REVIEW

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Microbiota and Digestive Metabolites Alterations in Functional Dyspepsia

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ABSTRACT

Functional dyspepsia (FD), a widespread and debilitating digestive disease, is thought to originate from disrupted gut-brain communication. The cause of FD is not completely understood, but recent evidence suggests it could be due to multiple factors and can vary among different patient groups. Factors like gut motility changes, increased sensitivity to pain in the gut, ongoing low-level inflammation, and increased gut permeability have all been linked to the development of FD. Additionally, changes in the gut microbiome have been suggested to play a significant role in the disease. The gut microbiota in the duodenum could either be a cause or a result of the immune and nervous system issues seen in FD, but the ways in which the gut flora in the small intestine affects gut function, digestive metabolites and symptoms are not yet clear, more studies being needed in order to completely assess the relationship between gastrointestinal microbiota and development and progression of FD.
This review summarizes the available research on the relationship between FD and the microbiota and examines the various treatments, including probiotics, that have been shown to relieve symptoms. Finally, suggestions for improving diagnosis and treatment for those with FD are presented.

Key words: functional dyspepsia – microbiota – metabolomics.

Abbreviations: EPS: epigastric pain syndrome; FD: functional dyspepsia; *H. pylori: Helicobacter pylori*; PDS: postprandial distress syndrome; ScFAs: short-chain fatty acids.

INTRODUCTION

Dyspepsia is a common symptom with a wide range of possible causes and underlying mechanisms. It affects up to 20% of the population worldwide, particularly women, smokers, and those taking nonsteroidal anti-inflammatory drugs. The exact prevalence of dyspepsia can vary depending on how it is defined. It can have a significant impact on a person's quality of life. The number of people who seek medical treatment for dyspepsia can range from 14-66% in different countries and ethnic groups [1-5].

The global occurrence of functional dyspepsia (FD) is 7.2% according to recent data [2]. Similar data was also confirmed in Romania, where the pooled prevalence of functional dyspepsia stands at 7.4% [3]. The underlying causes of FD are not entirely clear, but several theories have been proposed. These theories may differ depending on the subtype of FD [postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS)] [6]. Functional dyspepsia is suspected in patients that present symptoms such as feeling overly full after eating, feeling full too soon during a meal or experiencing pain in the upper stomach.

The diagnosis of FD is made when the patient meets certain symptom-based criteria and other potential causes of dyspepsia have been ruled out. This process includes taking a patient's history, conducting a physical examination, running laboratory tests, and performing an endoscopic examination to check for any underlying structural or organic issues that could be causing the symptoms.

The Rome IV criteria for FD define it as the presence of one or more of the following symptoms: feeling overly bothersome after eating, feeling full too soon during a meal, experiencing pain or burning in the upper stomach, and no

evidence of structural or organic disease that could be causing the symptoms [7]. According to the Rome IV guidelines, these symptoms should have been present for at least the last three months and onset of symptoms should have occurred at least six months before the diagnosis is made [7]. While these criteria for symptom frequency and duration are important for defining patient eligibility for research, in clinical practice, the diagnosis can be made without strictly adhering to them, based on the clinician's judgement. In addition, two subtypes of FD are recognized based on the predominant symptoms: PDS, which is characterized by bothersome feelings of fullness and/or early satiation after eating, and EPS, which is characterized by bothersome pain or burning in the upper stomach that is not limited to only occurring after eating. However, it is common for patients to have symptoms from both subtypes [6].

The human gastrointestinal tract is one of the largest interfaces in the body, with an area of 250-400 square meters. Over the course of a lifetime, a person's gastrointestinal tract will come into contact with a wide variety of microorganisms from the environment. These microorganisms can pose a significant threat to the integrity of the gut [8]. The gut microbiota plays a vital role in maintaining host physiology and homeostasis through various mechanisms such as maintaining gut barrier function, modulating host energy metabolism, providing a barrier against pathogenic organisms and modulating the host's immune response [9-12]. However, an altered microbial composition, or dysbiosis, can disrupt these beneficial functions and contribute to the development of various pathological conditions.

GUT MICROBIOTA AND FUNCTIONAL DYSPEPSIA

Long time it was considered that the stomach is sterile because of its low pH. In 1984 *Helicobacter pylori* (*H. pylori*) was discovered [13]. With the advent of new techniques of genomic amplification, a lot of microbacterial species and strains have been discovered in the stomach.

There is increasing attention being focused on the small intestine microbiome in relation to functional dyspepsia.

The gastrointestinal tract is a crucial point of contact between the human body and the external environment, featuring a diverse microbial community composed of over 1000 species of commensal bacteria. The composition of this microbiome can be impacted by various factors such as diet, environmental exposures, and medication, resulting in significant interindividual variation. The microbiome plays a crucial role in maintaining gut health, such as preserving the integrity of the epithelial barrier and modulating the mucosal immune system, allowing for tolerance towards both commensal microorganisms and digested food antigens. The main microorganisms found in the human gastrointestinal tract include Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes, making up over 98% of the total gut microbiota [14]. In healthy individuals, *Firmicutes* tend to predominate, followed by Actinobacteria and Bacteroidetes, as seen in fecal and intestinal biopsy samples [15]. When this balance is disrupted, it can result in pathological changes due to the dysbiosis.

The *Proteobacteria* phylum is present not only in the gastrointestinal tract, but also in various parts of the human body, such as the skin, mouth. These bacteria can either be symbiotic or pathogenic. An increase in the abundance of *Proteobacteria* is an indicator of dysbiosis in the gut microbiota and can serve as a potential diagnostic criterion. Actinobacteria is a phylum of Gram-positive bacteria known for the radially spreading growth pattern of their colonies. Bacteroidetes is a prevalent phylum in the gastrointestinal tract of both humans and animals, accounting for over 60% of the total gut microbiota. Bacteroidetes play a role in carbohydrate fermentation, nitrogenous substance utilization, and the biotransformation of bile acids and other steroids in the human gut [16-17]. Brown et al. described the taxonomy of the intestinal microbiota using the main bacterial phyla [18] (Table I).

Zhong at al. [19] showed an increased abundance of *Streptococcus* in patients with FD when compared to healthy controls and lower number of *Prevotella*, *Veillonella*, *Leptotrichia*, *Actinomyces* in these patients. The increased number of *Streptococcus* was further confirmed and positively correlated with the severity of upper gastrointestinal symptoms. It was also shown an increased abundance of *Firmicutes* genus [20]. Additionally, the beta diversity of the mucosal microbiota in the duodenum was found to be significantly different between patients and controls, despite unchanged alpha diversity, suggesting that the disease may be associated with a more complex change in the microbiota structure, rather than just alterations in the relative abundance of specific genera [20]. Dyspeptic patients showed an increase in anaerobic metabolism in the gastric microbial community along with a rise in *Pseudoclavibacter* and *Tannerella*, a heightened presence of *Veillonella*, *Cohnella*, *Sporolactobacillus*, and *Propionigenium* in saliva, and a greater occurrence of *Rothia*, *Clostridium*, *Haemophilus*, and *Actinobacillus* species in the duodenum [21].

Table I. Small intestinal microbiota that have key role in dysbiosis. Adapted from Brown et. al [18]

GRAM NEGATIVE		GRAM POSITIVE	
Bacteroidetes	Proteobacteria	Firmicutes	Actinobacteria
Prevotella	*Neisseria*	*Bacillus*	*Actinomyces*
Tannerella	*Shigella*	*Staphylococcus*	*Pseudiclavibacter*
Bacteroides	*Klebsiella*	*Cohnella*	*Rothia*
Porphyromonas	*Escherichia*	*Sporolactobacillus*	
	Enterobacter	*Lactobacillus*	
	Haemophilus	*Enterococcus*	
	Helicobacter	*Clostridium*	
	Campylobacter	*Faecalibacterium*	

In a recent study, a new strain of *Streptococcus* was isolated from the duodenal tissue of a dyspeptic patient and characterized through its genomic features. It was identified as a taxonomic match to *Streptococcus salivarius* [22]. Igarashi et al. showed increased levels of *Bacteroides*/*Proteobacteria* in patients with FD [23]. Microbial alterations in functional dyspepsia are shown in Table II.

Microbiota Metabolites and Functional Dyspepsia

The gut microbiome has a sophisticated metabolic system within the human body. It not only sustains its own growth and reproduction by utilizing energy sources, but also has the ability to produce a wide array of metabolites from the intestinal contents and the mucus secreted by the intestinal lining. These metabolites, including short-chain fatty acids (ScFA), cholic acid, choline byproducts, can impact human health both positively and negatively and are linked to the development and progression of many illnesses.

The primary producers of short-chain fatty acids (ScFAs) are bacteria from the *Clostridium* group within the *Firmicutes* phylum, as well as *Lactobacillus*, *Bifidobacterium*, *Eubacteriaceae*, and fecal bacteria. These microorganisms generate ScFAs from dietary fiber, resistant starch, oligosaccharides, and other indigestible compounds in the gut [24]. Research has demonstrated that ScFAs have the ability to maintain the pH level in the intestine, boost the absorption of water, sodium, calcium, magnesium, and other elements, and serve as a source of energy for up to 70% of the energy requirements of intestinal epithelial cells, with butyric acid being particularly significant [25]. Short-chain fatty acids have the ability to suppress the growth and proliferation of harmful bacteria and the activity of inflammation-causing substances in the intestine, thereby having an anti-inflammatory effect in the gut and are also capable of maintaining the integrity of gap junctions in the intestine [26].

Lipid metabolites, such as cholesterol, lipopolysaccharide (LPS), peptidoglycan, and sphingolipids, are produced primarily by bacteria including *Bifidobacterium*, *Lactobacillus*, *Enterobacteriaceae*, and *Clostridium*. Research has demonstrated that these metabolites can impact gut permeability and immune function. LPS, which is often produced as a result of the death and breakdown of Gram-negative bacteria, triggers the release of inflammatory factors such as tumor necrosis factor alpha (TNFα), interleukin-1β (IL-1β), interferon-gamma (IFNγ), and interleukin-8 (IL-8), leading to an immune response and inflammation [27].

The intestinal symbiotic bacteria *Bacteroidetes* and *Prevotella*ceae have been shown to produce sphingolipids. Animal studies have revealed that these lipids can exacerbate intestinal inflammation [28].

Clostridium sporogenes and *Escherichia coli* produce indole-derived metabolites through fermentation. These metabolites have the ability to regulate gastrointestinal disorders by influencing the brain-gut axis and guarding against stress-induced harm in the gut. Tryptophan, a key neurotransmitter involved in the regulation of central neurotransmission and gut function, is part of this process. Research has indicated that the gut microbiome can regulate the brain-gut axis through the metabolic processing of tryptophan [29].

***Helicobacter Pylori* and Functional Dyspepsia**

Studies have established a link between *H. pylori* infection and dyspeptic symptoms, with *H. pylori* infection being identified as a significant contributing factor in the development and progression of FD. The mechanism of action may involve inflammation of the gastrointestinal mucosa and disruptions to gut motility [30]. Follow-up studies on individuals infected with *H. pylori* showed that they have an increased risk of developing FD [31]. However, treatment aimed at eradicating *H. pylori* has been found to be effective in improving symptoms in patients with *H. pylori*-associated dyspepsia. *H. pylori* infection not only influences the gut microbiome but also microbial metabolism, which in turn can impact the occurrence and progression of FD through various pathways [32].

TARGETING MICROBIOTA AS A TREATMENT IN FUNCTIONAL DYSPEPSIA

Since dysbiosis of the gastrointestinal microbiota is closely related to the occurrence and progression of FD, regulation of the gastrointestinal microbiota becomes one of the potential therapeutic modalities for FD.

A clinical randomized control trial found that treatment of FD using a combination of probiotics (Bacillus coagulans, Bacillus clausii, and Bacillus subtilis) was more effective than a placebo in improving symptoms such as burping, bloating, belching, and acid reflux in patients. The results showed a significant difference between the treatment and placebo groups [16]. Another randomized controlled trial evaluated the efficacy of probiotics (*Bacillus coagulans* MY01 and *Bacillus subtilis* MY02) versus a placebo in treating FD patients. The results showed that the treatment group using probiotics was more effective than the placebo group, however, there was no significant difference observed in the efficacy between the

Table II. Microbial alterations in functional dyspepsia

Author, Year, Country	Increased Microbes	Decreased Microbes
Zhong et al., 2016, Australia [19]	*Streptococcus*	*Prevotella, Veillonella, Leptotrichia, Actinomyces*
Fukui et al., 2019, Japan [20]	*Firmicutes, Streptococcus*	
Wauters et al., 2021, Belgium [17]		Neisseria, Porphyromonas
Igarashi et al., 2017, Japan [23]	*Bacteroides/Proteobacteria*	

placebo group who were also taking proton pump inhibitors and the treatment group [17].

In a double-blind, randomized controlled trial, 116 individuals with functional dyspepsia (FD) who were negative for *H. pylori* infection were assigned to either consume a daily yoghurt containing *Lactobacillus gasseri* OLL2716 or a placebo (a fermented milk product without L. gasseri) for a 12-week period. The study found that there was no significant difference in the overall impact on gastric symptoms as assessed by a questionnaire where participants rated the severity of FD and accompanying symptoms (p=0.073). However, a higher elimination rate of FD symptoms was observed in the group taking probiotics (17.3% compared to 35.2% in the placebo group, p=0.048). This result was observed in participants with PDS but not in those with EPS [33].

Broad spectrum antibiotics were considered in order to target the more-prevalent species in patients with FD. Rifaximin is a broad-spectrum antibiotic that has large coverage, including gram-negative and gram-positive, aerobic and anaerobic bacteria that has minimal absorption in the digestive tract and also minimal systemic adverse effects. When given to patients with small intestinal bacterial overgrowth, rifaximin was superior in treating dyspeptic symptoms in 79% of patients, compared to 47% in placebo group [34]. There was a randomized, double-blind, placebo-controlled trial aimed at evaluating the efficacy and safety of rifaximin in the treatment of functional dyspepsia. The results of the study showed that rifaximin was more effective than placebo in providing adequate relief of dyspeptic symptoms at week 8. 78% of the subjects in the rifaximin group experienced adequate relief compared to only 52% in the placebo group (p=0.02). A similar trend was also observed in the preceding 4 weeks. Rifaximin was also found to be more effective than placebo in providing relief from belching and post-prandial fullness/bloating (PPF) in subjects at week 4. A subgroup analysis revealed that female subjects had a more significant response to rifaximin treatment, with more adequate relief of dyspeptic symptoms (GDS) at week 4 (76% vs. 42%, p=0.006) and week 8 (79% vs. 47%, p=0.008), as well as improvements in belching and PPF at week 4. The incidence of adverse effects was similar in both groups, indicating that rifaximin was generally well tolerated [35].

CONCLUSIONS

Several factors such as diet, lifestyle, medication, genetics, environmental conditions, and stress levels, can impact the composition and structure of the human gut microbiome.

The main mechanisms behind FD caused by dysbiosis of the gut microbiota can be broadly categorized by the abnormal composition and abundance of the gut microbiota itself that leads to digestive tract dysfunction, and secondly, by changes in metabolites due to the alteration of the gut microbiota result in abnormal digestive tract function.

Further research is needed to better understand the underlying mechanisms of FD by studying the small intestinal microbiome in combination with levels and functions of immune cells. This will lead to the development of more advanced diagnostic methods and effective therapeutic solutions for this debilitating condition.

Conflicts of interest: None to declare.

Author's contribution: R.A.F. and D.L.D conceived and designed the study. S.G and C.G. collected and analysed the data. R.A.F. Drafted the manuscript. S.G. edited the paper. D.L.D. revised the paper for intellectual content. All the authors approved the final version of the manuscript.

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