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Gastroesophageal reflux disease: From pathophysiology to treatment

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Abstract

This review focuses on the pathophysiology of gastroesophageal reflux disease (GERD) and its implications for treatment. The role of the natural anti-reflux mechanism (lower esophageal sphincter, esophageal peristalsis, diaphragm, and trans-diaphragmatic pressure gradient), mucosal damage, type of refluxate, presence and size of hiatal hernia, *Helicobacter pylori* infection, and Barrett's esophagus are reviewed. The conclusions drawn from this review are: (1) the pathophysiology of GERD is multifactorial; (2) because of the pathophysiology of the disease, surgical therapy for GERD is the most appropriate treatment; and (3) the genesis of esophageal adenocarcinoma is associated with GERD.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a very prevalent disease. Population studies have repeatedly shown GERD-related symptoms in a significant proportion of adults. The Montreal consensus conference defined GERD as "a condition which develops when the reflux of gastric contents causes troublesome symptoms and/or complications"^[1]. However, this definition did not include details of the pathophysiology of the disease and its implications for treatment. The Brazilian consensus conference considered GERD to be "a chronic disorder related to the retrograde flow of gastro-duodenal contents into the esophagus and/or adjacent organs, resulting in a spectrum of symptoms, with or without tissue damage"^[2]. This definition recognizes the chronic character of the disease, and acknowledges that the refluxate can be gastric and duodenal in origin, with important implications for the treatment of this disease.

This review focuses on the pathophysiology of GERD and its implications for treatment.

GERD - ROLE OF NATURAL ANTI-REFLUX MECHANISMS

Although all normal individuals experience some sort of "physiological" gastroesophageal reflux, a highly efficient barrier exists between the stomach and the esophagus. From the esophageal side, esophageal clearance is pro-

moted by peristalsis and salivary production. A valve mechanism exists between the esophagus and the stomach, formed by the lower esophageal sphincter (LES), the diaphragm, the His angle, the Gubaroff valve and the phrenoesophageal membrane.

Peristalsis

Esophageal peristalsis is an important component of the antireflux mechanism because it is the main determinant of esophageal clearance of the refluxate. Defective peristalsis is associated with severe GERD, both in terms of symptoms and of mucosal damage^[3]. As matter of fact, the composite reflux score (DeMeester score)^[4] includes in its calculation two indirect measurements of esophageal clearance (number of reflux episodes longer than 5 min and length of the longest episode). In addition, the average esophageal clearance time can be calculated by dividing the total minutes the pH is below 4 by the number of reflux episodes. This association also explains the high prevalence and severity of GERD in systemic diseases that affects peristalsis, such as connective tissue disorders^[5].

It is known that 40%-50% of patients with GERD have abnormal peristalsis^[3]. This dysmotility is particularly severe in about 20% of patients because of very low amplitude of peristalsis and/or abnormal propagation of the peristaltic waves (ineffective esophageal motility)^[6]. Esophageal clearance is slower than normal, therefore, the refluxate is in contact with the esophageal mucosa for a longer period of time and it is able to reach more often the upper esophagus and pharynx. Thus, these patients are prone to severe mucosal injury (including Barrett's esophagus) and frequent extra-esophageal symptoms such as cough^[6,7].

It is still unclear whether esophageal dysmotility is a primary condition that leads to GERD, or it is a consequence of esophageal inflammation. Medical therapy does not ameliorate esophageal peristalsis^[8,9]. However it has been shown that effective fundoplication improves the abnormal peristalsis in most patients^[10].

LES

Physiologically, the LES is a 3-4-cm-long segment of tonically contracted smooth muscle at the distal end of the esophagus^[11]. It is intuitive that the LES creates a high pressure zone between the esophagus and the stomach that prevents reflux. An effective LES must have an adequate total and intra-abdominal length, and an adequate resting pressure^[12]. However, a normal LES pressure does not exclude GERD, because abnormal transient relaxation might occur. Periodic relaxation of the LES in normal individuals has been termed transient lower esophageal sphincter relaxation (TLESR), to distinguish it from relaxation triggered by swallowing. TLESR accounts for the physiological reflux found in normal subjects. When it becomes more frequent and prolonged, TLESR can contribute to reflux disease, and this phenomenon appears to explain the reflux seen in the 40% of patients with GERD whose resting LES pressure is normal. What determines TLESR is unknown, but postprandial gastric

distention is probably involved^[11,13]. It has been shown that a mechanically incompetent LES is progressively associated with worse mucosal damage^[7].

At the present time, there are no medications used in clinical practice that act on the LES. Some studies are presently conducted using inhibitors of the GABA type B receptor, especially baclofen, but the effect of this medication is still not clear. These data underline that an incompetent LES represents a mechanical and permanent defect of the gastroesophageal barrier. Only fundoplication can correct the functional and mechanical profile of the LES, therefore resulting in control of any type of reflux from the stomach into the esophagus.

Diaphragm

The crus of the diaphragm provides an extrinsic component to the gastroesophageal barrier. This pinchcock action of the diaphragm is particularly important as a protection against reflux induced by sudden increases in intra-abdominal pressure^[13]. This mechanism is obviously disrupted by the presence and size of a hiatal hernia.

Increase of thoraco-abdominal pressure gradient

Abnormal gastric emptying might contribute to GERD by increasing intra-gastric pressure. Patients with suspected abnormal gastric emptying should be tested with nuclear markers^[14] or ultrasound^[15]. If slow emptying is diagnosed, appropriate therapy should be considered. Medication such as metoclopramide and Nissen fundoplication improve gastric emptying^[16].

There is also strong evidence of a possible link between obesity and GERD. Specifically, it has been shown that there is a dose-response relationship between increasing body mass index (BMI) and prevalence of GERD and its complications^[17-19]. Some studies have reported that morbidly obese patients with GERD have a higher incidence of incompetent LES, transient LES relaxation and impaired esophageal motility than non-obese patients with GERD^[8,20,21]. However, a detailed mathematical analysis has shown that the severity of GERD (based on the DeMeester score) is associated with BMI^[22], which suggests that obesity plays an independent role in the pathophysiology GERD, mainly through increased abdominal pressure^[18,23].

The association of different pulmonary diseases and GERD has recently gained renewed interest^[24]. It has been shown that patients with end-stage lung disease have a high prevalence of GERD; up to 70%^[25]. Although in these patients pan-esophageal motor dysfunction is frequently found^[25], a more negative thoracic pressure with an increase in the gradient between intra-gastric and intra-thoracic pressure might also contribute.

GERD: ROLE OF MUCOSAL DAMAGE

Increasing severity of esophagitis is associated with increasing acid exposure^[26]; however, erosive esophagitis is present in only 50% of GERD patients^[7]. Some experts believe that the erosive and non-erosive forms of the

disease might actually account for different subsets of the disease; others believe that they represent two different and progressive stages of the disease.

It is still unclear if mucosal inflammation is a cause or a consequence of GERD. Evidence has shown that esophagitis is associated with esophageal body dysmotility^[7]. However, it is still unclear if it is the cause or the effect of the altered peristalsis. We do know that medical therapy for GERD does not ameliorate esophageal peristalsis^[8,9], whereas surgical therapy clearly results in improvement^[10].

GERD: ROLE OF THE REFLUXATE

As previously mentioned, gastric and duodenal contents can reflux into the esophagus and adjacent organs. Gastric hydrochloric acid has long been recognized as harmful to the esophagus^[27]. However, gastro-esophageal refluxate contains a variety of other noxious agents, including pepsin^[26]. Currently, it is recognized that this component of the refluxate (commonly called bile reflux and identified by the Bilitec bile reflux monitor using bilirubin as a marker) is composed of bile salts and pancreatic enzymes^[26], and is also injurious to the esophageal mucosa. It causes symptoms^[28], and could be linked to the development of Barrett's esophagus^[29] and esophageal adenocarcinoma^[30].

Besides the constituents of the refluxate, symptom perception and mucosal damage also appear to be linked to the patterns of esophageal exposure and the volume of the refluxate. Individuals are more likely to perceive a reflux event if the refluxate has a high proximal extent and a large volume^[26].

Acid suppression is the main treatment for GERD. It has evolved from topical alkaline antacids to very effective proton pump inhibitors (PPIs). Several studies have shown the efficacy of PPIs in almost neutralizing gastric acid. These medications make the refluxate less aggressive, which leads to symptom amelioration and healing of esophagitis^[31]. However, they do not stop reflux or cure GERD, as different studies with intraluminal impedance technology have shown that PPI therapy alters the pH of the refluxate but does not change the occurrence and number of reflux episodes^[32,33]. Currently, there is no specific medication that controls non-acid reflux. On the other hand, fundoplication blocks any type of gastric refluxate because it restores the competence of the gastroesophageal junction.

GERD: ROLE OF HIATAL HERNIA

Hiatal hernia and GERD were once considered synonyms and hiatal hernia was considered a *sine qua non* condition for GERD to occur^[34,35]. Currently, it is well known that both conditions can exist independently. However, it is recognized that hiatal hernia disrupts most of the natural antireflux mechanisms, and is considered an independent factor for GERD^[26]. The simple presence of an abdominal portion of the esophagus is considered an antireflux mechanism, because it is submitted

to positive abdominal pressure and acts as a valve^[34]. In addition, TLESR seems to occur more frequently when a hiatal hernia is present. Not surprisingly, the presence and size of a hiatal hernia are associated with a more incompetent LES (the pinchcock action of the diaphragm is absent), defective peristalsis, more severe mucosal damage, and increased acid exposure^[36].

Hiatal hernia is associated with early recurrence and failure of medical therapy for GERD^[34]. The reduction of a hiatal hernia with narrowing of the esophageal hiatus is a key element in fundoplication and its omission or failure is a cause of recurrence of GERD.

GERD: ROLE OF *HELICOBACTER PYLORI*

The association of GERD and *Helicobacter pylori* (*H. pylori*) is very controversial. While some argue that the infection might play a role in the prevention of GERD by altering the nature of the refluxate (gastritis leading to achlorhydria), others find no link between the infection and esophageal diseases^[37,38].

Prevalence studies seem to suggest that *H. pylori* infection is inversely associated with reflux esophagitis in some populations^[37]. Eradication studies also suggest that *H. pylori* infection is protective with respect to GERD^[37].

If *H. pylori* protects against GERD, a logical assumption would be that it also protects against adenocarcinoma development. Furthermore, adenocarcinoma incidence is rising worldwide; however, the increasing pace is slow in underdeveloped countries, exactly where *H. pylori* incidence is higher. Indeed, the majority of epidemiological studies have found a protective association, and the results of three recently published meta-analyses have shown that *H. pylori* colonization of the stomach is associated with a nearly 50% reduction in cancer risk^[39].

GERD AND BARRETT'S ESOPHAGUS

The history of Barrett's esophagus has been complicated by different opinions on the genesis of the disease^[40]. Currently, it is unquestionable that Barrett's esophagus is an acquired disease caused by GERD, although risk factors and innate predisposition are still being scrutinized. Also, it is believed that most, if not all, esophageal adenocarcinoma arises in Barrett's mucosa^[41].

With regard to GERD pathophysiology, Barrett's esophagus represents an end stage form of the disease. It encompasses pan-esophageal motor dysfunction that is characterized by abnormalities in esophageal peristalsis, defective LES, and bile reflux^[42]. Most authors consider this form of GERD to be a surgical disease^[43], based on the aforementioned points.

FROM PATHOPHYSIOLOGY TO TREATMENT

The simultaneous use of intra-esophageal impedance and pH measurement of acid and non-acid gastroesophageal

reflux has clearly shown that treatment with PPIs only changes the pH of the refluxate, without stopping reflux through a functionally or mechanically incompetent LES^[44]. For instance, using this technology, Vela *et al*^[44] have shown that during treatment with omeprazole, postprandial reflux still occurs but it becomes predominantly non-acid. In a study in normal subjects, Vela and colleagues also have shown that baclofen, a GABA B antagonist, is able to reduce both acid and non-acid reflux by decreasing TLESR, the primary mechanism for both acid and non-acid reflux^[45]. This study signals an important shift toward treatment focused on the competence of the LES rather than the pH of the refluxate alone. This goal can also be achieved by fundoplication; an operation that can be done laparoscopically with a short hospital stay, minimal postoperative discomfort, fast recovery time and excellent results^[46-49]. Long-term studies have shown that fundoplication controls symptoms in 93% of patients after 5 years and in 89% after 10 years^[46]. The operation controls reflux because it improves esophageal motility, both in terms of LES competence and quality of esophageal peristalsis^[10]. Control of reflux is not influenced by the pattern of reflux, and is equally effective when reflux is upright, supine or bipositional^[47]. In addition, the operation is equally safe and effective in young or elderly patients^[48]. Concern has been raised about the presence of postoperative dysphagia. In our experience, this occurs in about 8% of patients, irrespective of the type of fundoplication, and it resolves spontaneously in all but a few patients in a few months, without requiring re-intervention^[49].

It is important to select the best treatment for the individual patient based on a review of symptoms, age, sex, esophageal function, and type of refluxate. We feel that laparoscopic fundoplication is indicated in the following circumstances: when heartburn and regurgitation are not affected by medical treatment; when it is thought that cough is induced by reflux (Mainie *et al*^[50] have shown that patients with a positive symptom index resistant to PPIs with non-acid or acid reflux demonstrated by multichannel intraluminal impedance-pH monitoring can be treated successfully by laparoscopic Nissen fundoplication); poor patient compliance; cost of medical therapy if more than one pill/day of PPI is needed (most insurance companies in the United States pay for one pill/day only); and postmenopausal women with osteoporosis. It has been shown that PPIs and histamine-2 receptor antagonists can increase the risk of hip and femur fractures^[51]. Therefore, medical treatment is not advisable for young and very symptomatic patients.

Finally, in a recently published meta-analysis of medical *vs* surgical management for GERD, Wileman *et al*^[52] have shown that, in adults, laparoscopic fundoplication is more effective than medical management for the treatment of GERD in the short to medium term. Surgery, however, carries some risk and its application should be individualized and the decision to undergo fundoplication should be based on patient and surgeon preference.

CONCLUSION

The pathophysiology of GERD is clearly multifactorial. While medical therapy can only affect gastric acid production, fundoplication restores the function of the LES and improves esophageal peristalsis. In addition, fundoplication stops any type of refluxate because it restores the competence of the gastroesophageal junction. It seems that fundoplication alone does not cause regression of Barrett's esophagus and does not prevent the development of adenocarcinoma. It will be important to study in patients with Barrett's esophagus the long-term effect of surgery in association with new treatment modalities such as radiofrequency ablation (RFA) and endoscopic mucosal resection (EMR). The combination should be more effective than monotherapy, because RFA and EMR eliminate the metaplastic or dysplastic epithelium, while fundoplication stops reflux, which is the original cause of Barrett's esophagus.

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