# Inflammation and Its Pathophysiological Role in Functional Dyspepsia

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## ABSTRACT

*Many individuals worldwide suffer from functional dyspepsia (FD), a chronic digestive disorder characterized by symptoms in the absence of observable structural abnormalities within the gastrointestinal system. This condition significantly impacts the quality of life and healthcare expenditures. Although the precise etiology of FD remains incompletely understood, recent research indicates that low-grade inflammation, particularly within the duodenum, constitutes a substantial component of its pathophysiology. Such inflammation involves immune system dysregulation, activation of mast cells and eosinophils, and the secretion of pro-inflammatory cytokines, which collectively contribute to duodenal inflammation. This inflammatory response disrupts the enteric nervous system and elevates visceral hypersensitivity. Hypersensitivity and diminished gastric motility are associated with dysbiosis of the gut microbiota and Helicobacter pylori infection, and these associations are mediated via the gut-brain axis. Increasing evidence suggests that alterations in the duodenal microbiota may underlie immunological irregularities and FD. Recent therapeutic approaches, including probiotics, antihistamines, and leukotriene inhibitors, have demonstrated promise in addressing the inflammatory pathways implicated in FD. The purpose of this review is to examine current evidence concerning the role of inflammation in the pathogenesis of FD and to consider its potential implications for the development of novel therapeutic strategies. A deeper understanding of these underlying processes may facilitate the development of effective, targeted treatments, thereby improving patient outcomes.*

***Keywords:*** *Functional Dyspepsia, Inflammation, Gut-Brain Axis, Gut Microbiota*

## ABSTRAK

*Banyak orang di seluruh dunia mengalami dispepsia fungsional (FD), suatu kondisi pencernaan kronis yang dapat terjadi meskipun tidak ditemukan kelainan struktural pada saluran cerna. Kondisi ini berdampak signifikan terhadap kualitas hidup dan menimbulkan beban besar pada sistem pelayanan kesehatan. Meskipun penyebab pasti FD belum sepenuhnya dipahami, penelitian terbaru menunjukkan bahwa inflamasi derajat rendah, terutama pada duodenum, memegang peranan penting dalam patogenesis FD. Pada kondisi ini terjadi disregulasi sistem imun, aktivasi sel mast dan eosinofil, serta produksi sitokin proinflamasi yang berkontribusi terhadap inflamasi duodenum. Proses inflamasi tersebut mengganggu sistem saraf enterik dan meningkatkan sensitivitas visceral. Hipersensitivitas dan penurunan motilitas lambung juga dikaitkan dengan disbiosis mikrobiota usus dan infeksi Helicobacter pylori melalui jalur komunikasi gut-brain axis. Semakin banyak*

*bukti menunjukkan bahwa perubahan komposisi mikrobiota duodenum dapat memicu kelainan imunologis dan berperan dalam timbulnya FD. Probiotik, antihistamin, dan inhibitor leukotrien merupakan beberapa contoh terapi yang belakangan ini menunjukkan potensi dalam penatalaksanaan FD dengan menargetkan jalur inflamasi yang mendasarinya. Tulisan ini bertujuan untuk meninjau bukti terkini mengenai peran inflamasi dalam patogenesis FD serta mengeksplorasi implikasinya terhadap strategi terapi baru. Dengan pemahaman yang lebih komprehensif mengenai mekanisme tersebut, terapi yang lebih efektif dan terarah dapat dikembangkan untuk meningkatkan luaran klinis pasien.*

***Kata Kunci:*** *Dispepsia Fungsional, Inflamasi, Gut-Brain Axis, Mikrobiota Usus*

## INTRODUCTION

Functional dyspepsia (FD) is among the most prevalent functional gastrointestinal disorders worldwide and imposes a significant burden on healthcare systems. A recent systematic review and meta-analysis of studies published between 1990 and 2020 identified an overall global prevalence of FD of approximately 8.4%. However, substantial heterogeneity was observed across different regions and diagnostic criteria. The prevalence varied by Rome criteria, with higher estimates under earlier definitions and lower estimates under Rome IV. Moreover, FD was found to be more prevalent in developing countries compared to developed nations and was more commonly observed in women than in men.[1]

FD is also linked to disproportionately elevated healthcare utilization. In a comprehensive retrospective study conducted in a secondary care gastroenterology setting, FD emerged as the most prevalent functional gastrointestinal disorder (FGID). Over fifty percent of patients with FGIDs experienced significant healthcare demands, characterized by frequent endoscopic or imaging procedures, recurrent unscheduled consultations, or hospital admissions. Importantly, FD was independently correlated with the highest healthcare burden relative to other FGIDs.[2]

Our understanding of the pathophysiology of FD remains incomplete, despite its relative prevalence. Currently, diagnosing and managing FD pose significant challenges because no identifiable anatomical or biochemical abnormalities can explain the persistent symptoms. Recent research increasingly emphasizes the role of low-grade inflammation, particularly in the duodenum, as a contributing factor to the etiology of FD.[3]

Emerging evidence indicates that dysbiosis of gut microbiota, infiltration of inflammatory cells, and compromised mucosal barrier integrity may be potential etiological factors in visceral hypersensitivity and motility disturbances observed in FD. Histamine, cytokines, and eosinophils serve as pro-inflammatory mediators that activate nociceptors, thereby amplifying pain perception and symptom severity. Therapeutic strategies targeting inflammation could offer a novel approach for the management of FD, as suggested by this inflammatory paradigm, which provides insights into the function of the gut-brain axis in this disease.[4]

This review of the literature will focus on the current understanding of inflammation's role in FD, examining recent discoveries in its pathophysiology and considering potential implications for diagnosis and future treatment strategies. It is anticipated that elucidating these processes will unveil new opportunities for more targeted and effective interventions in the management of FD.

## DEFINITION AND DIAGNOSTIC CRITERIA OF FUNCTIONAL DYSPEPSIA

Dyspepsia has evolved in its meaning over time. Historically, any complaint involving the upper gastrointestinal tract was classified as dyspepsia.[5] However, the terminology has become more precise. According to the Rome IV criteria, dyspepsia is diagnosed in individuals who exhibit at least one symptom, such as postprandial fullness, early satiation, epigastric discomfort, or a burning sensation in the epigastric region. A more practically relevant definition is provided by the American College of Gastroenterology and the Canadian Association of Gastroenterology. The presence of persistent epigastric discomfort for 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, sensations of fullness in the epigastrium, or vomiting, may coexist.[6] Dyspepsia is subsequently classified as either organic or functional. Dyspepsia associated with structural abnormalities or identifiable underlying causes is categorized as organic dyspepsia.[7]

FD, in accordance with the Rome IV Criteria, is characterized by dyspeptic symptoms that disrupt daily activities, manifest at least three days per week

over the past three months, and have persisted for a minimum of six months. These symptoms occur in the absence of structural abnormalities that could explain the presentation, as identified by upper gastrointestinal endoscopy. The diagnostic criteria for FD are outlined in **Table 1**.[8]

**Table 1. Diagnostic Criteria for Functional Dyspepsia Based on the Rome IV Criteria[8]**

| 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 |

## PATHOPHYSIOLOGICAL MECHANISMS OF FUNCTIONAL DYSPEPSIA

Although the precise pathophysiology of FD remains undefined, various interconnected pathways have been hypothesized. Symptoms such as early fullness, nausea, vomiting, bloating, and abdominal pain may result from visceral hypersensitivity and abnormalities in gastric motility, including reduced gastric accommodation and delayed gastric emptying.[3,9] An additional significant factor is the presence of Helicobacter pylori infection, which can induce inflammation of the gastric mucosa and neurons. This inflammatory response may persist long after bacterial eradication, leading to neuronal damage and gastrointestinal dysfunction.[10] Environmental and psychosocial factors, including dietary habits, smoking, alcohol consumption, medication use, toxin exposure, and psychological stress, may further exacerbate symptoms by compromising gut integrity and disrupting the gut–brain axis.[11] Recent review articles synthesizing evidence from multiple studies suggest that the duodenum plays a central role in the pathophysiology of functional dyspepsia, wherein low-grade inflammation, increased mucosal permeability, and altered luminal composition contribute to heightened duodenal sensitivity and symptom presentation.[12,13]

## THE ROLE OF INFLAMMATION IN FUNCTIONAL DYSPEPSIA

Although the absence of major structural abnormalities is a key diagnostic criterion for FD according to the Rome IV criteria, emerging evidence suggests that microscopic duodenal alterations may significantly influence its pathophysiology.[14] According to recent studies, one of the primary molecular pathways involved in FD is immunological dysregulation.[15]

### Immunopathology and Molecular Mechanisms

The two primary components of the human immune system are the adaptive and innate immune systems. The innate immune system comprises various biological mediators, including chemical and physical barriers, dendritic cells, plasma proteins, and natural killer (NK) cells. The adaptive immune system comprises two subsets: humoral immunity, mediated by antibody-producing B cells and plasma cells, and cellular immunity, governed by helper and cytotoxic T cells. Immune responses predominantly occur in the epithelial mucosa. The adaptive immune responses are facilitated by lymphoid tissues and lymph nodes associated with the intestines. The intestinal epithelium exhibits a higher density of T cells, whereas the lamina propria contains both B and T cells, as well as macrophages, eosinophils, and mast cells.

Proinflammatory mediators, including IL-8 (interleukin-8), MCP-1 (monocyte chemoattractant protein-1), TNF-α (tumor necrosis factor alpha), RANTES (regulated upon activation, normal T cell expressed and secreted), and IL-6 (interleukin-6), may be released when bacteria, allergens, dietary antigens, or other events compromise the integrity of the mucosa. Macrophages, eosinophils, B cells, T cells, and neutrophils are all stimulated by these proinflammatory mediators. Dendritic cells play a vital role as antigen-presenting cells in this process.[15] The schematic illustration of this process is shown in **Figure 1.**

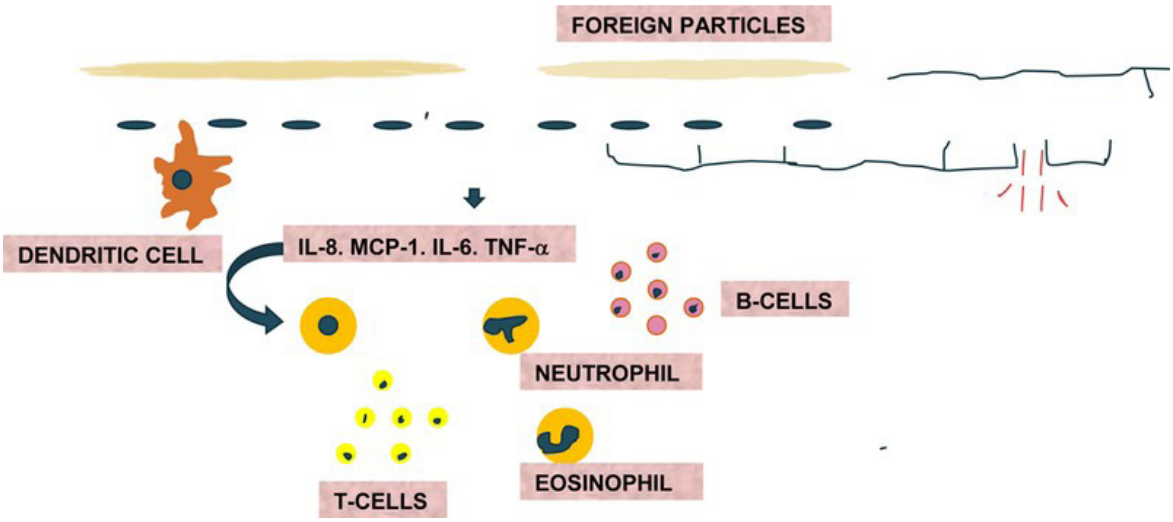


**Figure 1. Immune system activation within the intestine upon exposure to foreign substances. Upon exposure to a foreign antigen, early release of proinflammatory cytokines and chemokines, including IL-8, MCP-1, TNF-α, RANTES, and IL-6, initiates the recruitment and activation of innate and adaptive immune cells such as neutrophils, macrophages, eosinophils, and lymphocytes. Simultaneously, dendritic cell–mediated antigen presentation further enhances the inflammatory cascade.[15]**

## THE ROLE OF ENTERIC GLIAL CELLS IN NEUROIMMUNE MECHANISMS

Originating from the neural crest and organized into ganglia, enteric glial cells (EGCs) oversee the activity of intestinal smooth muscles, regulate blood vessel tone, facilitate glandular secretions, and support immune cell functions. Signals from the intestinal microenvironment, neuroplasticity, and the upregulation of immunoregulatory molecules are mechanisms through which EGCs contribute to immune modulation.[16] They are capable of producing nitric oxide, nerve growth factor, cytokines, and various inflammatory mediators.

Evidence from clinical studies underscores the involvement of enteric glial cells in the mechanisms underlying FD. Cirillo et al. documented neuronal alterations and gliosis in eighteen FD patients, accompanied by mast cell and eosinophil infiltration in the submucosa.[17] Similarly, Tanaka et al. observed that dyspeptic symptoms correlated with elevated levels of glial cell line-derived neurotrophic factor (GDNF).[18] It has been proposed that enteric glial cells (EGCs) are safeguarded from harm by GDNF secreted by eosinophils and epithelial cells in response to low-grade duodenal inflammation. These findings emphasize the bidirectional relationship between the gut's immunological and neurological systems.

The morphology and function of the Enteric Glial Cells (EGCs) may be influenced by mediators released into the gastrointestinal tract by individuals experiencing anxiety and stress, including glutamate, serotonin, corticosteroids, Corticotropin-releasing factor (CRF), and gamma-aminobutyric acid. Furthermore, by secreting cytokines such as IL-1, IL-6, Tumor Necrosis Factor Alpha (TNF-α), and GDNF, EGCs can modulate enteric nervous system function. These neuroimmune pathways may underlie the observed association between FD and low-grade duodenal inflammation, which may be attributable to allergens, atopic conditions, alterations in the gut microbiota, or post-infectious changes.[15]

## THE ROLE OF EOSINOPHILS AND MAST CELLS IN THE PATHOPHYSIOLOGY OF FUNCTIONAL DYSPEPSIA

Under normal physiological conditions, eosinophils are distributed throughout the gastrointestinal tract except the esophagus. Their recruitment is regulated by interleukin-5 (IL-5) and depends on α4β7 integrins and chemokine receptors for migration into the small intestine and colon.[14] Approximately 20% of leukocytes in the proximal small intestinal lamina propria are Th2 cells, which predominate over Th1 and Th17 cells. Eosinophils are activated by eotaxin through the STAT6 pathway following secretion of IL-4, IL-5, and IL-13 by Th2 cells. Although eosinophilic infiltration is classically associated with allergic and respiratory conditions, it is also observed in gastrointestinal diseases such as inflammatory bowel disease, disorders of gut–brain interaction, and eosinophil-associated gastrointestinal disorders.[14]

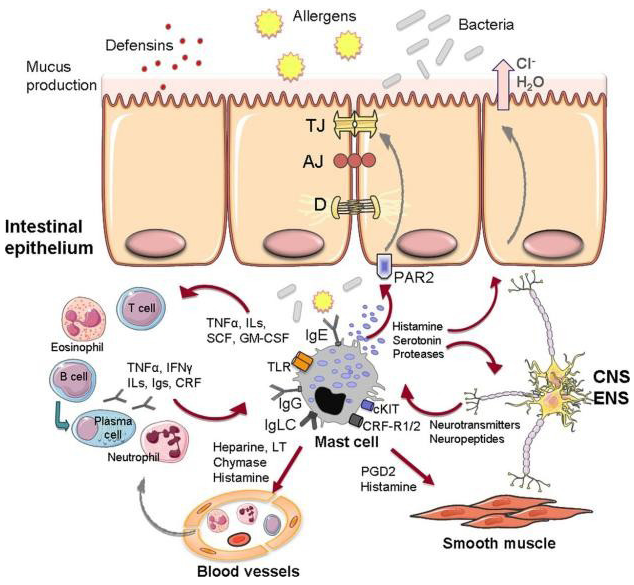


**Figure 2. The role of mast cells in alterations of duodenal mucosal barrier function. Luminal factors such as acid, food antigens, and microbial components impair duodenal epithelial barrier function, thereby activating mast cells through immune and innate pathways. Mast cell mediators alter epithelial permeability, neuromuscular function, and sensory nerve signaling.[21]**

In FD, eosinophil accumulation may be precipitated by food antigens or exposure to duodenal acid. Additionally, chronic Helicobacter pylori infection can induce secondary eosinophilia in the gastric and duodenal regions.[19] Recent evidence suggests that degranulation of duodenal eosinophils impairs mucosal barrier integrity and modulates neural and smooth muscle function, thereby contributing to symptom manifestation in functional dyspepsia.[20] Eosinophil granules comprise major basic protein (MBP), eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin. The release of interleukins, inflammatory cytokines, eotaxin, leukotriene C4, and transforming growth factor by activated eosinophils facilitates Th1/Th2 polarization, modifies smooth muscle contractility, enhances vascular permeability, and influences immune–neural interactions. Notably, MBP impacts peripheral neuronal plasticity and may play a crucial role in the etiology of visceral hypersensitivity.[15]

Mast cells are pivotal components of the immune system and are involved in FD and other functional gastrointestinal disorders. Mast cell activation has been associated with conditions such as inflammatory bowel disease, postoperative ileus, food allergies, visceral hypersensitivity, and neuromuscular dysfunction. In the gastrointestinal mucosa, mast cells are intimately connected with sensory nerve fibers expressing the transient receptor potential vanilloid 1 (TRPV1), thereby facilitating altered neuromuscular activity and pain perception in response to infection, stress, or emotional stimuli.[21] In FD, diminished expression of mast cell–regulated tight junction proteins, including claudin-8, zonula occludens-1 (ZO-1), and occludin, contributes to increased epithelial permeability and barrier dysfunction, consequently promoting duodenal inflammation.[22] Upon degranulation, mast cells release tryptase, which activates protease-activated receptor-2 (PAR-2) on enterocytes, leading to tight junction redistribution and an increase in macromolecular permeability. Additional mediators such as histamine and prostaglandin $D_2$ further influence epithelial secretion and permeability.[21,22]

## THE ROLE OF PRO-INFLAMMATORY CYTOKINES IN FUNCTIONAL DYSPEPSIA

Cytokines serve as pivotal mediators of immune responses and cellular signaling, playing a crucial role in inflammation-related modifications of gastrointestinal function. In cases of FD, cytokine activity driven by immune mechanisms may interfere with gastric physiology, influence enteric nervous system signaling, and induce neuronal injury, thereby perpetuating dyspeptic symptoms.[10] However, evidence from a meta-analysis by Du et al. indicated no significant differences in circulating IL-6 and IL-10 levels between patients with FD and controls. These findings imply that systemic cytokine alterations may not constitute the primary inflammatory mechanism in FD and instead underscore the significance of localized microinflammation, particularly involving mucosal immune cells such as eosinophils and mast cells.[23]

In addition to cytokines, matrix metalloproteinase-9 (MMP-9), primarily synthesized by macrophages, has been implicated in the inflammatory pathophysiology of *H. pylori*-associated FD. MMP-9 facilitates extracellular matrix degradation, mucosal apoptosis, and neuronal injury, processes that may contribute to ongoing symptoms even following the successful eradication of H. pylori.[10]

## GUT MICROBIOTA DYSBIOSIS, INFLAMMATION, AND FUNCTIONAL DYSPEPSIA: THE ROLE OF THE GUT-BRAIN AXIS

The gut microbiota plays a pivotal role in the gut–brain axis, a bidirectional communication network encompassing neural, hormonal, and immune pathways that connect the gastrointestinal tract to the central nervous system. Disruptions in this microbial

equilibrium, referred to as dysbiosis, may induce pathological alterations that negatively 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 demonstrated that the duodenal mucosa of patients with FD exhibits lower levels of *Actinomyces*, *Gemella*, *Haemophilus*, *Megasphaera*, *Mogibacterium*, and *Selenomonas*, and higher levels of *Fusobacteria*, *Alloprevotella*, *Corynebacterium*, *Peptostreptococcus*, *Staphylococcus*, *Clostridium*, and *Streptococcus*. Studies suggest that elevated levels of *Streptococcus* and *Prevotella* may correlate with increased symptom severity. *Furthermore, Veillonella*, *Prevotella*, and *Actinomyces* were all significantly decreased in the patient group compared to the healthy control cohort.[24]

Microbial dysbiosis in FD may influence neurotransmitter production and other signaling molecules, thereby contributing to impaired gastric motility, visceral hypersensitivity, and low-grade inflammation. Additionally, metabolic alterations arising in the gut may play a significant role. In one study, Wen et al. identified metabolic changes in the serum and urine of FD patients using liquid chromatography–mass spectrometry, with a notable reduction in L-glutamate, which emerged as a strong predictor of symptom severity.[26]

## CLINICAL IMPLICATIONS OF THE ROLE OF INFLAMMATION IN FUNCTIONAL DYSPEPSIA

Recognizing the role of inflammation in the pathogenesis of FD facilitates the development of more precise diagnostic and treatment approaches. Duodenal eosinophilia has been identified as a potential indicator of low-grade inflammation in postprandial distress syndrome, particularly among patients lacking *H. pylori* infection. Furthermore, studies have demonstrated that patients exhibiting duodenal eosinophilia respond positively to proton pump inhibitor (PPI) therapy after a course of 4–6 weeks. This observation suggests that eosinophilia may serve as a predictor of therapeutic benefit from PPI treatment.[27] Currently, pharmacological agents targeting low-grade duodenal inflammation are under development as potential therapeutic options for FD.

Low-grade duodenal inflammation is frequently associated with mucosal dysbiosis, which also appears to play a role in the pathogenesis of FD. The recognition of dysbiosis as a contributing factor presents new opportunities for therapeutic intervention.[19] In recent years, probiotics have garnered increased attention as a potential treatment modality for FD. Probiotics assist in restoring microbial balance, mitigate inflammation by modulating the gastrointestinal immune response, such as inhibiting Th17-related pathways, and improve intestinal barrier integrity 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, thereby impacting gut-brain axis communication and potentially reducing symptom intensity.[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]

Research is currently exploring pathways involving histamine and leukotrienes as potential therapeutic targets. The synthesis of histamine by basophils and mast cells in response to immunological stimuli may worsen FD symptoms by increasing inflammatory responses, gastric acid secretion, and altering gastric motility.[31] Antihistamines mitigate the inflammatory response by inhibiting histamine binding to its receptors. Given that histamine facilitates eosinophil recruitment and activation, antihistamines may provide symptomatic relief for FD by reducing duodenal inflammation and eosinophilic infiltration.[31,32]

Leukotrienes are inflammatory mediators derived from arachidonic acid through the lipoxygenase pathway. They contribute to the inflammatory process by augmenting immune cell recruitment, increasing vascular permeability, and promoting tissue inflammation. In the gastrointestinal tract, leukotrienes may intensify inflammation and potentially exacerbate FD symptoms. Leukotriene inhibitors function either by inhibiting the enzyme 5-lipoxygenase or by blocking leukotriene receptors. Emerging evidence suggests a role for low-grade duodenal inflammation in FD, making leukotriene inhibitors a potential therapeutic option. Nonetheless, further research is necessary to confirm their efficacy and safety within this context.[31]

## CONCLUSION

FD is a longstanding condition of the upper digestive tract, characterized by recurrent symptoms despite the absence of visible structural abnormalities. The underlying mechanisms are diverse and complex, including disturbances in gastric motility, heightened visceral sensitivity, and *H. pylori infection*. Psychosocial determinants and environmental exposures are also recognized as important contributors to its development. Increasing evidence highlights the contribution of low-grade duodenal inflammation, driven by immune dysregulation, mast cell and eosinophil activation, 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 lead to neuronal injury. Additionally, interactions between the immune system and enteric glial cells further sustain inflammation and visceral hypersensitivity. Dysbiosis of the duodenal microbiota has also emerged as a significant component, affecting the gut-brain axis and modulating immunological responses and motility. Collectively, these findings support a paradigm shift in understanding FD pathophysiology, moving from a purely functional model to an integrated immune-neuro-epithelial model.

Despite these advances, the clinical translation of inflammatory mechanisms in FD remains limited. This review attempts to synthesize current evidence on the mechanisms and the important role of duodenal inflammation in the pathophysiology of FD. A deeper understanding of these mechanisms may facilitate the development of biomarker-driven diagnosis and targeted therapies. Future therapeutic strategies, including anti-inflammatory agents and microbiota-modulating interventions, hold promise for improving outcomes by targeting the underlying inflammatory drivers of FD rather than focusing solely on symptom control.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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## AUTHOR CONTRIBUTIONS

CPS: original draft preparation, gathering of references, review and editing; IKM: conceptualization, review and editing, supervision

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