GERD pathogenesis, pathophysiology, and clinical manifestations

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a specific clinical entity defined by the occurrence of gastroesophageal reflux through the lower esophageal sphincter (LES) into the esophagus or oropharynx to cause symptoms, injury to esophageal tissue, or both. The pathophysiology of GERD is complex and not completely understood. An abnormal LES pressure and increased reflux during transient LES relaxations are believed to be key etiologic factors. Prolonged exposure of the esophagus to acid is another. Heartburn and acid regurgitation are the most common symptoms of GERD, although pathologic reflux can result in a wide variety of clinical presentations. GERD is typically chronic, and while it is generally nonprogressive, some cases are associated with development of complications of increasing severity and significance.

Gastroesophageal reflux disease (GERD), as generally defined, is a common condition that results from the reflux of gastric material through the lower esophageal sphincter (LES) into the esophagus or oropharynx, causing symptoms and/or injury to esophageal tissue.[1] The term encompasses both symptoms and pathophysiologic changes to the esophageal mucosa, which occur as a result of exposure of the distal esophagus to acidic gastric contents after episodes of gastroesophageal reflux.

While most people experience some degree of normal gastroesophageal reflux (ie, retrograde movement of gastric acid contents through the LES into the esophagus) about once every hour, such episodes are not generally associated with pathologic signs or symptoms. Heartburn may occur, especially after a meal. In most cases, however, such episodes of benign "physiologic" reflux are asymptomatic and characterized by rapid clearance from the distal esophagus.[2]

Pathologic gastroesophageal reflux results in a wide range of symptoms and esophageal pathologic changes characteristic of GERD. Pathologic reflux episodes are more frequent and of longer duration, and they can occur during the day and/or at night. Typically, they lead to chronic symptoms, inflammation, or esophageal mucosal damage.[3] GERD, therefore, is a clinical condition in which the symptoms of gastroesophageal reflux or its effects on esophageal tissue are severe enough to disrupt a patient's life or cause injury to esophageal tissue.

CLINICAL OVERVIEW OF GERD

The pathogenesis of GERD is multifactorial. Pathologic reflux is thought to occur when the injurious properties of refluxed gastric acid, bile, pepsin, and duodenal contents overwhelm normal esophageal protective antireflux barriers, such as esophageal acid clearance and mucosal resistance. The primary underlying mechanism causing pathologic reflux appears to be a defective LES, which increases the volume of acidic gastric contents that refluxes into the esophagus. This increase in acid volume tips the balance toward pathologic reflux by overwhelming the normal capacity of the esophageal mucosa to tolerate acid.[4]

A minority of patients with GERD (20%) have, as their primary underlying motility disorder, LES incompetence due to either decreased LES pressure (LESP), increased intra-abdominal pressure (as seen with obesity or pregnancy), or a shorter than normal (< 2 to 5 cm) LES.[3] Many patients with GERD, however, have normal LESP. In this group of patients, frequent transient LES relaxation (TLESR) is often

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found as the underlying cause of pathologic reflux.[5] Although the understanding of TLESRs remains incomplete, one of the main triggers is believed to be gastric distention caused by postprandial fullness or intragastric air. Although TLESRs are not more frequent in GERD, a higher proportion of them are accompanied by acid reflux.

While heartburn and acid regurgitation are the most commonly reported symptoms of GERD, they are not the only associated symptoms. Pathologic acid reflux can result in a wide spectrum of GERD clinical presentations, including dysphagia/odynophagia and noncardiac chest pain. Important extraesophageal symptoms include laryngitis, pharyngitis, chronic sinusitis, dental erosions, asthma, and chronic cough. Laryngeal or pulmonary symptoms, such as laryngitis, hoarseness, noncardiac chest pain, or asthma, can occur as a result of gastric acid reflux into the throat and vocal cords or down into the lungs. Pharyngitis can occur as a result of gastric acid reflux into the back of the throat, causing inflammation. Acid reflux due to GERD can also erode teeth.

While GERD is usually nonprogressive, in a minority of cases disease progression is associated with the development of complications. The range of GERD complications includes esophagitis, bleeding, esophageal erosions and ulcerations, stricture formation, Barrett's esophagus, and adenocarcinoma of the esophagus. Reflux-induced injury to esophageal tissue can result in tissue destruction and the development of esophageal erosions or ulcerations. Esophageal scarring, involving fibrous tissue deposition as a protective response to ulceration, can lead to the development of esophageal stricture. Replacement of ulcerated squamous epithelium by a metaplastic intestinal-type epithelium characterizes the development of Barrett's esophagus.

Barrett's esophagus, a serious complication of reflux esophagitis in severe, long-standing GERD, has been linked to a significant increase in the risk of esophageal adenocarcinoma.[6] In fact, symptomatic reflux has been identified as a strong risk factor for esophageal adenocarcinoma. In a population-based case-control study, a high percentage of esophageal adenocarcinoma cases were attributable to symptomatic reflux.[7] The complications of GERD are discussed in detail in the third article in this supplement.

GERD may also be a temporary condition associated with a specific triggering factor (eg, pregnancy), disappearing once that factor is removed. More typically, however, GERD is a chronic condition requiring continued management using medications (see the final article in this supplement) and lifestyle modifications. Selected patients with severe disease may benefit from surgery to prevent relapse.

A number of factors have been identified that suggest early recurrence: a hypotensive LES, long-standing symptoms, the need for long-term treatment to achieve initial symptom relief and healing, esophagitis having a high initial endoscopic grade, hiatal hernia, and the presence of persistent symptoms despite endoscopically documented esophagitis healing.[8] Pharmacotherapy, particularly the use of antisecretory agents, has probably modified the natural history of GERD. Proton pump inhibitor (PPI) use, in particular, has had an enormous impact on treatment, in providing significantly improved erosive esophagitis healing rates and better symptom control.[9]

Without maintenance therapy, most patients with erosive GERD, especially those with the greatest disease severity, will experience relapse within 3 months. Prompt recurrence has also been seen among a majority of patients receiving histamine$_2$-receptor antagonists (H_2RAs) for maintenance of esophagitis healing. Among patients with more mild esophagitis, relapse rates of 50% to 90% have been reported.

Among patients with nonerosive esophagitis but frequent heartburn, a symptom relapse rate of 75% was seen at 6 months.[10] Additional data from small studies of limited duration suggest that a minority of patients with nonerosive GERD will progress to erosive GERD. This finding needs to be confirmed, however, in larger studies of longer duration.[9] Therefore, an initial negative endoscopy does not preclude the development of erosive disease.

Compared with the pathophysiology, symptoms, and clinical course of GERD, the impact of GERD on quality of life is perhaps less well recognized. Numerous studies have documented how GERD reduces quality of life and the way in which effective treatment can yield significant benefit in measures of patient functioning and well-being.

PATHOGENESIS AND PATHOPHYSIOLOGY

A multifactorial etiology

Some degree of gastroesophageal reflux occurs normally in most individuals **(Figure 1)**. GERD is thought to develop when a combination of conditions occurs to increase the presence of refluxed

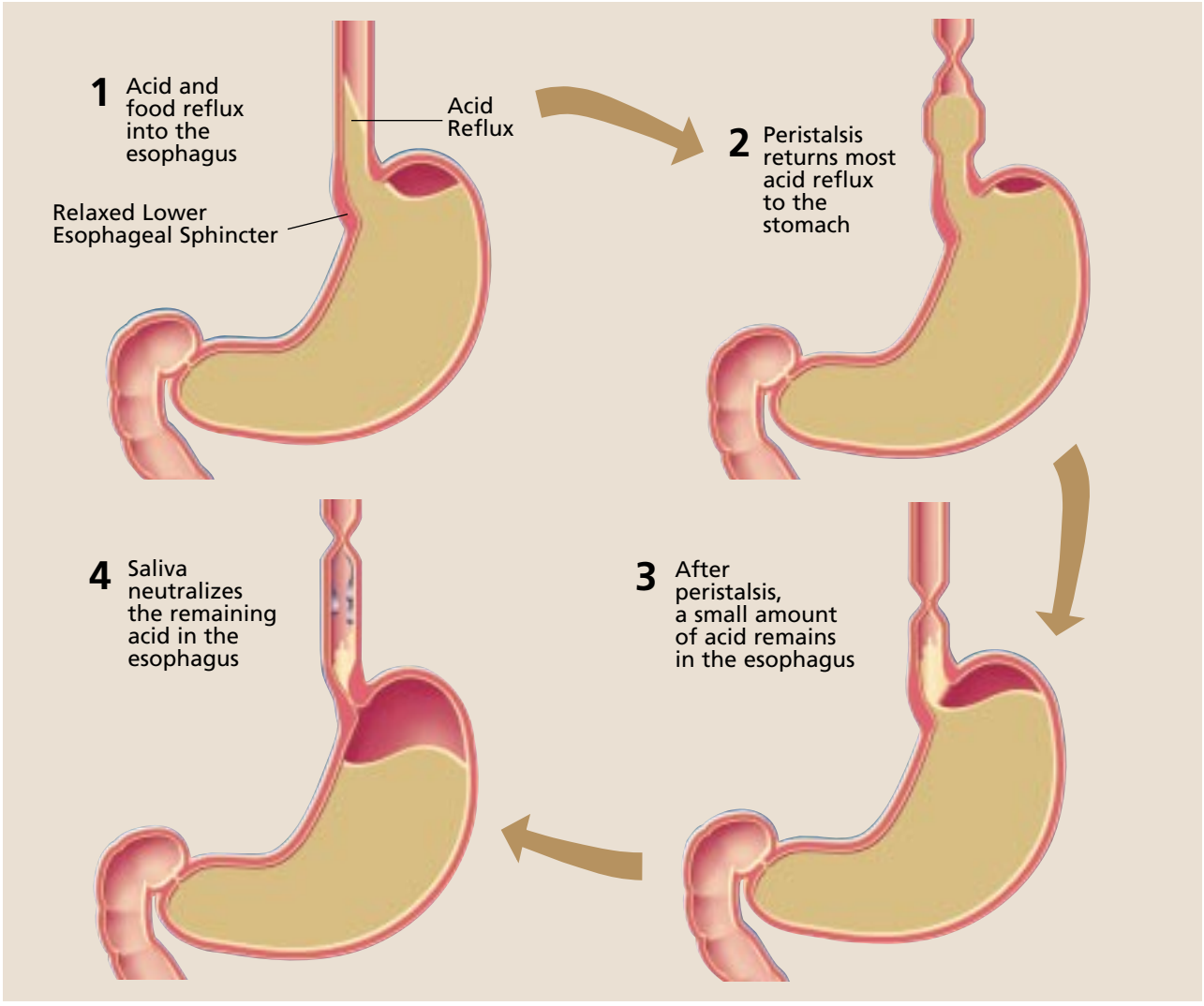

FIGURE 1. What happens during nonpathologic reflux.

acid in the esophagus to pathologic levels.[3] Aggressive mechanisms potentially harmful to the esophagus overwhelm protective mechanisms such as esophageal acid clearance and mucosal resistance, which normally help to maintain a physiologically balanced state. In this way, the pathogenesis of GERD is similar to that of other acid-secretory diseases, such as duodenal ulcer disease and gastric ulcer disease.[11]

Among the mechanisms thought to contribute to the development of GERD are TLESRs or decreased LES resting tone, impaired esophageal acid clearance, delayed gastric emptying, decreased salivation, and impaired tissue resistance **(Figure 2)**. Recent data also support the importance of the potency of the gastric refluxate as a contributory factor in some circumstances.[12] A significant defect in any one of these forces can alter the balance from a compensated state to a decompensated one. Manifestations of the decompensated state include symptoms and complications such as heartburn and esophagitis.[13]

Excessive acid reflux due to TLESRs is the most common causative mechanism **(Table 1)**.[14] A pathologically decreased LES resting tone is more common among patients with severe GERD, especially those with esophageal strictures or Barrett's esophagus.

Esophageal motility abnormalities (impaired peristalsis) are also commonly associated with severe esophagitis **(Figure 3)**.[15] Among both normal individuals and those with GERD, gastric disten-

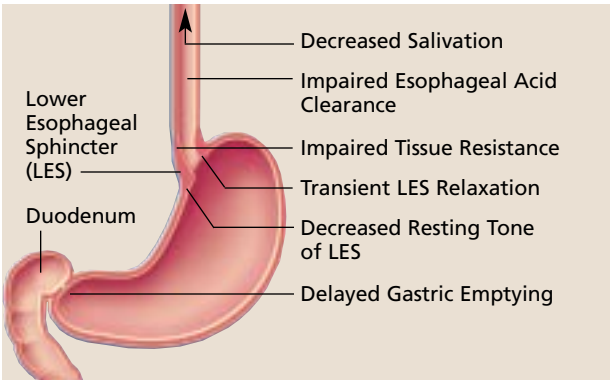

FIGURE 2. Possible etiologic factors involved in GERD.

TABLE 1
Mechanisms of gastroesophageal reflux in normal volunteers and in patients with GERD

Type	Normal volunteers	Patients with GERD
Transient lower esophageal sphincter relaxations (TLESRs)	94%	65%
Transient increase in intra-abdominal pressure	5%	17%
Spontaneous free reflux	1%	18%

tion is thought to contribute to the increase in reflux by significantly increasing the rate of TLESRs.[16] Thus, it is thought to be the trigger for TLESRs **(Figure 4)**.[17]

Secondary causes of GERD include reflux caused by acid hypersecretory states such as Zollinger-Ellison syndrome; connective-tissue disorders such as scleroderma; gastric outlet obstruction as caused by ulceration and stricture; and delayed gastric emptying due to conditions such as gastric stasis, neuromuscular disease, idiopathic gastroparesis, pyloric dysfunction, duodenal dysmotility, or duodenogastroesophageal bile reflux.

Increased intragastric pressure leading to GERD can be caused by obesity, pregnancy, or disruption of the normal receptive relaxation of the stomach following an increase in gastric volume.[3] Most patients with complicated GERD have a hiatal hernia, which, by displacing the LES segment of the distal esophagus, both reduces LES pressure and impairs acid clearance.[12]

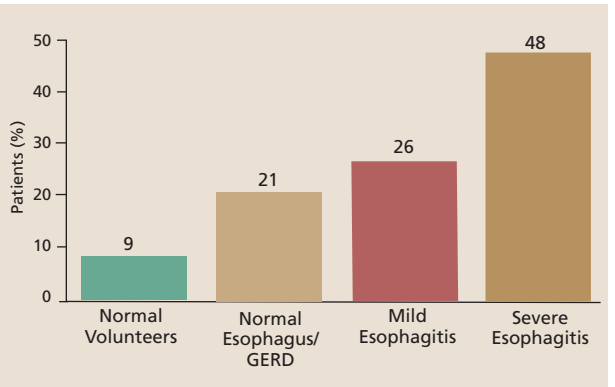

FIGURE 3. Proportion of subjects with esophageal motility abnormalities, by increasing severity of esophagitis. Reprinted from reference 15 with permission from the American Gastroenterological Association.

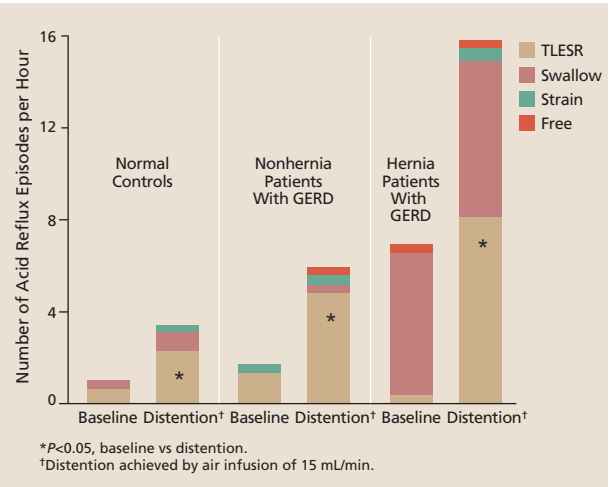

FIGURE 4. Relationship between gastric distention, the number of acid reflux episodes, and the reflux mechanism (TLESR = transient lower esophageal sphincter relaxation). Reprinted from reference 17 with permission from the American Gastroenterological Association.

Once reflux has occurred, impaired acid clearance prolongs exposure of the mucosa to the damaging effects of the refluxate.[16] Diminished peristaltic clearance is seen among approximately one half of patients with severe GERD.[15] Acid clearance is particularly impaired in patients with hiatal hernia.

Lower esophageal sphincter dysfunction

Perhaps the dominant pattern of dysfunction among patients with mild disease is an increased proportion of TLESRs accompanied by reflux. Patients with more severe disease typically have impaired LES resting tone, associated with a weak sphincter or other factors underlying a persistently reduced LES pressure.

TABLE 2
Substances that influence lower esophageal sphincter pressure (LESP)

	Increase LESP	Decrease LESP
Hormones	Gastrin, motilin, substance P	Secretin, cholecystokinin, glucagon, gastric inhibitory polypeptide, vasoactive intestinal polypeptide, progesterone
Neural agents	Alpha-adrenergic agonists, beta-adrenergic antagonists, cholinergic agonists	Alpha-adrenergic antagonists, beta-adrenergic agonists, cholinergic antagonists, serotonin
Medications	Metoclopramide, domperidone, prostaglandin $F_{2\alpha}$, cisapride	Nitrates, calcium channel blockers, theophylline, morphine, meperidone, diazepam, barbiturates
Foods	Protein	Fat, chocolate, ethanol, peppermint

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Normal LES function. The LES is a 3-cm to 4-cm segment of tonically contracted smooth muscle located at the gastroesophageal junction. It is one of two muscular valves located at either end of the esophagus that protect the airway from the reflux of injurious gastric contents. The LES is an anatomically complex zone, comprising two components: the true LES in the distal esophagus and the crural portion of the diaphragm. Both the LES and the diaphragm contribute to gastroesophageal sphincter competence. The LES must be dynamic to protect against reflux in a variety of situations, including swallowing, recumbency, and abdominal straining.

In normal digestion, relaxation of the LES prior to contraction of the esophagus allows food to pass through into the stomach. Constriction of the LES prevents regurgitation of stomach contents (food and acidic stomach juices) into the esophagus. Tonic contraction of the LES is a property of the muscle itself as well as its extrinsic innervation. Both myogenic and neurogenic mechanisms are involved in maintaining LES resting tone. LES tone is maintained or increased by release of acetylcholine. Relaxation of the LES occurs in response to nitric oxide release, as seen in response to swallowing.

In the resting state, the LES maintains a high-pressure zone that is 15 mm Hg to 30 mm Hg above intragastric pressures, depending on individual variability. Normal LESP varies with breathing, body position, and movement, in response to intra-abdominal pressure and gastric distention. The crural diaphragm can augment LESP to help prevent reflux during inspiration, when pressure in the intrathoracic region decreases. LESP also exhibits significant diurnal variation: it is lowest in the daytime and during the postprandial period and highest at night.[3] LESP is also influenced by various drugs, foods, and hormones **(Table 2)**.[13]

Transient lower esophageal sphincter relaxations. TLESRs are brief episodes of LES relaxation that are unrelated to swallowing or peristalsis **(Figure 5)**.[18,19] Lasting approximately 10 seconds to 35 seconds, TLESRs decrease LESP to the gastric level.[3] They occur via stimulation of vagal sensory and motor nerves in response to gastric distention.[2] Seen among individuals both with and without GERD, TLESRs do not always result in gastroesophageal reflux. Nevertheless, they are strongly associated with both physiologic and pathologic reflux.[20,21] In experiments involving simultaneous measurement of LESP and esophageal pH, most reflux episodes were found to be caused by spontaneous complete relaxations of an otherwise normal LES.[20]

In fact, TLESRs account for the vast majority of nonpathologic (ie, physiologic) reflux events. Peristalsis returns approximately 90% of refluxed acidic material to the stomach, and the remaining acid is neutralized by swallowed saliva during successive swallows. Among patients with GERD, TLESRs are considered the primary underlying cause of pathologic reflux in the presence of a normal resting tone. Patients with GERD have an equal frequency of TLESRs compared with normal individuals, although they have a higher percentage of TLESRs associated with reflux.[22] Thus, the time that gastric acid remains in contact with the esophageal mucosa is increased in patients with GERD, increasing their risk of symptoms and esophageal injury.

The proportion of reflux episodes due to TLESRs varies with GERD severity. Among healthy individuals, or those with GERD but no esophagitis, reflux occurs almost exclusively during TLESRs. In patients with erosive or ulcerative esophagitis, reflux occurs during TLESRs in only about one third of episodes. Data from a recent study comparing excess reflux among patients with GERD with and without a hiatal hernia show that TLESRs accounted for 32.8% of reflux episodes among patients with a hiatal hernia, compared with 60.2% among those without a hiatal hernia.[23]

Decreased LES resting tone. A minority of patients with GERD have a constantly weak, low-pressure LES, which permits reflux every time the pressure in the stomach exceeds the LESP. Among patients with such a defect, the absolute LESP necessary for GERD is less than 6 mm Hg.[12] A chronically decreased LES resting tone is usually associated with severe esophagitis. Severe impairment in basal LES tone may lead to more severe disease by allowing gastric contents to pass freely into the esophagus when the patient is supine.[8] Similarly, LES defects have been found among many patients with other GERD complications, such as esophageal stricture and Barrett's esophagus.

Factors that decrease LES tone include endogenous hormones (eg, progesterone in pregnancy), medications, and specific foods.[2] In patients with hiatal hernia, the true LES and the crural diaphragm are separated, which impairs acid clearance.

Increased esophageal acid exposure

Esophageal acid exposure is the percentage of time within a 24-hour period in which esophageal pH is less than 4. The degree of esophageal mucosal injury and the frequency and severity of symptoms such as heartburn, regurgitation, and pain are determined by the degree and duration of esophageal acid exposure. Esophageal acid exposure, in turn, is related to the pH of the refluxed gastric material.[24]

Among most patients with mild disease, esophageal acid exposure occurs predominantly during postprandial periods.[21] The pattern of esophageal acid exposure, in fact, has been linked to increasing GERD severity. Among 401 patients with increased esophageal acid exposure, divided into four groups according to their pattern of reflux (ie, postprandial, upright, supine, or bipositional), the risk of severe GERD increased progressively with the different reflux patterns, from postprandial to upright to supine to bipositional.[25]

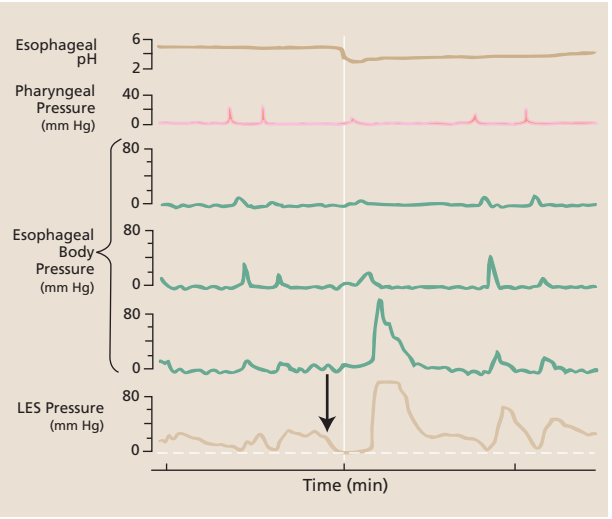

FIGURE 5. Gastroesophageal reflux occurring during transient lower esophageal sphincter (LES) relaxations. Shortly before reflux occurs (white vertical line), the LES abruptly relaxes (arrow) without an antecedent swallow. Intragastric pressure is indicated by the horizontal broken line. Reprinted from Gut 1988; 29:1020–1028,[19] with permission from the BMJ Publishing Group.

Normal acid clearance. The process of normal acid clearance involves peristalsis as well as the swallowing of salivary bicarbonate. Peristalsis clears gastric fluid from the esophagus, whereas the swallowing of saliva (pH of 7.8 to 8.0) neutralizes any remaining acid. Both primary and secondary peristalsis are essential mechanisms of esophageal clearance. Voluntary induced primary peristalsis occurs approximately 60 times per hour. Secondary peristalsis occurs in the absence of a pharyngeal swallow and can be elicited by esophageal distention or acidification, which occurs with acid reflux.[3] Salivation is crucial to the completion of esophageal acid clearance and the restoration of esophageal pH. Gravity also plays an important role in esophageal acid clearance.

Impaired acid clearance. Ineffective esophageal acid clearance increases esophageal acid exposure time in patients with GERD. In experimentally induced or spontaneous reflux, patients with GERD have been found to have acid clearance times that are two to three times longer than those of persons without GERD.[13] Impaired esophageal clearance can be caused by an increase in volume of the refluxate. Rarely, impaired esophageal acid clearance may be due to an underlying disease such as scleroderma. In some patients, esophageal body dysfunction can sub-

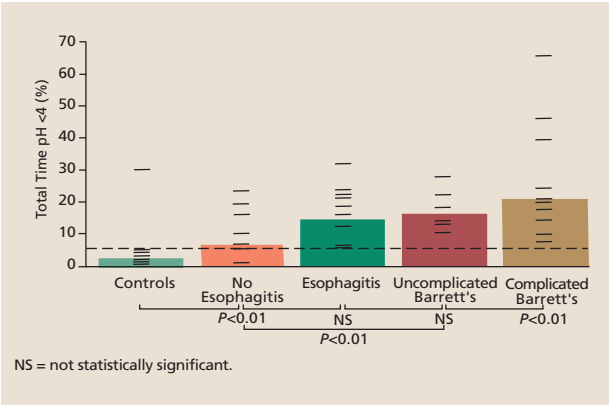

FIGURE 6. Duration during which pH was less than 4 among healthy controls and patients with various grades of GERD. Dashes represent data points for individual subjects; colored bars represent median value for the respective subject group. Horizontal dashed line represents the upper limits of normal acid reflux. Reprinted from reference 28 with permission from the American Gastroenterological Association.

stantially prolong the dwell time of acidic gastric contents in the esophageal lumen.[21]

Two mechanisms of impaired volume clearance have been identified: peristaltic dysfunction and re-reflux. Peristaltic dysfunction is characterized by failed peristalsis and low-amplitude contractions. Failed peristaltic contractions and hypotensive (< 30 mm Hg) peristaltic contractions lead to incomplete esophageal emptying.[26] Decreased amplitude of secondary peristaltic waves and segmental contractions have been demonstrated among some patients with GERD. Peristaltic dysfunction often increases with increasing severity of esophagitis. Re-reflux is associated with certain hiatal hernias, and certain types of hernias also impair esophageal emptying to varying degrees.[13]

The completion of esophageal acid clearance with restoration of esophageal pH depends on salivation. Normally, saliva can neutralize any residual acid coating the esophagus after a secondary peristaltic wave. Acid clearance is prolonged by a reduced salivary rate or by diminished salivary capacity to neutralize acid. Reduced salivation during, or immediately before, sleep accounts for markedly prolonged acid clearance times.[13] Reduced esophageal acid clearance during sleep appears to be a major causative factor in serious forms of GERD.[27] Reduced frequency of swallowing-induced peristalsis during sleep also prolongs esophageal acid exposure.

Duration of esophageal acid exposure. The duration of esophageal exposure to acid and other digestive juices is the primary cause of GERD symptoms and tissue injury. The longer the esophagus is exposed to acid (and also pepsin), the more severe the disease **(Figure 6)**.[28] Severe erosive esophagitis and Barrett's esophagus are associated with particularly high levels of acid exposure.

Symptom severity also progressively increases as esophageal acid exposure increases, whether patients have erosive esophagitis or a macroscopically normal esophagus.[21]

A pH of 4 appears to be the optimal threshold for differentiating between aggressive and nonaggressive reflux throughout a 24-hour period.[29] This was demonstrated in a meta-analysis of GERD treatment trials in which gastric acid suppression data were compared with clinical outcomes, showing that greater control of 24-hour intragastric acidity (determined by the length of time that intragastric pH was greater than 4) significantly improved healing rates at 8 weeks ($P < 0.05$).[19] However, symptom relief sometimes requires 24-hour control of intragastric acidity, since GERD patients can experience gastroesophageal reflux at any time of day.[24] These findings are reflected in the treatment goal of antisecretory agents, namely, to reduce esophageal acid exposure. If the intraesophageal pH can be maintained at or above 4 for the majority of a 24-hour period, most patients will remain symptom-free and experience complete healing of erosive lesions.

Characteristics of the refluxate. The development of GERD symptoms and the potency of the gastric refluxate (primarily acid and pepsin) in causing mucosal injury are highly dependent on intragastric pH and the amount of time the refluxate is in contact with the mucosa. Esophageal clearance time is also influenced by the pH of the refluxate. The lower the pH, the more time is needed for intraesophageal pH to return to 4 or above.[21]

The relationship between the degree of acidity and pain sensation was explored in a study by Smith and colleagues.[30] They observed a positive correlation between the time elapsed before esophageal pain was experienced and the pH of an infused solution. The most significant difference was found between pH 2 and pH 4. Between these acidity levels, the elapsed time to pain sensation increased progressively, eventually leveling off at a pH greater than 4.[30]

Similarly, the degree of mucosal damage can be markedly accelerated if the luminal pH is less than 2 or if pepsin is present in the refluxate. Studies have shown that the combination of acid and pepsin is

most injurious to esophageal mucosa.[12] The intragastric acidity threshold of pH 4 differentiates between aggressive and nonaggressive reflux in part because gastric refluxate with a pH less than 4 contains active pepsin. The enzymatic activity of pepsin is dependent on pH, and it is activated in an acidic environment. Refluxed bile or alkaline pancreatic secretions, however, may contribute in some cases. Increased amounts of bile acids have been found in the refluxate of GERD patients, especially those with Barrett's esophagus.[12] A recent study indicates, however, that isolated bile reflux does not result in esophagitis.[31] Pepsin is clearly the dominant player. The causative role of bile has not been established.

These observations have immediate clinical benefit. Antisecretory drugs have become the principal approach for treating reflux symptoms and esophagitis because they reduce the acidity of gastric juice and the activity of pepsin. They also reduce the volume of gastric juice available for reflux into the esophagus.[32]

The role of hypoacidity has also been demonstrated in new studies suggesting that colonization with *Helicobacter pylori* may protect against severe esophagitis and Barrett's esophagus. This protection is presumed to occur via mechanisms that promote hypoacidity. Eradication of *H pylori*, consequently, may aggravate GERD in susceptible patients.[12]

Timing of esophageal acid exposure. Among the majority of patients with GERD who have mild erosive esophagitis or no endoscopic abnormality, most reflux occurs after meals. Relatively little reflux occurs during the night. With increasingly severe cases of esophagitis, acid exposure progressively increases, primarily because of an increase in nocturnal reflux. Nighttime is also the longest period of unbuffered gastric acid secretion, owing to reduced acid neutralization by salivary bicarbonate during sleep. In addition, esophageal acid exposure clearance is reduced because of sleep's effects on esophageal motility.[21]

Other etiologic factors

Delayed stomach emptying. Delayed gastric emptying is present in 10% to 15% of patients with GERD.[12] It is believed to contribute to the development of a small proportion of cases by increasing the amount of fluid available for reflux and by the associated constant gastric distention. Potential causes of impaired gastric emptying include gastroparesis, as seen in patients with diabetes, and partial gastric outlet obstruction.[33]

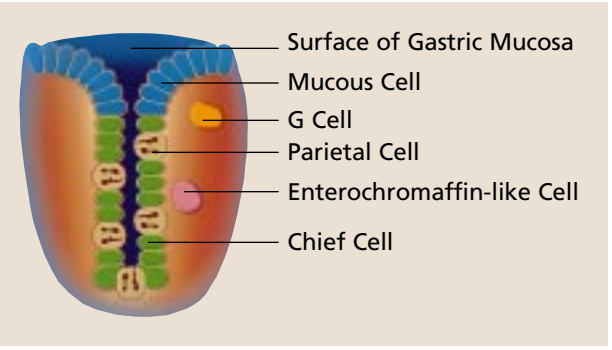

FIGURE 7. Schematic presenting a microscopic view of the gastric mucosa.

Impaired mucosal resistance. The ability of the esophageal mucosa to withstand injury is a determining factor in the development of GERD. Age and nutritional status seem to influence the ability of the mucosa to withstand injury. Esophageal tissue resistance to acid consists of cell membranes and intercellular junctional complexes, which protect against injury by limiting the rate of diffusion of hydrogen ions into the epithelium. The esophagus also produces bicarbonate and mucus. Bicarbonate buffers the acid, and mucus forms a protective barrier on the epithelial surface.

The sensitivity of the esophageal mucosa to damage from acid, pepsin, or bile is rather high. The level of resistance of the esophageal mucosa to acid damage is far less than that of the stomach lining. Esophageal damage occurs because the level of acid and pepsin present exceeds the level of mucosal protection. Pepsin in the acid refluxate can damage the esophageal mucosa by digesting epithelial protein. Enhanced mucosal sensitivity to acid can also be seen in association with chronic heartburn symptoms.[34]

Gastric acid production and regulation

Acid production by parietal cells. Deep within the lining of the stomach lie collections of cells organized into gastric glands, which secrete various substances into the stomach **(Figure 7)**, including mucus, hydrochloric acid (HCl), the hormone gastrin, histamine, pepsinogen, and intrinsic factor. Mucous cells, within gastric pits that open onto the surface of the stomach, secrete mucus. Specialized parietal cells, located in the deeper part of the gland, secrete HCl. Parietal cells also are thought to secrete intrinsic factor, which is needed for vitamin

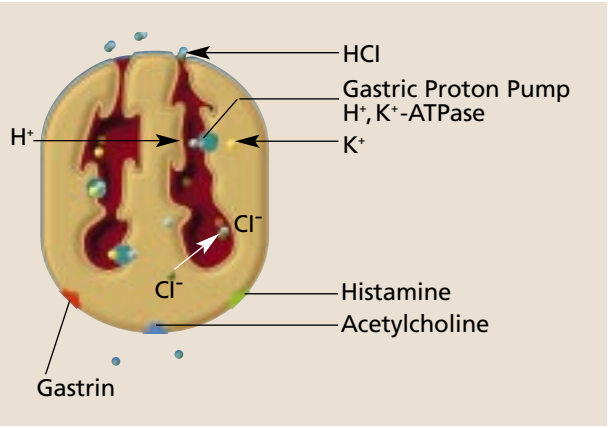

FIGURE 8. The gastric proton pump. The H^+, K^+-ATPase molecule, or gastric proton pump, exchanges H^+ for K^+, which, followed by the passive movement of Cl^- into the parietal cell lumen, leads to the production of HCl. Acid production within the parietal cell can be stimulated by the binding of gastrin, acetylcholine, or histamine to specific receptors on the cell surface.[42]

B_{12} absorption. G cells, located predominantly in the antrum of the stomach, secrete gastrin. Histamine is secreted by enterochromaffin-like cells, and chief cells secrete pepsinogen.

Parietal cells are stimulated to secrete HCl following activation of receptors for histamine$_2$, acetylcholine, and/or gastrin. When maximally stimulated, parietal cells can secrete HCl at concentrations that can lower the pH of gastric juice to 1 or less.[35] The stomach produces an average of 2 liters of HCl a day, which, in combination with the protein-splitting enzyme pepsin, breaks down chemicals in food.[35]

During a meal, the rate of acid production by parietal cells increases markedly, mediated by vagus nerves. Stomach distention, hydrogen ion concentration, and peptides send messages through long and short neural reflexes to increase gastrin release, which also increases acid production.

Acid regulatory pathways. Acid secretion by parietal cells is controlled by three acid regulatory pathways: the acetylcholine, gastrin, and histamine receptor pathways. These pathways, in turn, are stimulated by food via the vagus nerve. The sight, smell, and taste of food and its physical presence in the mouth, esophagus, and stomach all contribute to the stimulation of gastric acid secretion. Hormones also play a role, as nervous stimulation of cells in the antrum leads to the release of gastrin, which in turn stimulates further acid secretion into the stomach cavity.

Significant interaction and overlap occur among the three pathways. Acetylcholine release is stimulated by the sight, smell, and taste of food. Digested food in the stomach (containing dietary amino acids and proteins) chemically stimulates the release of gastrin from G cells in the gastric antrum. An elevated gastric pH also stimulates the release of gastrin.[36,37] A low gastric pH inhibits gastrin release by inducing the release of somatostatin from antral D cells, which in turn reduces gastrin release from G cells.[38] Stomach distention, triggering the release of acetylcholine, further stimulates G cells to produce gastrin. Gastrin travels through the bloodstream and binds to the gastrin receptor on the parietal cells, located in the gastric body and fundus. Both acetylcholine and gastrin stimulate enterochromaffin-like cells to release histamine.

The binding of acetylcholine, gastrin, or histamine to its receptor on the parietal cell initiates the process leading to acid production by altering the parietal cell's permeability to calcium ions. The resulting influx of calcium ions increases the intracellular calcium concentration, thereby activating intracellular protein phosphokinases. At the same time, a membrane-bound adenylate cyclase leads to the generation of cyclic adenosine monophosphate, which acts as a second messenger to activate protein phosphokinases.

The final step in gastric acid production occurs via the gastric acid (proton) pump, in the apical membrane of the parietal cell. The low gastric pH maintained by the proton pump allows balance between gastric acidity and mucosal defenses.[39]

The gastric proton pump. The hydrogen-potassium adenosine triphosphatase (H^+, K^+-ATPase) molecule, or gastric proton pump, comprises an enzyme system located on the secretory surface of the gastric parietal cell. It has two major components: a larger (alpha) subunit, containing approximately 1,000 amino acids with both transport and catalytic functions, and a smaller (beta) subunit, consisting of about 300 amino acids with structural and membrane-targeting functions.[40]

Each gastric parietal cell contains about 1 million acid pumps in its cytoplasmic membranes. Following the passive movement of potassium and chloride ions into the secretory canaliculus, the pumps are activated by translocation into canaliculi (resulting from the increase in protein phosphokinases described above) and by activation of a potassium and chloride ion transport pathway.[41] The primary function of the activated pump is to exchange

TABLE 3
The spectrum of GERD manifestations

Chest	Pulmonary	Oral	Throat	Ear
Heartburn	Asthma	Tooth decay	Globus sensation	Earache
Regurgitation	Cough	Gingivitis	Hoarseness	
Chest pain	Aspiration		Laryngitis	
Dysphagia/odynophagia				

hydrogen ions from the cytosol of the parietal cell for potassium ions from the secretory canaliculi using energy derived from the splitting of ATP. In the secretory canaliculus, the chloride ions combine with hydrogen ions to form HCl.

Regardless of the stimulus, the physical production of acid from the parietal cell via H^+, K^+-ATPase is the final common pathway for gastric acid secretion **(Figure 8)**.[42]

Direct inhibition of the proton pump inhibits acid secretion independent of the biochemical pathway involved in its activation. Drugs that target the proton pump are therefore more effective inhibitors of gastric acid secretion than are those that target histamine, gastrin, or acetylcholine receptors on the basolateral surface of the parietal cell. Consequently, PPIs, which inhibit the activity of H^+, K^+-ATPase, have been found to be more potent inhibitors of gastric acid secretion than other similar treatments (see the final article in this supplement).[43]

CLINICAL MANIFESTATIONS

The clinical spectrum of GERD

GERD is characterized by a wide variety of clinical symptoms and presentations, ranging from symptomatic reflux without macroscopic esophagitis to the chronic complications of esophageal mucosal damage.[44] Heartburn is the most common symptom of GERD. In some patients, heartburn may be accompanied by acid regurgitation, odynophagia, and dysphagia. Numerous esophageal manifestations of GERD can occur.

Depending on the extent to which refluxed acid reaches other nearby tissues, other types of symptoms may occur. The spectrum of GERD symptoms, therefore, is diverse **(Table 3)**.

Noncardiac chest pain associated with GERD presents as unexplained angina-type pain that can resemble a myocardial infarction. A wide range of pulmonary and otolaryngologic symptoms can occur.[45] In addition to laryngitis, pharyngitis, chronic cough, asthma, bronchiectasis, recurrent aspiration syndromes, globus, and dysphagia, extraesophageal manifestations of GERD can include nausea and vomiting and erosive changes in dental enamel.[6,46]

Symptom frequency also varies among patients. Some experience daily or weekly symptoms, while others have GERD symptoms a few times per month. Symptom frequency and severity do not correlate with the degree of esophageal mucosal changes apparent on endoscopy.[47] The most common complication of GERD is esophagitis, and its severity ranges from erythema in early disease to the development of endoscopic erosions or ulcerations of varying severity. More serious complications include obstruction caused by esophageal stricture formation, or Barrett's esophagus (see the third article in this supplement).

Complicated GERD is suggested by a number of early warning signs. Slowly progressive dysphagia, particularly for solids, suggests the presence of peptic strictures. Liquid and solid dysphagia suggests a GERD-related motility disorder. Odynophagia (otherwise, rarely present) suggests inflammation or ulceration, most frequently associated with infectious or pill-induced esophagitis. A GERD-related esophageal motility disorder is more often seen in patients who have associated respiratory symptoms. Occasionally, patients present with occult upper gastrointestinal bleeding or with iron-deficiency anemia. If patients have any of these warning signs, they should undergo prompt evaluation to rule out a diagnosis other than GERD.[48]

Heartburn and acid regurgitation

Heartburn is the most common symptom of GERD.

Its classic presentation is that of a retrosternal burning sensation that radiates to the pharynx. It usually occurs after meals (typically 30 to 60 minutes after eating) or upon reclining at night. It can also be aggravated by bending over.[33] Many patients can obtain relief by standing upright or taking an antacid to clear acid from the esophagus.

Heartburn is believed to be caused by acid stimulation of sensory nerve endings in the deeper layers of the esophageal epithelium. If an excessive amount of acid reflux enters the esophagus, prolonged contact with the esophageal lining will injure the esophagus and produce a burning sensation. For heartburn to occur, the refluxate must be sufficiently acidic.

Heartburn as the primary esophageal complaint has a high degree of reliability in diagnosing GERD. Many patients, however, have less-specific dyspeptic symptoms and may or may not have heartburn. Increasing frequency of heartburn (from occasional to occurring more than twice per week) suggests GERD. When both heartburn and regurgitation are present, a diagnosis of GERD can be made with greater than 90% certainty.[48] Patients who have both symptoms and acid reflux but normal esophageal acid exposure have been classified as having functional heartburn or "acid-sensitive esophagus." Patients with Zollinger-Ellison syndrome, however, may present with GERD symptoms only. Both heartburn and regurgitation are considered classic symptoms of GERD.[49]

Acid regurgitation is the effortless return of acidic gastric contents into the esophagus without nausea, wretching, or abdominal contractions. Like heartburn, regurgitation usually occurs after meals, especially after large ones, and may be exacerbated by recumbency, straining, or bending over.[50] If reflux of injurious acidic gastric contents extends beyond the esophagus to the lungs, larynx, pharynx, or oral cavity, extraesophageal GERD symptoms can occur.

Dysphagia and odynophagia

Dysphagia is the perception of impaired movement of swallowed material from the pharynx to the stomach. It affects more than 30% of patients with GERD. Its possible causes include peristaltic dysfunction, inflammation, peptic stricture, or a Schatzki ring.[15] Alternatively, if no physical abnormality is found, the cause may be abnormal esophageal sensitivity to movement of the bolus during peristalsis.[13]

Oropharyngeal dysphagia is the perception of impaired movement of a bolus from the oropharynx to the upper esophagus, whereas **esophageal dysphagia** is the perception of impaired transit through the esophageal body. The distinction can usually be made from a careful history.[33] Among patients with significant GERD, dysphagia is not uncommon and may indicate esophageal stricture. Among those with severe or recent-onset dysphagia, esophageal cancer must be ruled out.

Odynophagia is a sharp substernal pain that occurs during swallowing. The pain may be so severe as to limit oral intake. The cause of odynophagia is esophageal ulceration, especially in the setting of infectious esophagitis. It may also be caused by corrosive injury from ingestion of caustic substances or by pill-induced ulcers.[33]

Noncardiac chest pain

Noncardiac chest pain refers to unexplained substernal chest pain resembling a myocardial infarction without evidence of coronary artery disease. GERD is the most common gastrointestinal cause of noncardiac chest pain. The proximity of the esophagus to the heart and its shared visceral enervation are believed to be underlying factors. Pain is thought to occur as a result of stimulation of chemoreceptors or by esophageal distention. Actual microvascular angina independent of reflux might also be the cause.

Noncardiac chest pain can be sharp or dull and can radiate widely into the neck, jaw, arms, or back. One should also remember that substernal chest pain can be caused by cardiovascular disease. The patient's response to exercise is one aspect of the history that can help distinguish heartburn from heart disease or a myocardial infarction. Pain resulting from heart disease can be aggravated by exercise and possibly relieved by rest. Heartburn is less likely to be associated with physical activity, with the possible exception of bending over, which sometimes exacerbates heartburn.

Extraesophageal symptoms

Extraesophageal complications of GERD (see the following article in this supplement) have become increasingly well recognized. In up to half of the patients with such symptoms, GERD can be a causative or an exacerbating factor, especially if the symptoms are refractory. Because many of these patients do not experience the classic GERD symptoms of heartburn or regurgitation, the diagnosis is

often overlooked.[33] In many cases, the diagnosis rests on the outcome of empiric treatment.[2]

The most common extraesophageal symptoms associated with GERD are noncardiac chest pain, chronic hoarseness, chronic cough, and asthma.[51] Acid reflux into the lungs causes pulmonary symptoms such as chronic cough, intermittent wheezing, asthma, bronchitis, aspiration or recurrent pneumonia, and interstitial fibrosis. Acid reflux that reaches the mouth can erode dental enamel, causing tooth decay. Other oral symptoms include gingivitis, halitosis, aphthous ulcers, and water brash. Acid reflux into the throat causes sore throat and globus sensation. Vocal cord inflammation can produce chronic posterior laryngitis and hoarseness. Otalgia and hiccups are other possible extraesophageal symptoms.[48]

Symptom relapse and chronicity

We know that patients with reflux esophagitis have a high rate of endoscopic and symptomatic relapse if therapy is discontinued or if the drug dosage is decreased. Patients with higher grades of esophagitis are particularly likely to experience a recurrence if they are not given effective maintenance therapy. Data from numerous studies have yielded a recurrence rate of 80% or more (without maintenance therapy) within 6 months of discontinuing therapy among patients with relatively severe esophagitis.[52]

Acid suppression therapy can control symptoms and heal erosive esophagitis. Because it cannot correct underlying motility problems, however, relapse is common once treatment is discontinued. Even among patients with extraesophageal symptoms, symptom recurrence is common within months of discontinuing therapy. The clinical impression associated with GERD, therefore, is one of chronicity, although the expression of disease chronicity differs among patients. Most patients, particularly those with erosive esophagitis or extraesophageal disease, require continuous medical therapy or surgery for adequate symptom relief.[48]

EXACERBATING FACTORS

Potential GERD triggers or exacerbating factors include dietary and lifestyle factors (including specific foods, eating habits, obesity, alcohol consumption, smoking, physical activity, and sleeping position) as well as pregnancy, hormones, hiatal hernia, and certain medications.

While some of these factors are thought to play a significant and documented role in GERD pathogenesis or pathophysiology, others, primarily dietary and lifestyle factors, lack convincing or consistent documentation of a role in triggering or worsening GERD symptoms. This is because of the nature of the studies conducted, which have been generally small and inconclusive and have yielded conflicting results in different patient groups. The treatment of GERD, however, is oriented toward the individual patient's symptoms, and in practice this includes providing specific advice regarding individual dietary intolerances and lifestyle factors.[53]

A careful history can help to identify specific factors in individual patients, to avoid unnecessarily restricting patients who might not benefit from such measures. Therefore, while little consistent data support the role of lifestyle modifications alone as an effective treatment, avoidance of exacerbating factors can be helpful for individual patients.

Meals and specific foods

Meals are the major aggravating factor of GERD symptoms, since they stimulate the production of gastric acid available for reflux into the esophagus. Food in general (and large meals in particular) induces TLESRs. Meals eaten within 2 to 3 hours of bedtime (which increase acid availability at nighttime), or with alcohol, can predispose patients to nocturnal reflux.[48] Dietary fat in the duodenum also appears to be a strong reflux trigger, in part by impairing gastric emptying. In a recent study, however, no difference in postprandial LESP and GERD was seen among 12 healthy volunteers after consuming a high-fat meal compared with an isocaloric and isovolumetric low-fat meal.[54] The study authors concluded that it was inappropriate to advise patients to reduce the fat content of their meals, as least with regard to GERD symptom relief.

Specific foods that have been identified as potentially aggravating factors in certain patients include raw onions, chocolate, caffeine, peppermint, citrus juices, alcoholic beverages, tomato products, and spicy foods. Peppermint and chocolate are thought to lower LES tone, facilitating reflux. Citrus juice, tomato juice, and probably pepper can irritate damaged esophageal mucosa. Cola drinks, coffee, tea, and beer can have an acidic pH, lowering LESP to precipitate symptoms. Potential esophageal irritants should be restricted.[48]

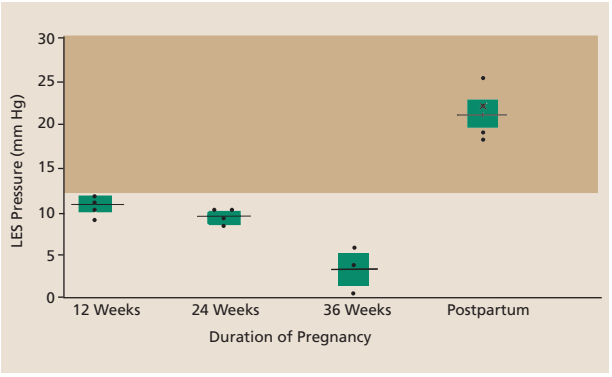

FIGURE 9. Effect of pregnancy on lower esophageal sphincter (LES) pressure. LES pressure data were recorded from 4 women during pregnancy and the postpartum period. The mean ± SEM for each time period is represented by the horizontal bars and green shaded areas. The area shaded in gold represents the range of LES pressures in normal nonpregnant women. Reprinted from reference 60 with permission from the American Gastroenterological Association.

Body weight

Obesity is thought to be another potential predisposing factor to gastroesophageal reflux or GERD, although data are somewhat conflicting. In a risk-factor analysis of a random sample of 1,524 residents of Olmsted County, Minn., obesity (body mass index > 30 kg/m^2) was found to be a strong risk factor for GERD.[55] In addition to obesity, other risk factors independently associated with frequent (at least weekly) symptoms included family history (suggesting a genetic component to GERD), a history of smoking, frequent alcohol consumption (> 7 drinks per week), and a higher degree of psychosomatic symptoms.[55]

A recent population-based study in Sweden among 820 adults conflicts with these findings. The Swedish researchers found no association between body weight and the severity or duration of reflux symptoms. They concluded that weight reduction might not be justifiable as an antireflux therapy.[56] Even so, it is commonly believed that weight reduction and exercise can have a favorable impact on reflux in obese persons. Others have found a significant association between weight loss and improvement of GERD symptoms, and recommend weight loss as a component of first-line management.[57]

Pregnancy

Pregnancy is the most common condition predisposing to GERD and is generally associated with symptomatic GERD (typically heartburn) rather than esophagitis.[58] Because heartburn affects approximately two thirds of all pregnancies, it is considered by many to be a normal occurrence during pregnancy. In most cases, symptoms occur for the first time during the pregnancy and subside soon after delivery. Recurrence is also a possibility with subsequent pregnancies. While symptoms may occur throughout the pregnancy, data are conflicting on whether they occur more frequently during the first and second trimesters or during the third.[59]

While the pathogenesis is thought to be multifactorial, the primary pathophysiology of GERD during pregnancy is probably that of decreased LESP resulting from the effects of progesterone and estrogen on LES function **(Figure 9)**.[58,60] The two hormones appear to act together, with progesterone acting as a mediator of LES smooth-muscle relaxation and estrogen as a "primer" of LES relaxation.[59] Mechanical factors, such as increased abdominal pressure due to enlargement of the uterus, are believed to play a somewhat smaller role. In most cases, patients can be treated with lifestyle and dietary modifications if symptoms are mild. Otherwise, nonsystemic medications (antacids or sucralfate) can also be safely prescribed for symptom relief. Except for severe or intractable cases, systemic therapy during pregnancy should be avoided.[59]

Hiatal hernia

A hiatal hernia is frequently found among patients with GERD.[47] The proximal stomach is dislocated through the hiatus of the diaphragm into the chest, and the crural diaphragm becomes separated from the LES **(Figures 10 and 11)**.[12] Viewed as part of a GERD continuum, a hiatal hernia is another factor disrupting the integrity of the gastroesophageal sphincter, resulting in increased esophageal acid exposure.[61] It may be a factor in GERD pathogenesis, especially if the patient has severe symptoms. Hiatal hernias are present in more than 90% of patients with severe erosive esophagitis, especially if complications are present, such as esophageal stricture or Barrett's esophagus.[33] Hiatal hernias, in fact, are found among most patients with Barrett's esophagus, and they likely contribute to its development.[62] Whether or not the hernia is an initiating factor in GERD, it clearly plays a role in sustaining GERD, accounting for the chronicity of the disease.[63]

Hiatal hernias are thought to promote GERD chronicity via anatomic changes to the gastroesophageal junction that ultimately result in reduced

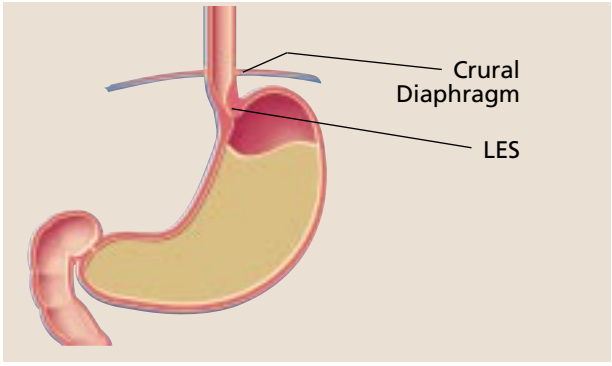

FIGURE 10. Normal antireflux barrier containing the lower esophageal sphincter (LES) and the crural diaphragm.[12]

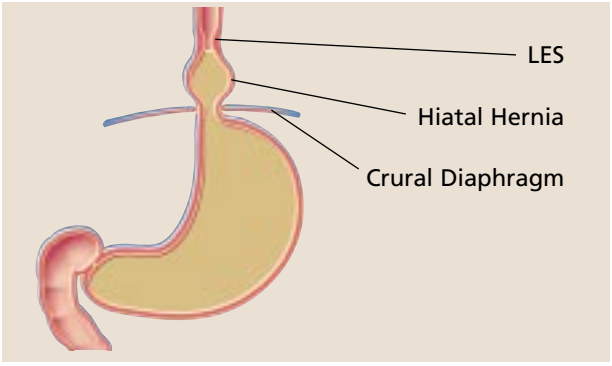

FIGURE 11. Hiatal hernia characterized by separation of the lower esophageal sphincter (LES) from the crural diaphragm.

esophageal acid clearance and increased esophageal acid exposure.[63] Depending on their size, hiatal hernias can displace and disable the diaphragmatic sphincter (the crural diaphragm) to increase susceptibility to reflux during sudden increases in intra-abdominal pressure. Large hiatal hernias also impair esophageal emptying during swallowing, thus prolonging acid clearance time.[61] Esophageal acid clearance might also be impaired by diaphragmatic contractions.[3]

Medications

A wide variety of medications can promote GERD symptoms as a result of their effects on gastric emptying of acid or by reducing LESP to promote reflux.[64] The use of hypnotics, neuroleptics, or antidepressants that affect wakefulness, LES tone, salivation, or esophageal motility may induce or exacerbate symptoms. Medications that can decrease LESP, leading to reflux, include anticholinergics, sedatives or tranquilizers (particularly benzodiazepines), tricyclic antidepressants, theophylline, prostaglandins, dihydropyridine calcium channel blockers (such as diazepam and alprazolam), alpha-adrenergic blockers, beta blockers, and progesterones. Potassium tablets, nonsteroidal anti-inflammatory drugs (NSAIDs), and alendronate can also cause esophagitis.[48]

NSAIDs disrupt tissue resistance, and more-severe cases of esophagitis might be more common among chronic NSAID users. In fact, a small but significant odds ratio of 1.4 for development of reflux esophagitis has been seen among patients with diseases commonly treating using NSAIDs, such as osteoarthritis, back pain, and tension headache.[65] Ingestion of alendronate by patients with osteoporosis can be associated with esophagitis and esophageal ulcer. Damage to the esophagus might occur as a result of toxicity from the medication itself as well as from nonspecific irritation caused by contact between the pill and the esophageal mucosa, as seen in other cases of pill esophagitis.[66]

Smoking

The relationship between cigarette smoking and GERD is somewhat unresolved. It has been controversial for decades, since a high statistical association was reported and subsequently challenged.[67]

A number of potentially contributory factors have been identified. Studies show that smoking decreases LESP, thereby promoting reflux, and predisposes to strain-induced reflux. Indeed, smoking has been found to be related to an increased number of reflux events in association with deep inspiration and coughing. Smoking might promote the movement of bile from the intestine to the stomach, which would increase the harmful properties of the refluxate. Smoking also prolongs acid clearance by inhibiting the secretion of saliva.[67] This increases the risk of direct esophageal injury, given that saliva secretion is normally a crucial component of the esophageal mucosal defenses.

Nevertheless, smoking is not considered a major risk factor for GERD, despite the impact of both smoking and nicotine on major GERD pathophysiologic factors. However, patients should be cautioned against smoking regardless of its possible contribution to GERD. Smoking cessation, in combination with appropriate pharmacologic therapy, could be beneficial.[67]

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