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Prediction, prevention and management of gastroesophageal reflux after per-oral endoscopic myotomy: An Update

Gastroesophageal reflux after POEM

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Abstract

Achalasia cardia, the most prevalent primary esophageal motility disorder, is predominantly characterized by symptoms of dysphagia and regurgitation. The principal therapeutic approaches for achalasia encompass pneumatic dilatation, Heller's myotomy, and the more recent per-oral endoscopic myotomy (POEM). POEM has been substantiated as a safe and efficacious modality for the management of achalasia. Although POEM demonstrates superior efficacy compared to pneumatic dilatation and an efficacy parallel to Heller's myotomy, the incidence of gastroesophageal reflux disease (GERD) following POEM is notably higher than with the aforementioned techniques. While symptomatic reflux post-POEM is relatively infrequent, the significant occurrence of erosive esophagitis and heightened esophageal acid exposure necessitates vigilant monitoring to preclude long-term GERD-related complications. Contemporary advancements in the field have enhanced our comprehension of the risk factors, diagnostic methodologies, preventative strategies, and therapeutic management of GERD subsequent to POEM. This review focuses on the limitations inherent in the 24-hour pH study for evaluating post-POEM reflux, potential modifications in the POEM technique to mitigate GERD risk, and the strategies for managing reflux following POEM.

Key Words: achalasia cardia; per-oral endoscopic myotomy; gastroesophageal reflux; esophagitis

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Core Tip: Per-oral endoscopic myotomy (POEM) has gained recognition as a primary therapeutic intervention for achalasia cardia. POEM is distinguished by its effectiveness and a commendable safety profile. However, gastroesophageal reflux disease (GERD)

has emerged as an important long term adverse event after POEM. Notably, the incidence of GERD is higher after POEM when compared to the other leading treatment modalities including pneumatic dilatation and Heller's myotomy with fundoplication. Since the introduction of POEM in 2010, there has been considerable advancement in our understanding of GERD after POEM. This article aims to elucidate the recent developments in predicting, preventing, assessing, and managing GERD subsequent to POEM intervention.

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INTRODUCTION

Per-oral endoscopic myotomy (POEM) is an established endoscopic treatment modality for achalasia and allied non-achalasia spastic esophageal motility disorders. Contemporary guidelines from leading gastrointestinal (GI) societies endorse POEM as a primary treatment option for achalasia.^[1-4] While the safety and efficacy of POEM are well-established, the emergence of postoperative gastroesophageal reflux disease (GERD) has become a prominent concern in recent literature.^[5] Studies employing endoscopic and pH monitoring studies have revealed a notably high incidence of GERD following POEM.^[5-7] Comparative analyses in randomized studies have demonstrated a significantly higher incidence of GERD in comparison to pneumatic dilatation (PD) and laparoscopic Heller's myotomy (LHM).^[8, 9] Consequently, recent research has increasingly concentrated on the prevention, diagnosis and management of GERD after POEM.

This review aims to provide an overview of the latest developments in predicting, preventing, evaluating, and managing GERD subsequent to POEM.

GERD is a frequent occurrence following POEM, with a higher incidence compared to PD and LHM. The effective identification of risk factors, the implementation of preventive measures, and timely intervention are essential to mitigate complications associated with prolonged esophageal acid exposure post-POEM.

POST-POEM REFLUX: SCOPE OF PROBLEM

POEM represents the most recent advancement among the available treatment options for achalasia cardia.^[10] Initial studies primarily concentrated on assessing the safety and the efficacy of POEM in providing symptomatic relief. Consequently, early investigations lacked comprehensive data on post-POEM reflux, resulting in a wide variation in reported GERD prevalence following the procedure.^[5] Recent research efforts have undertaken more rigorous evaluations of GERD post-POEM (Table 1). In a multicenter study involving 282 patients, post POEM reflux esophagitis and GERD on pH analysis was reported in 23.2% and 57.8% of patients, respectively.^[6] Nabi *et al* evaluated GERD in 209 consecutive patients who underwent POEM.^[11] A high DeMeester score (> 14.72), reflux esophagitis, and symptomatic GERD were identified in 47.9 %, 41.9 %, and 29.3 % of patients, respectively.^[11] Additionally, two randomized trials comparing POEM with PD and LHM reported reflux esophagitis in 41% and 44% of POEM cases, respectively.^[8, 9] Although reflux is common, severe reflux esophagitis (Los Angeles [LA] grade C or D) and symptoms of reflux are uncommon after POEM. Severe reflux esophagitis has been reported in 3.4% to 7.5% of cases across various studies.^[6, 7, 11, 12]

In contrast to the notable incidence of erosive esophagitis and increased esophageal acid exposure observed on pH analysis, the majority (60% to 80%) of patients remain asymptomatic for reflux.^[5, 6, 11] Karyampudi *et al* compared post POEM reflux with reflux in individuals without esophageal motility disorders.^[13] They concluded that despite more severe esophagitis, the symptoms in post-POEM reflux cases tend to be milder and the correlation between reflux and symptoms is weaker compared to controls.

In summary, while the occurrence of reflux esophagitis and increased esophageal acid exposure is high after POEM, symptomatic GERD is infrequent, and severe reflux esophagitis is not commonly observed in these cases.

RISK FACTORS FOR GERD AFTER POEM

Understanding the risk factors for GERD following POEM is crucial not only for preventive strategies but also for necessitating close monitoring. Various studies have

identified several risk factors associated with post-POEM reflux. These include a higher body mass index (BMI >35kg/m²), the presence of hiatal hernia, a low integrated relaxation pressure (IRP) post-POEM, pre-POEM lower esophageal sphincter (LES) pressures below 45 mmHg, low post-POEM LES pressure, and female gender.^[6, 14, 15] [16-21]

Additionally, certain technical aspects of the POEM procedure have been implicated in predisposing patients to GERD. These factors encompass long esophageal myotomy, posterior myotomy, full thickness myotomy and excess myotomy (>4 cm) on the gastric side.^[22, 23] A comprehensive study from Japan involving 2905 patients identified additional risk factors including age ≥65 years (relative risk [RR] 1.72), previous treatments (RR 2.21), Eckardt score ≥ 7 (RR 0.68), sigmoid-type achalasia (RR 1.40), and esophageal myotomy exceeding 10 cm (RR 1.59) as being associated with severe reflux esophagitis.^[7] Contrarily, other studies have not confirmed a correlation between post-POEM reflux and patient or procedural factors, including obesity, gender, full thickness myotomy, long esophageal myotomy and orientation of myotomy.^{[6, 11], [24, 25]} The divergent findings across different studies underscore that the prediction of GERD following POEM necessitates further exploration through high quality research. (Table 2)

EVALUATION OF GERD AFTER POEM

The assessment of GERD after POEM encompasses a multifaceted approach involving endoscopy, pH analysis, and symptom assessment through standardized questionnaires. (Figure1)

Symptoms

Published studies report symptomatic GERD in 16% to 40% of cases after POEM. Intriguingly, symptoms can be absent even in cases exhibiting severe reflux esophagitis and increased esophageal acid exposure on pH studies. The weak correlation between symptoms and both reflux esophagitis and increased esophageal acid exposure suggests that symptomatic presentation alone may not be a reliable indicator of GERD

after POEM. Therefore, proactive monitoring is advised regardless of the presence or absence of reflux symptoms after POEM.

Erosive esophagitis

Reflux esophagitis (LA grade \geq B) on endoscopy has been identified as an objective and reliable marker of GERD.^[26] However, the presence of ulcers with distinct endoscopic appearance is not uncommon after POEM and should be distinguished from reflux esophagitis. A comprehensive study from the United States involving 610 patients found solitary esophagogastric junction ulcers in 29% of the cases.^[12] The study posits that these ulcers might indicate ischemic, poorly healing mucosa rather than being a direct consequence of reflux esophagitis.

Esophageal acid exposure

The quantification of esophageal acid exposure is generally regarded as the definitive method for confirming GERD. However, several noteworthy considerations arise, particularly in the context of achalasia. Unlike typical GERD cases, achalasia patients have impaired peristalsis leading to significant stasis, which can lead to fermentation and subsequent esophageal acidification. As a result, there is a potential for misclassification of fermentation-induced esophageal acidification as GERD in this population.^[27, 28]

A detailed study focusing on reflux in treated achalasia patients revealed that most occurrences of esophageal acidification were not related to reflux.^[29] Automated pH analysis systems are unable to distinguish between true esophageal acid exposure and false GERD due to fermentation induced acidification. Therefore, manual interpretation of pH tracings becomes essential to differentiate between these two scenarios.^[30] Characteristic patterns of esophageal acid exposure in cases with achalasia include a) a rapid decline in pH to less than 3 with slow clearance, indicative of true GERD, and b) a gradual decrease in pH, seldom falling below 3.7, characteristic of fermentation secondary to food stasis.^[30] In a recent prospective study including 54 patients undergoing POEM, "true acid reflux" was identified in 29.6% of cases, in contrast to 64.8% as indicated on automated analysis.^[31] This finding underscores the

importance of manual review of pH tracings to accurately identify "true acid reflux" in patients with achalasia after POEM.

PREVENTION OF GERD AFTER POEM

Given the high incidence of GERD after POEM, the development of preventative measures is of paramount importance. However, the current body of research concerning preventive approaches for GERD after POEM is limited. The preponderance of existing studies have focused on assessing the clinical effectiveness of modified POEM techniques with only a few dedicated to evaluating their impact on the incidence of post-operative GERD.

While the clinical effectiveness of short esophageal myotomy (≤ 5 cm) and selective circular myotomy has been established as comparable to standard esophageal myotomy and full-thickness myotomy, their effect on post-operative GERD remains unclear.^[23, 32-34] Theoretically, short esophageal myotomy might facilitate partial recovery of peristalsis, potentially leading to reduced esophageal acid exposure.^[35] However, robust data are required to substantiate this theory. A retrospective study involving 237 patients noted partial peristaltic recovery in 22% of patients after POEM.^[36] Another study indicated a lower frequency of GERD symptoms and reflux esophagitis in patients exhibiting partial peristaltic recovery post-POEM, with preprocedural LES resting pressure and the Eckardt score predictive of this recovery.^[37] However, these findings require confirmation through high-quality clinical trials.

The role of longitudinal esophageal muscles in both health and disease remains an area of ongoing research. Longitudinal muscles are thought to contribute to esophageal shortening and may be implicated in the genesis of chest pain in achalasia patients.^[38] Interestingly, one study found a higher incidence of post-POEM reflux in cases who underwent full thickness myotomy.^[23] However, this finding is contrasted by another study that reported differing results.^[39]

Overall, the prevention of GERD following POEM is a complex issue that requires further exploration and validation through well-designed research studies.

Length of gastric myotomy

An extended gastric myotomy (3 vs 1.5 cm) has been shown to improve the results of LHM for achalasia.^[40] However, LHM typically includes a concurrent fundoplication procedure. In contrast, fundoplication is not performed in conjunction with POEM, and consequently, longer gastric myotomies in the context of POEM may increase the risk of developing GERD. ¹¹ Grimes *et al* assessed the impact of the gastric myotomy length on post POEM reflux.^[22] They found that gastric myotomy extending beyond 2.5 cm was associated with increased rates of moderate esophagitis (LA grade B). The authors also advocated the utilization of a double scope method to precisely control the gastric myotomy length. This technique not only assists in determining the myotomy length, but also aids in assessing the myotomy orientation.^[41] In a case control study, the incidence of reflux esophagitis was compared between patients with a short gastric myotomy (1 cm) and those with a standard gastric myotomy (2-3 cm).^[42] The study observed a significantly lower incidence of LA grade B or higher esophagitis in the short myotomy group (0% vs 30%, $P = 0.01$), along with lower mean GerdQ scores (6.5 vs 8.2, $P = 0.001$).^[42]

Sling fiber preservation

Other techniques for mitigating reflux involves preservation of sling fibers during posterior POEM and incorporating natural orifice transluminal endoscopic surgery fundoplication (NOTES-F) in anterior POEM. Sling fibers, crucial to the natural anti-reflux barrier, are visible towards the gastric side during posterior myotomy (Figure 2). Re-orienting the direction of myotomy during POEM can facilitate the preservation of these fibers.^[43] Tanaka *et al* reported a significant reduction in the frequency of grade B or higher reflux esophagitis in cases where sling fibers were preserved during posterior POEM (31.3% vs 58.1%).^[44] Shiwaku *et al* found that while overall rates of reflux esophagitis were similar between conventional and sling fiber preserving groups, severe esophagitis (LA grade C/D) was significantly less frequent in the latter (44.1% vs 18.5%).^[45] The gastroesophageal flap valve grade was better preserved in cases without severed sling fibers (4.4% vs 19.8%).^[45] In contrast, a randomized trial concluded that preserving sling fibers does not significantly impact

post POEM reflux esophagitis.^[46] This trial observed similar incidences of grade B or higher esophagitis (25.9% *vs* 31.6%), mean number of reflux episodes (48.2±36.6 *vs* 48.9±40.3), increased esophageal acid exposure (45.5% *vs* 31.7%) and high DeMeester scores (38.6% *vs* 41.5%) in both the groups.

Given that sling fibers cross the dissection field from left to right, performing a short gastric myotomy might be essential to preserve them.^[41] Stavropoulos *et al* highlighted this technique (anti-reflux POEM), where sling fibers are preserved by orienting the myotomy at 2 o' clock and limiting the length of gastric myotomy.^[47] The anti-reflux POEM group demonstrated significantly lower acid exposure (4.5% *vs* 10.3%, $p < 0.001$), fewer reflux episodes (31 *vs* 53, $P = 0.02$) and reduced GERD symptoms (5.2% *vs*. 18.1%) compared to controls.

NOTES-fundoplication

NOTES fundoplication has gained attention as a preventive measure for GERD following POEM. This procedure involves performing an anterior myotomy followed by dissection along the serosal side to access the peritoneum. A peritoneal opening is created and the anterior surface of the stomach is accessed. The left lobe of liver serves as a landmark in the peritoneal cavity. The anterior stomach wall is then pulled towards the myotomy site using a forceps or an endoclip. A second slim endoscope within the gastric lumen confirms the wrap formation. The wrap is secured using several endoclips over an endoloop along the serosal aspect of stomach and distal end of the myotomy. Subsequently, the endoloop is tightened and the excess portion is trimmed using a loop cutter. (Figure 3)

Inoue *et al* demonstrated the safety and feasibility of creating a fundoplication wrap with anterior POEM using an endoloop and endoclips in a proof-of-concept study.^[48] Bapaye *et al* later reported sustained wrap integrity in 82.6 % patients at a median follow-up of 12 months, with increased esophageal acid exposure and mild esophagitis in 11.1%, and 18.2% of patients, respectively.^[49] Despite the safety and feasibility in case reports and small case series, concerns have arisen regarding the durability of wrap.^[50-52] A retrospective study including 17 cases who underwent

NOTES fundoplication showed loosening of the fundal wrap in 29.4% and 41.2% patients at 1-month and 3 months, respectively.^[53] This aligns with observations of progressive increase in the incidence of GERD after LHM with fundoplication due to loosening of the wrap.^[54, 55] Refinement in NOTES-F procedure remains an active research.^[56] Given the low incidence of severe GERD (<10%) post-POEM, selecting the appropriate candidates for this procedure and conducting quality studies with long-term follow-up are essential before routine clinical implementation.

Other modifications in POEM technique, such as anterior *vs* posterior myotomy, and variations in myotomy length or thickness, have not shown substantial impact on the incidence of GERD.^[32-34, 39, 57-60] (Figure 4)

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MANAGEMENT OF GERD AFTER POEM

Proton pump inhibitors

Proton pump inhibitors (PPIs) are the primary treatment for GERD post-POEM. Studies show that post POEM reflux esophagitis responds well to PPIs and refractory GERD is distinctly uncommon after POEM.^[11, 12, 61] In two large studies, the response to PPIs in cases with erosive esophagitis after POEM was 81.4% and 87%, respectively.^[11, 12] Importantly, non-compliance to PPIs was the major reason in cases with residual esophagitis, emphasizing the importance of compliance in managing post-POEM GERD.

Device assisted endoscopic fundoplication

Device assisted endoscopic fundoplication has been increasingly recognized as a viable approach for managing GERD following POEM.^[62-65] A multicenter retrospective study explored the efficacy of transoral incisionless fundoplication (TIF) in a cohort of 12 patients who developed GERD after POEM.^[65] This study observed a marked reduction in the need for twice daily PPIs, alongside notable improvements in the frequency of daily symptoms and GERD Health-related Quality of Life scores, mean DeMeester scores, and mean percentage acid exposure time. In a separate randomized trial including 60 patients, Maydeo *et al* evaluated the effectiveness of endoscopic full thickness plication (EFTP) using the GERDx device (G-SURG GmbH, Seeon-Seebruck,

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Germany) in cases with PPI dependent GERD after POEM.^[66] At the 3-month follow-up, the study reported significant improvements in the EFTP group, with a notably higher proportion of patients exhibiting acid exposure time below 6% (69% vs. 10.3%). Additionally, the median GERDQ scores were significantly better in the EFTP group. However, it's important to note that while these results are promising, the study did not find a significant improvement in esophagitis, and a substantial portion of the EFTP group (28%) continued to require PPIs for symptom management.

Electrical stimulation

Electrical stimulation therapy (EST) has been effectively utilized for the treatment of GERD.^[67, 68] Emerging data suggest that EST of the LES may offer a potential therapeutic option for post POEM reflux.^[69, 70] In a porcine study, ² two electrical leads were implanted at the LES level and electrical stimulation applied with the Endostim system.^[69] ² After myotomy, the LES pressure significantly dropped to 10.60 ± 3.24 mmHg ($P = 0.03$). Subsequent to electrical stimulation, there was a substantial increase in LES pressure to 21.74 ± 4.65 mmHg ($P = 0.01$). These findings suggest that EST could play a significant role in the management of GERD after POEM, highlighting its potential to augment LES function and mitigate reflux symptoms.^[69]

NATURAL HISTORY OF GERD AFTER POEM

There is a significant body of research documenting the prevalence of GERD during brief follow-up, but long-term data on GERD progression and its consequences are relatively scarce. A large single-center study involving 610 patients reported the development of short segment Barrett's esophagus and peptic strictures in a small number of cases (five patients each) within 2 to 6 years after POEM.^[12] Similarly, others have also reported the development of Barrett's esophagus as a sequelae to post POEM reflux.^[71] Notably, these long-term sequelae of GERD were predominantly observed in patients who were noncompliant with PPIs.

Emerging evidence indicates that both the incidence and severity of reflux may reduce over time after POEM.^[12, 72, 73] In a study by Modayil *et al*, paired pH studies were conducted on 21 patients at a median of 5 months and 57 months after POEM.^[12] They

reported a significant reduction in the total number of refluxes (22 vs 66, $P = 0.001$), and DeMeester scores (21 vs 38, $P = 0.03$). Interestingly, 35% of patients with initially positive pH studies exhibited normalized results on long-term follow-up.^[12] The authors proposed that this improvement might be attributed to remodeling of gastroesophageal junction over time, a hypothesis supported by paired endoluminal functional lumen imaging probe(EndoFLIP) studies showing increased LES pressure and reduced cross sectional area, distensibility, and compliance of gastroesophageal junction several months after POEM.^[12] Further, a large multicenter Japanese study reported a significant decrease in the prevalence of symptomatic GERD at 5-year follow-up compared to 1-year after POEM.^[7] This suggests a generally favorable natural course of post POEM reflux implying that conservative management may often be adequate. In two long-term follow-up studies by Nabi *et al* and Simkova *et al*, the rates of symptomatic GERD and reflux esophagitis decreased over time, with a notable reduction in severe esophagitis (LA grades C/D).^{[74][73]} A recent systematic review and meta-analysis echoed these findings, showing a decrease in erosive esophagitis rates over time (28% at ≤ 6 months and 13% patients at ≥ 2 years).^[75] The landmark randomized trial comparing POEM to LHM, reported a reduction in the incidence of reflux esophagitis from 57% at one year to 44% at 2-years after POEM. In contrast, an increase was observed in the LHM group over the same period. This pattern aligns with previous studies which report a progressive increase in acid reflux after LHM at long-term follow-up.^[55]

In summary, while the incidence of endoscopic reflux appears to diminish over time after POEM, vigilant follow-up remains crucial. Ensuring adherence to PPI therapy is essential, given the potential development of Barrett's esophagus and peptic strictures as long-term complications of post-POEM reflux.

FUTURE PERSPECTIVES

In the era of precision medicine, the traditional approach of arbitrarily choosing a myotomy length (especially gastric) during POEM is being re-evaluated. The advent of technologies like EndoFLIP is paving the way for more objective criteria in

determining the length of myotomy. EndoFLIP facilitates intraoperative assessment of LES distensibility during POEM, enabling the tailoring of myotomies to achieve optimal distensibility while mitigating the risk of postoperative reflux.^[76] The potential of intraoperative impedance planimetry in predicting GERD after POEM has been explored in recent studies. Attar and colleagues reported that ² patients with a distensibility index ≥ 2.7 and a final cross-sectional area ≥ 83 were more likely to develop esophagitis after POEM.^[77] Similarly, post LHM distensibility index (DI) was higher in those who developed erosive esophagitis compared to ³ those without esophagitis (9.3 *vs* 4.8 mm(2)/mm Hg, $P < .05$).^[78] These studies suggest an association between EndoFLIP measurements and the risk of post-operative GERD. However, not all studies have confirmed the utility of EndoFLIP in predicting reflux after POEM, indicating a need for further high-quality research before its routine clinical application can be recommended. The future of POEM lies in integrating such advanced technologies with clinical practice, enhancing the precision and efficacy of treatments in esophageal motility disorders.

SUMMARY

GERD is a frequent occurrence following POEM, with a higher incidence compared to PD and LHM. The effective identification of risk factors, the implementation of preventive measures, and timely intervention are essential to mitigate complications associated with prolonged esophageal acid exposure post-POEM. There has been considerable advancement in understanding the factors predisposing to GERD, as well as in the diagnostic and therapeutic approaches following POEM. While modifications to the POEM technique have been shown to maintain efficacy, their impact on reducing the incidence of GERD post-procedure has not been as promising. However, conclusive evidence from high-quality research is needed before definitive conclusions can be drawn regarding the efficacy of these modified techniques in preventing GERD after POEM. (Figure 5)

CONCLUSION

GERD is a frequent occurrence following POEM, with a higher incidence compared to PD and LHM. The effective identification of risk factors, the implementation of preventive measures, and timely intervention are essential to mitigate complications associated with prolonged esophageal acid exposure post-POEM.

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