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Inflammatory Pathways in Functional Dyspepsia: From Mechanisms to Therapeutic Targets

ABSTRACT

Many people all around the globe suffer with functional dyspepsia (FD), a persistent gastrointestinal ailment. There may be no underlying structural issues, yet FD has a devastating impact on quality of life and healthcare costs. We still don't fully understand what causes FD, but new research points to low-grade inflammation, especially in the duodenum, as a major player. There is dysregulation of the immune system, activation of mast cells and eosinophils, and the production of pro-inflammatory cytokines in FD, which leads to inflammation in the duodenum. This inflammation disrupts the enteric nervous system and increases visceral sensitivity. Hypersensitivity and reduced stomach motility are linked to dysbiosis of the gut microbiota and *Helicobacter pylori* infection via the gut-brain axis pathway. More and more evidence points to changes in the duodenal microbiota as a cause of immunological abnormalities and FD. Probiotics, antihistamines, and leukotriene inhibitors are a few examples of the medicines that have recently shown promise in treating FD by addressing the underlying inflammatory pathways. Improving patient outcomes may be possible with the development of more effective and tailored treatment techniques made possible by a better knowledge of the inflammatory function in FD.

Keywords: *functional dyspepsia, inflammation, gut-brain axis, gut microbiota, anti-inflammatory therapy*

ABSTRAK

Banyak orang di seluruh dunia menderita dispepsia fungsional (FD), penyakit gastrointestinal persisten. Mungkin tidak ada masalah struktural yang mendasarinya, namun FD memiliki dampak yang menghancurkan pada kualitas hidup dan biaya perawatan kesehatan. Kami masih belum sepenuhnya memahami apa yang menyebabkan FD, tetapi penelitian baru menunjukkan peradangan tingkat rendah, terutama di duodenum, sebagai pemain utama. Ada disregulasi sistem kekebalan tubuh, aktivasi sel mast dan eosinofil, dan produksi sitokin pro-inflamasi di FD, yang menyebabkan peradangan di duodenum. Peradangan ini mengganggu sistem saraf enterik dan meningkatkan sensitivitas visceral.

Hipersensitivitas dan penurunan motilitas lambung terkait dengan disbiosis mikrobiota usus dan infeksi *Helicobacter pylori* melalui jalur sumbu usus-otak. Semakin banyak bukti menunjukkan perubahan mikrobiota duodenum sebagai penyebab kelainan imunologis dan FD. Probiotik, antihistamin, dan inhibitor leukotrien adalah beberapa contoh obat yang baru-baru ini menunjukkan hasil yang menjanjikan dalam mengobati FD dengan mengatasi jalur inflamasi yang mendasarinya. Peningkatan hasil pasien dapat dicapai dengan pengembangan teknik pengobatan yang lebih efektif dan sesuai kebutuhan, yang dimungkinkan oleh pemahaman yang lebih baik tentang fungsi inflamasi pada FD.

Kata kunci: dispepsia fungsional, inflamasi, gut-brain axis, mikrobiota usus, anti-inflamasi

INTRODUCTION

A large number of Asians suffer from functional dyspepsia (FD). The frequency of this condition is greater in Asian nations compared to Western countries, affecting about 10-20% of the population. Additional testing revealed FD in 43–79.5% of patients with dyspepsia in a research spanning nine Asian nations (China, Hong Kong, Indonesia, Korea, Malaysia, Singapore, Taiwan, Thailand, and Vietnam).¹⁵ This variation can be associated with hereditary variables, eating habits, or the frequency of *Helicobacter pylori* (*H. pylori*) infections.¹ Both urban and rural parts of Indonesia are afflicted by FD, which lowers quality of life and increases healthcare consumption. High healthcare costs and the detrimental effects on patients' mental health make FD, the most frequent functional gastrointestinal condition, the most expensive health problem in the world.²

We still don't fully understand the pathophysiology of FD, even though it's rather common. Currently, it is difficult to diagnose and treat FD since there are no known anatomical or biochemical abnormalities that would account for the persistent symptoms. The importance of low-grade inflammation in the etiology of FD,²² especially in the duodenum, is being more and more highlighted in recent investigations.³

Emerging evidence suggests that gut microbiota dysbiosis, inflammation cell infiltration, and compromised mucosal barrier integrity as potential causes of the visceral hypersensitivity and motility problems seen in FD. Histamine, cytokines, and eosinophils are pro-inflammatory mediators that activate nociceptors, which in turn increases the

intensity of pain perception and the severity of symptoms. Therapies that target inflammation may provide a new way to treat FD, according to this inflammatory paradigm, which sheds information on the gut-brain axis's function in the disease.⁴

This review of the literature will focus on the present knowledge of inflammation's function in FD, discussing new discoveries on its pathophysiology and discussing possible implications for diagnosis and future treatment methods. It is believed that by clarifying these processes, new avenues for more targeted and efficient interventions in FD management would become apparent.

DEFINITION AND DIAGNOSTIC CRITERIA OF FD

Dyspepsia has changed its meaning over time. Historically, any complaint involving the upper gastrointestinal tract was considered dyspepsia.⁵ However, the term has evolved into something more precise.²⁷ According to Rome IV criteria, dyspepsia is diagnosed in individuals presenting with at least one symptom such as postprandial fullness, early satiation, discomfort in the epigastrium, or a burning sensation in the epigastric region. A more practically relevant definition of dyspepsia is provided by the American College of Gastroenterology and the Canadian Association of Gastroenterology. The presence of persistent epigastric discomfort for a duration of one month or more is considered dyspepsia. Assuming epigastric pain is the primary complaint, additional symptoms of the upper gastrointestinal tract, such as nausea, vomiting, heartburn, a fullness sensation in the epigastrium, or vomiting, may coexist with this.⁶ Dyspepsia is then classified into organic and functional dyspepsia. Dyspepsia associated with structural abnormalities or identifiable underlying causes is categorized as organic dyspepsia.⁷

FD according to the Rome IV Criteria²⁹ is defined as dyspeptic symptoms that interfere with daily activities, occur at least three days a week for the past three months, and have been present for at least six months, all without signs of structural abnormalities that could explain the symptoms, as shown, for example, on upper gastrointestinal endoscopy. The diagnostic criteria for FD can be seen in Table 1.⁸

Table 1. Diagnostic criteria for functional dyspepsia based on the Rome IV criteria⁸

Diagnostic criteria	Description
1. One or more of the following:	
a. Bothersome postprandial fullness	A bothersome sensation of postprandial fullness that significantly interferes with daily activities
b. Bothersome early satiation	Early satiety, even after consuming a small amount of food
c. Bothersome epigastric pain	Pain in the epigastric area that is severe enough to disrupt daily activities
d. Bothersome epigastric burning sensation	A disturbing burning sensation in the epigastric region
2. No evidence of structural disease	No evidence of structural disease (including on upper endoscopy) that is likely to explain the symptoms
Symptoms duration	Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

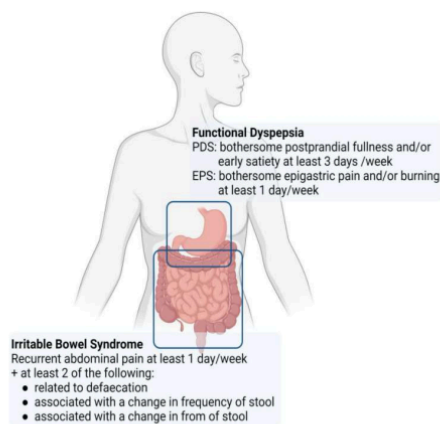


Figure 1. Rome IV criteria for functional dyspepsia and irritable bowel syndrome.

EPS, epigastric pain syndrome; PDS, postprandial distress syndrome.⁴

PATHOPHYSIOLOGICAL MECHANISMS OF OF FD

Although the exact pathophysiology of FD is still unclear, several interconnected pathways have been postulated. Early fullness, nausea, vomiting, bloating, and abdominal pain may be caused by visceral hypersensitivity and gastric motility abnormalities such as reduced gastric accommodation and delayed gastric emptying.^{3,9} A further major factor is the presence of *Helicobacter pylori* (H. pylori) infection, which may cause inflammation of the stomach lining and neurons. This inflammation can continue long after the bacteria have been eradicated, leading to neurons damage and gastrointestinal dysfunction.¹⁰ Environmental and psychosocial factors, including dietary habits, smoking, alcohol consumption, medication use, toxin exposure, and psychological stress, may exacerbate symptoms by altering gut integrity and disrupting the gut–brain axis.¹¹ According to new research, the duodenum ¹plays an important role in the development of FD symptoms due to ¹low-grade inflammation, increased mucosal permeability, and changed luminal contents, all of which make the duodenum more sensitive.^{12,13}

THE ROLE OF INFLAMMATION IN FD

Although the absence of major structural abnormalities is a defining diagnostic criterion for FD according to the Rome IV criteria, emerging evidence indicates that microscopic duodenal alterations may contribute substantially to its pathophysiology.¹⁴ According to recent research, one of the main molecular pathways driving FD is immunological dysregulation.¹⁵

Immunopathology and Molecular Mechanisms

The two main parts of the human ¹⁰immune system are the adaptive immune system and the innate immune system. A variety of biological mediators, including ¹²chemical and physical barriers, dendritic cells, plasma proteins, natural killer (NK) cells, and others, make up ⁹the innate immune system. There are two subsets of the adaptive immune system: humoral immunity, which is controlled by antibody-producing ⁹B cells and plasma cells, and cellular immunity, which is controlled by helper and cytotoxic T cells. Immune responses mostly manifest in the epithelial mucosa. The lymphoid tissues and lymph nodes connected to the

intestines are responsible for the adaptive immune responses. The intestinal epithelium has a higher concentration of T cells, whereas the lamina propria has both B and T cells as well as macrophages, eosinophils, and mast ²⁰ cells.

Proinflammatory mediators including IL-8, MCP-1, TNF- α , RANTES, and IL-6 may be released when bacteria, allergens, dietary antigens, or other events disrupt the integrity of the mucosa. Macrophages, eosinophils, B cells, T cells, and neutrophils are all stimulated by these proinflammatory mediators. Dendritic cells play a crucial role as antigen-presenting cells in this process.¹⁵

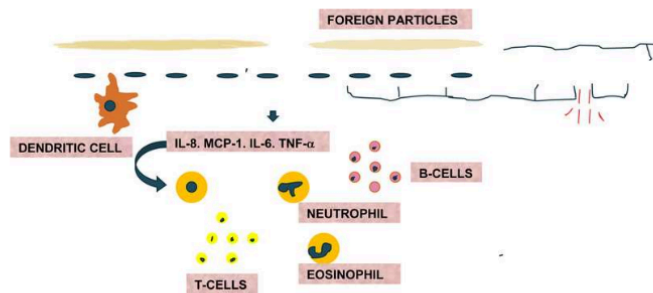


Figure 2. Immune system activation within the intestine upon exposure to foreign substances.¹⁵

The Role of Enteric Glial Cells in Neuroimmune Mechanisms

Originating from the neural crest and organized into ganglia, enteric glial cells (EGCs) govern the action of the smooth muscles of the intestines, the tone of the blood vessels, the production of glandular secretions, and the function of immune cells. Intestinal microenvironment cues, neuroplasticity, and upregulation of immunoregulatory molecules are ways in which EGCs contribute to immune modulation.¹⁶ They have the ability to produce nitric oxide, nerve growth factor, cytokines, and other inflammatory mediators.

Evidence from clinical studies highlights the involvement of enteric glial cells in the mechanisms underlying FD. Cirillo et al. reported neuronal alterations and gliosis in 18 FD patients, accompanied by mast cell and eosinophil infiltration within the submucosal layer.¹⁷ Similarly, Tanaka et al. found that dyspeptic symptoms were associated with ⁵ higher levels of glial cell line-derived neurotrophic factor (GDNF).¹⁸ It was proposed that EGCs are

protected from harm by GDNF released by eosinophils and epithelial cells in response to low-grade duodenal inflammation. These results highlight the two-way nature of the connection between the gut's immunological and neurological systems.

The shape and function of the EGCs may be affected by mediators released into the gut by anxious and stressed individuals, including glutamate, serotonin, corticosteroids, CRF, and gamma-aminobutyric acid. Finally, by secreting IL-1, IL-6, TNF- α , and GDNF, EGCs are capable of regulating the functions of the enteric nervous system. These neuroimmune pathways may be responsible for the association between FD and low-grade duodenal inflammation, which may be caused by allergens, atopy, changes in the gut microbiota, or changes that occur after an infection.¹⁵

The Role of Eosinophils and Mast Cells in the Pathophysiology of FD

Under normal physiological conditions, eosinophils are distributed throughout the gastrointestinal tract, with the exception of the esophagus. Their recruitment is regulated by interleukin-5 (IL-5) and depends on $\alpha 4\beta 7$ integrins and chemokine receptors for migration into the small intestine and colon.¹⁴ Approximately 20% of the leukocytes in the proximal small intestine lamina propria are Th2-cells, as opposed to Th1 or Th17 cells, which predominate in the immunological profile there. Activation of eosinophils occurs via the STAT6 pathway in response to eotaxin, facilitated by ¹⁸Th2 cells releasing IL-4, IL-5, and IL-13. While eosinophilic infiltration is most often associated with respiratory conditions including asthma, atopic dermatitis, and allergic rhinitis, it may also be seen in gastrointestinal illnesses such as inflammatory bowel disease, gut-brain connection disorders, and eosinophil-related gastrointestinal disorders.¹⁴

Food allergies or duodenal acid reflux might cause eosinophil accumulation in FD. Long-term infection with *H. pylori* may trigger eosinophil accumulation in the stomach and duodenum, representing a secondary inflammatory process.¹⁹ Symptoms like bloating and stomach discomfort are caused by the disruption of mucosal integrity, structural and neurological changes, neural activation, and smooth muscle contraction caused by degranulation of duodenal eosinophils.²⁰ In addition to ⁸eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxic, granules containing eosinophils also include ⁸major basic protein (MBP). The polarization of the immune system into Th1 and Th2 is

driven by the production of interleukins, inflammatory cytokines, eotaxin, leukotriene C4, and transforming growth factor by activated eosinophils. Changes in smooth muscle contractility, increased vascular permeability, and altered immune-neural interactions are all brought about by these mediators. Specifically, MBP affects neuronal plasticity in the periphery and could play a significant role in the onset of visceral hypersensitivity.¹⁵

Another important kind of immune cell that is involved with FGIDs, such as FD, are mast cells. The activation of these pathways is associated with a variety of gastrointestinal disorders, including inflammatory bowel disease, postoperative ileus, food allergies, visceral hypersensitivity, and neuromuscular dysfunction. The presence of sensory nerve fibers carrying neuropeptides, such as visceral afferents expressing transient receptor potential vanilloid 1 (TRPV1), is adjacent to mast cells in the gastrointestinal mucosa. This anatomical relationship facilitates altered neuromuscular activity and pain perception in response to infection, stress, or emotional triggers.²¹ Reduced expression of mast cell-regulated epithelial tight junction proteins in FD patients increases epithelial permeability and barrier dysfunction, which in turn promotes inflammation in the duodenum. These proteins include claudin-8, zonula occludens-1 (ZO-1), and occludin.²² Upon degranulation, mast cells release tryptase, which activates protease-activated receptor-2 (PAR-2) on enterocytes, leading to tight junction redistribution and enhanced macromolecular permeability. Additional mediators, including histamine and prostaglandin D₂, further regulate epithelial water and chloride secretion as well as permeability.^{21,22}

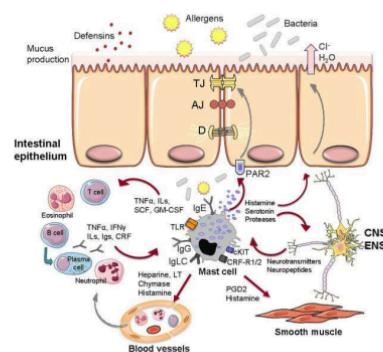


Figure 3. The role of mast cells in alterations of duodenal mucosal barrier function.²¹

The Role of Pro-Inflammatory Cytokines in FD

Proteins known as cytokines are essential in immune responses and other signal transduction processes. Cytokines mediate immune-driven inflammation that can alter gastric physiology, affect the enteric nervous system, and contribute to neuronal injury, thereby sustaining dyspeptic symptoms.¹⁰ However, according to a 2018 meta-analysis, IL-6 and IL-10 levels did not differ significantly between patients with FD and control groups. These results highlight the possibility that local microinflammatory processes—such as infiltration of eosinophils and mast cells—play a greater role in the disorder than systemic cytokine fluctuations.²³

Matrix metalloproteinase-9 (MMP-9), which is mostly made by macrophages, promotes neuronal damage, mucosal apoptosis, and extracellular matrix degradation in *Helicobacter pylori*-associated FD, which may cause symptoms to persist long even after bacterial eradication.¹⁰

Gut Microbiota Dysbiosis, Inflammation, and FD: The Role of the Gut-Brain Axis

The gut microbiota plays a central role within the gut-brain axis, a bidirectional communication system involving neural, hormonal, and immune pathways that link the gastrointestinal tract with the central nervous system.¹¹ Disruptions in this microbial balance, known as dysbiosis, can trigger pathological changes that adversely affect digestive function, emotional regulation, and overall health.²⁴

Alterations in duodenal microbial composition have been associated with the manifestation of FD symptoms and a reduced quality of life.²⁵ Research has shown that the duodenal mucosa of FD patients had lower levels of *Actinomyces*, *Gemella*, *Haemophilus*, *Megasphaera*, *Mogibacterium*, and *Selenomonas*, and higher levels of *Fusobacteria*, *Alloprevotella*, *Corynebacterium*, *Peptostreptococcus*, *Staphylococcus*, *Clostridium*, and *Streptococcus*.²⁵ Studies indicate that higher levels of *Streptococcus* and *Prevotella* may be associated with greater symptom severity. *Veillonella*, *Prevotella*, and *Actinomyces* were all significantly lower in the study group compared to the healthy control group.²⁴

Microbial dysbiosis in FD may influence neurotransmitter production and other signaling molecules, contributing to impaired gastric motility, visceral hypersensitivity, and

low-grade inflammation. Gut-derived metabolic changes may also play a role. In one study, Wen et al. identified metabolic alterations in serum and urine of FD patients using liquid chromatography–mass spectrometry, with reduced L-glutamate emerging as a strong predictor of symptom severity.²⁶

CLINICAL IMPLICATIONS OF THE ROLE OF INFLAMMATION IN FD

Acknowledging the role of inflammation in FD pathogenesis facilitates the development of more precise diagnostic and treatment strategies. Duodenal eosinophilia ²⁵has been identified as a potential marker of low-grade inflammation in postprandial distress syndrome, particularly among patients without *H. pylori* infection. Moreover, studies have shown that patients with duodenal eosinophilia exhibit a positive response to ²⁶proton pump inhibitor (PPI) therapy after 4–6 weeks of treatment. This suggests that the presence of eosinophilia may serve as a predictor of benefit from PPI therapy.²⁷ Currently, drugs targeting low-grade duodenal inflammation are being developed as a potential therapy for FD.

Low-grade duodenal inflammation is frequently accompanied by mucosal dysbiosis, which also appears to contribute to FD pathogenesis. The identification of dysbiosis as a contributing factor opens new avenues for treatment.¹⁹ In recent years, probiotics have gained attention as a potential treatment for FD. Probiotics help reestablish microbial equilibrium, attenuate inflammation through modulation of the gastrointestinal immune response—such as suppressing Th17-related pathways—and ²¹enhance intestinal barrier function by upregulating tight junction proteins.⁴

The short-chain fatty acids and other metabolic byproducts of these cells enhance epithelial function and reduce bacterial adherence. Furthermore, probiotics modulate immunological responses and neurotransmitter synthesis, which impacts gut-brain axis communication and may reduce the intensity of symptoms.²⁸ Nevertheless, the mechanisms underlying their efficacy remain incompletely defined, and clinical outcomes have been inconsistent due to variability in probiotic strains, dosing regimens, and treatment duration.²⁹ Moreover, survival of probiotic organisms in the acidic gastric environment poses a challenge, emphasizing the need for acid-resistant formulations.³⁰

Pathways involving histamine and leukotrienes are also being considered as potential therapeutic targets. The production of histamine by basophils and mast cells in response to immunological stimuli may exacerbate FD symptoms by increasing inflammation, acid secretion from the stomach, and changes in gastric motility.³¹ Antihistamines lessen the inflammatory response by preventing histamine from attaching to its receptors. Because histamine promotes eosinophil recruitment and activation, antihistamines may alleviate FD symptoms by lowering duodenal inflammation and eosinophilic infiltration.^{31,32}

Leukotrienes are inflammatory mediators derived from arachidonic acid via the lipoxygenase pathway. They contribute to inflammation by enhancing immune cell recruitment, increasing vascular permeability, and promoting tissue inflammation. In the gastrointestinal tract, leukotrienes may exacerbate inflammation and potentially worsen FD symptoms. Leukotriene inhibitors act either by inhibiting the enzyme 5-lipoxygenase or by blocking leukotriene receptors. With growing evidence implicating low-grade duodenal inflammation in FD, leukotriene inhibitors could represent a potential therapeutic option. However, additional ² research is required to establish their efficacy and safety in this context.³¹

CONCLUSION

FD refers to a long-standing condition of the upper digestive tract, characterized by recurring symptoms despite the absence of visible structural abnormalities. The underlying mechanisms are diverse and complex, including disturbances in gastric motility, heightened visceral sensitivity, and infection with *Helicobacter pylori*. Psychosocial determinants and environmental exposures are also recognized as important contributors to its development. Increasing evidence highlights the contribution ³⁰ of low-grade duodenal inflammation, driven ³ by immune dysregulation, activation of mast cells and eosinophils, and the release of pro-inflammatory mediators. These processes disrupt epithelial integrity, increase intestinal permeability, and alter motility and sensitivity, ultimately leading to symptom generation.

Neuroinflammation, potentially initiated by *H. pylori* infection, may cause neuronal injury, while interactions between the immune system and enteric glial cells further perpetuate inflammation and visceral hypersensitivity. Dysbiosis of the duodenal microbiota

also becomes an important component, impacting the gut-brain axis and regulating immunological responses and motility.

A more comprehensive understanding of these inflammatory pathways may facilitate the development of targeted diagnostic and therapeutic strategies. The presence of duodenal eosinophilia, especially in patients with postprandial distress syndrome, has been proposed as both a diagnostic marker and an indicator of therapeutic responsiveness. Future approaches—such as anti-inflammatory agents and microbiota-modulating interventions—hold promise for improving outcomes in FD by addressing underlying inflammatory mechanisms.

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