Review article

Kosin Medical Journal 2023;38(2):98-106
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.23.115

KMJ
KOSIN MEDICAL JOURNAL

Revolutionizing gut health: exploring the role of gut microbiota and the potential of microbiome-based therapies in lower gastrointestinal diseases

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The gut microbiota comprises a collection of microorganisms residing in the human digestive system, including bacteria, viruses, and fungi. These microbes have critical roles in food breakdown, immune system regulation, and the production of essential nutrients. Several lower gastrointestinal (GI) diseases, including inflammatory bowel disease, irritable bowel syndrome, and colorectal cancer, have been associated with dysbiosis, which refers to an imbalance in the gut microbiota. Additionally, the gut microbiome and its microbial compounds affect disease development and the host's immune response. Alterations in the gut-brain axis microbiome are also implicated in lower GI diseases. Therefore, microbiome-based therapies that regulate the gut microbiota (e.g., fecal microbiota transplantation and probiotics) are essential for the prevention and treatment of these diseases. This review aims to highlight the significance of gut microbiota and microbiome-based therapies in managing lower GI diseases.

Keywords: Fecal microbiota transplantation; Gastrointestinal diseases; Gastrointestinal microbiome; Probiotics

Introduction

The human body consists of 3.7×10^{13} cells [1], whereas approximately $3.8\times10^{13-14}$ bacteria reside in the body [2,3]. Most regions of the human body harbor bacteria, but the colon and skin host the highest proportion of bacterial populations. With emerging interest in the human microbiota, numerous studies have been conducted over the last two decades. There has been much interest in their origin, roles, and potential therapeutic applications. In recent studies, connections have been uncovered between the gut microbiota and a range of disease categories, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), type 2 diabetes, obesity, allergies, asthma, cardiovascular disease, rheumatoid arthritis, autism spectrum disorder, anxiety, and depression [4,5]. In this context, our focus is specifically on exploring the involvement of the gut microbiota in lower gastrointestinal (GI) diseases and examining the potential of microbiome-based therapies for these conditions.

The origin and transmission of gut microbiota

Traditionally, the uterine environment is considered sterile; however, recent studies have shown a low abundance

Received: March 24, 2023; **Revised:** June 13, 2023; **Accepted:** June 14, 2023
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of bacteria in healthy uteri [6,7]. During delivery, neonates are exposed to a wide variety of microbes, and the neonatal microbiota can be determined using the delivery method. The microbial communities of infants born through vaginal delivery resemble the vaginal microbiota of their mothers, whereas infants born via cesarean section (C-section) exhibit similarities to their mother's skin surface microbiota [8]. However, if C-section infants are exposed to maternal vaginal fluids during birth, their microbiota can develop to be more akin to that of vaginally delivered infants [9]. Breastfeeding has been observed to correlate with higher levels of Bifidobacterium species, while the cessation of breastfeeding prompts accelerated maturation of the gut microbiota, characterized by a significant increase in Firmicutes [10]. Throughout an individual's lifespan, the composition of the gut microbiota can be influenced by various environmental factors, including diet, leading to significant implications for health and the risk of developing specific diseases [11,12].

The transmission of bacteria involves the excretion of fecal material by the host, along with the survival and persistence of bacteria in the external environment, which ultimately leads to the ingestion and colonization of a new host. Individuals within a community who can serve as sources or sinks of bacteria during transmission, commonly known as reservoirs, also play a crucial role in the transmission process [13]. Through the analysis of over 9,700 human metagenomes, which included computational strain-level profiling, researchers discovered over 10 million bacterial strains that were shared among individuals. These strains exhibited transmission patterns from mother to infant, within households, and across populations. Mothers and infants shared the highest percentage of microbiome strains, showing approximately 50% similarity until 1 year of age. The oral microbiome was more horizontally transmitted than the gut microbiota, with a higher degree of strain-sharing observed among those who lived together for a longer period. In contrast, the strain-sharing rate was almost 0% for unrelated individuals in different populations or even in different villages of the same population [14].

Microbial diversity of gut microbiota

Even among healthy individuals, there is a significant variation in microbial diversity and abundance of specific microbial species [15]. This essential knowledge enables researchers to gain a fundamental understanding of the structural and functional configurations of microbial communities in healthy populations, paving the way for future research on the epidemiological, ecological, and translational applications of the human microbiome.

In general, high microbial diversity is associated with good health and stability [16,17]. The gut microbiota in diseases, such as obesity, IBD, and diabetes, and the skin microbiota in conditions, such as atopic dermatitis and psoriasis, demonstrate a relative lack of diversity [18]. This may compromise the ability of the community to resist pathogens. However, the principle that high microbial diversity is linked to good health does not apply to all areas of the body. For example, high vaginal diversity has been linked to conditions, such as vaginal inflammation and pre-term birth [19,20]. Interventional studies have shown that a significant increase in dietary fiber can temporarily reduce microbial diversity. This is because microbes that break down fibers become more abundant, leading to a shift in composition, and ultimately resulting in reduced diversity owing to competitive interactions [21].

Microbial diversity and composition are influenced by various factors. A population-based metagenomic analysis showed that age and sex were not only correlated with gut microbial diversity but also with composition and functional richness [22]. The gut microbial diversity of a long-living population older than 90 years was greater than that of younger people in Chinese and Italian cohorts [23]. According to the findings of the Human Microbiome Project Consortium, the community types detected in stool samples were linked to sex, with males having a threefold higher likelihood of community type D, characterized by reduced levels of *Bacteroides* and elevated levels of *Prevotella* [24]. The usage of antibiotics has been associated with a reduction in gut microbial diversity, and various medications including proton pump inhibitors, metformin, statins, and laxatives have significant effects on the gut microbiota. Additionally, specific food choices can influence gut microbial diversity, with buttermilk consumption being linked to higher diversity and high-fat milk consumption associated with lower diversity. Furthermore, intake of coffee, tea, and red wine has been associated with increased microbial diversity, while a diet rich in carbohydrates has

been associated with lower microbial diversity.

An overview of how the gut microbiota is related to the lower GI diseases

The human GI tract is a large microbial ecosystem. Dysbiosis is a condition that arises when there is an imbalance in the microbial community that usually resides in the human body, leading to disruption in the composition or function of the microbiota. This can result in negative health outcomes [25]. Gut dysbiosis has been linked to lower GI diseases, such as IBD, IBS, and colorectal cancer (CRC).

Individuals with IBD tend to display a specific pattern of intestinal dysbiosis, characterized by a decrease in the diversity of commensal bacteria, particularly in the two most prevalent groups, Firmicutes and Bacteroides, which typically constitute the bulk of the normal gut flora [26,27]. Moreover, several studies have reported a possible association between Crohn's disease (CD), a form of IBD, and an elevated relative proportion of Enterobacteriaceae in the gut [28,29]. A shift towards facultative anaerobes at the expense of obligate anaerobes is frequently observed in the gut microbiota of patients with IBD. Additionally, molecular disruptions in microbial transcription and changes in the metabolite pools, including acylcarnitines, bile acids, and short-chain fatty acids (SCFAs), are observed, as well as alterations in the levels of antibodies present in the host's serum [30]. During periods of disease activity, there is an increase in temporal variability, and microbes demonstrate distinct changes in their taxonomic, functional, and biochemical profiles. During investigations into the role of dysbiosis as a potential causative factor in IBD, researchers have postulated that bile acid metabolism might play a role in the underlying mechanism of dysbiosis-related IBD. In a recent study, it was revealed that certain human gut bacteria and their corresponding enzymes can transform secondary bile acids into two compounds, 3-oxoLCA and isolithocholic acid (isoLCA), which were found to be capable of inhibiting the differentiation of Th17 cells. Furthermore, the study also revealed that patients diagnosed with CD had notably lower levels of 3-oxoLCA and isoLCA compared to individuals without the condition [31].

The gut-brain axis is a bidirectional communication network that connects the gut and brain. Studies have shown that imbalances in the gut-brain axis can contribute to the development of GI disorders and neurodegenerative diseases, such as IBS [32]. Several studies have linked the pathogenesis of IBS to dysbiosis, a condition characterized by reduced microbial diversity and richness. This shift is a result of the displacement of commensal bacteria by pathogenic microbes in the gut [33,34]. A comprehensive systematic review found that individuals with IBS tend to have elevated levels of, *Lactobacillaceae*, *Bacteroidales*, and *Enterobacteriaceae* while the abundance of *Faecalibacterium*, *Bifidobacterium*, and *Clostridiales* is reduced when compared to healthy individuals [35]. In contrast, a recent study conducted in Sweden, involving a random population sample of 3,556 individuals, did not identify a specific microbiota signature associated with IBS [36]. Another study suggested that alterations in the mycobiome of patients with IBS and the emergence of visceral hypersensitivity indicate that fungal dysbiosis may contribute to the development of IBS [37].

Studies using Sequencing techniques have revealed alterations in the microbial composition and ecological patterns in patients with CRC, and functional research in animal models has revealed the contributions of certain bacteria, including *Fusobacterium nucleatum*, *Escherichia coli*, and *Bacteroidetes fragilis*, to CRC carcinogenesis [38,39]. A meta-analysis was conducted on eight diverse fecal shotgun metagenomic studies on CRC, which considered various confounding factors. The analysis identified a core set of 29 species that exhibited significantly higher abundance in the metagenomes of individuals with CRC [40]. A recent study discovered that the gut microbiota within neoplastic tissues was heterogeneous and correlated with the development of CRC [41]. Moreover, studies have indicated changes in enteric virome profiles within the mycobiome, with an observed increase in the abundance of specific viruses or fungi in the microbiota of individuals with CRC [42,43]. Two significant classes of metabolites, SCFAs and bile acids are highly influenced by the diet and gut microbiota. Research has demonstrated that butyrate, a type of SCFA can modulate regulatory T cells and promote the apoptosis of CRC cell lines, and reduced SCFAs have been associated with populations at high risk of CRC [44,45]. In addition, populations at a higher risk of developing CRC have been found to have elevated levels of secondary bile acids, including deoxycholic acid [46].

Fecal microbiota transplantation for lower GI diseases

Fecal microbiota transplantation (FMT) is a medical procedure that involves transferring fecal material from a healthy donor into a recipient's GI tract. The purpose of FMT is to restore microbial diversity and promote health-associated functions within the recipient's gut. FMT has shown remarkable efficacy in treating *Clostridium difficile* infection (CDI) and is currently being investigated as a potential therapeutic approach for managing a variety of other diseases. The objective is to explore the potential benefits of FMT in addressing different conditions beyond CDI that are characterized by disruptions or imbalances in the gut microbiota. A Cochrane review, with a small number of identified studies and uncertainty regarding the rate of serious adverse events, showed that FMT may increase the rates of clinical remission in patients with mild to moderate ulcerative colitis (UC) [47]. A pilot randomized controlled study evaluated the successful colonization of donor microbiota at 6 weeks in patients with CD; however, this was not achieved in any patient [48]. In this open-label prospective study, the efficacy and safety profile of FMT in patients diagnosed with IBD and two or more confirmed CDI episodes within 12 months were investigated [49]. Additionally, the analysis of fecal and colonic mucosa samples taken from patients who underwent FMT for active UC showed that remission was linked with the presence of *Eubacterium* and *Roseburia* species, biosynthesis of SCFA, and secondary bile acids. Conversely, remission was negatively correlated with *Fusobacterium*, *Sutterella*, and *Escherichia* species, as well as elevated levels of heme [50]. A randomized trial conducted on patients with treatment-refractory IBS characterized by predominant bloating revealed that FMT had a positive impact on symptom relief compared to placebo, and the response was linked to the composition of the gut microbiota before FMT [51]. In contrast, another randomized trial demonstrated that although FMT can alter the gut microbiota of patients with IBS, such changes are insufficient to improve the clinical symptoms of IBS [52]. FMT has shown potential in reducing the activation of pro-carcinogenic pathways, along with inflammatory and proliferative pathways, as well as microbiota-induced genotoxicity. This makes it a promising treatment option for CRC. However, the efficacy of FMT in managing CRC remains largely unexplored. A bioinformatic and functional study provided evidence that *F. nucleatum* can activate autophagy and promote resistance to chemotherapy in CRC, suggesting that the modulation of the gut microbiota can have an impact on the treatment outcomes of patients with CRC [53]. A recent study using FMT in patients with immunotherapy-refractory melanoma showed that FMT and reinduction of anti-PD-1 (programmed cell death-1) immunotherapy induced one complete remission and two partial responses in 10 patients [54]. Another study demonstrated that FMT combined with anti-PD-1 immunotherapy provided clinical benefits in six out of 15 patients. These studies found that patients who responded to treatment showed a higher abundance of microorganisms that were previously linked to a positive reaction to anti-PD-1 treatment, a boost in the activation of $CD8^+$ T cells, and a lower frequency of interleukin-8 expressing myeloid cells [55].

Recent guidelines recommend FMT only for patients with multiple recurrences of CDI who have not responded to appropriate antibiotic treatments. Moreover, it is recommended that both the donor and the donor fecal specimens undergo appropriate screening before performing FMT [56]. There have been three safety warnings regarding the risk of transmitting pathogenic *E. coli* from the donor to FMT recipients and the possibility of transmitting severe acute respiratory syndrome coronavirus 2 [57-59]. Since then, enhanced donor screening and validated stool tests have been performed for potential transmission. A prospective cohort study including 609 patients who underwent FMT reported the safety of FMT in both the short- and long-term. The study had a median follow-up period of 3.7 years. In this study, infections, mainly due to recurrent CDI, were reported in 11.8% of the patients. However, it is important to note that only one patient reported an infection within 1 month following FMT, and none of the reported deaths were found to be associated with FMT [60]. FMT has also been explored as a potential treatment for adverse effects of immunotherapy, such as colitis. In a report describing two human cases, FMT was successfully used to treat refractory immunotherapy-associated colitis. Notably, changes in gut microbial composition were correlated with the complete resolution of colitis in both cases [61].

Although FMT has shown remarkable efficacy and a low rate of serious adverse events, there are still challenges that

need to be addressed, such as the unpleasantness associated with receiving odorous feces and the potential risk of transferring harmful microorganisms. However, a new method of FMT involving the capsule-mediated delivery of a concentrated fecal suspension was studied [62-64]. This approach was designed to reduce discomfort and make the treatment more convenient and allow for self-administration without the assistance of a physician. Another alternative therapeutic tool to traditional FMT is the use of sterile fecal filtrate, which involves filtering and removing live microorganisms from stool components [65].

Probiotics in the prevention and treatment of lower GI diseases

Probiotics are defined as living microorganisms that, when administered in sufficient quantities, confer health benefits to the host. They are frequently used to maintain healthy microbiota or restore microbial balance when bacterial homeostasis is disrupted [66]. However, the efficacy and safety of probiotics in various conditions, including constipation-predominant IBS, IBD, and CRC, continue to be a matter of debate. Recently, the American Gastroenterological Association technical review on probiotics has suggested that probiotics can only be conditionally recommended for the prevention of CDI. The current evidence is insufficient to fully support the use of probiotics for the treatment of other diseases, including CDI, UC, CD, and IBS [67]. A systematic review and meta-analysis showed that probiotics can improve stool frequency and consistency without causing serious adverse events for constipation-predominant IBS, but it did not find any significant differences in abdominal pain/bloating or quality-of-life scores [68,69]. Another systematic review and meta-analysis of VSL#3 also did not find clear effectiveness for IBS symptoms [70]. The use of probiotics for IBS has only been recommended in clinical trials [67]. In patients with active UC, probiotics have shown limited or no effect in inducing clinical remission when compared to the medication 5-aminosalicylic acid (5-ASA). However, when used in combination with 5-ASA, probiotics may lead to a slight improvement in the induction of remission of active UC [71]. The effectiveness of probiotics in maintaining remission in patients with UC remains unclear [72]. In relation to inducing remission in CD, the effectiveness and safety of probiotics are uncertain due to the limited available evidence [73]. A systematic review and meta-analysis examining the efficacy of probiotics in IBD found no evidence supporting the superiority of probiotics over placebo in inducing remission in active UC and CD [74]. The use of probiotics in patients with UC or CD has been recommended only in clinical trials [67]. The efficacy of probiotics in CRC has only been evaluated in a limited number of clinical trials.

Lactobacillus casei was found to reduce the occurrence rate of moderate- or high-grade dysplastic tumors in patients that had at least two colorectal tumors removed, but not the overall number of tumors [75]. A recent randomized trial demonstrated that the administration of probiotics reduced the incidence and severity of chemotherapy-induced diarrhea in patients with CRC who underwent radical surgery and chemotherapy. Furthermore, probiotic administration has been linked to an augmentation in microbial diversity and the production of SCFAs, which have been shown to have protective effects against CRC [76]. However, further clinical trials are required to verify the efficacy of probiotics in patients with CRC. In a systematic review published in the Cochrane database, which analyzed 82 studies involving 12,127 participants, primarily children, it was concluded that there was no significant difference in the occurrence of diarrhea lasting longer than 48 hours between those who took probiotics and those who received a placebo or no additional treatment. This conclusion was based on two studies conducted in high-income countries, involving 1,770 children. Furthermore, the review found uncertain evidence regarding the effect of probiotics on the duration of diarrhea symptoms, as the data from six studies involving 3,058 individuals were of low certainty [77].

To mitigate the risks associated with the transfer of pathogens, considerable research and development efforts have been directed toward identifying specific bacterial strains that could be utilized as targeted therapeutics. Next-generation probiotics (live biotherapeutics) contain live organisms, typically bacteria, that are used to prevent, treat, or cure human diseases or medical conditions and are not classified as vaccines [78]. They are different from traditional probiotics because they are specific microbes intended to colonize the gut, and have well-established clinical benefits for treating specific diseases [79]. Engineered live biotherapeutics have the potential to provide living medicines that can detect within a patient's body,

respond directly to the disease site, and address concerns related to systemic exposure and toxicity. Genetically modified strains have been created as antimicrobial agents for the intestine and have undergone preclinical evaluations [80]. However, several steps are necessary before they can be introduced to patients. These include undergoing clinical trials and obtaining approval from appropriate regulatory authorities.

Conclusions

The role of gut microbiota in maintaining health and contributing to disease is complex and dynamic, and there is still much to be learned. It is increasingly being recognized as a potential biomarker that can be utilized for screening, stratification prior to treatment, and monitoring treatment response. In addition, manipulating the microbiota holds promising potential for disease prevention and therapeutic improvements. However, the field of gut microbiota research has many unresolved issues, including the precise causal relationship between gut microbiota and various disease states, as well as a lack of detailed information at the microbial strain level. Integrating artificial intelligence and machine learning with gut microbiota data has the potential to greatly improve our understanding of the relationship between gut microbiota and disease, as well as to develop personalized medicine based on an individual's unique microbiota. However, it is crucial to approach these new technologies with caution and to ensure that they are used ethically and responsibly.

Article information

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This study was supported by a National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT), No. 2020R1C1C1012694.

Author contributions

Conceptualization: YEP, JHK. Data curation: YEP, JHK. Writing – original draft: YEP, JHK. Writing – review & editing: YEP, JHK. Approval of final manuscript: all authors.

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