A New Paradigm Shift in Gastroparesis Management

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INTRODUCTION

Gastroparesis is a dysmotility disease, defined by delayed gastric emptying in the absence of mechanical obstruction. With a rising prevalence over the past decade, gastroparesis has become a burden to both the patients and healthcare system. The hospitalization rate has alarmingly increased with a mortality rate of up to 3.2%. With limited available therapeutic options, patients with gastroparesis not only have impaired quality of life, but also with shorter survival. Advanced age at diagnosis and uncontrolled diabetes are the key poor prognostic factors.

Gastric motility is a complex process that involves a concert orchestration of motor, secretory, and neuromodulating activities, making it almost impossible for any single intervention to effectively target the entire gastric emptying mechanism. Only 70% of patients adequately respond to dietary modification and medical management. Most prokinetic and antiemetic medications are limited by their adverse effects. These limitations underscore the need for an alternate therapeutic options. Fortunately, with better understanding of the pathophysiology and pathogenesis of the disease, new treatments have emerged and have shown promising efficacy even in patients with refractory symptoms. The scope of this article will focus on recent advances in diagnosis and management of gastroparesis.

EPIDEMIOLOGY

The true prevalence of gastroparesis is difficult to be accurately assessed. It is estimated that only one-ninth of the patients with high likelihood of having gastroparesis was actually worked up for and diagnosed. One of the key challenges is the lack of well-designed epidemiologic study using both verified gastroparetic symptoms and validated gastric emptying scintigraphy as diagnostic criterion. Few existing data reported a prevalence of 10 to 38 per 100,000 population with predominance in female and type I diabetic patients.

These existing epidemiological data are mainly in Caucasian population. The prevalence of gastroparesis in...
minority groups such as Hispanics, Africans, and Asian population are largely unknown. Among patients with diabetes, gastroparesis is far more prevalent in diabetes type 1 (30% to 50%) with a cumulative risk of 5.2%, compared to diabetes type 2 (15% to 30%) with a lower cumulative risk of 1.1%. As for gender inequity, women are at a 4-fold increased risk to developed gastroparesis with an incidence of 9.8 per 100,000 person years—partly can be explained by cyclic rises of progesterone, a key relaxant of gastric smooth muscle which induces overall gut hypomotility. Advanced age has also been shown to increase risk of gastroparesis with an incidence of 10.5 per 100,000 person years in patients older than 60 years old. It is hypothesized that older age carries more likelihood of being exposed to infections, drugs, and neuropathogenic factors.

Emerging data has suggested a very close relationship between functional dyspepsia and gastroparesis that many believe they are two different entities of the same spectrum. A significant portion of gastroparesis patients are known to overlap with functional dyspepsia, especially in patients with mildly delayed gastric emptying (<20% retention at 4 hours).

Functional dyspepsia is defined by bothersome upper gastrointestinal symptoms, which are postprandial fullness, early satiety, epigastric pain, or epigastric burning, in the absence of structural or metabolic etiology. While pain and burning sensation are not included in gastroparesis cardinal symptoms, but up to 90% of gastroparetic patients suffer from epigastric pain which can be misdiagnosed as functional dyspepsia. The prevalence of functional dyspepsia is estimated to be 10%, 3 to 7 times higher than that of gastroparesis.

Sensorimotor symptoms of upper gastrointestinal tract lack enough specificity to help reliably differentiate functional dyspepsia from gastroparesis. Vice versa, six out of nine symptoms of gastroparesis cardinal symptoms index (GCSI) overlap with symptoms of functional dyspepsia. In addition, majority of gastroparesis patients meet ROME IV criteria for functional dyspepsia while 30% of patients with functional dyspepsia have delayed gastric emptying, raising a question on how many have been misdiagnosed as one another. Due to such complex diagnostic paradigm, true prevalence of gastroparesis is likely to be inaccurately estimated. Regardless, the hospitalization rate of gastroparesis has amplified 158% from 1994 to 2005 with an astounding 3.5 billion US dollar healthcare expenditure in the United States, putting in a perspective on the significant increase in medical and economical from this debilitating disease.

PATHOPHYSIOLOGY

A wide range of gastric neuroimmunologic abnormalities are found in patients with gastroparesis. The conventional pathogenesis of gastroparesis focuses on a disruption of interstitial cells of Cajal network and vagal nerve injury, especially in patients with diabetic gastroparesis and postsurgical gastroparesis, while loss of synaptic vesicles and increased proinflammatory M1 macrophage are more commonly seen in patients with idiopathic gastroparesis. The discovery of smooth muscle cells, interstitial cells of Cajal, PDGFRα+ cells syncytium as the main gastric pacemaker unit (Fig. 1) and the neuronal-specific autoantibodies targeting gastric myenteric ganglion have shifted our understanding from the disease of dysmotility to a spectrum of neuroimmunologic dysfunction with a component of autoimmunity (Fig. 2).
ies, not only help us better understand the pathogenesis, but also open the possibilities of targeted immunotherapy in selected refractory cases. 38,39

Gastric motility involves three main mechanisms; (1) fundic accommodation, (2) gastric phasic contraction, and (3) antro-pyloro-duodenal coordination. 6,40 Once food bolus passes through the esophagus, the fundus relaxes increasing gastric volume while maintaining intragastric pressure. Impairment of fundic accommodation can cause nausea from unaccommodated intragastric pressure. 41

Once food bolus enters the stomach, fundic tone increases at the same time as myenteric interstitial cell of Cajal generates slow wave contraction that leads to propagated smooth muscle contraction to capture food that is pushed from fundus into gastric body and antrum against a closed pylorus. Such to-and-fro movement allows mechanical grinding and enzyme mixture of the food bolus back and forth until small particle homogenous chyme is achieved. 42 This process is controlled by magnitudes of gastric hormones, primarily by cholecystokinin (CCK) as the main inhibitor of gastric emptying and orexigenic hormones such as ghrelin and motilin as an accelerator of gastric emptying (Fig. 3). 43 CCK release is triggered by fat and protein content in ingested food. It stimulates contraction of pylorus and relaxation of proximal stomach (fundic accommodation), thereby delaying gastric emptying via vagal afferent nerve. 44 Ghrelin and motilin act directly on ghrelin and motilin receptor in the stomach and small intestine to stimulate muscular contraction thereby playing an important role in the regulation of interdigestive gastrointestinal motility and indirectly causes rhythmic contraction to accelerate gastric emptying and increase appetite. 43,45 They are targets of prokinetics such as relamorelin and erythromycin 43 as shown in Fig. 3. Abnormal level of neurotransmitters responsible for enteric muscle contraction such as ghrelin, motilin, and substance P can lead to pylorospasm. 46 Imbalance of these gastric hormones can cause impaired fundic accommodation, pylorospasm, and gastric dysmotility leading to gastroparesis. 43,46

The composition of chyme determines neurohormonal response for pancreatic enzyme secretion and relaxation of the pylorus, an event that occurs at the same time as duodenal contraction, allowing food passage into the small intestine. Antroduodenal motility is therefore one of the key process that determines the pace of gastric emptying. 47

Fig. 2. Neuroimmunologic and histologic injury in the pathogenesis of gastroparesis. ICC, interstitial cell of Cajal; nNOS, neuronal nitric oxide synthase; HO1, heme oxygenase-1.
All key gastric dysmotility including antroduodenal hypomotility, impaired fundic accommodation, and pylorospasm interact with one another (Fig. 3) and such dysmotility can result from multiple causes including, diabetes with microvascular complications, vagal nerve injury, viral infections, i.e., cytomegalovirus, Epstein-Barr virus, metabolic disorders, neuromuscular disorders, certain medications, certain abdominal and thoracic surgery such as solid organ transplantation, Roux-en-Y gastric bypass, esophagectomy, etc. as described in Table 1.4,12,17,51 However, despite better understanding of its pathophysiology, majority of gastroparesis are still from an unknown cause.4,17

The cardinal symptoms of gastroparesis are essential in making the diagnosis. These symptoms do not stem from delayed gastric emptying alone, but also from a complex spectrum of neuromuscular dysfunction.

The gold standard method for assessment of gastric emptying remains scintigraphy study using a validated 4-hour T99 labeled solid meal technique according to the Tougas protocol.32,53 However, such time-consuming nuclear study poses certain dilemmas, i.e., (1) gamma-camera for T99 scintigraphy is costly and not readily available in many centers; (2) because of the 4-hour standardization, testing can be limited to only one to two patients per day; (3) radiation exposure is of concern for many women in reproductive age which represent the majority of gastroparesis patients; (4) low fat, low caloric conventional egg-based meal does not represent a general daily meal for most patients which may cause false negative in patients with mild delayed gastric emptying. Due to aforementioned limitations, repeating the study multiple times to monitor progression or treatment response are not prac-

**DIAGNOSIS**

Diagnosis of gastroparesis requires three main criteria; (1) gastroparetic symptoms, (2) absence of mechanical obstruction, and (3) demonstrable delayed gastric emptying.52
Table 1. Etiology of Gastroparesis

| Etiology of gastroparesis | Specific causes |
|---------------------------|-----------------|
| Diabetes                  | Diabetes type II (5 times more common than type I) |
| Postinfectious            | Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus |
| Vagal nerve injury        | Pylorus-preserving Whipple, Lung transplantation, Esophagectomy, Roux-en-Y gastric bypass, Cholecystectomy, Nissen fundoplication |
| Metabolic disorders       | Hypokalemia, Hypomagnesemia, Hypophosphatemia, Hypothyroid, Cystic fibrosis |
| Musculoskeletal disorder  | Scleroderma, Amyloidosis, Mixed connective tissue disease |
| Neurological disorder     | Parkinson’s, Autoimmune gastrointestinal dysmotility |
| Medication-induced        | Opioid, Anti-cholinergic agents, Tricyclic antidepressant, Calcium channel blocker, Octreotide, Levodopa, Lithium, Glucagon-like peptide-1 analogs, Cyclosporine |
| Idiopathic                | Accounts for 30% to 50% of cases |

Recently, alternative methods such as carbon-13 labeled breath test and wireless motility capsule (WMC) study have emerged to overcome the limitations of gastric emptying scintigraphy. The concept of breath testing is to assess the time carbohydrate-base substrate is digested and absorbed in the small intestine. The tagged substrate can be a medium-chain fatty acid such as octanoic acid or an edible algae such as commercialized Spirulina platensis. Once the carbohydrate-base substrate is digested and absorbed in proximal small intestine, $^{13}$C then undergoes hepatic metabolism into tagged $^{13}$CO$_2$, which can be detected in the patient’s exhaled gas using mass spectrometry method. Timing of $^{13}$CO$_2$ detection after meal ingestion can be analyzed for gastric emptying time.

Compared to a nuclear study, breath test is more simple, reproducible, and much more economical since it does not require any special hardware equipment however, gastric outlet obstruction needs to be excluded first. Although not as extensively validated, the results of $^{13}$C breath test has shown to correlate well with scintigraphy study and has recently been approved by U.S. Food and Drug Administration. The limitation of the $^{13}$C breath test is that it cannot demonstrate the gastric region affected such as impaired fundic accommodation versus poor pyloric clearance. Moreover, the results should be interpreted with caution in patients with liver and lung pathology where false positive can occur. In addition, 39% of gastroparesis patients, especially in those with diabetes or scleroderma, may have concurrent small bowel bacterial overgrowth, a condition that can accelerate small bowel absorption process thus producing false negative results.

WMC assesses global motility function including gastric emptying and small bowel transit time by measuring changes in pH, temperature, and pressure. The limitation of the WMC is that the emptying of a non-digestible foreign body like a wireless capsule does not reflect the true emptying of a regular meal. Therefore, WMC only showed moderate correlation with the gold standard 4-hour scintigraphy study with 75% agreement ($\kappa$=0.42), 65% sensitivity, and 87% specificity. In addition to global gastric emptying, regional function assessment is of new diagnostic concept that can be helpful for targeted therapy and is of prognostic value. It can be evaluated by both scintigraphy study and by WMC while targeted physiologic evaluation of the pylorus can be evaluated by impedance planimetry using endoscopic functional lumen imaging probe (EndoFLIP). The degree of delayed gastric emptying does not always correlate with symptoms severity certain symptoms correlate with proximal and distal gastric retention. Delayed proximal gastric emptying generally causes more symptoms including nausea, vomiting, abdominal distension, and acid reflux while early satiety is more likely to be associated with delayed distal gastric emptying.

Localized gastric scintigraphy can serve not only as a surrogate for regional gastric digestive mechanism, but also as a predictor for responses to gastroparesis therapy. For example, Acotiamide, a medication that targets to improve fundic accommodation may be preferred in patients with delayed proximal gastric emptying or pylorus-directed therapy is predicted to yield clinical response in patients with high retention index. Therefore, regional emptying data should be retrieved when able as they can provide additional important information for selecting appropriate therapy.

Gastric accommodation is a different parameter than proximal delayed gastric emptying but certainly share a similar mechanism. It can be assessed using single-photon emission computed tomography or magnetic resonance imaging. Scintigraphy test may be able to crudely screen impaired fundic accommodation by measuring the size of
the proximal stomach immediately after radiolabeled meal ingestion.66

| Mechanism                        | Medication                              |
|----------------------------------|-----------------------------------------|
| Anti-dopaminergic receptor       | Domperidone, Levosulpiride, Metoclopramide, Itofpride |
| Cholinergic agonist (acetylcholinesterase inhibitor and muscarinic receptors antagonist) | Acotiamide, Itofpride |
| Motilin agonist                  | Erythromycin, Azithromycin              |
| Cannabinoid receptor agonist     | Tetrahydrocannabinol, Cannabidiol        |
| Serotonin modulators             |                                         |
| SHT3 antagonist                  | Alosetron, Ondansetron                  |
| SHT3 agonist-Ach modulator       | Prucalopride, Mosapride, Levosulpiride, Metoclopramide, Velusetrag |
| 5HT4 agonist                    | Buspirone, Acotiamide                   |
| Ghrelin agonist                  | Buspirone, Ulimorelin                   |
| Neurokinin antagonist            | Aprepitant, Tradipitant                 |

Ach, acetychololine.

**TREATMENT**

Careful restoration of water and electrolyte balances with close monitoring of refeeding syndrome is the cornerstone of initial treatment. Special attention should be made on the patient’s glycemic control due to high risk of hypoglycemia, diabetic ketoacidosis, and hyperglycemic-induced exacerbation of gastroparetic symptoms.67

Dietary modification with small frequent meals of low-fat, low-caloric, low-fiber diet should be adopted by all patients.67 Vigorous chewing of ingested food into small particles can also reduce reflux and gastroparetic symptoms.68 Unfortunately, despite nutritional counseling, majority of the patients will remain symptomatic and require medical therapy.7

1. Pharmacotherapy

Medical treatment of gastroparesis is largely limited by long-term adverse effects of available medications, tachyphylaxis, and availability.7 Prokinetics remain the mainstay of pharmacotherapy.8 Other centrally-acting medications such as muscarinic cholinergic receptor antagonist, SHT3 receptor antagonists, and phenothiazines have antiemetic effects which can be used for symptomatic relieve as described in Table 2 and Fig. 4.69

1) Anti-dopaminergic receptor

Among all pharmacotherapies for gastroparesis, metoclopramide is the most commonly used as it is the only available Food and Drug Administration-approved medi-

**Fig. 4.** Mechanism of available pharmacotherapies for gastroparesis. THC, tetrahydrocannabinol; CBD, cannabidiol; D2RA, dopamine D2 receptor; NK1, neurokinin 1; Sub-P, substance P; M1M2, muscarinic 1 and muscarinic 2 receptors; Ach, acetychololine; Ach-R, Ach receptor; AchE, acetycholinesterase.
cation in the United States. Its 12-week black box warning due to extrapyramidal side effects is the main limitation for long-term use. It also has weak effects on 5HT₃ and 5HT₁ receptors accelerating gastric emptying. Domperidone, though is available in Europe and Asia, carries a low but significant risk of QTc prolongation and sudden cardiac death. Advantage of domperidone is that it does not cross blood brain barrier thus having much lower risk for extrapyramidal side effects. Levsulpiride increases lower esophageal sphincter pressure and inhibits dopamine D₂ receptors on both stomach and small intestine. All three anti-dopaminergic agents have dual-antiemetic activities as they bind both central (chemoreceptor trigger zone in the area postrema) and peripheral (enteric) dopamine receptors and prokinetic properties since they antagonize dopamine receptors in the central nervous system as well as in the gastrointestinal tract where dopamine augments inhibitory effects on gastrointestinal motility.

2) Serotonin modulators
Pharmacologic agents targeting serotonin receptors such as 5HT₁₆, 5HT₁₅, and 5HT₁₃ have seen the most progress among pharmacotherapy of gastroparesis. 5HT₁₃ receptor agonist and motilin receptor agonists such as prucalopride, mosapride, levsulpiride, and velusetrag have been used to relieve bloating and early satiety with varying clinical response. Prucalopride has shown to be effective for gastroparesis in a predominantly female idiopathic gastroparesis cohort. Since it is currently used for constipation, it would be ideal for gastroparesis patients who also have colonic inertia.

5HT₁₆ receptor antagonists such as ondansetron and alosetron primarily work centrally via afferent vagal nerve thus exerting antiemetic effect with little prokinetic property. Advantage of medication in this group is their availability in non-oral route of administration. Ondansetron is available in both oral disintegrating tablet and intravenous form, while granisetron is available in a transdermal delivery system.

Acotiamide, an agent with both selective and reversible acetylcholinesterase inhibition, also exhibit 5HT₁₆ agonistic activity. It is mainly used for epigastric pain syndrome and is not well studied in gastroparesis but its ability to improve fundic accommodation and reduce postprandial antral pressure has been an attractive property for gastroparesis patients. Patients with anxiety disorder can benefit from 5HT₁₆ anxiolytic agent such as Buspirone that can exert fundic relaxation effect and improve postprandial symptoms, especially for those with concomitant functional dyspepsia.

3) Neurokinin 1 inhibitor
Neurokinin 1 (NK1) inhibitor is a novel agent with selective high-affinity antagonist of substance P and NK1 receptors with little or no affinity to serotonin or dopamine receptors. Drugs in this class include aprepitant and tradipitant, which are used commonly for chemotherapy-induced nausea. Recent studies have demonstrated their efficacy in improving GCISI with a potential benefit in functional accommodation.

4) Ghrelin agonist
Ghrelin agonist such as relamorelin can stimulate gastric body and antral contraction, thereby accelerating gastric emptying. The results of phase IIa and IIb randomized controlled trials among patients with diabetes have been quite promising. Its lack of cardiovascular or extrapyramidal adverse effect make relamorelin an appealing option for patients with diabetic gastroparesis with concurrent constipation.

5) Cannabinoid receptor agonist
The role of medical marijuana has been under debate for years. Although a long chronic use of marijuana is associated with cannabinoid hyperemesis syndrome but the centrally acting effect of tetrahydrocannabinol is, in itself, antiemetic and analgesic. A recent study revealed that gastroparesis patients with concomitant use of cannabis tend to have shorter hospitalization duration and even with lower in-patient mortality rate. Another questionnaire-based study showed that there was no difference in gastric emptying between cannabis and non-cannabis users but improved gastroparesis symptoms were reported among those who use cannabinoids. Proper dosing of tetrahydrocannabinol and cannabidiol is the cornerstone of its use and remains to be verified in larger randomized controlled studies.

6) Antidepressants
Traditionally, antidepressant and neuromodulators have been used to alleviate gastroparesis symptoms with varying success. Tricyclic antidepressant, though can be useful in functional dyspepsia, has shown to have little effects in gastroparesis. Its anticholinergic property can also delay gastric emptying and generally should be used only for mild gastroparesis or functional dyspepsia with overlapping gastroparesis symptoms. Noradrenergic and specific serotonergic antidepressant such as mirtazapine, however, has demonstrated promising results in improving nausea, loss of appetite, and weight gaining benefit in an open-label study. Antipsychotic agents such as haloperidol and levsulpiride have been shown to improve nausea and pain
in gastroparesis patients via their anti-dopaminergic effects.\textsuperscript{92,93}

Non-intravenous parenteral route is essential for assuring adequate delivery of the medication in nausea-predominant patients. Nasal metoclopramide, transdermal granisetron, and subcutaneous relamorelin offer practical alternatives to conventional peroral medications.\textsuperscript{94} When cannabinoid is considered, smoked cannabis offers better bioavailability compared to oral route due to a lack of first-pass effect through the liver.\textsuperscript{95}

The selection of medication depends on the presenting symptoms. For nausea/vomiting which stems from a combination of increased intragastric pressure and efferent signal via central vomiting center in the medulla, dopamine receptor antagonist such as metoclopamide, domperidone, and phenothiazines and serotonin modulator such as ondansetron and granisetron are generally the first-line agents.\textsuperscript{96} Conventional antispasmodic agents with anticholinergic property such as hyoscyamine, dicyclomine, and peppermint oil can be used for abdominal pain. Bloating and early satiety are more resilient symptoms as they are associated with impaired fundic accommodation, a mechanism with no specific targeted therapy.

2. Endoscopic therapy

As pyloric dysfunction is one of the main pathogeneses of gastroparesis, all available endoscopic therapies aim to mechanically disrupt pyloric muscle, a mechanism which has been proven to impact not only pyloric clearance, but also global gastric emptying.\textsuperscript{22,96,97} Available endoscopic modalities include intramuscular pyloric botulinum injection, transpyloric stenting, pyloric dilation, and gastric peroral endoscopic pyloromyotomy (G-POEM).\textsuperscript{76} Pylorospasm is defined as a high-amplitude long contraction of pyloric muscle and is associated with muscular fibrosis and loss of interstitial cell of Cajal.\textsuperscript{98}

Recent studies on surgical pyloroplasty and transpyloric stenting demonstrated an improvement of both GCSI and gastric emptying,\textsuperscript{99-102} however, randomized controlled trials of intrapyloric botulinum injection failed to show symptomatic improvement compared to sham saline injection despite improvement in gastric emptying.\textsuperscript{102,104,105} Intrapyloric botulinum injection is no longer recommended by the American College of Gastroenterology, while transpyloric stent is associated with risk of stent migration and not considered a long-term solution.\textsuperscript{8,104,105}

Currently, the most promising endoscopic therapy is G-POEM, also known as peroral endoscopic pyloromyotomy, which is a novel therapy for refractory gastroparesis.\textsuperscript{106-109} Available data on G-POEM is only for short-term outcomes with the longest follow-up data of 3 years.\textsuperscript{110} Although more than a thousand patients have been reported worldwide, the follow-up data were mainly from retrospective non-controlled studies with a few small non-controlled prospective trials.\textsuperscript{22,96,106,110,111}

The procedural techniques of G-POEM have been refined over time. Current recommendation is to perform selective circular pyloromyotomy to minimize the risk of perforation and that there is no difference in clinical outcomes between anterior and posterior approach, nor is there any difference in the patient’s position.\textsuperscript{22,112-114} Although general anesthesia is the standard mode of anesthesia for G-POEM however, recent study has demonstrated that the procedure can be safely carried out with conscious sedation.\textsuperscript{115}

Despite its technical challenges that demands expertise in third space endoscopy, technical success of G-POEM has been reported at almost 100%.\textsuperscript{22,76,108,109,111} It is important to recognize that these results were likely subject to publication bias and all procedures were performed by expert endoscopists who are highly experienced in submucosal endoscopy. The learning curve of the procedure, even in the experts’ hands, was estimated to be at 18 procedures.\textsuperscript{116}

Pyloric parameters such as cross-sectional area and diameter are shown to be inversely associated with cardinal symptoms of postprandial fullness and early satiety.\textsuperscript{49} Poor pyloric compliance and distensibility are also associated with severity of gastroparesis symptoms and delayed gastric emptying time.\textsuperscript{55} These findings can explain the mechanism of how pyloromyotomy can improve global gastric emptying and gastroparesis symptoms.

Five recent large meta-analyses have reiterated clinical efficacy of G-POEM in both short and mid-term follow-up with significantly improved both GCSI score and gastric emptying scintigraphy.\textsuperscript{117-119} Mohan et al.\textsuperscript{117} demonstrated that G-POEM has comparable clinical success, technical success, and adverse event rate to surgical pyloroplasty with shorter procedural time. Despite limited long-term data and much more complex pathophysiology, the long-term efficacy of G-POEM for gastroparesis has been quite encouraging with significantly improved symptoms and quality of life in 73% to 85.7% of patients at up to 36-month follow-up period,\textsuperscript{22,96,97,106,110,113} which was surprisingly comparable to the 72.7% to 87% clinical success rate of its predecessor, POEM for achalasia.\textsuperscript{120,121} Overall adverse events rate of G-POEM is low, ranging from 0% to 6.7%.\textsuperscript{96,108,113,114,122} Serious adverse events included gastrointestinal bleeding, pyloric ulcer, and tension c Kapneritoneum. Unusually high rate of perforation (20%) was reported in one study,\textsuperscript{111} which could have been attributed to full-thickness pyloromyotomy technique used.
Due to limited therapeutic options and growing number of patients suffering from refractory gastroparesis, G-POEM was quickly adopted.\textsuperscript{20,96,97,106,112,113,122-124} Data from Asian population is sparse and is mainly from India and Korea.\textsuperscript{106,111} This reporting disparity reflects the varying prevalence among different ethnicities. The role of G-POEM awaits further large, randomized, sham-controlled trials to verify these results.

One of the recent advances in endoscopic evaluation and management of gastroparesis is the advent of impedance planimetry using EndoFLIP\textsuperscript{5} that allows real-time evaluation of pyloric physiology and function. Pyloric compliance and distensibility have been shown to play a predictive role of clinical response to pylorus-directed therapy.\textsuperscript{52,111,125,126}

G-POEM decreases pyloric pressure, increased pyloric distensibility, increased pyloric cross-sectional area, as well as the GCSI.\textsuperscript{111} The distensibility cutoff of 9.2 mm\textsuperscript{2}/mm Hg yielded a specificity of 100% and a sensitivity of 72% for clinical response while the outcomes were more favorable in patients with diabetic gastroparesis.\textsuperscript{111} Subsequent studies on impedance planimetry measurements reaffirmed similar correlation between an increased pyloric distensibility and improved gastroparesis symptoms, whether the pyloromyotomy was performed by G-POEM or by an EsoFLIP-controlled pyloric dilation.\textsuperscript{127-129} Gastric emptying was also found to be decreased after G-POEM when improved pyloric indices and symptoms were observed.\textsuperscript{129,130} Although there is prognostic benefit of intra-procedural pyloric evaluation using EndoFLIP\textsuperscript{5}, the cost-effectiveness of its routine use remains to be further verified.\textsuperscript{52}

3. Gastric electrical stimulator

Gastric electrical stimulation (GES) involves surgically implanted neurostimulator to the gastric wall. The amplitude, frequency, and direction of these electrical activities can be adjusted to help control the gastric emptying.\textsuperscript{88,131} The device has been approved for patients with nausea-predominant diabetic gastroparesis who do not respond to medical therapy.\textsuperscript{132} However, the efficacy of GES in recent randomized controlled trials were rather disappointing with no significant improvement of symptom severity or significant superiority to sham intervention.\textsuperscript{7,133,134} In addition, the implantation and device-associated adverse effects such as pocket infection, sepsis, pulmonary embolism, stroke, or even death have been reported.\textsuperscript{132} Shen et al.\textsuperscript{135} conducted a comparative study between GES and G-POEM and demonstrated that G-POEM had higher and more durable clinical response with 76% response rate at 24-month follow-up and lower adverse event rate (4.3% vs 26%). Currently, the indication for GES is rather limited only for patients with nausea-predominant diabetic gastroparesis.

4. Surgical therapy

Although surgery can serve as a rescue therapy in those who do not respond to medication and pyloromyotomy, it is imperative to reevaluate these patients preoperatively and exclude other causes of gastroparesis-like symptoms such as small bowel dysmotility, overlapped functional dyspepsia, etc. Surgical intervention includes surgical pyloroplasty, total gastrectomy, and subtotal gastrectomy with Roux-en-Y gastrojejunostomy reconstruction. While gastrectomy with surgical gastrojejunostomy can be a durable therapeutic option but it carries significant risk with some studies reported as high as 23% morbidity and 3% mortality rate.\textsuperscript{136,137} Although endoscopic ultrasound-guided gastrojejunostomy can offer less-invasive mean to provide pyloric-bypass anastomosis, high quality studies on its long-term safety and patency are still lacking.\textsuperscript{137}

A study comparing G-POEM with surgical pyloroplasty showed G-POEM had average shorter operative time, less intra-procedural blood loss, shorter hospital stay, lower adverse event rate, and lower intensive care unit admission rate.\textsuperscript{138} Recent systematic review comparing GES, surgical pyloroplasty, and gastrectomy showed favorable outcomes in pyloric intervention group.\textsuperscript{136}

Pyloromyotomy can be repeated in patients with recurrent symptoms.\textsuperscript{22} Combined therapy can also be complementing to each other. Surgical pyloroplasty with gastric pacemaker has shown to improve gastroparesis symptoms.\textsuperscript{99} Total gastrectomy serves as a last resort for the patients who continue to suffer from refractory symptoms despite optimal therapy.\textsuperscript{114}

As exciting as these novel breakthroughs are, a few shortcomings on gastroparesis studies remain: (1) there is no validated gold standard treatment that new therapeutic intervention can be compared with; (2) objective outcomes such as gastric retention rate does not correlate well with gastroparesis symptoms; (3) clinical response is mainly measured by GCSI which is subjective and is limited by recall bias; (4) even with an increasing prevalence, gastroparesis is still a rare disease and novel therapies are limited by the device and expertise availability, making large-scale trials very challenging; (5) most existing studies included only patients with severe refractory disease, subjecting the results to overinflated improvement due to regression to the mean phenomenon; or (6) sham-controlled randomized prospective studies with long-term follow-up are direly lacking. Until more robust data is available, caution should be made when adopting these novel modalities into routine clinical practice.
CONCLUSIONS

With recent advances in unfolding the complex pathophysiology of gastroparesis, more practical diagnostic modalities, and minimally invasive therapeutic options, management paradigm of gastroparesis has shifted significantly with an aim to become curative and more individualized. As more long-term data from randomized trials are emerging, the armamentarium of gastroparesis management will continue to evolve.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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