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Pathophysiology of Gastroesophageal Reflux Disease

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The pathogenesis of gastroesophageal reflux disease (GERD) is complex and involves changes in reflux exposure, epithelial resistance, and visceral sensitivity. The gastric refluxate is a noxious material that injures the esophagus and elicits symptoms. Esophageal exposure to gastric refluxate is the primary determinant of disease severity. This exposure arises via compromise of the anti-reflux barrier and reduced ability of the esophagus to clear and buffer the refluxate, leading to reflux disease. However, complications and symptoms also occur in the context of normal reflux burden, when there is either poor epithelial resistance or increased visceral sensitivity. Reflux therefore develops via alterations in the balance of aggressive and defensive forces.

Keywords: Esophageal Motility; Esophageal Sensitivity; Acid Exposure; Transient Lower Esophageal Sphincter Relaxations; Hiatal Hernia.

Gastroesophageal reflux disease (GERD) is defined as the presence of symptoms or complications that are directly related to the retrograde flow of gastric contents into the esophagus.[1] A certain degree of reflux is normal—development of GERD requires either increased esophageal exposure to gastric juice or a reduced threshold for epithelial injury and symptom perception. This balance among reflux exposure, epithelial resistance, and visceral sensitivity is delicate, and can be altered by perturbations in physiologic and anatomical factors that either promote or impede reflux into the esophagus, or protect or injure the epithelium from exposure to gastric juice.

Under normal circumstances, reflux into the esophagus is prevented by the anti-reflux barrier, which is a complex anatomic zone made up of multiple components, including the lower esophageal sphincter, the extrinsic crural diaphragm, and the supporting structures of the gastroesophageal flap valve. When these protective components are compromised, the deleterious effects are additive, resulting in increasing numbers of reflux events and increasingly abnormal esophageal reflux exposure. When gastric juice enters the esophagus, protective factors help clear the refluxate from the esophagus and protect the epithelium. Breakdown of these protective forces promotes reflux disease. However, complications and symptoms can also occur in individuals with a normal reflux burden, when there is either poor epithelial resistance or increased visceral sensitivity. The pathogenesis of reflux disease is therefore complex and determined by interactions among multiple aggressive and defensive factors.

We review the pathophysiology of GERD in the context of abnormalities related to reflux exposure and abnormalities related to epithelial resistance and visceral hypersensitivity. These exist in a continuum that determines severity of reflux disease. It is important to consider this balance in attempting to understand mechanisms of pathogenesis in each patient.

Reflux Exposure

GERD develops via reflux of noxious gastric juice into the esophagus.[1] Excessive reflux exposure is normally prevented as a function of the anti-reflux barrier and the direct result of an impaired anti-reflux barrier is an increased number of reflux events via an increasing diversity of mechanisms of reflux. Once reflux has occurred, injury and symptoms are regulated by the duration of exposure and causticity of the gastric juice. The duration of reflux exposure is determined by the effectiveness of esophageal reflux clearance, the dominant determinants of which are peristalsis, salivation, and the presence of a hiatus hernia. Abnormalities of esophageal clearance are probably the major determinants for development of esophagitis, whereas esophageal sensitivity is a major determinant of GERD symptom perception.

Abbreviations used in this paper: **EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; NERD, nonerosive reflux disease; PAR2, protease-activated receptor 2; PPI, proton pump inhibitor; tLESR, transient lower esophageal sphincter relation; TRVP1, transient receptor potential vanilloid type-1.**

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Gastric Refluxate

Gastric juice is a noxious blend of acid, bile, and digestive enzymes that help digest food so that it can be delivered to the small intestine. This material is caustic and can therefore injure most epithelial layers unless proper protective measures are in place to buffer the acid and protect the mucosa from inflammation and other direct effects of the refluxate. Although all of the components can injure and irritate the esophagus, acid is the primary determinant of esophagitis and reflux symptoms. However, studies have indicated that abnormal acid secretion is not the primary defect of GERD, because gastric acid secretion is similar between asymptomatic individuals and GERD patients.[2]

Although hypersecretory states, such as Zollinger-Ellison disease, are associated with severe reflux disease, the mere presence of normal gastric juice in the esophagus is enough to injure and irritate the esophagus. Despite the multitude of studies in animal models, human translational investigations, and clinical trials focused on acid suppression, many people have been misled into thinking that GERD can result from too little acid in the stomach. Some researchers have advocated for recklessly increasing acid levels in patients with GERD using various concoctions with pH values <4.0. These approaches have placed patients with severe GERD at high risk for complications and death, and should be aggressively discouraged. Acid suppression is the first-line treatment for GERD, based on sound experimental and clinical data.

In addition to acid, other components of gastric juice, such as bile, digestive enzymes, microbial pathogens, and other noxious factors can damage the esophagus and cause symptoms.[3–6] In patients given high doses of proton pump inhibitors (PPIs), gastric juice typically remains acidic, termed *weakly acidic reflux*. Reflux of weakly acidic gastric content has been implicated in the generation of symptoms (regurgitation, based primarily on the volume delivered into the esophagus, and possibly oropharynx, but also heartburn) and lesions.[7] Pepsin also contributes to mucosal injury—even small amounts can injure the esophagus.[5,6] However, this effect is most deleterious in an acidic environment, because most pepsins are inactive at pH 4.5–7.0.[5,6]

Bile acids can alter the integrity of the mucosal barrier by disrupting cell function and damaging membrane structure.[4] Bile is secreted into the proximal small intestine. However, abnormal secretory patterns and antro-duodenal dysmotility can increase the amount of bile in the stomach. Esophageal exposure to bile mixed with acid is associated with more severe grades of esophagitis[3,4] and this is believed to be related to a shift toward higher levels of conjugated bile acids. Analyses of the association of acid and bile reflux (quantified using bilirubin absorbance) with GERD lesions support the hypothesis that the presence and severity of erosive esophagitis depend mostly on acid reflux, whereas the presence of Barrett's esophagus depends on exposure to acid and bile.[8] Although, bile acids and pepsin are important constituents of a noxious gastric refluxate, there are no treatments that target these components. Treatment has focused on acid suppression and anti-reflux procedures.

Although there has been substantial interest in the effects of the microbiome on development of gastrointestinal disease, there have been few studies of the roles of bacteria in development of GERD, outside of its well-established relationship with *Helicobacter pylori* infection. Studies have associated changes in the esophageal microbiota with GERD, and especially with Barrett's esophagus.[9] Further studies are needed to clarify whether these contribute to development or are consequences of reflux.

Epidemiology studies have reported inverse time trends in the prevalence of GERD and *H pylori*–related peptic ulcer disease, indicating an interaction that involves the pattern of gastritis.[10,11] It appears that body-predominant *H pylori* decreases gastric acid secretion by reducing the overall volume of parietal cell mass, whereas antral-predominant *H pylori* increases acid secretion, based on alterations in negative feedback inhibition via D-cell interference in the antrum. Regardless, perturbations of other components of reflux pathophysiology are required for reflux disease to develop; abnormal acid secretion in and of itself is inadequate to induce symptoms of GERD.

The distribution and volume of gastric juice within the stomach may also be important in the pathogenesis of GERD. Although many patients with GERD have abnormal gastric emptying,[12] it is difficult to prove that this causes GERD—gastric emptying studies are typically reserved for patients with refractory disease and those with nausea and vomiting. More recently, there has been interest in the distribution of gastric juice in terms of its relationship to the postprandial acid pocket[13] and anatomical variants, such as the cascade stomach (retroflexed gastric fundus, which preferentially fills upon ingestion).[14] The acid pocket is a gastric juice layer that resides above the ingested food bolus and is positioned just below the esophagogastric junction (EGJ) in normal postprandial conditions. Studies have shown that the acid pocket is associated with proximal extension in GERD, and that the position of the acid pocket is altered in patients with hiatus hernia to promote acid reflux.[15] These findings support that the role of the proximal stomach in GERD, but studies are needed to better understand how gastric accommodation and distribution of the acid pocket can alter GERD severity.

Reflux Events

Reflux exposure begins with reflux events; the anti-reflux barrier is the primary determinant of reflux event burden and the mechanisms of reflux. The anti-reflux barrier is a complex anatomic high-pressure zone that arises via synergy between the lower esophageal sphincter and the crural diaphragm.[16] The function of this barrier is maintained by the architecture of the gastroesophageal flap valve,[17] which is supported by the phrenoesophageal ligament and the gastric sling fibers of the gastric cardia. These supporting structures help maintain position of the intrinsic lower esophageal sphincter within the extrinsic crural diaphragm, such that the 2 can overlap and create a more effective barrier. Severity of reflux correlates with the severity of dysfunction of each of the individual component of the anti-reflux barrier.