Prevalence and Clinical Significance of Esophagogastric Junction Outflow Obstruction in Patients with Gastroesophageal Reflux Disease

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Abstract

Background: *The clinical significance of Esophagogastric Junction Outflow Obstruction (EGJOO) in patients with Gastroesophageal Reflux Disease (GERD) is unclear given the inherent contradictory pathophysiology of the lower esophageal sphincter (LES) for each condition. Recently, the Chicago Classification version 4.0 (CCv4.0) has updated the diagnostic criteria for EGJOO to address these inconsistencies; however, its applicability to patients with GERD is uncertain. The aim of this study was to investigate the prevalence of EGJOO in symptomatic GERD patients using CCv4.0 in comparison to Chicago Classification version 3.0 (CCv3.0) criteria.*

Methods: *We analyzed prospectively collected data from 364 patients seen in a tertiary referral multidisciplinary center focused on GERD, which was confirmed with elevated GERD questionnaire scores, abnormal pH-metry, biopsy-confirmed Barrett's esophagus, and/or erosive esophagitis. High-resolution esophageal manometry (HREM) was performed as clinically indicated. EGJOO was diagnosed according to CCv3.0 (EGJOO CCv3.0) and CCv4.0 (EGJOO CCv4.0)*

Key Results: *Of 147 patients presenting with GERD symptoms, 64 patients had confirmed GERD and abnormal HREM, and 26/64 (41%) had EGJOO CCv3.0. Seventeen of these 26 patients had both supine and upright swallows performed and only 5/17 (29%) had EGJOO CCv4.0. All 5 patients (100%) with EGJOO CCv4.0 had secondary causes for outlet obstruction.*

Conclusions: *Using the new CCv4.0, the prevalence of true EGJOO in GERD patients is less than of what was initially defined using CCv3.0 (18%). Routine upright swallows with HREM, and confirmatory non-manometric tests, may minimize the misdiagnosis of EGJOO in the setting of confirmed GERD.*

Keywords *Esophagogastric junction outflow obstruction, high-resolution esophageal manometry, lower esophageal sphincter, Integrated Relaxation pressure, Gastroesophageal Reflux Disease.*

Introduction

Gastroesophageal Reflux disease (GERD) is a common, complex disorder defined by symptoms or complications resulting from the reflux of gastric continents into the esophagus and possibly into the larynx or lung.[1-4] The most fundamental abnormality in GERD is thought to be from an incompetent esophagogastric junction (EGJ).[5] Since its inception in the 1990s, high-resolution esophageal manometry (HREM) has become the global standard to evaluate esophageal motility disorders assessing EGJ function. Aside from examination of esophageal motility in patients with dysphagia or those considered for anti-reflux surgery, its role in the evaluation of GERD patients has not been fully elucidated.[6-8]

EGJ outflow obstruction (EGJOO) is a relatively new diagnostic entity that has evolved through the various versions of the Chicago Classification. EGJOO describes an obstruction at the level of the EGJ, resulting in high intrabolus pressure.[9] Previously, the Chicago Classification (CCv3.0) defined EGJOO as the inability of the lower esophageal sphincter (LES) to relax appropriately, based on an elevated integrated relaxation pressure (IRP) in the setting of preserved peristalsis; however, this ignored the large proportion of those that were asymptomatic and the possible artifactual effects of the crura on the IRP.[10] Recently, the Chicago Classification version 4 (CCv4.0) specifically addressed these pitfalls in CCv3.0 such that now a diagnosis of manometric EGJOO must include: (1) supine and upright swallows with an elevated median IRP (>15 supine, >12 upright), and (2) elevated intrabolus pressure in at least two swallows. Manometric EGJOO requires confirmatory testing with timed barium esophagram and/or functional luminal imaging probe (FLIP). Clinically relevant EGJOO requires the addition of symptoms such as dysphagia and/or non-cardiac chest pain in conjunction with the manometric findings. [11]

The clinical significance of EGJOO in patients with GERD has not been well-defined. Prior studies reported up to 45% of patients with GERD have non-obstructive dysphagia, but specific disorders of EGJ outflow were not evaluated.[12] Most patients with EGJOO present with dysphagia that improves with either expectant management or targeted treatment to reduce the LES IRP via smooth muscle relaxants, botulinum toxin injections, pneumatic dilations, per-oral endoscopic myotomy (POEM) or laparoscopic myotomy.[13] However, up to 13% of these patients also report reflux symptoms.[14-19] With HREM evaluation, the finding of an elevated IRP, suggesting incomplete LES relaxation, appears to be counterintuitive since most studies involving HREM and GERD reveal esophageal hypomotility and LES hypotension.[20-23] One explanation for the paradoxical diagnoses may reside in the incomplete diagnostic criteria for EGJOO from CCv3.0. To date, the newly released CCv4.0 criteria for EGJOO has not been evaluated in patients with reflux.[24-27]

This study aimed to evaluate the prevalence and characteristics of patients diagnosed with GERD and EGJOO using CCv3.0 as well as CCv4.0. We hypothesized that the newer guidelines would reveal a lower prevalence of EGJOO in patients with GERD compared to that of CCv3.0, thereby impacting subsequent surgical or endoscopic treatments of the EGJ for GERD and EGJOO.

Materials and Methods

This is a prospective cohort study involving patients evaluated and treated at The Johns Hopkins Heartburn Center, which was established in 2017 as a multidisciplinary tertiary referral center aimed at clinical excellence and research focused on GERD and its associated complications. Institutional Review Board (IRB) approval was obtained for prospective data collection and use for research. All patients provided written informed consent.

Patients were referred for symptoms of GERD and completed GERD quality of life questionnaires at the time of the clinic visit, including the standardized and validated GERD-Health Related Quality of Life (GERD-HRQL) and the Reflux Symptom Index (RSI).[28,29]

All patients underwent endoscopy with biopsy, video fluoroscopic barium ("cine")-esophagram, pH testing by wireless telemetry capsule or pH/impedance, and FLIP as clinically indicated. Confirmed GERD was defined as pathologic reflux based on elevated GERD questionnaire scores, presence of reflux esophagitis during endoscopy, biopsy proven Barrett's esophagus, and/or abnormal pH testing (elevated number of reflux episodes, and/or abnormal acid exposure time pH < 4 of > 6%).

HREM was performed if the patients were considered for endoscopic or operative anti-reflux treatment, and/or reported dysphagia as part of their symptoms. HREM was performed using Medtronic ManoScan™ ESO high-resolution manometry catheter (Minneapolis, MN, USA). Once placement of catheter was confirmed, 10 liquid swallows were performed in the supine position at 30-second intervals. This sequence was followed with multiple rapid swallows, to evaluate esophageal peristaltic reserve. Next, the patient was positioned upright 90 degrees and 5 additional liquid swallows were performed before the catheter was gently removed. Manometric EGJOO was defined using CCv3.0 and CCv4.0. Of these patients, the manometry studies were re-read by physicians with expertise in esophageal motility, and median IRP results in the upright position were calculated. Those with EGJOO CCv4.0 were further reclassified as either "secondary EGJOO", based on history of a mechanical etiology (hiatal hernia, eosinophilic esophagitis)

extrinsic compression or known opiate exposure, or "Idiopathic EGJOO", for which no etiology is found. [30]

All data were entered into an online secure database (Research Electronic Data Capture or REDCap, Vanderbilt University, Nashville, Tennessee). Categorical and numerical data from baseline patient characteristics and HREM results were analyzed using parametric and non-parametric methods, where appropriate. Statistical analysis was performed with IBM SPSS for Windows (version 25, SPSS Inc., Chicago, IL, USA).

Results

From 2017 to 2019, 364 patients were seen in the Heartburn Center for symptoms of GERD, and 147 (40%) had confirmed GERD and underwent HREM. Sixty-four of these patients (64/147 – 44%) had an abnormal HREM and 26/147 (18%) were diagnosed with EGJOO CCv3.0. After excluding patients who did not have an upright swallow, 17 patients were included in the final cohort used for our analysis (Figure 1).

Baseline characteristics of the EGJOO CCv3.0 Cohort are detailed in Table 1. Among the 17 EGJOO CCv3.0 patients, the median IRP was 18 before upright swallows (interquartile range (IQR) of 5.3). Ten (58.8%) patients had a hiatal hernia (range 1-3cm). Fifteen (57.7%) patients had a diagnosis of EGJOO alone, one patient (3.9%) also had a diagnosis of concurrent ineffective esophageal motility (IEM), and one patient (3.9%) had concurrent Jackhammer esophagus. Ten (34.6%) had both EGJOO and hiatal hernia.

Of the 17 patients with EGJOO CCv3.0, four patients did not correct IRP with upright swallows. When considering EGJOO CC v4.0, five (29%) patients met most criteria for EGJOO CCv4.0. All patients had a secondary cause for obstruction: 2 with hiatal hernias, 1 on opiates, 2 with extrinsic compression from a gastric band or vascular abnormality, [30] but not all had supportive tests, such as a barium esophagram or a FLIP.

Figure 1. Flow diagram of GERD patients diagnosed with EGJOO. CC, Chicago Classification; EGJOO, esophagogastric outlet obstruction; IRP, integrated relaxation pressure; HREM, high-resolution esophageal manometry

Table 1: Patient Characteristics

	EGJOO CCv3.0 (n=26)	EGJOO CCv3.0 with upright swallows (n=17)	EGJOO CCv4.0 (n=5)
GENDER			
Male, n (%)	10 (38.5)	4 (23.5)	0
Female, n (%)	16 (61.5)	13 (76.5)	5 (100)
AGE, mean ± SD	53.4 ± 12.4	53.9 ± 12.7	49.6 ± 10.7
BMI, mean ± SD	28.4 ± 7.5	28.3 ± 7.4	33.2 ± 8.4
Hiatal Hernia, n (%)	12 (46.2)	10 (58.8)	3 (60%)
Dysphagia n (%)	12 (46.2)	9 (52.9)	5 (100%)
Median IRP (IQR)			
Supine	18.05 (5.4)	18 (5.3)	18.1 (4.6)
Upright	12.9 (8.3)	12.9 (8.3)	16.5 (3.3)
HREM findings			
EGJOO alone, n (%)	15 (57.7)	7 (41.2)	2 (40)
EGJOO + IEM, n (%)	1 (3.85)	1 (5.9)	1 (20)
EGJOO + JH, n (%)	1 (3.85)	1 (5.9)	0
EGJOO + HH, n (%)	9 (34.6)	8 (47)	2 (40)

BMI = body mass index; IRP = integrated relaxation pressure; IQR = interquartile range; IEM = ineffective esophageal motility; JH= Jackhammer's esophagus; EGJOO = esophagogastric junction outlet obstruction

Discussion

To our knowledge, this is the first prospective study evaluating the prevalence of patients dually diagnosed with GERD and EGJOO using the new CCv4.0. We found that coexistence of EGJOO and GERD is uncommon and even more so with CCv4.0. Specifically, the prevalence of EGJOO CCv3.0 is 18%, and although we cannot definitively quantify the prevalence of CCv4.0, we know that the prevalence is significantly lower based upon the new exclusion criteria. In our representative cohort of 17 patients with EGJOO CCv3.0, only 29% met criteria for EGJOO CCv4.0. Furthermore, all patients with EGJOO CCv4.0 were found to have secondary causes for obstruction thereby leaving zero patients that have primary, or idiopathic EGJOO. Therefore, CCv4.0 emphasizes the rarity of EGJOO in GERD which supports our original hypothesis given the contradictory LES dysfunction of both disorders.

The new criteria for diagnosing EGJOO in CCv4.0 is more restrictive as previously highlighted and further delineates between manometric EGJOO, confirmed EGJOO, and clinically relevant EGJOO.[11] These changes were made to increase diagnostic yield with a higher level of sensitivity of EGJOO in the setting of dysphagia. [31-33] Although CCv4.0 has improved the diagnostic evaluation of EGJOO, the significance of EGJOO in confirmed GERD patients is unclear and treatment regimens remain controversial. Between 30-40% of patients with GERD will not respond to lifestyle changes or pharmacologic treatment, and thus may be candidates for surgical or endoscopic intervention to augment the EGJ resistance and restore the normal anti-reflux barrier.[33] A dual diagnosis of GERD and EGJOO uncovers a diagnostic and therapeutic dilemma, as management of EGJOO involves decreasing LES pressure whereas treatment of GERD involves augmenting the EGJ barrier. Our data show that patients with GERD and EGJOO initially diagnosed by CCv3.0 might have been overlooked for therapeutic endoscopic or surgical interventions.[14-19]

In a recent prospective study, patients with EGJOO and GERD who underwent laparoscopic Nissen fundoplication (LNF) had similar improvements in both GERD and rates of dysphagia when compared to those post LNF without EGJOO.[19] Although these results suggest a concomitant diagnosis of EGJOO and GERD, the diagnosis of EGJOO should not preclude surgical or endoscopic treatment for GERD. Newer technology, such as FLIP, has a promising future for the diagnosis and treatment of EGJOO as it has the ability to directly measure EGJ distensibility and potentially rule out artifact, although more studies are needed.[27] Until the diagnosis of true EGJOO and its role in GERD is better understood, more studies are needed to discern the efficacy of the surgical or endoscopic treatments in these patients.

The strengths of our study include its prospective data collection, routine assessment of symptomatic GERD patients with standardized patient-reported GERD surveys, pH-metry, endoscopy, biopsy, and use of HREM when clinically appropriate, as well as esophageal motility expertise allowing re-evaluation of HREM studies. Our study does have a few limitations. Our study is relatively small, as a third of the patients initially diagnosed with EGJOO CCv3.0 did not have an upright study, and CCv4.0 could not be applied. Therefore, the true prevalence of true EGJOO using CCv4.0 could not be calculated in our study population. Therefore, our study has limited generalizability to the symptomatic GERD population in the community that are not undergoing routine extensive evaluation and testing. Secondly, one patient with EGJOOv4.0 was taking opiates, which are known to be associated with EGJOO among other motility abnormalities.[34,35]

In conclusion, EGJOO is uncommon in the setting of GERD. Compared to CCv3.0, CCv4.0 minimizes the misdiagnosis of EGJOO that could hinder appropriate candidates from undergoing endoscopic or surgical

evaluation for refractory GERD. Larger prospective studies involving defined patient populations undergoing routine HREM using the new criteria are needed to optimize HREM diagnosis EGJOO particularly in GERD.

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