The Role Of Motility And Gastric Acid Secretion in The Pathophysiology of Gastroesophageal Reflux Disease (GERD)

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ABSTRACT

Introduction: Gastroesophageal reflux disease (GERD) is a chronic disorder of the upper gastrointestinal tract that involves a complex interaction between physiologic and pathologic factors. The two main components that play a role in this dynamic are gastric motility and acid secretion.

Methods: This review used a narrative literature review approach by searching the current scientific literature from various databases between 2015-2024.

Discussion: Normal gastric motility maintains gastric emptying efficiency and lowers the risk of reflux, while disorders such as delayed gastric emptying increase intragastric pressure and trigger reflux. Excessive secretion of gastric acid, especially HCl and pepsin, amplifies the aggressive nature of gastric contents and exacerbates damage to the esophageal mucosa. These two aspects interact to create an imbalance between protective and aggressive factors in GERD.

Conclusion: The interplay between gastric motility and acid secretion plays a key role in the transition from physiologic to pathologic mechanisms in GERD, so a thorough understanding of both is important in diagnosis and treatment strategies.

Keywords: GERD, gastric motility, acid secretion, acid reflux, pepsin

Introduction

Gastroesophageal reflux disease (GERD) is one of the upper gastrointestinal disorders whose prevalence continues to increase globally, influenced by modern lifestyles and obesity.[1] This disease is characterized by the rise of acidic stomach contents into the esophagus, and can cause classic complaints such as heartburn and regurgitation, as well as other manifestations that interfere with the quality of life of sufferers.[2,3] Although it appears to be a local disorder of the esophagus, the pathological process of GERD is closely related to the physiological dynamics occurring in the stomach, particularly motility and acid secretion.[4,5]

Normal gastric motility plays an important role in the efficient emptying of the stomach into the duodenum, thereby preventing an increase in intragastric pressure that can trigger reflux.[6] Conversely, motility disorders such as antral hypomotility or delayed gastric emptying have been shown to exacerbate the tendency for gastric acid reflux. On the other hand, excessive gastric acid secretion, particularly in the form of HCl and pepsin enzymes, contributes significantly to damage to the esophageal mucosa when reflux occurs. This secretory activity is influenced by neural, hormonal, and local regulation, and can be exacerbated by external factors such as diet, stress, and consumption of certain medications.[7]

Understanding the close relationship between gastric motility and acid secretion in the physiological and pathological mechanisms of GERD is important for informing diagnostic approaches, therapeutic strategies, and the prevention of long-term complications. Therefore, this article aims to review and summarize the latest scientific literature on the role of gastric motility and acid secretion in the physiological and pathophysiological dynamics of GERD through a narrative literature review approach.

Methods

This article was compiled using the narrative review method by examining relevant literature related to gastric motility and secretion physiology and its relationship to the pathophysiology of gastroesophageal reflux disease (GERD). Data sources were obtained from scientific databases such as PubMed, ScienceDirect, and Google Scholar, with publication time limits between 2015 and 2024 to ensure the latest information.

Stomach Motility Physiology

Stomach motility is an important aspect of gastrointestinal physiology that reflects the ability of the stomach's smooth muscles to perform coordinated contractions in order to receive, mix, and gradually empty the stomach's contents into the duodenum. This process consists of three main phases, namely receptive relaxation, mixing, and gastric emptying. The receptive relaxation phase allows the stomach to store food without significantly increasing intraluminal pressure, while the mixing phase facilitates the mixing of food bolus with enzymes and stomach acid. Furthermore, in the gastric emptying phase, the stomach contents are gradually emptied into the small intestine.[1]

This motility pattern involves coordination between the activity of the smooth muscles of the stomach and a complex nervous and hormonal regulatory system. The enteric nervous system (ENS) acts as the main regulator of intrinsic gastrointestinal motility. The ENS consists of two main plexuses, namely the myenteric plexus (Auerbach), which regulates smooth muscle movement and the coordination of sphincter relaxation, such as the pylorus and ileocecal sphincter, and the submucosal plexus (Meissner), which is responsible for mucosal secretion and local blood flow regulation. These two plexuses work synergistically with the autonomic nervous system. Parasympathetic activation via the vagal nerve is known to be excitatory to gastric motility, while sympathetic stimulation tends to inhibit smooth muscle contractility and glandular secretion. Parasympathetic activation via the vagal nerve is known to be excitatory to gastric motility, whereas sympathetic stimulation tends to inhibit smooth muscle contractility, gastric gland secretion, and local vascular perfusion.[2]

In addition to neural influences, various neurotransmitters also play an important role in regulating motility. Acetylcholine and serotonin are excitatory neurotransmitters that can increase gastric motor activity, while vasoactive intestinal peptide (VIP), nitric oxide (NO), and norepinephrine are known to be inhibitory and play a role in decreasing gastric smooth muscle contractility.[2]

Hormonally, gastric motility is influenced by several digestive hormones that act both locally and systemically. Gastrin, secreted by G cells in the gastric antrum in response to gastric distension or the presence of peptides in the lumen, functions to stimulate gastric acid secretion and accelerate gastric emptying into the duodenum. Conversely, hormones such as cholecystokinin (CCK), gastric inhibitory peptide (GIP), and secretin have inhibitory effects on gastric emptying. All three are released primarily when there is fat or acid in the chyme, with the aim of slowing the flow of stomach contents into the duodenum so that

digestion and absorption can be optimized. On the other hand, the hormone motilin plays a role in stimulating inter-digestive contraction waves known as the migrating motor complex (MMC), which occurs approximately every 90 minutes during the interdigestive phase and serves to clear food residues before the next eating cycle begins.[3]

In addition to neural and hormonal factors, recent studies have shown that neuroimmune processes play an important role in regulating gastric motility. Activation of macrophages during the inflammatory process is known to cause degeneration of enteric neurons.[4] This results in decreased gastric smooth muscle contractility and has the potential to worsen motility disorders, especially in pathological conditions or other functional disorders of the stomach.[5]

Physiology Of Gastric Acid Secretion

Gastric acid secretion, particularly hydrochloric acid (HCl), is a complex physiological process controlled by interactions between the nervous system, hormonal system, and local mediators. The three main stimuli involved in the activation of HCl secretion are acetylcholine (released by parasympathetic nerve endings via the vagal nerve), gastrin (secreted by G cells in the gastric antrum), and histamine released by enterochromaffin-like (ECL) cells in the gastric mucosa.[6] These three work synergistically to stimulate parietal cells to activate the H^+/K^+-ATPase proton pump located on the apical membrane of parietal cells, which is the key to the excretion of hydrogen ions (H^+) into the stomach lumen.[6]

H^+ ions secreted into the lumen originate from the hydration of carbon dioxide (CO_2) and dihydrogen monoxide (H_2O) in the cytoplasm of parietal cells, which is catalyzed by the enzyme carbonic anhydrase to form carbonic acid (H_2CO_3). This carbonic acid (H_2CO_3) then dissociates into H^+ ions and bicarbonate (HCO_3^-) ions. H^+ ions are pumped into the stomach lumen via the H^+/K^+- ATPase proton pump with the help of energy from ATP. Meanwhile, HCO_3^- ions are transported out of the cell into the blood circulation through exchange with Cl^- (chloride) ions in the basolateral membrane using an antiporter. The Cl^- ions then passively diffuse into the stomach lumen through chloride channels and combine with H^+ to form stomach acid (hydrochloric acid/HCl).[6,7]

This process also gives rise to a phenomenon called the alkaline tide, which is a temporary increase in blood pH after eating, due to the excretion of bicarbonate ions into the systemic circulation. This phenomenon can even cause an increase in urine pH after eating, which is a physiological indicator of gastric secretory activity.[7]

The role of gastrin in regulating gastric acid secretion is not limited to its direct effect on parietal cells, but also works indirectly by stimulating ECL cells to release histamine. This histamine enhances the activation of proton pumps and increases overall gastric acid production. This mechanism demonstrates the close relationship between the hormonal and nervous systems in integrally regulating gastric secretory function.[8]

In addition to hydrochloric acid, pepsin is also an important component released into the gastric lumen and plays a role in protein digestion. Pepsin is a proteolytic enzyme that is activated from its inactive form, pepsinogen, in a highly acidic environment (pH <3). Although the pH increases after food enters the stomach, pepsin remains stable up to a pH of 6.5 and can be reactivated when the pH decreases. This is important in the context of gastroesophageal reflux, because pepsin carried in the stomach contents can remain active or be reactivated in the esophagus during acid reflux. Therefore, pepsin is considered an important mediator in the pathogenesis of mucosal damage in gastroesophageal reflux disease (GERD).[9]

Pathomechanism of Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disease characterized by regurgitation of acidic and enzymatic stomach contents into the esophagus due to dysfunction of the anti-reflux barrier at the esophagogastric junction (EGJ).[10] The main mechanism of reflux is dysfunction of the lower esophageal sphincter (LES), particularly in the form of transient LES relaxation or transient lower esophageal sphincter relaxation (TLESR). Transient lower esophageal sphincter relaxation (TLESR) is a physiological process that normally occurs after eating or when the stomach is distended, but in GERD patients, its duration and frequency increase pathologically. As a result, increased intragastric pressure, whether due to large food intake, abdominal obesity, or increased intra-abdominal pressure such as in pregnancy and ascites, makes it easier for stomach contents to rise into the esophagus.[11]

Anatomical factors such as hiatal hernia contribute to LES incompetence. This hernia disrupts the anatomical position of the crural diaphragm, which should support the EGJ as a barrier against high pressure. As a result, mechanical resistance to reflux weakens, especially when the patient is lying down or reclining. In addition, structural abnormalities such as a shorter-than-normal LES (<3 cm) have also been associated with a decrease in anti-reflux barrier function.[11,12]

Impaired gastric motility, such as delayed gastric emptying, causes retention of chyme and increased gastric pressure. Antral hypomotility, often found in patients with functional dyspepsia, gastroparesis, or diabetes mellitus, increases the risk of recurrent reflux by prolonging the contact time between gastric contents and the EGJ. On the other hand, esophageal motility disorders, such as weakened peristalsis or decreased saliva production, inhibit the cleansing and acid neutralization processes by the esophageal mucosa, thereby reducing the esophageal mucosa's protection against gastric acid reflux.[13,14]

The main aggressive components of gastric reflux are gastric acid and the proteolytic enzyme pepsin. Pepsin remains active at pH 6.5 and can become active again when the environment becomes more acidic, making it dangerous even after HCl secretion is suppressed. In addition to working in the lumen, pepsin can also enter mucosal cells through endocytosis and remain active in the acidic endosomal environment, which prolongs damage to the esophageal tissue.[14]

Chronic exposure to acid and pepsin causes a mucosal inflammatory response characterized by the release of cytokines and chemokines, as well as the recruitment of inflammatory cells such as T cells. This inflammatory process is mediated by the activation of molecular pathways such as Hypoxia -Inducible Factor-2 alpha (HIF-2α) and transcription factor NF-κB, which promote the production of proinflammatory cytokines and esophageal epithelial apoptosis.[14] If chronic, the esophageal mucosa may undergo metaplasia, i.e., a change from squamous epithelium to intestinal- type columnar epithelium, a pre-neoplastic condition known as Barrett's esophagus. The presence of Barrett's significantly increases the risk of esophageal adenocarcinoma, with patients experiencing weekly GERD symptoms having up to a six-fold higher risk of developing this condition compared to the general population.[15]

Risk factors that increase susceptibility to GERD are diverse and multifactorial. Unhealthy lifestyles such as smoking, alcohol consumption, caffeine, chocolate, and foods high in fat and spice can decrease LES tone and stimulate gastric acid secretion. Lack of physical activity and eating large meals, especially at night, also exacerbate symptoms. Obesity, especially central obesity, is one of the main risk factors due to increased intra-abdominal pressure. In addition, consumption of certain medications, such as anticholinergics, nitrates, beta-agonists, calcium channel blockers, and theophylline, has been shown to decrease LES pressure or slow gastric emptying. Hormonal factors such as increased progesterone levels during pregnancy or postmenopausal estrogen therapy also

contribute to decreased LES function. Psychosocial stress and depression have a direct effect on visceral sensitivity and gastrointestinal motility, making patients more susceptible to GERD manifestations.[16]

Clinical Manifestations of Gastroesophageal Reflux Disease (GERD)

Clinically, GERD is characterized by two main symptoms, namely regurgitation and heartburn. Regurgitation describes the condition of stomach contents rising into the esophagus or even into the oral cavity, often accompanied by a bitter and sour taste. Meanwhile, heartburn is a burning sensation in the retrosternal or epigastric region that can radiate to the chest. Both symptoms are characteristic, but they can resemble cardiovascular symptoms such as angina pectoris, often causing undue concern in patients. Fear of possible heart disease or cancer that has not been clinically proven can worsen the perception of the disease and impact the patient's quality of life.[17,18]

On the other hand, GERD is also closely related to psychological factors. Many patients experience anxiety and depression, either as a result of recurring and disturbing symptoms, or as factors that actually worsen somatic stomach complaints. A population study in the United States showed that GERD patients with comorbid anxiety (13%) and depression (13%) had a significant decrease in mental component summary (MCS) quality of life scores, by −10.8 and −6.3 points, respectively, which increased dramatically to −42.8 when both affective disorders were present simultaneously. This two-way relationship between emotional disorders and gastric complaints underscores the importance of a holistic approach to GERD management, which includes addressing both physical and psychological aspects.[17,18]

Complications Of Gastroesophageal Reflux Disease (GERD)

The global prevalence of GERD continues to increase, influenced by changes in lifestyle, diet, and high rates of obesity. If not treated properly, GERD can cause serious complications, both within the esophageal system and outside of it. One of the most common local complications is reflux esophagitis, which is inflammation of the esophageal mucosa due to chronic irritation by HCl and gastric enzymes. Long-term esophagitis can develop into esophageal ulcers, and during the healing process, it can cause strictures due to fibrosis. Esophageal strictures cause narrowing of the lumen and dysphagia, and increase the risk of aspiration.[19]

Prolonged acid exposure can also cause squamous epithelial metaplasia to become columnar epithelium, a histological change known as Barrett's esophagus. Barrett's is a precancerous condition that has the potential to progress to esophageal adenocarcinoma, although not all GERD patients will experience this change. Therefore, early detection and monitoring through esophageal endoscopy are very important, especially in patients with chronic symptoms or high-risk factors.[20]

In addition to local complications in the esophagus, GERD can also cause extraesophageal manifestations involving the respiratory system and oral cavity. Acid reflux reaching the upper respiratory tract can cause chronic inflammation and mucosal irritation, leading to symptoms such as chronic cough, asthma, pharyngitis, laryngitis, sinusitis, and tooth erosion. Repeated exposure of the respiratory tract and oral cavity mucosa to acid has the potential to progressively damage tissue and cause persistent respiratory symptoms.[20]

Conclusion

Impaired gastric motility and increased gastric acid secretion directly contribute to the development of GERD through increased intragastric pressure and abnormal LES relaxation. Repeated acid and pepsin reflux can damage the esophageal mucosa, trigger inflammation, and increase the risk of complications such as esophagitis and Barrett's esophagus. The interaction between the two is an important basis for understanding the physiological and pathological mechanisms of GERD.

Conflicts of Interests

There are no conflicts of interest.

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References

1. Fuchs KH, Babic B, Breithaupt W, Varga G, Babic T. Severity of GERD and disease progression. *Dis Esophagus.* 2021;34:1–10. doi:10.1093/dote/doab006.
2. Henning M, Wahba J, Kumar S, Singh R, Rajpal S, Malik M, et al. Association between anxiety and reflux symptoms in patients with gastroesophageal reflux disease: a prospective cohort study. *Cureus.* 2024;16(11):e73391. doi:10.7759/cureus.73391.
3. Azer SA, Hashmi MF, Reddivari AKR. Gastroesophageal reflux disease (GERD). In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2025 Oct 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441938/
4. Sihombing JA, Ningsih Y, Harahap D, et al. *Penyakit sistem pencernaan.* Purbalingga (ID): Eureka Media Aksara; 2025 [cited 2025 Oct 9].
5. Savarino E, Bredenoord AJ, Fox M, Pandolfino JE, Roman S, Gyawali CP. Advances in the physiological assessment and diagnosis of GERD. *Nat Rev Gastroenterol Hepatol.* 2017;14(11):665–76. doi:10.1038/nrgastro.2017.130.
6. Hall JE, Hall ME. *Guyton and Hall textbook of medical physiology.* 14th ed. Philadelphia (PA): Elsevier; 2021.
7. Nirwan JS, Hasan SS, Babar ZUD, Conway BR, Ghori MU. Global prevalence and risk factors of gastro-oesophageal reflux disease (GORD): systematic review with meta-analysis. *Sci Rep.* 2020;10:5814. doi:10.1038/s41598-020-62795-1.
8. Prawira MD, Sueta MAD. Konsep patofisiologi motilitas gastrointestinal. *Cermin Dunia Kedokteran.* 2020;47(1):7–10.
9. Parikh A, Thevenin C. Physiology, gastrointestinal hormonal control. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Oct 9]. Available from: https://www.ncbi.nlm.nih.gov/books/
10. Breßer M, et al. Macrophage-induced enteric neurodegeneration leads to motility impairment during gut inflammation. *EMBO Mol Med.* 2025;17(2):301–35. doi:10.1038/s44321-024-00189-w.
11. Wang Y, Chen JDZ, Nojkov B. Diagnostic methods for evaluation of gastric motility—a mini review. *Diagnostics (Basel).* 2023;13(4):803. doi:10.3390/diagnostics13040803.
12. Tobias A, Sadiq NM. Physiology, gastrointestinal nervous control. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2025 Oct 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537082/

13. Tortora GJ, Derrickson B. *Principles of anatomy and physiology.* 14th ed. Hoboken (NJ): John Wiley & Sons; 2014 [cited 2025 Oct 9]. Available from: https://www.wiley.com
14. Chen D, Hagen SJ, Boyce M, Zhao CM. Neuroendocrine mechanism of gastric acid secretion: historical perspectives and recent developments in physiology and pharmacology. *J Neuroendocrinol.* 2023;35(11):e13305. doi:10.1111/jne.13305.
15. Li C, Cao X, Wang H. Pathogenesis of pepsin-induced gastroesophageal reflux disease with advanced diagnostic tools and therapeutic implications. *Front Med (Lausanne).* 2025;12:1516335. doi:10.3389/fmed.2025.1516335.
16. Sihombing JA, Ningsih Y, Harahap D, et al. *Penyakit sistem pencernaan.* Purbalingga (ID): Eureka Media Aksara; 2025.
17. Argüero J, Sifrim D. Pathophysiology of gastro-oesophageal reflux disease: implications for diagnosis and management. *Nat Rev Gastroenterol Hepatol.* 2024;21:282–93. doi:10.1038/s41575-023-00897-7.
18. Eusebi LH, et al. Effect of gastro-esophageal reflux symptoms on the risk of Barrett's esophagus: a systematic review and meta-analysis. *J Gastroenterol Hepatol.* 2022;37:1507–16. doi:10.1111/jgh.15902.
19. Alwhaibi M. Anxiety and depression and health-related quality of life in adults with gastroesophageal reflux disease: a population-based study. *Healthcare (Basel).* 2023;11(19):2637. doi:10.3390/healthcare11192637.
20. Khieu M, Goosenberg E. Barrett esophagus. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Oct 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430979/