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Original Article

Esophageal Hypocontractile Disorders and Hiatal Hernia Size Are Predictors for Long Segment Barrett's Esophagus

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Background/Aims
Presently, there is paucity of information about clinical predictors, especially esophageal motor abnormalities, for long segment Barrett's esophagus (LSBE) as compared with short segment Barrett's esophagus (SSBE). The aims of this study are to compare the frequency of esophageal function abnormalities between patients with LSBE and those with SSBE and to determine their clinical predictors.

Methods
This was a multicenter cohort study that included all patients with a diagnosis of BE who underwent high-resolution esophageal manometry. Motility disorders were categorized as hypercontractile disorders or hypocontractile disorders and their frequency was compared between patients with LSBE and those with SSBE. Multivariable logistic regression modeling was used to calculate the odds of being diagnosed with LSBE relative to SSBE for demographics, comorbidities, medication use, endoscopic findings, and the type of motility disorders.

Results
A total of 148 patients with BE were identified, of which 89 (60.1%) had SSBE and 59 (39.9%) LSBE. Patients with LSBE had a significantly larger hiatal hernia and higher likelihood of erosive esophagitis than patients with SSBE ($P = 0.002$). Patients with LSBE had a significantly lower mean LES resting pressure, distal contractile integral, distal latency, and significantly higher failed swallows and hypocontractile motility disorders than those with SSBE ($P < 0.05$). Hiatal hernia and hypocontractile motility disorder increased the odds of LSBE by 38.0% and 242.0%, as opposed to SSBE.

Conclusions
The presence of a hypocontractile motility disorder increased the risk for LSBE. Furthermore, the risk for LSBE was directly associated with the length of the hiatal hernia.
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Key Words
Barrett's esophagus; Esophagitis; Hernia, hiatal; Manometry

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Introduction

Barrett's esophagus (BE) is defined as ≥ 1 cm extension of salmon-colored mucosa into the tubular esophagus proximal to the esophagogastric junction (EGJ) with biopsy proven intestinal metaplasia.[1-3] BE represents the replacement of normal squamous epithelium with metaplastic columnar epithelium appearing as salmon colored mucosa on white-light endoscopy.[2,3] Barrett's esophagus can further be classified as short segment (< 3 cm) and long segment (≥ 3 cm) based on endoscopic visualization. Risk factors for BE include long standing gastroesophageal reflux disease (GERD), male gender, smoking, Caucasian ethnicity, central obesity, and age over 50 years. The presence of BE increases the risk of esophageal adenocarcinoma by 11-fold.[3-9] BE is identified in approximately 6-8% of patients with chronic GERD.[10]

It has been hypothesized that impaired esophageal motility may lead to prolonged exposure of the distal esophageal mucosa to the noxious effect of gastric refluxate, contributing to the pathogenesis of BE.[11] Only recently have studies shown that esophageal dysmotility is a significant contributing factor to worsening reflux and thus the development of BE.[12-14] The most frequent motor disorders observed in these studies were ineffective esophageal motility (IEM), fragmented peristalsis, absent contractility and hypotensive lower esophageal sphincter.[11,15] It is still unknown whether esophageal motility disorders are the cause, or the consequence, of chronic gastroesophageal reflux.[11] Studies comparing esophageal function abnormalities between patients with long versus short segment BE are relatively scarce and were primarily performed using conventional manometry.[8] Consequently, we aimed to compare the frequency of esophageal motor disorders using high-resolution esophageal manometry (HREM) between patients with short segment BE (SSBE) and long segment BE (LSBE). In addition, we aimed to determine which clinical and demographic characteristics predict the presence of LSBE.

Materials and Methods

This was an international, multicenter study utilizing patients' data from 5 medical centers. Three sites were in the United States and 2 in Mexico. Participating Unites States sites used the SlicerDicer tool in Epic to query the medical record system for all patients with BE who underwent HREM. Sites outside the United States queried their respective medical record systems for the same criteria. Barrett's esophagus was defined per the 2016 American College of Gastroenterology guidelines, which require both endoscopic and histologic documentation of columnar epithelium with intestinal metaplasia extending into the tubular esophagus ≥ 1 cm proximal to the EGJ. BE patients were subdivided into those with short (< 3 cm) and long (≥ 3 cm) segment based on their upper endoscopy results.

Inclusion criteria were patients over the age of 18 who have undergone HREM within the last 7 years (January 1st, 2013-November 1st, 2019) and have been diagnosed with Barrett's Esophagus prior to undergoing HREM. Reasons for exclusion included age younger than 18 years, less than 1 cm of intestinal metaplasia within the esophageal mucosa, and missing data.

Demographics collected included patient age, sex, BMI, and smoking status. Associated comorbidities of interest were diabetes mellitus, heart disease, hypertension, hypothyroidism, rheumatic disorders (systemic lupus erythematosus, scleroderma, Sjögren syndrome, and rheumatic arthritis), GERD, and alcohol abuse. Medications identified in our query were categorized as proton pump inhibitors (PPIs), histamine 2 blockers, sucralfate, neuromodulators (gabapentin, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants), antispasmodics, smooth muscle relaxants (beta blockers, calcium channel blockers, nitroglycerine, and sildenafil), opioids, and prokinetics (Metoclopramide and erythromycin). Endoscopic features included in our query were hiatal hernia size (in centimeters; defined as displacement of the EGJ ≥ 1 cm proximal to the diaphragmatic hiatus), presence of erosive esophagitis, presence of dysplasia, and whether a fundoplication had been performed. Manometry measurements included median integrated relaxation pressure (IRP), mean lower esophageal sphincter (LES) resting pressure, LES residual pressure, distal contractile integral (DCI), contractile front velocity (CFV), distal latency, and percent weak swallows, failed swallows, and large breaks. Motility disorders were defined by the Chicago classification version 3.0 and categorized as hypercontractile disorders (distal esophageal spasm, jackhammer esophagus, esophagogastric junction outflow obstruction, and achalasia type 3), or hypocontractile disorders (absent contractility, IEM, and fragmented peristalsis). Achalasia types 1 and 2 were excluded from this analysis.

The study was approved by the institutional review board of the coordinating center of the study, MetroHealth Medical Center (IRB19-00873), and by all respective institutions providing patient data. Written consent from participants was not required because it was a chart review study and patient data were anonymized to protect confidentiality. The IRB also reviewed and approved the study

protocol, ensuring that it adhered to ethical guidelines for research involving human subjects.

Statistical Methods

R (Vienna, Austria) was used for all analysis. Packages used included Base for summary statistics, chi-square, *t* test, and regression. Summary statistics for continuous variables were reported as mean ± SD. Categorical variables were reported as proportions. Chi-square test was used for categorical variables, *t* test for normally distributed continuous variables, and Mann-Whitney *U* test for non-normal distributed data.

Multivariable logistic regression models were used to calculate the odds of being diagnosed with short segment relative to long segment Barrett's esophagus for the following variables: demographics (age, BMI, and smoking status), comorbidities (diabetes mellitus and rheumatic disorders), medications (neuromodulators, antispasmodics, baclofen, smooth muscle relaxants, opioids, and prokinetics), endoscopic findings (hiatal hernia and erosive esophagitis), and motility disorders (hypocontractile and hypercontractile). Continuous variables included age, BMI, and hiatal hernia size. All other variables were treated as categorical (yes/no). Statistical significance was set at 0.05 and all tests were 2-sided.

Results

A total of 148 patients with BE were identified who underwent manometric testing, of which 89 (60.1%) had short segment BE and 59 (39.9%) had long segment BE (Table 1). There were no significant differences in sex or BMI between the 2 groups, however, smoking was significantly more common among LSBE patients (SSBE, 21.3% and LSBE, 37.3%). Significant differences in comorbidities included diabetes mellitus (SSBE, 20.2% and LSBE, 6.8%) and hypertension (SSBE, 32.6% and LSBE, 15.3%). The most common comorbidity for SSBE was hypertension and alcohol use. The most common comorbidity for LSBE was alcohol use. Significant differences in medication use included neuromodulators (SSBE, 24.7% and LSBE, 8.5%), and smooth muscle relaxants

Table 1. Comparison of Demographics and Clinical Characteristics Between Patients With Short Segment Versus Those With Long Segment Barrett's Esophagus

Variable	Short segment Barrett's esophagus (n = 89)	Long segment Barrett's esophagus (n = 59)	*P*-value
Demographics			
Age (yr)	58.1 ± 12.3	56.2 ± 12.8	0.367
Sex (male)	42 (47.2)	34 (57.6)	0.242
BMI (kg/m^2)	28.6 ± 5.9	27.5 ± 7.9	0.341
Smoking	19 (21.3)	22 (37.3)	0.040
Comorbidities			
Diabetes mellitus	18 (20.2)	4 (6.8)	0.032
Heart disease	4 (4.5)	7 (11.9)	0.116
Hypertension	29 (32.6)	9 (15.3)	0.021
Hypothyroidism	4 (4.5)	4 (6.8)	0.713
Rheumatic disorder	6 (6.7)	5 (8.5)	0.755
GERD	1 (1.1)	1 (1.7)	1
Alcohol use	28 (31.5)	23 (39.0)	0.380
Medications			
PPI	76 (85.4)	51 (86.4)	1
H2RA	9 (10.1)	3 (5.1)	0.364
Sucralfate	1 (1.1)	1 (1.7)	1
Neuromodulators	22 (24.7)	5 (8.5)	0.016
Antispasmodics	3 (3.4)	1 (1.7)	1
Smooth muscle relaxants	26 (29.2)	7 (11.9)	0.015
Opioids	8 (9.0)	1 (1.7)	0.087
Prokinetics	7 (7.9)	6 (10.2)	0.768

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; H2RA, histamine H2 receptor antagonists; BMI, body mass index.
Data are presented as mean ± SD or n (%).

Table 2. Comparison of Endoscopic Findings Between Patients With Short Segment Versus Those With Long Segment Barrett's Esophagus

Variable	Short segment Barrett's esophagus (n = 89)	Long segment Barrett's esophagus (n = 59)	*P*-value
Endoscopic findings			
Hiatal hernia (cm)	1.17 ± 1.59	2.11 ± 1.89	0.002
Esophagitis	17 (19.1)	26 (44.8)	0.001
Barrett's length (cm)	1.56 ± 0.51	4.19 ± 1.47	< 0.001
Presence of dysplasia	6 (6.7)	6 (10.2)	0.209
Surgical fundoplication	11 (12.4)	7 (11.9)	> 0.999

Data are presented as mean ± SD or n (%).

Table 3. Comparison of Esophageal Manometric Metrics and Diagnoses Between Patients With Long Segment Versus Those With Short Segment Barrett's Esophagus

Variable	Short segment Barrett's esophagus (n = 89)	Long segment Barrett's esophagus (n = 59)	*P*-value
Median IRP	9.02 ± 10.17	6.71 ± 5.73	0.082
Mean LES resting pressure	25.91 ± 16.14	14.74 ± 9.08	< 0.001
LES residual pressure	7.21 ± 7.27	3.85 ± 3.56	0.001
DCI	1748.20 ± 1592.79	860.22 ± 1152.21	< 0.001
CFV	4.50 ± 4.47	3.51 ± 2.01	0.087
Weak swallows	15.37 (23.37)	22.14 (22.86)	0.093
Failed swallows	18.54 (28.20)	35.00 (35.68)	0.005
Large breaks	7.56 (21.81)	13.21 (22.08)	0.140
Distal latency	7.02 ± 2.29	6.18 ± 2.59	0.053
Motility disorders			
Hypercontractile disorders	8 ± 9.00	1 ± 1.69	0.087
Hypocontractile disorders	33 ± 37.08	40 ± 67.80	< 0.001

IRP, integrated relaxation pressure; LES, lower esophageal sphincter; DCI, Distal contractile integral; CFV, contractile front velocity.
Data are presented as mean ± SD or n (%).

(SSBE, 29.2% and LSBE, 11.9%).

Mean hiatal hernia size (SSBE, 1.17 cm and LSBE, 2.11 cm; $P = 0.002$) and the presence of erosive esophagitis (EE; SSBE, 19.1% and LSBE, 44.8%; $P = 0.001$) were significantly different between both groups (Table 2). Manometric testing revealed significant differences between both groups for mean LES resting pressure, LES residual pressure, DCI, and percent failed swallows. Hypocontractile motility disorders were significantly more common in LSBE as compared with SSBE (67.8% vs 37.1%, respectively, $P \leq 0.001$) (Table 3).

On univariate analysis, the presence of diabetes mellitus and use of neuromodulators decreased the odds for LSBE, with an OR of 0.29 (95% CI, 0.08-0.83) and 0.30 (95% CI, 0.10-0.80), respectively. Neither of these variables were statistically significant on multivariable analysis (Table 4). The presence of EE increased the risk for LSBE, with an OR of 3.39 (95% CI, 1.63-7.22), however, this was also not significant on multivariable analysis. All other variables attaining significance had a similar direction and magnitude in the univariable and multivariable regression models.

On multivariable analysis, patients with hiatal hernia had a 38.0% (OR, 1.38; 95% CI, 1.09-1.79) increase in the odds for LSBE, as opposed to SSBE, for every 1 cm increase in hernia size (Table 4). The presence of a hypocontractile motility disorder increased the odds for LSBE, as opposed to SSBE, with an OR of 3.42 (95% CI, 1.50-8.17). No statistically significant correlations were found for all other variables examined.

Discussion

This is the first study that assessed clinical predictors for LSBE using HREM data. We demonstrated that hypocontractile motility disorders and hiatal hernia size were strong predictors for the pres-

Table 4. Multivariable Analysis of the Predictors for Long Segment Barrett's Esophagus

Variable	Short segment Barrett's esophagus (n = 89)	Long segment Barrett's esophagus (n = 59)	Adjusted OR multivariable	CI lower bound (2.5%)	CI upper bound (97.5%)
Demographics					
Age (yr)	58.1 ± 12.33	56.2 ± 12.79	1.00	0.97	1.03
BMI (kg/m^2)	28.6 ± 5.93	27.5 ± 7.86	1.01	0.95	1.07
Smoking	19 (21.3)	22 (37.3)	1.00	0.37	2.62
Comorbidities					
Hypertension	29 (32.6)	9 (15.3)	0.60	0.16	2.07
Diabetes mellitus	18 (20.2)	4 (6.8)	0.49	0.09	2.26
Rheumatic disorder	6 (6.7)	5 (8.5)	0.94	0.16	5.65
Medications					
Neuromodulators	22 (24.7)	5 (8.5)	0.32	0.08	1.15
Antispasmodics	3 (3.4)	1 (1.7)	1.68	0.06	20.53
Smooth muscle relaxants	26 (29.2)	7 (11.9)	0.45	0.11	1.69
Opioids	8 (9.0)	1 (1.7)	0.19	0.01	2.11
Prokinetics	7 (7.9)	6 (10.2)	0.79	0.19	3.33
Endoscopic findings					
Hiatal hernia (cm)	1.17 ± 1.59	2.11 ± 1.89	1.38	1.09	1.79
Esophagitis	17 (19.1)	26 (44.8)	2.38	0.90	6.47
Motility disorders					
Hypercontractile disorders	8 (9.00)	1 (1.69)	0.67	0.03	5.27
Hypocontractile disorders	33 (37.08)	40 (67.80)	3.42	1.50	8.17

BMI, body mass index.
Data are presented as mean ± SD or n (%).

ence of LSBE. Savarino et al[14] have shown that among all GERD phenotypes, BE had the highest rate of hypocontractile esophageal motility disorders (42.0%) as compared with EE and non-erosive reflux disease (NERD) (38.0% and 19.0%, respectively). Furthermore, the presence of hiatal hernia was significantly higher in BE than EE and NERD patients (82.0% vs 70.0% vs 58.0%, respectively; $P < 0.05$). Moreover, Gutschow et al[16] reported more esophageal motility disorders in BE patients than in EE and NERD (27.3% vs 6.7% vs 16%, respectively). Using conventional esophageal manometry, Loughney et al[17] reported that those with LSBE had lower amplitude contractions as compared to SSBE and controls.

The aforementioned studies established the relationship between BE and esophageal motor disorders, specifically those with reduced esophageal amplitude contractions. While our study demonstrated that hypocontractile motility disorders are highly predictive of LSBE, it is unclear from our study or the literature if the presence of a hypocontractile motility disorder is a risk for BE development or a consequence of it. The concept that BE develops in patients with abnormal clearance of acid reflux due to esophageal motor abnormalities, especially if the result in a high esophageal acid dwell time, is physiologically feasible. The absence of properly occlusive peristaltic waves and a weak lower esophageal sphincter may facilitate the injurious effect of noxious substances in the refluxate on the esophageal mucosa. This may eventually lead to the replacement of normal esophageal squamous epithelium by metaplastic columnar epithelium.

Recognizing that the length of BE directly correlates with the degree of esophageal acid exposure suggests that this is the underlying mechanism for the development of LSBE, the type of BE that is more commonly associated with the emergence of adenocarcinoma of the esophagus.[7,18]

The presence of hiatal hernia is highly prevalent among patients with BE (up to 96.0%).[19] The close relationship between hiatal hernia and BE has been previously described in the literature as well as the correlation between LSBE and hiatal hernia length. A meta-analysis has shown that the presence of hiatal hernia is associated with an increased risk of developing BE (OR, 3.94; 95% CI, 3.02-3.96).[20] It has also been demonstrated that the length of hiatal hernia is significantly greater in BE patients than in controls (96.0% vs 42.0%, respectively; $P < 0.001$), those with EE ($P < 0.003$) or patients with NERD ($P < 0.005$).[21] Dickman et al[8] demonstrated

that there is a significant correlation between LSBE and hiatal hernia length ($r = 0.22$, $P < 0.01$), presence of dysplasia ($t = -2.3$, $P < 0.05$), histamine H2 receptor antagonists use ($t = 1.98$, $P < 0.05$), and nonsmoking ($t = -2.5$, $P < 0.05$), while SSBE was correlated with PPI use ($t = 1.96$, $P < 0.05$. Similarly, we found that LSBE was associated with a significantly longer hiatal hernia than SSBE. In addition, with every 1 cm increase in hiatal hernia length (OR, 1.44; 95% CI, 1.12-1.88) there is a greater risk for having LSBE. Like previous studies, we demonstrated a close relationship between hiatal hernia length and the likelihood of having LSBE.

Our study also demonstrated that mean LES resting pressure and DCI were significantly lower in those with LSBE as compared to patients with SSBE. The finding that LES residual pressure was significantly lower in LSBE versus SSBE patients is likely because the mean LES basal pressure was already significantly lower in LSBE subjects. Furthermore, LSBE patients had a significantly higher percent of failed swallows and presence of hypocontractile esophageal motility disorder as compared to those with SSBE. Two thirds of the LSBE patients, as compared to one third of the SSBE patients, had a hypocontractile motor disorder, primarily IEM. This is the first study to report that the more severe the BE (LSBE) the greater the likelihood patients will demonstrate an esophageal motor abnormality. Other investigators have shown that the LES is more "defective" or weaker in patients with LSBE as compared to those with SSBE.[22-27] It has been hypothesized that hypocontractility, in addition to the presence of a hiatal hernia, increases esophageal acid dwell time and thus the likelihood of esophageal mucosal injury.[22] As previously mentioned, several studies have shown that there is a close correlation between esophageal acid exposure and the length of BE.[5,7] It remains to be determined, though, which is the "chicken and which is the egg."

Our study has a number of limitations. It was a retrospective cohort study, and as such causation cannot be proven with respect to the effect of our predictors on LSBE and SSBE. Furthermore, since our study was conducted using chart review, deficiencies and incorrect documentation of demographics, comorbidities and medications may be present. However, one of the study strengths is the multi-center source of the collected data, suggesting a more diverse patient population.

In conclusion, we demonstrated that hypocontractile motility disorders, primarily IEM, and hiatal hernia, increase the risk for LSBE. Esophageal motor abnormalities, primarily reduced esophageal body and LES function, are significantly more common in LSBE as compared with SSBE. These esophageal function findings may explain the higher esophageal acid and non-acid exposure in patients with LSBE as compared to those with SSBE.

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Conflicts of interest: None.

Author contributions: Fahmi Shibli performed study conceptualization and design, data collection, statistical analysis, and manuscript preparation; Ofer Z Fass performed statistical analysis, manuscript preparation and editing; Oscar Matsubara Teramoto, José M Remes-Troche, Vikram Rangan, and Michael Kurin performed data collection and manuscript editing; and Ronnie Fass performed study conceptualization, manuscript editing, and project supervision.

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