Physiology and Pathogenesis of Gastroesophageal Reflux Disease

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KEYWORDS

• Gastroesophageal reflux disease • GERD • Heartburn • Pathology of GERD
• Pathogenesis of GERD

KEY POINTS

- Gastroesophageal reflux disease (GERD) represents a wide range of pathologic conditions that are poorly understood.
- Reflux of gastric acid most commonly presents as heartburn, but GERD can also be associated with bile (alkaline) reflux, gastric or esophageal distention, and motility disorders.
- Pain associated with gastroesophageal reflux is secondary to the stimulation and activation of mucosal chemoreceptors by acid; the lower esophageal sphincter (LES) plays a vital role in the frequency and severity of GERD.
- Development of Barrett esophagus is believed to be due to repeated and uncontrolled acid exposure of the distal esophagus resulting in metaplasia, which can progress to dysplasia of the epithelium of the distal esophagus.

INTRODUCTION: NATURE OF THE PROBLEM

GERD is a common problem treated by primary care physicians. It is estimated that up to 20% of Americans experience symptomatic GERD weekly and that an even higher percentage of people have heartburn monthly.[1] The cost of managing a disease of this prevalence is substantial, with estimates of direct and indirect costs exceeding $14 billion in the United States, 60% of which is accounted for by medication costs.[2] Although the physiology and pathogenesis of GERD are poorly understood, heartburn, the most common symptom, occurs in most patients and is thought to be due to the stimulation and activation of mucosal chemoreceptors in the distal esophagus.[3] The

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pain associated with heartburn is usually due to gastric acid present in the esophagus, but it can also be due to bile salt irritation of the esophagus, esophageal distention, and motility disorders of the distal esophagus.[4] There has been an alarming increase in the prevalence of GERD in the United States over the past 2 decades, and although the cause is likely multifactorial and our understanding of GERD has improved, 2 factors that seem to have contributed most are the obesity epidemic and improvements in diagnostic techniques, with the routine use of endoscopy becoming more commonplace.[5,6]

The wide range of symptoms from mild to severe heartburn with or without acid exposure in combination with the multifactorial nature of GERD makes understanding this disease challenging. GERD and its associated symptoms occur as the end product of a collection of anatomic and/or physiologic abnormalities. Under normal circumstances, the intra-abdominal pressure is positive, whereas the intrathoracic pressure is negative, a physical principle that should promote reflux of gastric contents into the esophagus. Not surprisingly, small amounts of reflux occur throughout the day in everyone, but pathologic GERD is prevented by the normal anatomy and physiology of the esophagus, LES, diaphragm muscles at the hiatus, and the stomach. In general, pathologic reflux is most commonly a consequence of the breakdown of the normal reflux barrier of the LES, but it can also result from factors that increase the pressure gradient between the abdomen and thorax (eg, morbid obesity and pregnancy) or dysmotility of the esophagus, hiatus musculature, and/or the stomach. This article examines the physiology of GERD and the pathologic conditions resulting from it.

PHYSIOLOGY OF THE DISTAL ESOPHAGUS

The distal esophagus and LES are dynamic and interrelated (**Fig. 1**). The antireflux mechanism of the esophagus consists of the LES, the angle of His, and the muscle fibers of the diaphragm. The LES is 2 to 4 cm in length of the distal esophagus and is composed of tonically contracted circular smooth muscle located within the diaphragm hiatus.[7,8] Gastroesophageal reflux occurs when there is inappropriate relaxation of the LES permitting gastric acid to enter the distal esophagus, stimulating the chemoreceptors and causing irritation, leading to the manifestation of symptoms. In addition, several drugs can alter the LES tone (**Table 1**) and affect the natural defenses of the esophagus to induce heartburn; however, more commonly, many different foods can trigger heartburn (**Box 1**). As mentioned, other key contributors to reflux in addition to the drugs and foods listed are factors that increase intra-abdominal pressure, overcoming the antireflux barrier, such as pregnancy or obesity.[9]

The LES is a circular muscle layer of the distal esophagus that generates a resting pressure higher than the intra-abdominal pressure.[7] The LES resting pressure is normally sufficient to prevent reflux of gastric contents into the esophagus thereby preventing symptomatic heartburn, but during times of increased abdominal pressure (ie, Valsalva maneuver, lifting, Trendelenburg position, and pregnancy) other mechanisms aid in preventing reflux.[10] The left and right crural muscles of the diaphragm constitute the second mechanism of defense to protect the esophagus from reflux. The crural muscles and the LES are anatomically connected by the phrenoesophageal ligament (**Fig. 2**) and give the esophagus 2 distinct but interactive mechanisms to prevent reflux of stomach contents into the esophagus.[11]

Swallowing is a complex physiologic process that results in the propulsion of the food bolus from the pharynx into the esophagus and then into the stomach. This process can be started consciously or reflexively by stimulation of areas of the mouth or pharynx. Pharyngeal activity during swallowing stimulates the esophageal phase and

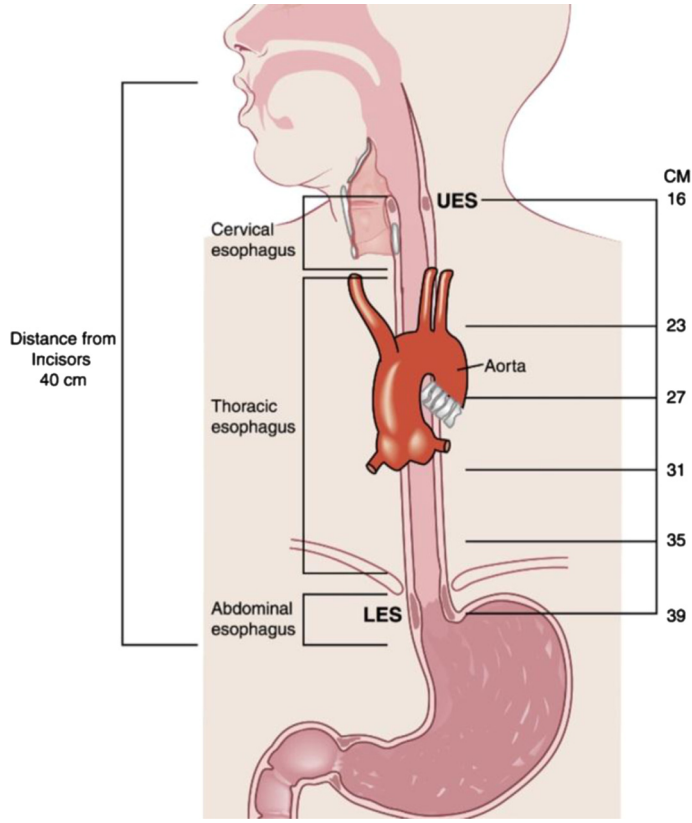

Fig. 1. Schematic view of the esophagus. The esophagus is approximately 40 cm from the incisors to the bottom of the LES. UES, upper esophageal sphincter. (*From* Patel D, Vaezi MF. Normal esophageal physiology and laryngoesophageal reflux. Otolaryngol Clin North Am 2013;46:1025; with permission.)

Table 1
Effect of drugs on the lower esophageal sphincter tone

Increase	Decrease	No Change
Metoclopramide	Atropine	Propranolol
Domperidone	Glycopyrrolate	Oxprenolol
Prochlorperazine	Dopamine	Cimetidine
Cyclizine	Sodium nitroprusside	Ranitidine
Edrophonium	Ganglion blockers	Atracurium
Neostigmine	Thiopental	?Nitrous oxide
Succinylcholine	Tricyclic antidepressants	
Pancuronium	β-Adrenergic stimulants	
Metoprolol	Halothane	
α-Adrenergic stimulants	Enflurane opioids	
Antacids	?Nitrous oxide	
	Propofol	

? indicates possibly.

Data from Sharma VK. Role of endoscopy in GERD. Gastroenterol Clin North Am 2014;43(1): 39–46.

Box 1
Foods that are commonly associated with heartburn

Alcohol, particularly red wine

Black pepper

Garlic

Raw onions

Spicy foods

Chocolate

Citrus fruits

Coffee

Tea

Soda

Peppermint

Tomatoes

Data from Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1383–91; and Vaezi MF. The Esophagus: Anatomy, Physiology, and Diseases. In: Flint PW, Haughey BH, Lund VJ, et al., editors. Cummings Otolaryngology: Head and Neck Surgery. 5th edition. Philadelphia: Mosby Elsevier; 2010. p. 953–80.

because of the helical arrangement of the circular smooth muscle, the esophageal body functions as a "worm drive" propulsive pump. The esophageal phase of swallowing moves food from the esophagus into the stomach and accomplishes this against a pressure gradient of 12 mm at rest (−6 mm Hg pressure in the thoracic cavity and +6 mm Hg pressure in the abdominal cavity).[11] The upper esophageal sphincter (UES) closes rapidly after the initiation of a swallow, and the contraction that follows relaxation of the UES proceeds down the esophagus as a peristaltic wave.[11] When present, defects in primary and secondary peristalsis contribute to GERD, so understanding the physiology in a patient with GERD is essential.

The symptoms resulting from GERD are because of mucosal injury and are directly related to the frequency of reflux events, the duration of mucosal acidification, and the

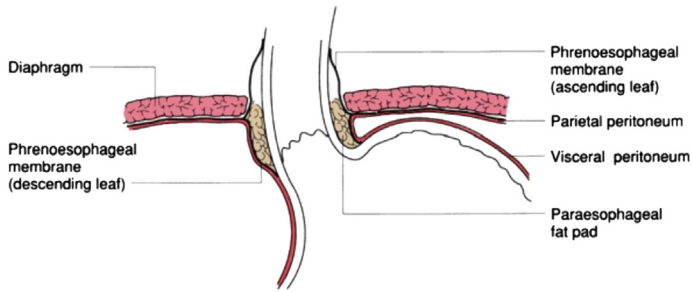

Fig. 2. Attachments of the phrenoesophageal membrane. (*From* Peters JH, Watson TJ, DeMeester TR. Esophagus: anatomy, physiology and gastroesophageal reflux disease. In: Greenfield LJ, editor. Surgery: scientific principles and practice. 3rd edition. Philadelphia: Lippincott Williams and Wilkins; 2001. p. 660; with permission.)

caustic potency of the refluxate.[12] The esophageal mucosa in normal individuals exists in a milieu that constantly fluctuates between damaging and protective forces. The main mechanism that leads to most physiologic reflux events is termed transient lower esophageal sphincter relaxations (TLESRs).[13] TLESRs are the normal gastric venting mechanism of the stomach, and a normal TLESR event is activated by different stimuli such as distension of the stomach. In patients with GERD there is an increased percentage of TLESRs predisposing to symptomatic heartburn. The main relaxation is mediated through the vagus nerve, which inhibits the crural fibers of the diaphragm (**Fig. 3**).[14–16] The overexaggeration of this phenomenon is seen in patients with a hiatal hernia and can contribute to significant heartburn symptoms.

HIATAL HERNIA

There are 4 types of hiatal hernias (**Fig. 4**). Type 1 hiatal hernias are called sliding hiatal hernias with upward migration of the LES. Type 2 hiatal hernias are called paraesophageal hiatal hernias and have a normal gastroesophageal junction (GEJ) location below the diaphragmatic hiatus with migration of gastric fundus through the hiatus. Type 3 hiatal hernias represent a combination of type 1 and 2 hernias with both the GEJ and gastric fundus migrating through the diaphragmatic hiatus. The last and rarest is the type 4 hiatal hernia, which involves herniation of other abdominal organs such as the colon or the spleen. The most common type of hiatal hernia is type 1, which is seen in 90% of patients with a hiatal hernia.[15] The disruption of the crural muscle and the phrenoesophageal ligament secondary to the hiatal hernia creates a proximal pouch in the distal esophagus. This pouch has been termed an acid pocket and can cause an increased environment for acid exposure.[16] Development of a hiatal hernia is

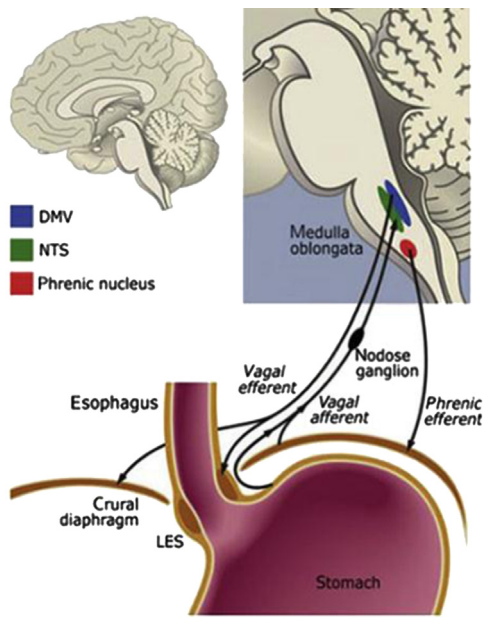

Fig. 3. Neural pathway involved in TLESRs. DMV, dorsal motor nucleus of the vagus nerve; NTS, nucleus of the solitary tract. (*From* Boeckxstaens GE, Rohof WO. Pathophysiology of gastroesophageal reflux disease. Gastroenterol Clin North Am 2014;43(1):17; with permission.)

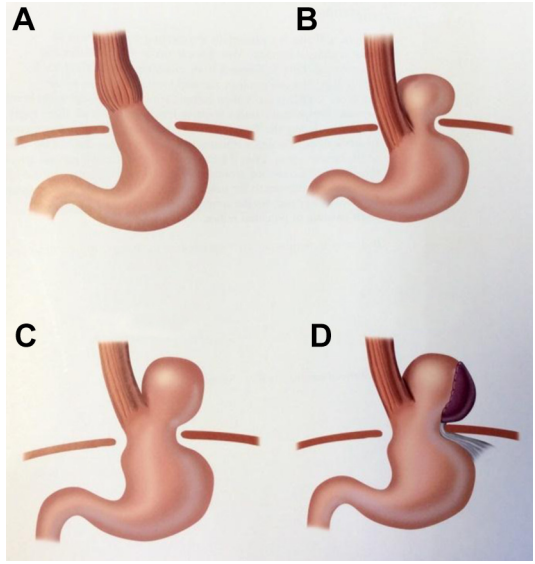

Fig. 4. Types of hiatal hernias. (*A*) Type I (sliding hiatal hernia); (*B*) type II (paraesophageal hernia). (*C*) type III (mixed type); (*D*) type IV (complex with other organs in hernia). (*From* Laparoscopic paraesophageal hernia repair. In: Jones DB, Maithel SK, Schneider BE, editors. Atlas of minimally invasive surgery. 1st edition. Woodbury (CT): Cine-Med, Inc; 2006. p. 129; with permission.)

poorly understood but is more common in obese patients,[17] and a hiatal hernia greater than 2 cm is associated with a greater incidence of erosive esophagitis and Barrett esophagus. Repeated shortening of the esophagus as a result of swallowing or retching and loss of elasticity of the phrenoesophageal ligaments are thought to be primary contributors to the formation of a hiatal hernia.

Hiatal hernias disrupt the normal anatomic and physiologic mechanisms of the LES and TLESRs. There is a reduction in LES length and pressure and alterations of esophageal peristalsis that can result in increased acid exposure at the distal esophagus contributing to mucosal injury.[15] In sliding hiatal hernias (type I), there is a circumferential weakness of the phrenoesophageal ligament leading to migration of the esophagogastric junction in a craniad direction into the lower mediastinum. Type II (paraesophageal) hernias result from local weakness of the phrenoesophageal ligament laterally resulting in migration of the fundus into the lower mediastinum.[18]

GASTRIC FUNCTION

The third and often overlooked component of GERD is the contribution of gastric function. Delay in gastric emptying can cause prolonged gastric retention of food, which in turn increases the propensity for GERD. With this phenomenon, there is an increase in the gastroesophageal pressure gradient, gastric volume, and the volume of potential refluxate.[16] Normal peristaltic movement in the stomach is important for the clearance and propulsion of liquids and solids toward the pylorus. Patients with gastroparesis often feel bloated and full because of the resultant poor emptying of the stomach, and this may lead to heartburn symptoms. It is important to distinguish between gastroparesis and gastric outlet obstruction because the treatment algorithm is different

for both groups and a preoperative upper endoscopy should be done in the workup of these patients.[19] Gastric outlet obstruction can be caused by ulcer disease, large gastric polyps, or cancer, and the subsequent poor gastric emptying can lead to gastric distention pressures that overcome the LES closing pressure and result in GERD. Gastric emptying studies should be carried out in any patient with a history of abdominal bloating before antireflux surgery or a preoperative esophageal manometry that is incongruous with the diagnosis of GERD. A scintigraphy test of a solid-phase meal rather than a liquid meal is the gold standard for the diagnosis of gastroparesis.[20] Gastric emptying of liquids may seem normal even in patients with advanced gastroparesis, and gastroparesis is seen more often in patients with GERD than in those without GERD.[21]

TREATMENT OPTIONS

While the surgical treatment of GERD is comprehensively addressed in the remainder of this article, it is essential to remember that nonsurgical therapy is the mainstay of initial treatment. However, several published trials have supported the premise that surgery results in similar resolution of GERD symptoms as medical therapy. In a recent study by Rossetti and colleagues[22] comparing medical versus surgical therapy for GERD in 301 patients, there was not a significant improvement of quality of life scores (36-Item Short Form Health Survey and Health Related Quality of Life) in the medical versus the surgical group at 1 year in patients with documented acid reflux.

In the LOTUS (Long-Term Usage of Esomprazole versus Surgery) trial, one of the largest prospective randomized trials, 554 patients with documented GERD were randomly assigned to receive either esomeprazole (20–40 mg/d) or laparoscopic antireflux surgery. The conclusion from this multicenter trial was that both medical and surgical antireflux therapies result in most patients remaining in symptom remission at 5 years.[23]

The long-term use of proton pump inhibitors has been shown to increase the risk of hip fractures, community-acquired pneumonia, diarrhea, and drug interactions especially in patients taking clopidogrel.[24] Patients with refractory GERD despite high-dose protein pump inhibitor therapy remain a treatment dilemma, and a pH study is indicated to provide clarity regarding whether symptoms are related to acid reflux. Talaie and colleagues[25] studied 48 patients with refractory GERD, and they had a mean DeMeester score of 10.06 (standard deviation = 10.48). The study demonstrated that most of patients with refractory GERD did not have acid reflux. Patients with refractory heartburn should undergo impedance pH monitoring while on acid suppressive therapy to best clarify the relationship between symptoms and acid or nonacid reflux. Patients with acid or nonacid reflux that either fails or does not respond to medical therapy may benefit from an antireflux operation. Unfortunately, unlike acid reflux for which there is effective medical therapy, options are limited for patients with nonacid reflux and antireflux surgery may be the best option.

SPECIAL CIRCUMSTANCES

Barrett Esophagus

Barrett esophagus is the most feared consequence of longstanding GERD because there is a small but real risk of conversion to adenocarcinoma. The progression to Barrett esophagus (metaplastic columnar mucosa) from the normal esophageal stratified squamous epithelium is seen with repeated and untreated acid exposure of the distal esophagus. The prevalence of Barrett esophagus varies between studies, but it has been estimated that 5.6% of the adult population in the United States has the

disease.[26] The risk of developing esophageal adenocarcinoma in patients with nondysplastic Barrett esophagus is only 0.1% to 0.3% per year, but male sex and the presence of long-segment Barrett esophagus increases this risk. The standard workup of a patient suspected of having Barrett esophagus starts with a standard esophagogastroduodenoscopy and a systematic biopsy protocol with the finding of columnar epithelium proximal to the GEJ. Esophageal biopsies should demonstrate intestinal metaplasia with the presence of goblet cells to make the diagnosis of Barrett esophagus. The proximal extent of the columnar metaplasia above the GEJ determines whether there is long-segment ($\geq$3 cm) or short-segment (<3 cm) Barrett esophagus.[26] To prevent the progression to Barrett esophagus, the 3 main pathophysiologic causes of GERD (ie, dysfunctional esophageal motility, a weakened LES, and impaired gastric emptying) discussed previously need to be evaluated and treated if present. Interestingly, routine screening of patients with GERD symptoms may have a low yield because most patients with short-segment Barrett esophagus have no GERD symptoms and up to 40% of patients with esophageal adenocarcinoma have no history of symptomatic GERD. The rate of progression to adenocarcinoma is estimated to be approximately 6% per year if high-grade dysplasia is present. Traditionally, esophagectomy was the recommended treatment for patients with high-grade dysplasia, but more recently endoscopic resection and ablation have become more commonplace to eradicate dysplasia. The mainstay of treatment is the use of proton pump inhibitors and modulation of the proinflammatory mechanisms. Antireflux surgery for Barrett esophagus has been shown to be equally effective in the LOTUS trial.[27] The current recommendation for patients with low-grade dysplasia is endoscopic surveillance at 6- to 12-month intervals or endoscopic ablative therapy. Patients with nondysplastic metaplasia should undergo routine surveillance, but currently ablation therapy is not indicated.[26]

Upright Versus Supine Reflux

Upright versus supine GERD symptoms differ in presentation, pathophysiology, and management options. Patients who have upright reflux generally reflux during the day, whereas those who have supine reflux generally have GERD symptoms at night.[28] Relaxation pressure, distal latency, and distal contractility are significantly lower in the upright position when compared with supine.[29] In general, patients with supine reflux tend to have weakness of the LES, can have bipositional GERD (upright and supine), and tend to have more severe GERD. Patients with upright daytime GERD tend to have reflux primarily because of the TLESRs discussed earlier and, generally, have less severe disease. Interestingly, TLESRs are decreased in the supine position, so patients with normal LES function tend not to reflux in the supine position; however, if the LES is defective as in patients with supine reflux, TLESRs are a nonfactor.[28]

Extraesophageal Manifestations of gastroesophageal reflux disease

Some of the more common extraesophageal complications of GERD include aspiration pneumonia, reflux-induced asthma, reflux cough syndrome, and laryngitis.[30] Asthma, chronic cough, and laryngitis have been shown to have a direct correlation with GERD, whereas aspiration pneumonias are usually multifactorial.[31] The usual management is medical therapy with the mainstay of treatment being proton pump inhibitors. Antireflux surgery should be offered if medical therapy is ineffective, if patients cannot or will not take medications, or if complications of reflux worsen in spite of adequate medical therapy (ie, volume regurgitation and aspiration). Unfortunately, treatment outcomes and benefits for these extraesophageal manifestations of GERD are less predictable than for heartburn or esophagitis symptoms.

Laryngopharyngeal reflux (LPR) is an extraesophageal variant of GERD, because the main symptomatic region involves the larynx and the pharynx. Heartburn and regurgitation are the hallmark symptoms of GERD in contrast to the symptoms of LPR, which often include hoarseness, chronic cough, sore throat, globus pharyngeus ("lump in the throat"), and frequent throat clearing. Recognition of LPR as an extraesophageal variant of GERD has increased, and approximately 10% of all otolaryngology clinic patients overall and 50% of patients with voice complaints have been diagnosed with LPR.[32]

Eosinophilic Esophagitis

Eosinophilic esophagitis (EOE) is a chronic, immune-antigen-mediated disease recognized with increasing frequency that is often confused with GERD. This disease is characterized by symptoms of esophageal dysfunction clinically and by eosinophil-predominant inflammation on endoscopic biopsy. EOE can cause dysphagia and food impaction in both adults and children, and the diagnosis requires an esophageal biopsy of the esophageal epithelium with 15 or more eosinophils per high-power field (HPF).[33] Eosinophils are not present in normal mucosa, but eosinophilic infiltration can occur from various diseases, such as GERD, eosinophilic gastroenteritis, collagen vascular disease, achalasia, and parasitic infections. Eosinophils can be observed in the mucosa in small numbers ($\leq$4 per HPF) in GERD, but the characteristic appearance of EOE such as longitudinal furrows is not seen in GERD.[34] The importance of EOE in the discussion of GERD is that it occurs with increasing frequency and patients with EOE are often treated for GERD and fall into the category of patients with "GERD unresponsive to medical therapy." Therefore, any patient who is refractory to medical therapy who has dysphagia should be evaluated for EOE.

SUMMARY

GERD remains one of the most common gastrointestinal problems. The heartburn a patient feels is related to multiple factors of which fluctuations in LES pressures is the most important. The diagnosis, treatment, and follow-up of these patients with GERD are significant burdens to our health care system, as is evident from the fact that some of the most costly and commonly prescribed medications in the United States are proton pump inhibitors. There are many options to treat GERD including medical and surgical options, but it is unlikely that one option will be best for every patient. More studies are being conducted in this field to improve understanding of this complex disease process.

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