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ORIGINAL ARTICLE

Gender, medication use and other factors associated with esophageal motility disorders in non-obstructive dysphagia

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Abstract

Background: High-resolution esophageal manometry (HREM) is the diagnostic test of choice for evaluation of non-obstructive dysphagia. Studies regarding the predictors of esophageal dysmotility are limited. Therefore, our aim was to study the prevalence of and factors associated with esophageal motility disorders in patients with non-obstructive dysphagia.

Methods: We performed a retrospective review of all patients with non-obstructive dysphagia who underwent HREM in a tertiary center between 1 January 2014 and 31 December 2015. After obtaining IRB approval (16–051), clinical records were scrutinized for demographic data, symptoms, medication use, upper endoscopic findings and esophageal pH findings. HREM plots were classified per Chicago Classification version 3.0. Primary outcome was prevalence of esophageal motility disorders; secondary outcomes assessed predictive factors.

Results: In total, 155 patients with non-obstructive dysphagia (55 ± 16 years old, 72% female) were identified. HREM diagnosis was normal in 49% followed by ineffective esophageal motility in 20%, absent contractility in 7.1%, achalasia type II in 5.8%, outflow obstruction in 5.2%, jackhammer esophagus in 4.5%, distal esophageal spasm in 3.9%, fragment peristalsis in 1.9%, achalasia type I in 1.9%, and achalasia type III in 0.6%. Men were five times more likely to have achalasia than women [odds ratio (OR) 5.3, 95% confidence interval (CI): 2.0–14.2; $P = 0.001$]. Patients with erosive esophagitis (OR 2.9, 95% CI: 1.1–7.7; $P = 0.027$) or using calcium channel blockers (OR 3.0, 95% CI: 1.2–7.4; $P = 0.015$) were three times more likely to have hypomotility disorders.

Conclusion: From this study, we concluded that HREM diagnosis per Chicago Classification version 3.0 was normal in 49% of patients with non-obstructive dysphagia. Male gender, erosive esophagitis and use of calcium channel blockers were predictive of esophageal motility disorders.

Key words: Impaired swallowing; high-resolution esophageal manometry; esophageal motility disorders

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Introduction

Dysphagia is a frequent symptom of esophageal motility disorders. Following initial evaluation with barium swallow or esophagogastroduodenoscopy (EGD), esophageal manometry is traditionally used to evaluate non-obstructive dysphagia [1]. In studies using conventional manometry, 53% of patients with non-obstructive dysphagia demonstrated abnormal manometric findings, the most frequent of those being nonspecific esophageal motility disorders, followed by achalasia and nutcracker esophagus [2]. Improvement in pressure sensors in high-resolution esophageal manometry (HREM), now located 1 cm apart compared to 4–5 cm in conventional manometry, has allowed HREM to become the most sensitive test to diagnose esophageal motility disorders [3]. This notion has been supported in a study where HREM was compared to conventional line tracings [4]. This study showed that the odds of an incorrect esophageal motility diagnosis and incorrect identification of a major motility disorder were over three times higher with line tracing than with HREM. In a randomized control trial comparing HREM to conventional manometry, HREM led to increased diagnostic yield for achalasia and more frequent confirmation on a repeat study [5]. Therefore, the authors concluded that motility disorders may be identified earlier with HREM than with conventional manometry.

In 2007, the Chicago Classification of esophageal motility was developed to categorize esophageal motility disorders by HREM, facilitating interpretation of swallows and creating a hierarchical analysis [6]. Since the initial consensus, two iterations of the Chicago Classification have been published, the most recent summarized as version 3 [7]. When performing HREM and applying metrics set by the newest criteria, we are limited on up-to-date data regarding the prevalence and predictors of esophageal motility disorders. A randomized control trial of HREM on 123 patients with unexplained dysphagia revealed 27% with hypomotility disorders, 26% with achalasia and normal study in 28% of patients [5]. However, this study did not address predicting factors for esophageal dysmotility.

Based on this literature review, we presume that only a certain subset of patients have an abnormal motility study even though HREM is known to improve diagnostic yield of motility disorders. Identifying the clinical characteristics of these patients can lead to more prudent use of this technology. Therefore, we aimed to determine the prevalence of esophageal motility disorders applying the newest Chicago Classification version 3.0 and identify factors associated with abnormal HREM study.

Patients and methods

All adults (≥18 years of age) with persisting dysphagia symptoms, no structural lesions on EGD within 1 year before or after HREM and referred for HREM at our institution from 1 January 2014 through 31 December 2015 were eligible for inclusion. Patients with known esophageal motility disorders prior to HREM (e.g. achalasia), structural lesions seen on EGD to explain dysphagia symptoms, prior esophageal or gastric surgeries and known eosinophilic esophagitis were excluded. The study was conducted with approval by the institutional review board. Informed written consent was not obtained given the retrospective nature of this study.

Study design

Charts of patients meeting inclusion criteria were reviewed. HREM studies were reviewed and interpreted per Chicago Classification version 3.0. To assess various predictors of abnormal esophageal motility disorders, baseline variables such as age, gender, race, smoking, alcohol abuse and medication use including proton pump inhibitors, histamine receptor antagonists, opioids, antidepressants and calcium channel blockers were obtained. Other variables obtained were comorbidities including hypertension, diabetes mellitus, stroke/transient ischemic attack and coronary artery disease, patient symptoms of weight loss, heartburn, acid regurgitation and chest pain and endoscopic and ambulatory esophageal pH monitoring data.

HREM studies were performed using the ManoScan system (Medtronic, Minneapolis, MN) after patients were off motility altering drugs for appropriate intervals. Data were categorized by basal lower esophageal sphincter (LES) pressures, LES integrated relaxation pressures, distal contractile integral (DCI), distal latency (DL), number and type of swallows. Each study was analysed using ManoScan software (Medtronic, Minneapolis, MN).

A subset of patients also underwent pH monitoring typically off acid suppression with Bravo pH wireless capsule (Medtronic, Minneapolis, MN) placed 6 cm proximal to the esophagogastric junction (EGJ) and attached to the mucosal wall by a vacuum pump or 24-hour Versaflex disposable pH catheter (Medtronic, Minneapolis, MN). Data were categorized by type of pH testing (24 vs 48 hours), total % time spent in reflux, upright % time spent in reflux, supine % time spent in reflux and DeMeester score.

Outcomes measurement

Esophageal motility disorders were grouped into four categories: absence of esophageal motility disorder (normal manometry), achalasia/EGJ outflow obstruction, hypermotility disorders (distal esophageal spasm, jackhammer esophagus) and hypomotility disorders (ineffective esophageal motility, fragmented peristalsis or absent contractility). The latter two categories were a merge of multiple diagnoses, as these disorders are rare and commonly require similar management. The primary outcome of this study was measuring the prevalence of esophageal motility disorders after HREM in non-obstructive dysphagia. Secondary outcomes were quantifying differences among motility disorders and predicting factors for each group.

Statistical analysis

Data are presented as median (25^{th}, 75^{th} percentiles) or frequency (percent). Univariable analysis was performed to assess differences between the four motility groups. Non-parametric Kruskal-Wallis tests were used to compare continuous variables and Pearson's chi-square tests or Fisher's Exact tests were used for categorical factors. When there was evidence to suggest a difference between at least two groups, post-hoc comparisons were performed and a Bonferroni correction was used.

Logistic regression analysis was performed to assess possible predictors of each disorder. For this, we evaluated the odds of having each particular motility disorder as opposed to not having it [e.g. achalasia vs no achalasia (normal, hyper and hypo combined)]. Final multivariable models were chosen using the branch-and-bound algorithm of Furnival and Wilson to identify the best three models [with the highest likelihood score (chi-square) statistic] composed of two parameters

for achalasia, five parameters for hypomotility and up to seven parameters for normal manometry; these models were further explored and the Akaike information criterion and log likelihood statistics were used to choose the final model. All analyses were performed using SAS (version 9.4, The SAS Institute, Cary, NC) and a $P < 0.05$ was considered statistically significant.

Results

One hundred fifty-five patients met study criteria. The mean age was 55 ± 16 years and the majority were women (72.3%). There were 100 (64.5%) patients presenting with solid-food dysphagia only, 5 (3.2%) patients presenting with dysphagia to liquids only and 50 (32.3%) with dysphagia to both liquids and solids.

Prevalence of esophageal motility disorders

The manometric diagnosis was normal in 76 patients. The most frequent abnormality was ineffective esophageal motility in 31 patients, absent contractility in 11, achalasia type I in 3, Type II in 9, type III in 1, EGJ outflow obstruction in 8, jackhammer esophagus in 7, distal esophageal spasm in 6 and fragment peristalsis in 3 patients (Figure 1).

Differences among motility disorders

For the purpose of our study, patients were categorized into four groups: normal ($n = 76$), achalasia/EGJ outflow obstruction ($n = 21$), hypermotility (distal esophageal spasm or jackhammer) ($n = 13$) or hypomotility (absent contractility, ineffective esophageal motility or fragmented peristalsis) ($n = 45$). Patients with achalasia were more likely to be male ($P = 0.002$). Differences in race ($P = 0.83$), smoking status ($P = 0.28$) and history of alcohol use ($P = 0.20$), however, were not seen between the four groups. Additionally, we did not observe significant distinctions in symptoms of weight loss ($P = 0.53$), chest pain ($P = 0.41$) and heartburn ($P = 0.64$), as well as comorbidities of hypertension ($P = 0.32$), diabetes ($P = 0.48$), stroke ($P = 0.61$) and coronary artery disease ($P = 0.92$) (Table 1).

As depicted in Table 2, on comparing endoscopic findings among the groups, we observed that patients with achalasia were more likely to have a dilated esophageal lumen on EGD ($P = 0.01$). Forty-three patients underwent esophageal biopsy during EGD, with the majority showing reflux-related changes. Given the overall low numbers in each category, however, further subgroup analysis regarding predictors was not performed. Similarly, pH data were available in 35 patients. No differences were observed and further subgroup analysis was not performed given the overall low numbers.

Factors associated with motility disorders

Patients with normal esophageal manometry were less likely to use calcium channel blockers [odds ratio (OR) 0.28, 95% confidence interval (CI): 0.11–0.71, $P = 0.01$] or demonstrate a dilated esophageal lumen on EGD (OR 0.21, 95% CI: 0.06–0.76, $P = 0.02$) (Table 3). After adjusting for age and comorbidities, a normal manometry diagnosis continued to have a negative association with these factors (OR 0.29, 95% CI: 0.11–0.79, $P = 0.015$ and OR 0.25, 95% CI: 0.06–0.96, $P = 0.44$, respectively). Chest pain was more likely to be associated with normal manometry (OR 2.1, 95% CI: 0.96–4.4). This finding, however, fell short of statistical significance ($P = 0.065$).

Patients using calcium channel blockers were almost three times more likely to have hypomotility esophageal disorders (OR 2.6, 95% CI: 1.1–6.0, $P = 0.03$). Erosive esophagitis was another factor found to be associated with these disorders (OR 2.6, 95% CI: 1.07–6.5, $P = 0.04$) (Table 3). After adjusting for opiate use, patients with erosive esophagitis (OR 2.9, 95% CI: 1.1–7.7, $P = 0.027$) or using calcium channel blockers (OR 3.0, 95% CI: 1.2–

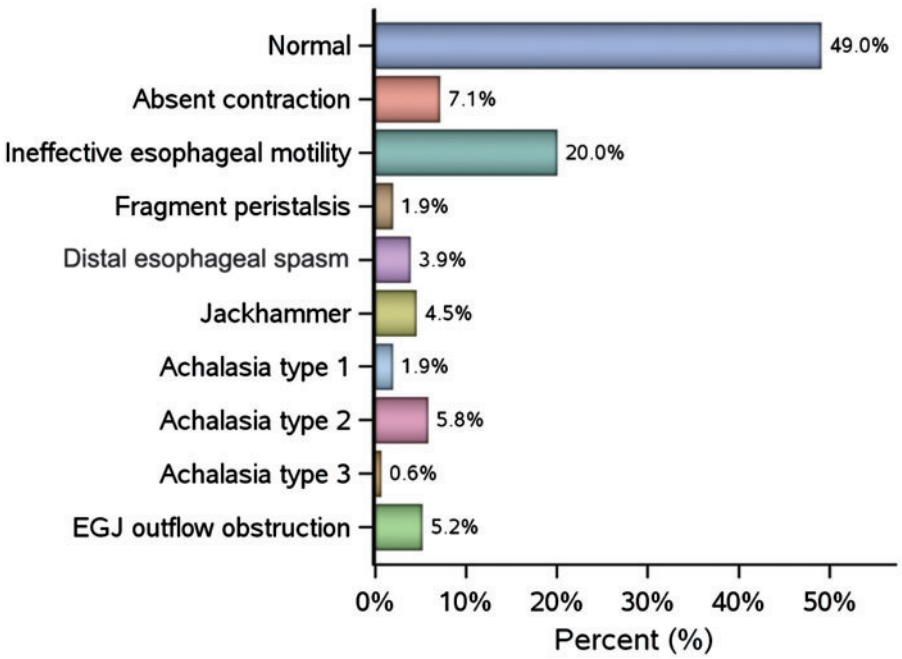

Figure 1. Prevalence of motility disorders following high-resolution esophageal manometry (HREM). Percent (%) = various manometric findings out of all patients with non-obstructive dysphagia ($n = 155$). Left column represents all possible diagnostic findings by HREM following Chicago Classification version 3.0. EGJ, esophagogastric junction.

Table 1. Demographic and clinical characteristics of patients with non-obstructive dysphagia

	Normal manometry (N = 76)	Achalasia/EGJ outflow obstruction (N = 21)	Hypermotility disorders (N = 13)	Hypomotility disorders (N = 45)	P-value
Demographics and social habits					
Age (years)	56 [42.5, 66]	64 [42, 75]	59.0 [47, 63]	56.0 [40, 68]	0.44[c]
Gender					0.002[a]
Female	60 (78.9)	8 (38.1)	11 (84.6)	33 (73.3)	
Male	16 (21.1)	13 (61.9)[d]	2 (15.4)[e]	12 (26.7)[e]	
Race					0.83[b]
White	58 (79.5)	16 (76.2)	12 (92.3)	39 (86.7)	
Black	13 (17.8)	4 (19.0)	1 (7.7)	5 (11.1)	
Other	2 (2.7)	1 (4.8)	0 (0.0)	1 (2.2)	
Smoking					0.28[a]
Never	46 (60.5)	8 (38.1)	9 (69.2)	28 (62.2)	
Past	23 (30.3)	11 (52.4)	4 (30.8)	11 (24.4)	
Current	7 (9.2)	2 (9.5)	0 (0.0)	6 (13.3)	
Alcohol use	32 (43.8)	9 (45.0)	3 (23.1)	19 (43.2)	0.55[a]
Symptoms and comorbidities					
Weight loss	18 (23.7)	3 (14.3)	2 (15.4)	13 (28.9)	0.53[a]
Chest pain	42 (55.3)	8 (38.1)	8 (61.5)	21 (46.7)	0.41[a]
Reflux	57 (75.0)	13 (61.9)	9 (69.2)	34 (75.6)	0.64[a]
Hypertension	27 (35.5)	12 (57.1)	6 (46.2)	20 (44.4)	0.32[a]
Diabetes	9 (11.8)	5 (23.8)	3 (23.1)	7 (15.6)	0.48[a]
Stroke	7 (9.2)	2 (9.5)	2 (15.4)	2 (4.4)	0.61[a]
Coronary artery disease	10 (13.2)	4 (19.0)	2 (15.4)	6 (13.3)	0.92[a]
Medications					
Proton pump inhibitors	54 (71.1)	13 (61.9)	10 (76.9)	29 (64.4)	0.70[a]
H2 receptor antagonist	15 (19.7)	3 (14.3)	5 (38.5)	13 (28.9)	0.27[a]
Opiates	24 (31.6)	6 (28.6)	7 (53.8)	10 (22.2)	0.18[a]
Antidepressant medications	27 (35.5)	7 (33.3)	6 (46.2)	22 (48.9)	0.44[a]
Calcium channel blockers	7 (9.2)	4 (19.0)	4 (30.8)	13 (28.9)[d]	0.03[a]

Statistics presented as Median [P25, P75] or Number (%). P-values:
[a]Pearson's chi-square test.
[b]Fisher's Exact test.
[c]Kruskal-Wallis test.
[d]Significantly different from Normal.
[e]Significantly different between Hypermotility or Hypomotility and Achalasia/EGJ.
[f]Significantly different between Hypomotility and Hypermotility. A significance level of 0.008 was used for pairwise ad-hoc comparisons. EGJ, esophagogastric junction.

7.4, $P = 0.015$) were three times more likely to have hypomotility disorders.

Patients of male gender (OR 5.6, 95% CI: 2.1–14.9, $P < 0.001$), past smoking history (OR 3.0, 95% CI: 1.1–8.1, $P = 0.03$) and a dilated esophageal lumen on EGD (OR 5.0, 95% CI: 1.6–15.6, $P = 0.01$) were more likely to have manometric findings consistent with achalasia (Table 3). On multivariate analysis, male gender (OR 5.3, 95% CI: 2.0–14.2, $P = 0.001$) remained predictive of achalasia and presence of a hiatal hernia was protective of achalasia (OR 0.2, 95% CI: 0.04–0.91, $P = 0.04$). Multivariable logistic regression analysis was performed for achalasia and hypomotility but not for hypermotility because only 13 patients were found in this group.

Discussion

In this study on patients presenting with non-obstructive dysphagia, we report the prevalence of esophageal motility disorders and factors associated with esophageal dysmotility. Nearly half the patients were found to have normal manometry, followed by ineffective esophageal motility, achalasia, EGJ outflow obstruction, jackhammer esophagus, distal esophageal spasm and fragment peristalsis in decreasing order. Male gender, calcium channel blocker use, erosive esophagitis and dilated esophageal lumen were factors associated with esophageal dysmotility.

Previous studies evaluating the prevalence of motility disorders in patients presenting with non-obstructive dysphagia revealed varying prevalence of dysmotility. In a study using conventional manometry, the most prevalent finding was normal study in 47% of patients followed by nonspecific esophageal motility disorders in 39% and achalasia in 36% of patients [2]. In a landmark study of 400 patients, HREM study was normal in 22.7% of patients, showed achalasia or variants in 29% of patients and hypomotility disorders in 25.5% of patients [6]. However, this study population included not only patients presenting with dysphagia, but also those with chest pain or known motility disorders or prior surgery—groups that we excluded in our study. Recently, the superiority of HREM analysis over conventional manometry in unexplained dysphagia was compared. In doing so, Roman *et al.* also demonstrated the absence of motility disorders and nonspecific disorders were frequently encountered with conventional manometry and HREM (52 and 12% vs 28 and 3%, respectively), suggesting a common trend of normal manometric findings in non-obstructive dysphagia [5]. Although the study of Roman *et al.* applied HREM in

Table 2. Esophagogastroduodenoscopy, high-resolution esophageal manometry (HREM) and pH findings of patients with non-obstructive dysphagia

	Normal manometry (*N* = 76)	Achalasia/EGJ outflow obstruction (*N* = 21)	Hypermotility disorders (*N* = 13)	Hypomotility disorders (*N* = 45)	*P*-value
Endoscopic findings					
Any abnormality	22 (28.9)	6 (28.6)	6 (46.2)	20 (44.4)	0.25[a]
Esophagitis	8 (10.5)	2 (9.5)	2 (15.4)	11 (24.4)	0.18[a]
Barrett's esophagus	1 (1.3)	0 (0.0)	0 (0.0)	1 (2.2)	0.99[b]
Schatzki ring	11 (14.5)	1 (4.8)	2 (15.4)	6 (13.3)	0.69[a]
Dilated esophageal lumen	3 (3.9)	6(28.6)[d]	2(15.4)	5(11.1)	0.01[a]
Ringed appearance	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.99[b]
Esophageal ulcers	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0.51[b]
Esophageal diverticulum	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.99[b]
Hiatal hernia	27 (35.5)	2 (9.5)	4 (30.8)	18 (40.9)	0.08[a]
Esophageal histological findings					0.06[b]
Normal	16 (57.1)	3 (50.0)	–	2 (22.2)[d]	
Reflux changes	11 (39.3)	1 (16.7)	–	6 (66.6)	
Barrett's esophagus	1 (3.6)	2 (33.3)	–	1 (11.1)	
Findings on HREM					
Basal UES pressure, mmHg	55.0 [39.4, 72.7]	50.9 [39.6, 74.6]	55.8 [19.1, 65.5]	57.4 [36.7, 93.5]	0.60[c]
Basal LES pressure, mmHg	25.4 [15.7, 38.8]	42.7 [35.3, 54.6][d]	26.1 [15.8, 40.7]	14.0 [7.3, 24.5][d, e]	<0.001[c]
Residual LES pressure, mmHg	3.0 [1.5, 6.1]	20.8 [15.1, 23.7][d]	7.0 [4.7, 8.4][d, e]	1.9 [0.3, 4.5][e, f]	<0.001[c]
Distal contractile integral	1721.6 [1141.1, 2446.2]	1172.6 [675.7, 3737.4]	3782.1 [1303.5, 8624.4]	441.7 [317.4, 690.4][d, e, f]	<0.001[c]
Contractile front velocity	3.3 [2.7, 4.3]	8.0 [3.1, 21.5]	3.1 [2.4, 5.2]	3.0 [2.4, 4.2]	0.09[c]
Average intrabolus pressure	11.7 [7.7, 14.6]	24.0 [18.5, 30.2][d]	13.5 [12.4, 15.5][e]	10.1 [7.5, 14.2][e]	<0.001[c]
Distal latency	6.7 [5.8, 7.7]	5.6 [3.8, 6.5][d]	5.3 [4.7, 7.0]	7.1 [6.3, 7.9][e]	0.001[c]
pH Testing	*N* = 16	*N* = 5	*N* = 4	*N* = 10	
Total % of time pH ≤4	2.8 [0.25, 9.0]	3.3 [1.00, 14.2]	8.2 [0.30, 17.7]	2.9 [1.6, 12.2]	0.78[c]
Abnormal total reflux	6 (37.5)	2 (40.0)	2 (50.0)	4 (36.4)	0.99[b]
Upright % time spent in reflux	2.2 [0.25, 9.6]	5.1 [1.5, 14.2]	5.6 [0.40, 13.6]	3.5 [1.00, 16.5]	0.71[c]
Abnormal upright reflux	6 (37.5)	2 (40.0)	2 (50.0)	4 (36.4)	0.99[b]
Supine time spent in reflux (%)	0.00 [0.00, 4.7]	0.30 [0.20, 14.2]	7.9 [0.15, 25.0]	1.6 [0.00, 2.5]	0.48[c]
Abnormal supine reflux	5 (31.3)	2 (40.0)	2 (50.0)	2 (18.2)	0.67[b]
DeMeester score	10.4 [1.5, 25.9]	11.8 [4.6, 58.2]	29.2 [2.1, 68.6]	12.0 [7.2, 35.0]	0.74[c]
Abnormal DeMeester score	8 (50.0)	2 (40.0)	2 (50.0)	4 (36.4)	0.96[b]

Statistics presented as Median [P25, P75] or Number (%). *P*-values:
[a]Pearson's chi-square test.
[b]Fisher's Exact test.
[c]Kruskal-Wallis test.
[d]Significantly different from Normal.
[e]Significantly different between Hypermotility or Hypomotility and Achalasia/EGJ.
[f]Significantly different between Hypomotility and Hypermotility. A significance level of 0.008 was used for pairwise ad-hoc comparisons. EGJ, esophagogastric junction; LES, lower esophageal sphincter; UES, upper esophageal sphincter.

assessing prevalence, there is a paucity of data regarding what clinical factors predict esophageal motility disorders in patients presenting with non-obstructive dysphagia. A few studies reported effects of opiates, skeletal muscle relaxants and diabetes as factors associated with esophageal dysmotility [8–10].

We found that calcium channel antagonist use is associated with ineffective esophageal motility. Calcium channel antagonists function by inhibiting intracellular calcium uptake and can inhibit esophageal peristalsis and lower LES pressures [11]. Therefore, this therapy has been applied in distal esophageal spasm and jackhammer esophagus, ameliorating chest pain and dysphagia symptoms [12]. Therefore, it was not unexpected for us to find hypomotility disorders, including absent peristalsis, fragmented peristalsis and ineffective esophageal motility disorders, occurring more frequently with exposure to calcium channel antagonists ($P = 0.015$). Furthermore, we observed the known relationship between hypomotility esophageal disorders and erosive esophagitis. In fact, an estimated 21–49% of patients with ineffective esophageal motility have a concomitant diagnosis of gastroesophageal reflux disease (GERD) [13]. Chronic acid exposure is hypothesized to lead to irreversible changes in esophageal motor function [13], resulting in lower LES pressures and decreased esophageal peristaltic wave amplitudes, longer durations of contractions and slower velocity of propagation [14]. These associations have led to more frequent presence of erosive esophagitis in hypomotility esophageal disorders, as evident in our study.

Important predicting factors observed among patients with achalasia were male gender, non-smoker or remote history and a dilated esophagus on EGD. Male gender as a predictive factor for achalasia in patients presenting with non-obstructive dysphagia is surprising. Available data suggest that achalasia has equal prevalence in men and women [15]. In contrast, if a hiatal hernia was found on EGD, this factor was found to predict against achalasia. This rarity of achalasia and presence of hiatal hernia has been well documented, dating back to the 1960s. Binder *et al.* reviewed a series of patients with achalasia diagnosed by a combination of clinical history, esophagrams, EGD

Table 3. Univariable analysis of factors associated with esophageal motility disorders

Factor	Normal manometry		Achalasia/ EGJ outflow obstruction		Hypomotility disorders		Hypermotility disorders	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (5-year increment)	0.95 (0.86–1.05)	0.35	1.1 (0.96–1.3)	0.13	0.97 (0.87–1.08)	0.62	1.06 (0.88–1.3)	0.52
Male vs female	0.51 (0.25–1.06)	0.07	5.6 (2.1–14.9)	<0.001	0.93 (0.42–2.0)	0.85	0.45 (0.10–2.1)	0.31
Caucasian race	0.69 (0.30–1.6)	0.39	0.65 (0.21–1.9)	0.44	1.6 (0.59–4.2)	0.36	2.8 (0.34–22.2)	0.34
Past smoking	0.87 (0.43–1.7)	0.68	3.0 (1.1–8.1)	0.03	0.65 (0.29–1.5)	0.3	0.61 (0.18–2.1)	0.42
Current smoking	0.86 (0.29–2.6)	0.78	1.6 (0.30–8.4)	0.58	1.5 (0.49–4.6)	0.48	0.61 (0.18–2.1)	0.42
Alcohol use	1.2 (0.61–2.2)	0.66	1.2 (0.45–3.0)	0.77	0.81 (0.40–1.7)	0.57	0.39 (0.10–1.5)	0.16
Weight loss	1.05 (0.50–2.2)	0.89	0.51 (0.14–1.8)	0.3	1.07 (0.53–2.2)	0.85	0.58 (0.12–2.7)	0.49
Chest pain	1.4 (0.75–2.6)	0.29	0.55 (0.21–1.4)	0.21	1.5 (0.70–3.4)	0.29	1.6 (0.50–5.1)	0.43
Reflux	1.2 (0.61–2.5)	0.56	0.55 (0.21–1.4)	0.23	0.78 (0.39–1.6)	0.49	0.82 (0.24–2.8)	0.76
Hypertension	0.59 (0.31–1.1)	0.11	2.0 (0.80–5.2)	0.13	1.2 (0.55–2.7)	0.63	1.2 (0.39–3.8)	0.75
Diabetes	0.57 (0.23–1.4)	0.22	1.9 (0.62–5.8)	0.26	1.01 (0.39–2.6)	0.99	1.7 (0.44–6.8)	0.43
Stroke	1.2 (0.40–3.9)	0.72	1.2 (0.24–5.7)	0.84	0.42 (0.09–2.0)	0.27	2.2 (0.43–11.0)	0.35
Coronary artery disease	0.85 (0.34–2.1)	0.72	1.5 (0.46–5.0)	0.5	0.90 (0.33–2.5)	0.84	1.1 (0.23–5.4)	0.9
Proton pump inhibitors	1.3 (0.65–2.5)	0.48	0.72 (0.28–1.9)	0.49	0.78 (0.37–1.6)	0.5	1.6 (0.42–6.1)	0.49
H2 receptor antagonists	0.68 (0.32–1.4)	0.31	0.51 (0.14–1.8)	0.3	1.5 (0.70–3.4)	0.29	2.2 (0.68–7.3)	0.18
Opiates	1.1 (0.57–2.2)	0.74	0.91 (0.33–2.5)	0.85	0.56 (0.25–1.3)	0.16	3.0 (0.94–9.4)	0.06
Antidepressants	0.69 (0.36–1.3)	0.27	0.72 (0.27–1.9)	0.5	1.7 (0.83–0.4)	0.15	1.3 (0.42–4.1)	0.64
Calcium channel blockers	0.28 (0.11–0.71)	0.01	1.08 (0.33–3.5)	0.9	2.6 (1.1–6.0)	0.03	2.2 (0.62–7.7)	0.22
Endoscopic abnormalities	0.60 (0.31–1.2)	0.13	0.72 (0.26–2.0)	0.52	1.8 (0.88–3.7)	0.11	1.7 (0.53–5.3)	0.38
Erosive esophagitis	0.50 (0.20–1.3)	0.14	0.57 (0.12–2.6)	0.47	2.6 (1.07–6.5)	0.04	1.05 (0.22–5.1)	0.95
Schatzki ring	1.3 (0.51–3.4)	0.57	0.30 (0.04–2.4)	0.26	1.06 (0.38–2.9)	0.92	1.3 (0.26–6.1)	0.78
Dilated esophageal lumen	0.21 (0.06–0.76)	0.02	5.0 (1.6–15.6)	0.01	1.1 (0.37–3.4)	0.84	1.7 (0.33–8.3)	0.53
Hiatal hernia	1.2 (0.63–2.4)	0.53	0.18 (0.04–0.81)	0.03	1.6 (0.78–3.3)	0.2	0.89 (0.26–3.0)	0.85

OR, odds ratio; CI, confidence interval; EGJ, esophagogastric junction.

and manometric studies [16]. Authors measured the frequency of a hiatal hernia among the population and noted that, in 43 subjects, only one demonstrated hiatal hernia on barium esophagram. Furthermore, in 1987, Taub *et al.* described similar findings after reviewing cases of achalasia. These findings, in addition to our study, suggest the presence of a hiatal hernia in patients with esophageal symptoms may reduce the likelihood of finding achalasia on HREM [17].

The main strength of our study is the careful selection of the patient population. We excluded all patients with known esophageal motility disorders or prior gastroesophageal surgery, which may impact the findings. We included only patients who had an EGD within 1 year of HREM and confirmed lack of structural lesions after reviewing all endoscopic reports. Nonetheless, our study is not without limitations. First, the study population is derived from a single tertiary care referral center where over 1000 HREM studies are performed per year and may not be generalizable to other practice settings. Since this is a retrospective review, it does not account for inter-observer variability and lacks standardization in interpretation. To overcome this shortcoming, we reinterpreted all HREM plots using Chicago Classification version 3. Also, approximately half the patients did not have a motility disorder diagnosed on HREM. Adding impedance may improve the sensitivity of diagnoses of bolus transit abnormalities as demonstrated in a recent study [18]. Last, HREM interpretation was not blinded, as investigators were aware of the patients' clinical case and history, thus introducing a possibility for bias.

In conclusion, our study demonstrated nearly 50% of patients with non-obstructive dysphagia were found to have functional dysphagia with normal HREM, therefore lacking an esophageal motility disorder to explain symptoms. Certain patient-related factors such as male gender, calcium channel antagonist use and endoscopic findings such as erosive esophagitis and dilated esophageal lumen may be considered while referring patients for HREM.

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