on AEs of FMT showed that the incidence rate of AEs and severe AEs related to FMT are 28.5% and 9.2%, respectively [60]. The same study also revealed that occurrence of the AEs are more frequent in upper GI administration route than lower one [60]. The variety of AEs have a wide range from minor like bloating, abdominal discomfort, transient fever, and nausea/vomiting to serious AEs such as pneumonia, sepsis, transmission of enteric pathogens, and post-infectious IBS [61].

Conclusion

Gut microbiota dysbiosis correlates with different diseases, including digestive and non-digestive ones. Also, the gut microbiota plays roles in immune systems by different mechanisms like production of cytokines. As a result, FMT can be used as a novel treatment for COVID-19. Pre-clinical and clinical studies should be conducted to investigate the safety and efficacy of FMT and further underlying mechanisms of FMT in patients with COVID-19. Also, developing indications for suggesting FMT for patients affected with SARS-CoV-2 should be considered in further studies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110476.

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