



Management of reflux after peroral endoscopic myotomy

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Peroral endoscopic myotomy (POEM) has emerged as an attractive treatment option for patients suffering from achalasia. The endoscopic nature of the procedure prevents an accompanying fundoplication to decrease post-procedure gastroesophageal reflux (GER). A large amount of literature exists reporting incidence of post-POEM GER but differences in the metric used to report GER, short follow-up and infrequent objective measuring creates wide variation in this data. Moderately sized multi-institutional trials and meta-analysis that use the most sensitive metric of GER suggest the incidence is close to 50%, which is significantly higher than traditional Heller myotomy with fundoplication. Although chronic GER has serious risks and implications in this patient population, many studies report complete subjective and objective resolution with anti-reflux medications. Novel endoscopic fundoplication technologies are emerging but their role in post-POEM GER is yet to be determined.

Keywords: Peroral endoscopic myotomy (POEM); reflux; myotomy; Heller

Received: 30 October 2018; Accepted: 14 January 2019; Published: 01 February 2019.

doi: 10.21037/jxym.2019.01.02

View this article at: <http://dx.doi.org/10.21037/jxym.2019.01.02>

Introduction

Heller myotomy has long been established as effective surgical treatment for achalasia. Soon after the procedure's adoption, reports of postoperative pathologic gastroesophageal reflux (GER) created controversy among surgeons; some surgeons attributed reflux to an overzealous myotomy while others insisted that it was an unavoidable result of the procedure (1-4). Reflux after myotomy makes physiologic sense because although obliterating the lower esophageal sphincter allows passage of food and resolution of dysphagia, it also weakens the anatomic mechanism that protects the distal esophagus from caustic gastric contents. The controversy was ultimately settled after numerous studies demonstrated the necessity of an accompanied fundoplication during myotomy; fundoplication effectively reduced post-operative GER without affecting dysphagia scores or recurrence (5-10).

Interestingly, the impressive technologic and technical

advent of the peroral endoscopic myotomy (POEM), an incisionless procedure that boasts a comparable success and complication rate as Heller myotomy (11-13), has resurfaced the problem encountered by the first esophagomyotomy surgeons twenty years earlier. The endoscopic nature of the procedure prevents a concomitant anti-reflux procedure. Additionally, some argue that this approach does not necessarily warrant an anti-reflux procedure, as the spared longitudinal muscles fibers, intact phrenoesophageal ligament, and preserved nervous complex of the gastroesophageal (GE) junction protect against significant reflux (14-18). This review will discuss the definition, incidence, diagnosis, implications, and treatment of post-POEM GER.

Definition

Before discussing the incidence of post-POEM GER, it is important to acknowledge the variation in how GER is measured across studies and recognize that this may account

Table 1 Patients reporting symptomatic reflux after POEM, excluding studies with n<50, follow-up <3 months (16,17,21-31)

Author	Year	Study type	Region	Patients evaluated (n)	GER rate	Follow-up (months)	Definition	Discharge on PPI
Li	2013	RC, SI	China	121	16.5%	Mean 10.5	GERDQ \geq 7	2 weeks, double dose
von Renteln	2013	PC, 5 centers	USA, Europe	70	33%	3	Clinical symptoms	–
				61	30%	6	Clinical symptoms	–
				51	37%	12	Clinical symptoms	–
Cai	2014	RCT, SI	China	100	7%	Median 11.5	Clinical symptoms	8 weeks, regular dose
Ling	2014	PC, SI	China	87	10.3%	Mean 14.4	Clinical symptoms	2 weeks, regular dose
Sharata	2015	PC, SI	USA	81	9%	Mean 21.5	Clinical symptoms	–
Inoue	2015	PC, SI	Japan	289	19.4%	12 to 24	Clinical symptoms	–
				61	21.3%	36	Clinical symptoms	–
Tang	2016	PC, SI	China	67	6.0%	12	Clinical symptoms	2 weeks, regular dose
Shiwaku	2016	PC, SI	Japan	70	7.1%	3	Clinical symptoms	4 weeks, regular dose
Familiari	2016	PC, SI	Italy	103	18.4%	Mean 7.6	GERDQ >7	–
Ramchandani	2016	RC, SI	India	102	21.6%	Mean 13.4	Clinical symptoms	–
Hungness	2016	PC, SI	USA	111	28%	Mean 24	GERDQ >7	6 months, regular dose
Werner	2016	RC, 3 centers	USA, Europe	79	24.1%	3 to 6	Clinical symptoms	2 weeks, double dose
				78	31.6%	12 to 18	Clinical symptoms	2 weeks, double dose
				80	37%	Mean 29	Clinical symptoms	2 weeks, double dose
Nabi	2017	PC, SI	India	261	16.8%	12	Clinical symptoms	–

PC, prospective cohort; RC, retrospective cohort; SI, single institution; POEM, peroral endoscopic myotomy.

for the wide range of incidence reported in the literature. Assessments may include symptom questionnaires, proton pump inhibitor (PPI) use, endoscopic evidence of reflux esophagitis, or 24-hour pH abnormalities. Thus, it is no surprise that large meta-analyses differ depending on which metric is used (19). In fact, the most objective measure of GER, abnormal pH levels, tends to be the least reported outcome metric after POEM (13,20). Additionally, some selection bias where only symptomatic patients undergo testing, may further obscure the data. Lastly, the relative novelty of POEM prevents a fair long-term comparison to laparoscopic Heller myotomy (LHM) and long-term incidence of GER after POEM remains unknown.

Incidence and diagnosis of reflux

Symptoms

The greatest amount of literature on post-POEM GER

uses symptoms as a marker of reflux (*Table 1*). Most studies use clinical symptoms such as regurgitation, heartburn, and retrosternal pain, though some have adopted standardized reflux score such as GERDQ, GERSS, and GERD-HRQL. Interestingly, many patients experience these symptoms pre-operatively as a result of achalasia and it is unclear how this affects the true rate of reflux. In the current literature, post-POEM GER ranges from 6% to 37%. Studies with the largest sample sizes (n>100) place the incidence between 16–22% (17,21-25). A true conclusion from this data should be drawn carefully, as the majority of POEM studies have less than 1-year follow-up. Additionally, some but not all patients are discharged on varying lengths and doses of PPI prophylaxis, which may alter symptomatology. Recently, a large meta-analysis using 2,142 patients with an average of 7.6 months of follow-up after POEM, found the incidence of symptomatic GER to be lower, at 8.8% (20). This discrepancy may be partially explained by the predominantly Asian populations in many of these studies; Asian countries

Table 2 Los Angeles classification of esophagitis based on endoscopy

Grade	Description
Grade A	One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length
Grade B	One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds
Grade C	Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference
Grade D	Mucosal breaks which involve at least 75% of the esophageal circumference

have lower prevalence of GER and less GER-pathogenetic factors such as different lifestyles and eating habits (32).

Even if symptomatic GER after POEM is as low as 8.8%, it is important to recognize that the correlation between symptomatic and pathologic GER, evidenced by esophagogastroduodenoscopy (EGD) or pH monitoring, is questionable. Jones *et al.* (33) tested for correlation between GERSS/GERD-HRQL surveys and pH testing in 43 patients after POEM. They found poor correlation with either survey; most alarming was that asymptomatic patients comprised 50% of those with pathologic acid reflux. Multiple other studies demonstrated similar findings (23,34-38). The variation in methods of measuring symptoms as well as poor correlation of symptoms to pathologic GER suggests that the best measure of post-POEM GER is not subjective, but objective.

Esophagitis

Esophagitis diagnosed on endoscopy works nicely as an objective measure of pathologic GER. In POEM literature, esophagitis is most commonly measured with the Los Angeles (LA) classification during endoscopy (Table 2). The classification groups the degree of esophageal erosion into mild (A, B) and more severe (C, D). In large studies that impose universal post-POEM endoscopy, the rate of esophagitis ranges from 6 to 64.7% (Table 3). It is important to note that although all these studies required post-procedure EGD regardless of symptoms, not all had 100% compliance and thus some bias affects this data; a patient who is having symptoms of reflux is more likely to be willing to undergo endoscopy than a patient who is asymptomatic. Regardless, the rate of esophagitis is quite high across these studies but the majority of patients exhibited only mild esophagitis (class A or B). The meta-analysis by Akintoye *et al.* again seems to settle a bit lower than the rest of the literature. They found the average incidence of esophagitis in 1,762 patients to be 13% with 8.4-month follow-up. Using

esophagitis on EGD as a marker for GER is imperfect as the grading is somewhat subjective and it requires an invasive procedure with inherent risks. Additionally, one could argue that esophagitis is actually the consequence of reflux and thus not the most sensitive marker; the most sensitive marker would objectively detect reflux in real-time.

pH monitoring

Schlottman *et al.*, in a large meta-analysis, reminds physicians that POEM is a new technology and thus should be evaluated with the most sensitive and accurate test (13). Exposure of the esophagus to gastric contents is most accurately measured by pH probe studies. The invention of wireless probes that can collect up to 96 hours of data has allowed an increasing amount of post-POEM pH data to emerge. Most post-POEM studies use a DeMeester score of greater than 14.7 or an esophageal pH of less than 4 for greater than 5% of the study period to classify as abnormal acid exposure, which is consistent with non-POEM-related GER literature. Incidence of abnormal pH studies in POEM patients ranges from 15–88% (Table 4). This parameter, more so than symptoms of esophagitis, is affected by smaller sample size ($n=23-103$) and short follow-up (only two studies with a mean follow up of greater than 10 months). The Akintoye meta-analysis estimates abnormal acid exposure of 47% in 336 patients at an average follow-up for 8.6 months. It should be emphasized that the most objective, sensitive test for post-POEM GER not only demonstrates an alarmingly high rate of GER but that both symptomatic and endoscopic markers seem to drastically underestimate it.

Rate of GER in LHM; how does POEM compare?

Despite the seemingly high rate of GER after POEM, it is important to remember that myotomy even with fundoplication has a fairly high rate of post-procedure GER as well. Studies examining GER after LHM suffer from

Table 3 Patients with esophagitis by EGD after POEM, excludes studies with n<50 (21-27,29-31,39)

Author	Year	Study type	Region	Total patients (n)	Patients with EGD (n)	Esophagitis rate	Follow-up (months)	LA classification [n]
Li	2013	RC, SI	China	131	121	5.79%	Mean 10.5	“A or B”
Von Renteln	2013	PC, 5 centers	USA, Europe	70	70	42%	3	A [21], B [9], C [0], D [0]
Cai	2014	RCT, SI	China	100	100	10%	3 to 6	–
Sharata	2015	PC, SI	USA	100	73	27.4%	6	A [15], B [3], C [2], D [0]
Inoue	2015	PC, SI	Japan	500	414	64.7%	2	A [140], B [107], C [20], D [1]
					191	59.2%	12 to 24	A [68], B [25], C [15], D [5]
Ramchandani	2016	RC, SI	India	220	84	16.6%	Mean 13.4	A [10], B [4], C [0], D [0]
Familiari	2016	PC, SI	Italy	103	103	20.4%	Mean 7.6	A [9], B [6], C [5], D [1]
Werner	2016	RC, 3 centers	USA, Europe	85	68	36.8%	3 to 6	A [14], B [11], C [0], D [0]
					72	37.5%	12 to 18	A [14], B [9], C [2], D [1]
Shiwaku	2016	PC, SI	Japan	105	70	6%	3	A [31], B [8], C [3], D [0]
Nabi	2017	PC, SI	India	408	227	18.1%	12	A [26], B [11], C [3], D [1]
Kumbhari	2017	RCC, 7 centers	USA, Europe, Asia	467	233	23.2%	Median 12	A [27], B [14], C [9], D [4]

RC, retrospective cohort; PC, prospective cohort; RCT, randomized control trial; RCC, retrospective case-control; SI, single institution; LA, Los Angeles; POEM, peroral endoscopic myotomy; EGD, esophagogastroduodenoscopy.

Table 4 Patients with abnormal pH testing after POEM, excluding studies with n<20 (23,25,27,33,35,38-42)

Author	Year	Study type	Region	Total patients (n)	Patients with pH testing (n)	Abnormal pH	Follow-up (months)	Abnormal pH definition
Chan	2016	RC, SI	China	56	34	15%	6	>14.7 DeMeester
Nabi	2017	PC, SI	India	408	92	28.3%	3	>14.7 DeMeester
Filicori	2018	RC, SI	USA	40	26	38%	6	>14.7 DeMeester
Sharata	2015	PC, SI	USA	100	68	38.2%	6	>14.7 DeMeester
Bhayani	2014	PC, SI	USA	101	23	39%	Median 6.8	>14.7 DeMeester
Wang	2016	RC, SI	China	56	32	40.6%	Mean 39.3	Esophageal pH <4 for >5% of the 24-h period
Familiari	2016	PC, SI	Italy	103	103	50.5%	Mean 7.6	Esophageal pH <4 for >5% of the 24-h period
Kumbhari	2017	RCC, 7 centers	USA, Europe, Asia	467	282	57.8%	Median 12	>14.7 DeMeester
Jones	2016	PC, SI	USA	43	26	58%	6	>14.7 DeMeester
Khashab	2016	RC, SI	USA	60	25	88%	Mean 3.9	Abnormal acid exposure

RC, retrospective cohort; PC, prospective cohort; RCC, retrospective case-control; SI, single institution; POEM, peroral endoscopic myotomy.

Table 5 GERD after per-oral endoscopic myotomy as compared with Heller myotomy with fundoplication: a systematic review with meta-analysis by Repici *et al.* 2018 (47)

Procedure	Symptomatic GER	Esophagitis on EGD	Abnormal pH
POEM	19.0%	29.4%	39.0%
Studies	17	12	5
Total patients (n)	1,275	1,056	289
Follow up (months)	Not stated	9.3	Not stated
LHM	8.8%	7.6%	16.8%
Studies	20	5	14
Total patients (n)	1,136	752	1,022
Follow up (months)	Not stated	26.6	22.8

GERD, gastroesophageal reflux disease; GER, gastroesophageal reflux; EGD, esophagogastroduodenoscopy; POEM, peroral endoscopic myotomy; LHM, laparoscopic Heller myotomy.

the same pitfalls that afflict post-POEM studies. Multi-institutional studies that use abnormal pH as a marker for GER place the true incidence of GER after LHM as high as 21–42% (43–45). A well-executed retrospective review of prospectively collected data by Bhayani *et al.* (40) demonstrated similar incidence of GER after LHM and POEM as assessed by 24-hour pH studies (32% LHM *vs.* 39% POEM; $P=0.7$) and other studies corroborate these findings (11,12,46).

Despite this, the two largest and most recent meta-analyses designed to address this question suggest that the rate of post-POEM GER is significantly higher than for LHM, as many surgeons originally suspected (13,47). *Table 5* summarizes the results from Repici *et al.*, which demonstrated significantly higher rates of GER across subjective and objective markers for POEM patients when compared to LHM. Analysis from Schlottman *et al.* (13) tells a similar story. POEM was found to have significantly higher rates of esophagitis on EGD (22.4% POEM *vs.* 11.5% LHM) and abnormal acid exposure in pH studies (47.5% in POEM *vs.* 11.1% in LHM). Both analyses include thousands of patients and likely represent the most accurate estimate of post-POEM GER in comparison to LHM.

Implications of post-POEM GER

Regardless of variation in the reported incidence of post-POEM GER, it is undeniable that reflux after POEM affects a sizeable number of patients and the clinical implications of this are yet to be determined. This is particularly important as most long-term failures after treatment

of achalasia are related to complications of reflux (36). Perhaps the more concerning risk is that of Barrett's esophagus and progression to esophageal adenocarcinoma. Leeuwenburgh *et al.* examined a cohort of achalasia patients treated with pneumatic dilation at an impressive 8.9 years of average follow-up. They found that 8.4% of their cohort developed Barrett's esophagus and 7% of that group developed esophageal adenocarcinoma (48). Studies looking specifically at rates of Barrett's esophagus after POEM are sparse but early results seem to suggest that this is more than just a theoretical risk (26). In fact, the implications of post-POEM GER are so great that a recent publication in *Endoscopy* asked if reflux has the potential to "kill POEM" and warned surgeons to monitor these patients carefully (19).

Treatment of post-POEM GER

In almost all studies where post-POEM GER was diagnosed, patients were treated with PPIs. Numerous studies conclude that GER was easily controlled in this manner with symptom resolution in all patients (16,20,21,27,28,38,49–53). Additionally, a handful of studies documented objective evidence of GER resolution with PPI treatment, usually by repeat EGD (23,35,36,54). These studies varied in terms of PPI dosing and length of therapy but most used double dose PPI for 6 weeks if endoscopic esophagitis was found.

With such a high efficacy of PPIs in post-POEM GER, a logical conclusion might be to universally prescribe PPIs for POEM patients. Lifelong PPI therapy has

drawbacks however. Firstly, patient compliance is a major issue especially because the majority of these patients are asymptomatic. Additionally, there are increasing concerns for serious side effects with long-term PPI use secondary to vitamin deficiencies, bone fractures, kidney disease, community acquired pneumonia, and increasing rates of *Clostridium difficile* infections (55-59).

The barriers to medical treatment of post-POEM GER might make surgical treatment a reasonable option. If a patient's reflux is severe and refractory, one could certainly offer a laparoscopic fundoplication; this has been demonstrated to be a safe and successful treatment method in a handful of patients (60,61). Obviously, requiring a laparoscopic procedure after POEM is not ideal and obviates the endoscopic benefit of the initial procedure.

An endoscopic fundoplication would be most ideal and the relatively novel transoral incisionless fundoplication (TIF) is an attractive option (Esophyx; EndoGastric Solutions, Redmond, WA, USA). This fully endoscopic procedure creates an anti-reflux barrier through creation of a valve 2 to 4 cm in length with a 270 degree or greater circumferential wrap (62). A 2013 systematic review of 551 patients with GER who underwent TIF demonstrated a PPI discontinuation rate of 67% and a 72% patient satisfaction rate. Unfortunately, pH metrics failed to show normalization in this group (63). Notwithstanding, using TIF to treat post-POEM GER has been published in a small case series. Tyberg *et al.* demonstrated 100% PPI discontinuation in five patients that underwent TIF after POEM. At 3-month EGD, all patients had resolution of esophagitis. Unfortunately, pH metrics after TIF were not measured (64).

Other endoscopic options for GER management exist and could theoretically be used to treat post-POEM GER. The Stretta system (Restech Mederi-RF, Houston, TX, USA) uses radiofrequency ablation to create thermal effect below the mucosa at the GE junction and restore the reflux barrier (65). In non-POEM patients, this technology has been fairly well studied. A recent meta-analysis by Fass *et al.*, containing 2,468 patients (4 randomized controlled trials, 23 cohort studies, and 1 international registry) showed that Stretta improved GERD-HRQL score by 14.6 points ($P<0.001$) and 51% of patients discontinued PPIs ($P<0.001$). In a smaller subset of patients, Stretta lowered the incidence of esophagitis by 24% ($P<0.001$) and DeMeester score by 13.79 ($P<0.001$) (66). Data looking at Stretta specifically for post-POEM GER has yet to be published.

The Anti-Reflux Mucosectomy (ARMS) involves endoscopic resection of gastric and esophageal mucosa in crescentic fashion which causes remodeling of the gastric cardia flap valve (67). There is little literature on outcomes but the pilot study is encouraging, showing significant improvement in abnormal acid exposure as documented by pH monitoring. Other therapies involving electrical stimulation and magnets are emerging in animal models as well (68,69). It is important to remember that the goal of treating post-POEM GER is objective improvement in reflux because subjective markers in achalasia patients are inconsistent and inaccurate. None of the endoscopic therapies presented above have demonstrated efficacy to this regard leading some to argue that none of them are indicated after POEM until more data become available. To this same end, no endoscopic GER therapy, except for a small case series of TIF patients, has been used in post-POEM GER specifically, and thus the safety and efficacy in this patient population remains unknown.

Recommendations

The post-POEM GER literature suffers from wide variation in methods of measuring GER and thus the true incidence of reflux in these patients is unknown. However, in summing large multicenter studies and current meta-analyses, a significant proportion, possibly more than half of POEM patients, will have pathologic reflux as documented by the most sensitive marker, pH monitoring. This incidence is likely higher than that seen in the current standard, LHM. Thus, the authors conclude that all patients who undergo POEM should be discharged on daily PPI for 6 to 12 months followed by a 96-hour pH study. If the study is positive, then the standard of care is to continue PPI or undergo a laparoscopic anti-reflux procedure in addition to screening EGD every 5 years. If the pH test is negative, the PPI is stopped and repeat testing is only done for patients who develop symptoms. This group should also undergo EGD every 5 years. Similar standards are being adopted by many major medical centers across the world and has the potential to prevent serious complications of uncontrolled post-POEM GER (26,33,34,36,39,41,47).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (David W. Rattner, Ozanan Meireles) for the series “Update on the Diagnosis and Treatment of Achalasia” published in *Journal of Xiangya Medicine*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jxym.2019.01.02>). The series “Update on the Diagnosis and Treatment of Achalasia” was commissioned by the editorial office without any funding or sponsorship. M. Ujiki reports reports personal fees from Olympus, personal fees and membership from Boston Scientific, personal fees from Apollo, personal fees from Medtronic, personal fees from Gore Medical, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jxym.2019.01.02

Cite this article as: Callahan ZM, Su B, Ujiki M. Management of reflux after peroral endoscopic myotomy. *J Xiangya Med* 2019;4:6.