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Mechanisms of Barrett's esophagus (clinical): LES dysfunction, hiatal hernia, peristaltic defects

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Summary

Barrett's esophagus, with the potential to develop into esophageal adenocarcinoma (EAC), is a major complication of gastroesophageal reflux disease (GERD). However, about 50% of patients developing EAC had no known GERD beforehand. Hence, while GERD symptoms, esophagitis, and Barrett's have a number of common determinants (esophagogastric junction (EGJ) incompetence, impaired esophageal clearance mechanisms, hiatus hernia) they also have some independent determinants. Further, although excess esophageal acid exposure plays a major role in the genesis of long-segment Barrett's esophagus there is minimal evidence supporting this for short-segment Barrett's. Hence, these may have unique pathophysiological features as well. Long-segment Barrett's seems to share most, if not all, of the risk factors for esophagitis, particularly high-grade esophagitis. However, it is uncertain if EGJ function and acid clearance are more severely impaired in patients with long-segment Barrett's compared to patients with high-grade esophagitis. With respect to short-segment Barrett's, the acid pocket may play an important pathogenic role. Conceptually, extension of the acid pocket into the distal esophagus, also known as intra-sphincteric reflux, provides a mechanism of acid exposure of the distal esophageal mucosa without the occurrence of discrete reflux events, which are more likely to prompt reflux symptoms and lead to the development of esophagitis. Hence, intra-sphincteric reflux related to extension of the acid/no acid interface at the proximal margin of the acid pocket may be key in the development of short segment Barrett's. However, currently this is still somewhat speculative and further studies are required to confirm this.

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Keywords

Barrett's esophagus; hiatal hernia; hypotensive esophagogastric junction; acid pocket; esophageal clearance

Introduction

Barrett's esophagus (BE) is considered a major complication of gastroesophageal reflux disease (GERD) and characterized as a premalignant lesion because of its potential to evolve into esophageal adenocarcinoma (EAC). Consistent with cancer pathogenesis in other organs, the proposed pathogenesis is a progression from inflammation to metaplasia to dysplasia to carcinoma [1]. Genetic and acquired modifiers act along this sequence making progression more or less likely. With respect to genetics, male gender, non-hispanic white ethnicity, family history and advancing age all increase the risk [2]. With respect to acquired modifiers, GERD and its associated risk factors dominate: obesity, hiatal hernia, smoking, *H. pylori* eradication (or absence). Hence, within these constraints, it seems reasonable to conclude that GERD severity plays a central role in the genesis of BE and EAC. Consistent with that hypothesis, high quality epidemiological studies have established chronic GERD symptoms as a risk factor for EAC [3, 4]. However, those same studies have also uniformly observed that pre-existing GERD symptoms are not universal and about 50% of EAC cases arise in individuals reporting no significant GERD history [5]. Hence, in considering mechanisms of BE and EAC, one has to accept that although there are common elements with the pathogenesis of GERD symptoms, there are also independent determinants. Specifically, since most BE is short segment and most EAC occurs in close proximity to the native squamocolumnar junction (SCJ), that microenvironment becomes a central focus. Anatomical and physiological conditions that promote the exposure of this vulnerable region to gastric juice likely also promote the development of BE, irrespective of whether or not GERD symptoms coexist.

GERD pathophysiology involves an interplay between factors promoting reflux of gastric juice proximal to the SCJ and defensive forces retarding movement of gastric content proximal to the SCJ or neutralizing it after the fact: esophagogastric junction (EGJ) competence, esophageal clearance and gastric acid secretion are all involved [6]. Intimately entwined in this pathogenesis are perturbations related to hiatal hernia. Recently the dynamics of the acid pocket, acid secreted postprandially that layers on top of gastric chyme, has been added as a determinant of where the acid/no acid interface localizes [7]. The aim of this review is to discuss how these pathophysiological factors might play a role in the genesis of BE.

The esophagogastric junction

The EGJ is the barrier against reflux of gastric content into the esophagus. It is mainly composed of the lower esophageal sphincter (LES) and the crural diaphragm. EGJ anatomy and physiology are complex, but warrant careful consideration. The esophagus enters the abdomen through a teardrop-shaped opening, the diaphragmatic hiatus, which is formed by the right diaphragmatic crus originating from lumbar vertebral bodies and forming a loop

around the distal esophagus. The esophagus is normally anchored to the diaphragm at the hiatus by the phrenoesophageal membrane, which also closes the potential space between the esophagus and the margins of the hiatus. The phrenoesophageal membrane is formed by fused elements of the peritoneum and the parietal pleura, inserting circumferentially into the esophagus at the level of SCJ. At the distal extreme of the esophagus, the thickened muscularis propria corresponds to the LES. Together, the right diaphragmatic crus, the phrenoesophageal membrane, and the LES form the EGJ.

In absence of swallowing, the EGJ is closed and the pH interface between the gastric and esophageal pH environments is precisely localized at the SCJ; a relationship that has been carefully studied by relating to positions of the intraluminal pH transition, a mucosal clip affixed to the SCJ and the intraluminal high-pressure-zone (HPZ) of the EGJ with fluoroscopy (Figure 1) [8]. A corollary of these relationships is that the distal aspect of the EGJ HPZ normally resides distal to the SCJ and that the proximal margin of the HPZ is normally 1-1.5 cm proximal to the SCJ. During swallowing, the LES relaxes and the EGJ opens. Alternatively, transient LES relaxations (tLESRs) can occur in absence of swallowing; they correspond to the physiological mechanism of belching, but also represent a major mechanism of gastroesophageal reflux [9, 10]. Major distinctions between swallow-induced relaxation and tLESRs are: 1) the crural diaphragm is inhibited with tLESR, but not swallow-induced LES relaxation, 2) tLESRs persist significantly longer than the roughly 6 seconds of relaxation associated with a swallow, and 3) tLESRs also entail contraction of the longitudinal muscle of the esophageal muscularis propria.

Hiatus hernia

Hiatal hernia is a condition in which elements of the abdominal cavity, most commonly the stomach, herniate through the esophageal hiatus into the mediastinum [11]. The major sub-categorization is between sliding hernias, which are most pertinent to reflux pathogenesis and paraesophageal hernias, which involve either inversion of the stomach as it herniates, or involvement of other organs. Sliding hernia is part of a continuum of anatomic disruption of the native EGJ also involving dilatation of the diaphragmatic hiatus and circumferential laxity of the phrenoesophageal ligament. This causes progressive exaggeration of the 'physiologic herniation' that occurs with swallowing as the cardia of the stomach herniates symmetrically upward in conjunction with contraction of the esophageal longitudinal muscle. When fully established, sliding hiatal hernia is characterized by a separation between the LES and the crural diaphragm, which normally work in synergy to augment the anti-reflux barrier [12]. Hence, with hiatus hernia, the mechanistic profile of reflux events extends to mechanisms other than tLESR, specifically strain-induced reflux and even swallow-induced reflux. This is especially true in a recumbent posture. Equally important, hiatus hernia profoundly disrupts the normal process of acid clearance by permitting the 'rereflux' of gastric juice into the distal esophagus during swallow-induced LES relaxation, a circumstance normally prevented by crural diaphragm contraction.

Epidemiologically, the incidence of hiatal hernia increases with age and with body mass index (BMI). Kyphosis and scoliosis also favor the occurrence of hernia [13]. Finally, thoraco-abdominal trauma (secondary to road traffic accidents, or falls from height) and

complications of surgery (antireflux procedures, esophagomyotomy, or partial gastrectomy) are risk factors for the occurrence of both sliding and paraesophageal hernias [14].

Diagnosis of hiatal hernia

There is no gold standard for diagnosis of a sliding hiatal hernia because it is not inherently a dichotomous condition. Rather, it is a progressive degradation of normal anatomy that becomes increasingly obvious as it progresses. The most accurate diagnosis is achieved during surgery in the region of the EGJ with the caveat that hiatal hernia might be intermittent.

Sliding hiatus hernia is diagnosed endoscopically when the apparent separation between the SCJ and the diaphragmatic impression exceeds 2 cm. However, the level of accuracy associated with this was apparent in a recent study performed among Barrett's esophagus experts and community hospital endoscopists that showed absolute agreement in the assessment of hiatal hernia length to be 63% (95% confidence interval (CI) 56-70) compared to 74% (95%CI 68-80) and 68% (95% CI 62-75) for the assessment of circumferential and maximal Barrett's esophagus length respectively according to the Prague Classification [15]. Confounding factors that help explain the discrepancies are that Barrett's mucosa can make it difficult to ascertain the location of the native SCJ and that an extremely patulous hiatus makes it difficult to precisely localize the diaphragmatic pinch. Finally, excess insufflation of the stomach can exaggerate the apparent size of the hernia. Another approach to the endoscopic grading of sliding hernia is to assess the appearance of the EGJ from a retroflexed position and to incorporate an assessment of hiatal integrity along with the assessment of axial displacement.

Barium swallow examination identifies the relative position of the EGJ and the diaphragmatic hiatus (Figure 2). A muscular ring (the A ring) can be visible during swallowing demarcating the superior margin of the LES. A second ring (the B ring) corresponds to the SCJ; a B ring with an internal aperture <13 mm is called a Schatzki ring. A separation exceeding 2 cm between the A and B ring is required to define a sliding hernia. However, these rings are not always present and not always easy to identify. In their absence, the demonstration of gastric rugal folds traversing the diaphragm is used as the defining criterion for hiatal hernia.

Finally, separation between LES and crural diaphragm can be evidence using high resolution manometry (HRM). Combining many closely spaced pressure sensors and topographic plotting methods (Clouse plots), HRM facilitates the localization of discrete elements within the EGJ. Hence, distinct EGJ morphologic subtypes have been described using HRM [16] (Figure 3). With type I EGJ morphology, there is complete overlap of the crural diaphragm and LES with no spatial separation evident on the Clouse plot and no double peak on the associated spatial pressure variation plot. With type II EGJ morphology, the LES and CD are separated (double-peaked spatial pressure variation plot), but the nadir pressure between the two peaks does not decline to gastric pressure: the separation between the pressure peaks is 2 cm or less. With type III EGJ morphology, the LES and CD are clearly separated as evidenced by a double-peaked spatial pressure variation plot and the nadir pressure between the peaks equal to or less than gastric pressure. Type III EGJ morphology is further divided

into subtypes IIIa and IIIb. With type IIIa the pressure inversion point remains at the CD level, while in type IIIb it is located at the LES level. Type II and type III EGJ morphology correspond to manometric hiatal hernia. On average, patients with GERD have significantly greater LES-CD separation than controls [16]. It is important to note that this separation can fluctuate over time during long-interval manometric recordings and gastro-esophageal reflux episodes preferentially occur in the hernia configuration rather than when in type I morphology [17].

Association with Barrett's esophagus

Hiatal hernia is commonly encountered in patients with Barrett's esophagus; up to 96% of patients in one estimate [18-20]. A recent meta-analysis found that hiatal hernia was associated with an increased risk of Barrett's esophagus (odds ratio (OR) 3.94, 95% confidence interval (CI) 3.02-5.13) [21]. This risk was even present after adjusting for BMI and reflux symptoms (OR=2.99, 95%CI 2.24-3.96). Hiatal hernia size was also greater in patients with Barrett's esophagus than in controls (for example mean length 3.95 cm versus 2.81 cm in the study of Cameron [18], $p<0.005$). Interestingly, a Japanese series found that kyphosis, which is a risk factor for hiatal hernia, might also be independently associated with the occurrence of long-segment Barrett's esophagus [22].

Some authors propose that hiatal hernia increases the risk of progression to esophageal adenocarcinoma. A case-control study found that the size of hiatal hernia was associated with the occurrence of high-grade dysplasia (OR 1.20, 95% CI 1.04-1.39 versus patients with Barrett's esophagus, $p=0.013$) [23]. In another series of 550 patients with Barrett's esophagus, the size of hiatal hernia (>6 cm) was independently associated with progression to high-grade dysplasia or adenocarcinoma (OR = 4.51, 95%CI 1.18-17.15) [24]. However, that association disappeared when patients without dysplasia and with low-grade dysplasia were entered in the model. That finding was confirmed in another series of 713 patients with Barrett's esophagus with no dysplasia or low-grade dysplasia; the size of hiatal hernia was not predictive of progression to high-grade dysplasia or adenocarcinoma (OR 0.9, 95% CI 0.7-1.2, ns) after 4 years of follow-up [25]. Finally, in another case-control study, hiatal hernia was associated with the occurrence of GERD and Barrett's esophagus but not with high-grade dysplasia or esophageal adenocarcinoma [26]. In summary, the role of hiatal hernia in the development of Barrett's esophagus is clear, but its role in the progression to high-grade dysplasia and adenocarcinoma is questionable.

EGJ morphologic alteration apart from hiatus hernia

Attempts have been made to characterize EGJ morphological changes in GERD patients short of hiatal hernia. Using magnetic resonance imaging and HRM, Curcic *et al.* demonstrated that the esophagogastric insertion angle was more obtuse in GERD patients than in healthy subjects [27] in conjunction with altered gastric orientation within the abdomen. Associate with this, the dimensions of EGJ opening during reflux events were greater in GERD patients than in controls. This observation is consistent with the increased EGJ distensibility observed in patients with GERD compared to controls using a hydrostat [28] or endoscopic functional luminal imaging probe (EndoFLIP®) [29]. To our knowledge,

there are no published studies comparing EGJ morphology and distensibility in patients with Barrett's esophagus and controls or GERD patients.

Hypotensive EGJ

The LES and crural diaphragm normally work synergistically as an anti-reflux barrier. Several studies have found a relationship between severe erosive esophagitis and diminished LES pressure [30-32]. Diminished EGJ pressure has also been demonstrated with high-resolution manometry, a technique that allows differentiation between the LES and diaphragmatic contributions to the EGJ [16, 33]. Pandolfino *et al.* showed that patients with GERD had significantly less inspiratory augmentation of EGJ pressure compared to controls [16]. Using a logistic regression model that simultaneously examined expiratory LES pressure, LES-crural diaphragm separation and inspiratory EGJ augmentation, while controlling for age and BMI, only inspiratory augmentation had a significant independent association with objectively defined GERD. These findings have recently been extended using 3D-HRM showing that the dominant constituent of EGJ pressure at rest is attributable to the diaphragm in control subjects [34]. Hence, it is becoming increasingly clear that morphological changes at the hiatus play an important role in the pathogenesis of GERD.

New HRM metrics are being evaluated to assess EGJ integrity as an antireflux barrier. These metrics are analogous to the distal contractile integral in that they integrate EGJ contractility across the length of the EGJ and over a period of time. Studies vary as to whether the period of time included in the calculation is arbitrary or indexed to the respiratory cycle. The isobaric contour threshold at which EGJ pressure is measured also differs among studies. Hoshino *et al.* described the lower esophageal sphincter pressure integral (LESPI) measured at 20-mmHg isobaric contour and within a 10-s window without swallowing [35]. Nicodème *et al.* proposed to use EGJ contractile integral (EGJ-CI) which was measured at 2 mmHg above the gastric pressure for a period of 3 respiratory cycles [34]. Finally Gor *et al.* slightly modified the calculation of EGJ-CI by measuring the pressure at the threshold of gastric pressure [36]. In each of these analyses, EGJ contractility was found to be lower in patients with pathological esophageal acid exposure compared to patients with normal acid esophageal exposure.

Hypotensive EGJ and Barrett's esophagus

Similar to GERD patients in general, patients with Barrett's esophagus frequently exhibit a hypotensive EGJ. Hypotensive LES was observed more frequently in patients with Barrett's esophagus (90% of females and 91% of males) compared to patients with reflux symptoms without Barrett's esophagus (76% of females and 63% of males) [37]. Moreover, Lord *et al.* reported that patients with Barrett's esophagus had a significant lower LES resting pressure compared to patients with non-erosive reflux disease (median LES pressure 5.2 mmHg vs 8.4, $p<0.05$) or to patients with esophagitis healed on proton pump inhibitors (7 mmHg, $p<0.05$) [38]. However, median LES resting pressure was similar among patients with Barrett's esophagus and patients with persistent esophagitis despite PPI therapy (5.2 mmHg vs 5.5, ns). Lee *et al.* made similar observations in Chinese patients: LES resting pressure was significantly lower in patients with Barrett's esophagus compared to patients with grade A or B esophagitis (mean pressure 8.9 mmHg vs 15.5, $p<0.05$), but not to patients with

grade C or D esophagitis (11.1 mmHg, ns) [39]. Hence, LES (EGJ) hypotension is seemingly more of a risk factor for severe GERD, rather than specifically for Barrett's esophagus. In a large series of 506 patients with abnormal esophageal acid exposure on 24-h pH monitoring, multivariate analysis demonstrated that abnormal bilirubin exposure was the only factor independently associated with Barrett's esophagus [37]. A defective LES, defined by a resting pressure <6 mmHg, overall length <2 cm and/or abdominal length <1 cm, was not independently associated with Barrett's esophagus in that series. Similarly, contrary to esophageal acid exposure, resting LES pressure was not independently associated with Barrett's esophagus in a series of 422 patients with suspected GERD [40]. However, all of these studies were performed with conventional manometry. Using HRM, Kumar *et al.* demonstrated that patients with Barrett's esophagus had the lowest LES pressure compared to controls, to patients without GERD and to patients with GERD [41]. However, there was no comparison made between patients with severe esophagitis (grade C and D) and patients with Barrett's esophagus in that study.

Finally, it is important to note that patients with long-segment Barrett's esophagus have been reported to have a significantly lower LES pressure than patients with short-segment Barrett's esophagus [42]. In a series of 147 Barrett's patients, the extent of intestinal metaplasia correlated strongly with esophageal acid exposure ($r=0.71$, $p<0.001$) and inversely with LES pressure ($r=0.36$, $p<0.001$) [43]. Consequently, although it has been a rather consistent observation that a hypotensive LES or EGJ plays an important role in the occurrence of severe esophagitis and Barrett's, the association with Barrett's may be limited to individuals with long-segments as opposed to short-segments of metaplasia. This leaves open the intriguing possibility that these two are mechanistically distinct in their pathogenesis.

Transient LES relaxations

tLESRs are the major mechanism of reflux demonstrable in long-interval manometry studies. They are triggered by gastric distension induced by food, liquid, or gas. Although the overall number of tLESRs is not consistently increased in GERD patients compared to control subjects, the number of reflux-associated tLESRs is consistently greater in GERD patients [30, 44]. To our knowledge there are no data concerning the frequency of, or characteristics of, tLESRs in patients with Barrett's esophagus.

The acid pocket

Although historically recognized as pertinent to the pathogenesis of peptic ulcer disease [45], the acid pocket has recently been rediscovered as pertinent to GERD. The acid pocket is comprised of the pool of acid secreted in response to eating that localizes on top of ingested chyme serving and serves as the reservoir for postprandial acid reflux [7]. Fletcher *et al.* first coined the term 'acid pocket' to describe this phenomenon, characterizing it as collection of highly acidic, unbuffered gastric juice adjacent to the EGJ in the postprandial period [46]. Several lines of evidence implicate the acid pocket as the source for postprandial acid reflux: 1) the time course of acid pocket formation correlates with that of postprandial acid reflux events [47]; 2) paradoxically, the gastric cardia become more acidic

than the more distal stomach after the meal [48]; and 3) there is a good correlation between the pH within the acid pocket and the nadir pH of reflux events in the distal esophagus [49].

Another intriguing aspect of the acid pocket pertinent to GERD is the precise localization of the acid/no acid interface at its proximal margin. Fletcher et al first suggested that the acid pocket might extend into the distal esophagus in their original report [46]. However, that result was likely attributable to a methodological problem and a definitive demonstration of this phenomenon came from Pandolfino et al in experiments that localized the proximal acid/no acid interface of the acid pocket utilizing concurrent HRM, fluoroscopy, a mucosal clip demarcating the position of the SCJ, and a pH electrode pull-through [8]. Those studies suggested that proximal migration of the acid/no acid interface proximal to the SCJ was a finding unique to GERD patients, particularly when they were in a supine posture (Figure 4). Recognizing that this was occurring with a closed lumen, those authors suggested that this was better described as an 'acid film' rather than an acid pocket, a phenomenon subsequently referred to as intra-sphincteric reflux. Also supportive of this concept, Beaumont et al utilize scintigraphy to study the formation of the acid pocket and the influence of hiatal hernia on its localization [47]. They were able to demonstrate that the acid pocket extended continuously above the diaphragm in 40% of patients with large hiatal hernia (>3 cm) and migrated intermittently above the diaphragm in the remainder [47]. On the other hand, the acid pocket was mainly localized immediately distal to the SCJ in healthy volunteers and patients with small hiatal hernia.

The above observations suggest a mechanism wherein the most distal squamous mucosa of the esophagus becomes exposed to gastric juice *without the occurrence of discrete reflux events*. Hence, the determinants of acid exposure in the intrasphincteric segment are distinct from the determinants of reflux symptoms such as heartburn, regurgitation, and chest pain, which generally occur with the extension of reflux into the proximal esophagus. However, intra-sphincteric reflux is potentially of great pathophysiological significance with respect to mucosal pathology, likely explaining why metaplasia of the distal esophagus is most prevalent at, and immediately proximal to, the SCJ and can occur in subjects without reflux symptoms or conventional evidence of reflux disease. It is provocative to note that since bile acids have been detected within the acid pocket of healthy volunteers [50] this may explain the occurrence of short segment Barrett's esophagus in essentially asymptomatic individuals. However, there are currently no data to support such speculation. It has, however, been demonstrated that acid exposure is significantly greater in the distal and intrasphincteric segment of the esophagus [42, 51-53]. Fletcher *et al.* showed that the 24-h esophageal acid exposure was greater 0.5 cm compared to 5 cm above the SCJ [52]. Intra-sphincteric acid exposure also occurs mainly postprandially [17] and has been shown to occur as a consequence of tightening a belt around the abdomen, reinforcing the concept that there are the distinct determinants of acid exposure in this region differ compared to the more proximal esophagus [54].

Esophageal peristaltic function

Many GERD patients exhibit delayed esophageal clearance which can be a major determinant of esophageal mucosal lesions [55]. Impaired esophageal peristaltic function

can cause delayed esophageal clearance thereby playing a role in the occurrence of esophagitis and Barrett's esophagus.

Using HRM Pohl *et al.* found that the transition zone, corrected for the length of the esophagus, was similar in length but longer in duration in patients with GERD symptoms compared to controls [56]. On the other hand, Porter *et al.* demonstrated that patients with GERD more frequently had fragmented peristalsis (analogous to a longer transition zone) than controls [57]. The difference between the 2 studies might be explained by the fact that Pohl *et al.* selected patients on the basis of clinical symptoms while Porter *et al.* studied patients with abnormal esophageal acid exposure or erosive esophagitis. Taking into account abnormal esophageal acid exposure and the presence of esophagitis, Ribolsi *et al.* showed that patients with erosive esophagitis exhibited more frequently breaks in the contractile front (>2 cm at 20 mmHg isobaric contour) than patients without esophagitis [58]. They also noticed that patients with more than 20% of swallows with large breaks (>5 cm at 20 mmHg isobaric contour) had higher esophageal acid exposure and worse bolus clearance time in the supine position compared to patients without large breaks. Finally, failed peristalsis was more frequent after drinking 200-ml water in patients with erosive esophagitis compared to patients with non-erosive reflux disease [33]. This may be reflective of poor 'peristalsis reserve' in patients with erosive esophagitis. Consequently, it has been a consistent observation that patients with erosive esophagitis exhibit more defects in peristalsis than patients with non-erosive reflux disease.

Esophageal peristaltic function and Barrett's esophagus

Using conventional manometry, Lee *et al.* showed that distal esophageal contractile amplitude was significantly lower in patients with Barrett's esophagus compared to patients with grade A or B esophagitis [39]. However, the percentage of patients with ineffective esophageal motility was not significantly different between the 2 groups (46.7% vs 64.3%). Savarino *et al.* confirmed that esophageal motility disorders were more frequently encountered in patients with Barrett esophagus compared to patients with non-erosive reflux disease (42% of patients with ineffective esophageal motility and 14% of patients with nutcracker esophagus or distal esophageal spasm vs 19% and 16% respectively, $p < 0.05$) [59]. However, the distribution of motility disturbances was similar to those observed in patients with erosive esophagitis. Using impedance manometry in the same series, the percentage of patients with incomplete bolus transit was greater among patients with Barrett's esophagus than among patients with non-erosive reflux disease (56% vs 20%, $p < 0.05$), but not among patients with esophagitis (54%).

Using high resolution manometry, Kumar *et al.* showed that the length and duration of transition zone were greater in patients with GERD or Barrett's esophagus compared to controls and patients without GERD [41]. Patients with Barrett's esophagus exhibited the longest and lengthiest transition zone; however, no comparison was made between patients with erosive esophagitis and patients with Barrett's esophagus.

While patients with long-segment Barrett's exhibited greater esophageal acid exposure than patients with short-segment Barrett's, no difference was observed concerning esophageal contractile activity in a series of 46 Brazilian patients [60]. On the other hand, Loughney *et*

al. observed lesser esophageal peristaltic amplitude in patients with long-segment Barrett's compared to controls [42]; a difference that was not observed in a comparison with short-segment Barrett's patients. Consequently, even if peristaltic abnormalities are frequently observed in patients with Barrett's esophagus, it is unclear if these abnormalities are a hallmark of severe GERD or if they are independently associated with the genesis of Barrett's.

Conclusion

Hiatal hernia, hypotensive EJG and peristaltic dysfunction are involved in the pathophysiology of GERD as well as in the pathophysiology of Barrett's esophagus; hiatal hernia might even be independently associated with the development of Barrett's mucosa. However, it does not seem that hiatal hernia might is a risk factor for progression to high-grade dysplasia and adenocarcinoma. Hypotensive EGJ and peristaltic dysfunction are clearly associated with the occurrence of severe GERD and esophagitis; they were also frequently encountered in patients with Barrett's. Nonetheless, it does not seem that they are more frequent in patients with Barrett's mucosa than in patients with grade C or D esophagitis. The magnitude of EGJ and peristaltic dysfunctions might contribute to the extent of intestinal metaplasia. Finally, the acid pocket may be an important determinant in the genesis of short-segment Barrett's. However, although some supportive evidence for that hypothesis exists, this remains speculative and further studies are required to fully define the role of acid pocket in the genesis of Barrett's esophagus.

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Practice points

Hiatal hernia is independently associated with the occurrence of long-segment Barrett's esophagus

Hypotensive EGJ and peristaltic dysfunction are risk factor for the occurrence of esophagitis and long-segment Barrett's esophagus

Extension of the proximal margin of acid pocket above the SCJ (intra-sphincteric reflux) as seen in GERD patients may facilitate the development of short-segment Barrett's

Research agenda

The EGJ function should be studied using high resolution manometry and new metrics in patients with Barrett's esophagus and compare with patients with severe GERD

The position of the acid pocket might be studied in patients with short-segment Barrett's esophagus and compare to controls and GERD patients

The role of EGJ dysfunction, peristaltic defect and acid pocket might be evaluated in the progression to dysplasia and adenocarcinoma

Figure 1.

Representative pH tracing during a pH catheter pull-through performed in a control subject. The squamocolumnar junction (SCJ) was previously located with an endoscopic clip. The acid pocket is defined as the region between the proximal pH transition point and the distal pH step-up. Modified from Pandolfino et al, Am J Gastroenterol 2007 [8].

Figure 2.

Hiatal hernia on barium swallow examination. A muscular ring demarcating the proximal margin of the lower oesophageal sphincter and called A ring, might be visible during swallowing as well as a second ring, the B ring, that corresponds to the SCJ. By convention the distinction between normal and hiatus hernia is a 2cm separation between the B ring and the hiatus. In the absence of a B ring, which is only variably present, the globular structure seen radiographically that forms above the diaphragm and beneath the tubular oesophagus during deglutition is more accurately termed the phrenic ampulla. In such cases, the demonstration of rugal folds traversing the diaphragm is used as the defining criterion for hiatus hernia.

Figure 3.

Esophagogastric junction (EGJ) morphology subtypes. For each panel the instantaneous spatial pressure variation plot corresponding to the red line on the pressure topography plot is illustrated by the black line on the right. The two main EGJ components are the lower esophageal sphincter (LES) and the crural diaphragm (CD), which cannot be independently quantified when they are superimposed as with a type I EGJ (Panel A). The respiratory inversion point (RIP), shown by the horizontal dashed line, lies at the proximal margin of the EGJ. During inspiration (I) EGJ pressure increases whereas it decreases during expiration (E). Type II EGJ morphology is illustrated in Panel B. Note the 2 peaks on the instantaneous spatial variation plot; the nadir pressure between the peaks is greater than the intra-gastric pressure. Panels C and D correspond to type III EGJ pressure morphology defined as the presence of 2 peaks of the instantaneous spatial pressure variation plot with a nadir pressure between the peaks equal to or less than intragastric pressure. The RIP is proximal to the CD with type IIIa (Panel C) whereas it is proximal to the LES in type IIIb (Panel D).

Figure 4.

Representative examples of combined, fluoroscopic, manometric and pH pull-through data from a control subject and a GERD patient. This figure illustrates the relative positions of the SCJ, proximal pH transition point (dot) and the EGJ high pressure zone (orange band) during the post prandial state in supine and upright position. The pH transition point occurs below the upper margin of the EGJ high-pressure zone in the control subject but proximal to the SCJ in the GERD patient. Modified from Pandolfino et al, *Am J Gastroenterol* 2007 [8].