Management of Gastroparesis

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Abstract: Gastroparesis is a gastrointestinal motility disorder characterized by nausea, vomiting, early satiation, postprandial fullness, bloating, and upper abdominal pain. The diagnosis requires documented delay in gastric emptying with an optimal test such as scintigraphy or stable isotope gastric emptying breath test in the absence of mechanical obstruction. The pathophysiologic mechanisms of gastroparesis are multifactorial, including antroduodenal hypomotility, pylorospasm, impaired gastric accommodation, and visceral hypersensitivity. The etiologies of gastroparesis are broad, but the most common subtypes are idiopathic, diabetic, and postsurgical. Less frequent etiologies are neurodegenerative disorder (Parkinson disease), myopathies (scleroderma, amyloidosis), and neoplastic syndrome. Symptoms of gastroparesis can be refractory and challenging to manage, leading to reduced quality of life and significant health care expenditure. This article introduces the epidemiology, clinical presentation, diagnosis, and differential diagnoses of gastroparesis, followed by a focused discussion on its management, including nutritional support, prokinetic and antiemetic agents, and emerging interventions directed at the pylorus. Robust sham-controlled trials are needed to evaluate the long-term efficacy of gastric peroral endoscopic myotomy. A multidisciplinary approach with individualized strategies based on characterization of the pathophysiology is deemed necessary to enhance clinical outcomes.

Keywords
Gastric emptying, gastric accommodation, visceral hypersensitivity, nutritional support, prokinetics, gastric peroral endoscopic myotomy

Gastroparesis is a gastric motility disorder characterized by upper gastrointestinal symptoms, including nausea, vomiting, early satiation, postprandial satiety, bloating, belching, and epigastric pain. Gastroparesis is associated with delayed gastric emptying in the absence of mechanical obstruction.[1] Although nausea and vomiting are considered the cardinal symptoms of gastroparesis,[2] other symptoms overlap frequently with functional dyspepsia, especially postprandial distress syndrome.[3] Abdominal pain was reported in up to 90% of patients with gastroparesis assessed at tertiary care centers in the National Institutes of Health (NIH) Gastroparesis Consortium, and 41% of those patients were chronically dependent on opioids.[4-6] The epidemiology, clinical presentation, diagnosis and differentials, and management of gastroparesis are discussed in this review article.

Epidemiology and Impact

The prevalence of gastroparesis was estimated to be 13.8 (95% CI, 12.6-15.1) per 100,000 persons, with the standardized incidence of 1.9 (95% CI, 1.4-2.3) per 100,000 person-years in 2016, based on the UK Clinical Practice Research Datalink.[7] Another study, based on Olmsted County, Minnesota, reported a prevalence of 24.2 per 100,000 persons and incidence of 6.3 per 100,000 person-years, both with a significant female predominance.[8] However, the true prevalence of gastroparesis may be much higher (estimated to be 1.8%, with only 0.2% formally diagnosed) owing to a significant portion of individuals with suspected symptoms not receiving confirmatory gastric emptying tests.[9]

The etiologies of gastroparesis are broad, but the most common subtypes are idiopathic, diabetic, and postsurgical (fundoplication, bariatric procedures), followed less frequently by neuropathic (Parkinson disease, paraneoplastic syndrome) and myopathic (scleroderma, amyloidosis) gastroparesis.[10]

Like most gastrointestinal motility disorders, gastroparesis is rarely considered a life-threatening condition. However, patients with gastroparesis have significantly lower overall survival than age- and sex-specific reference populations.[8] This is particularly true for patients with diabetic gastroparesis, presumably owing to concurrent comorbidities.[7,8] Furthermore, gastroparesis-related emergency department visits doubled and hospital admissions tripled from 2006 to 2013, with dramatically increased costs associated with hospitalizations.[11,12] Gastroparesis symptoms lead to reduced activities of daily living in 67.5%, lowered annual income in 28.5%, and disability in 11% of patients,[13] along with significant caregiver fatigue.[14]

Clinical Manifestations and Differential Diagnoses

In clinical practice, gastroparesis symptom severity can be tracked using the validated Gastroparesis Cardinal Symptom Index (GCSI),[15] and the 36-Item Short Form Survey can be used to assess a patient's physical functions and emotional, mental, and social health.[15] An upper gastrointestinal endoscopy or other imaging should first be pursued to rule out mechanical obstruction. Retained food in the stomach seen with esophagogastroduodenoscopy has a limited diagnostic value for predicting delayed gastric emptying.[16] Despite significant symptom overlap, gastroparesis is distinguished from functional dyspepsia by objectively delayed gastric emptying, measured by gastric emptying scintigraphy (GES) using a ^{99m}technetium-labeled test meal[1,17,18] or by the stable isotope gastric emptying breath test (GEBT) using ^{13}C-Spirulina.[19] A robust cutoff criterion for objective gastric emptying delay is 25% residue in the stomach at 4 hours postmeal.

In addition to functional dyspepsia, gastroparesis symptoms also overlap with other functional gastrointestinal disorders such as cyclic vomiting syndrome, cannabinoid hyperemesis, and rumination syndrome. These entities can be differentiated from gastroparesis based on history and patterns of symptoms. Cyclic vomiting syndrome is characterized by episodic bouts of nausea and vomiting and acute autonomic disturbances, interspersed with periods of baseline health. Cannabinoid hyperemesis occurs in patients with prolonged history (2-10 years) of nearly daily high-dose cannabis use and resolves with cessation.[20] Patients with rumination syndrome present with repetitive, effortless regurgitation of gastric contents (partially recognizable food) within 30 minutes after a meal that is not preceded by nausea or retching and sometimes involves reswallowing of the food.[21]

Diagnosis

A recent publication from the NIH Gastroparesis Consortium of patients with delayed or normal gastric emptying during different measurements obtained over time questioned the role of GES as well as the diagnosis of gastroparesis.[3] However, scintigraphy is considered the gold standard for measuring gastric emptying of solids and is endorsed by national societies for identifying abnormal gastric motor functions.[1] Scintigraphy is also used to investigate pathophysiologic mechanisms that might contribute to patients' symptoms and to evaluate the efficacy of prokinetic agents.[1] The most widely used test meal is a 256-kilocalorie, low-fat (2%) meal consisting of Egg Beaters (ConAgra Foods), toast, jam, and water, with delay identified by gastric retention greater than 60% at 2 hours or greater than 10% at 4 hours postmeal,[3] based on the 95th percentile in a multicenter study consisting of 123 healthy controls. However, a recent observation of 31 healthy controls at 1 center showed the 75th and 95th percentiles of gastric retention at 4 hours postmeal to be greater than 13% and greater than 23%, respectively.[22] Indeed, a thoroughly validated alternative meal consisting of 2 scrambled eggs, a slice of whole-wheat toast, jam, and milk, which has higher calories (300 kilocalories) and higher fat (30%) and is arguably more representative of a typical American meal, provides a more significant challenge test for assessing gastric motor function and defines delayed gastric emptying as gastric retention greater than 75% at 2 hours postmeal and greater than 25% at 4 hours postmeal.[18] Medications that alter gastric motility, such as metoclopramide, domperidone, erythromycin, narcotics, glucagon-like peptide-1 agonists, and

anticholinergics, should be withheld for 48 to 72 hours before the examination.

Stable isotope GEBT is a US Food and Drug Administration (FDA)-approved alternative to GES for evaluation of gastric emptying. Based on the principle that the rate of gastric emptying of ^{13}C substrate incorporated in the solid test meal is reflected by breath excretion of $^{13}CO_2$, premeal breath samples are collected after an 8-hour fast, followed by additional samples collected over 4 hours after eating the test meal. Involving no radiation exposure, GEBT can be safely used in pregnant or breastfeeding women or in children.[23]

The wireless motility capsule (WMC) is another FDA-approved modality to measure gastric emptying. The WMC directly measures the emptying of a relatively large indigestible solid object, and emptying has been shown to correlate with phase 3 of the migrating motor complex rather than the gastric emptying of a digestible, food-based solid meal.[24] The principle of this test is based on the precipitous rise in pH as the capsule empties from the acidic gastric lumen into the bicarbonate-rich duodenum. A systematic review reported a sensitivity of 59% to 86% and specificity of 64% to 81% as compared with 4-hour GES.[25] There is also little association of gastroparesis symptoms with the WMC profiles.[26] Thus, the accuracy of the WMC for diagnosis of gastroparesis is still debated.

Management

The management of gastroparesis can be challenging and involves a comprehensive, multimodal approach of nutritional support, dietary modification, suppressing or eliminating symptoms, and identifying and treating the underlying pathophysiologic mechanisms.

Hydration and Nutrition

For patients with severe fluid or metabolic derangements (ketoacidosis, uremia, hypoglycemia, hyperglycemia) owing to nausea and vomiting, restoration of hydration and electrolyte balance needs to be pursued in the appropriate setting (ie, through a peroral or, if necessary, intravenous [IV] route).[27]

Evidence from the NIH Gastroparesis Consortium showed that up to 64% of patients with gastroparesis consume caloric-deficient diets, defined as less than 60% of the estimated total energy requirements. Vitamin (A, B6, C, K) and mineral (iron, potassium, zinc) deficiencies are common. This documented experience showed that only one-third of 305 enrolled patients were taking vitamin supplements, 32% had nutritional consultation after diagnosis, and a mere 2% were following dietary modification or the gastroparesis diet.[28] The initial step of dietary modification involves cooking nondigestible fiber and mechanically homogenizing solids to a small particle size. In a randomized, controlled trial of 56 patients in Sweden with diabetic gastroparesis, this dietary modification was shown to significantly reduce the severity of nausea, vomiting, postprandial fullness, bloating, and regurgitation/heartburn.[29]

If the patient is unable to consume adequate calories through solid food or a homogenized diet, stepwise nutritional interventions are recommended, including the use of liquid meals, oral nutrition supplements, enteral nutrition, and parenteral nutrition.[30] Percutaneous jejunal feeding has been shown to be safe, allows patients to gain weight, and can be discontinued after an average of 20 months.[31] However, a trial of nasojejunal feeding should precede percutaneous placement of the jejunal feeding tube, as some patients have coexistent intestinal dysmotility or may not tolerate the rate of calorie infusion required, which would preclude jejunal feeding. Parenteral nutrition is reserved for temporary use in patients with severe nutrition deficiency, and chronic use should be avoided because of increased risk of complications such as infections and thromboses.[32,33]

Pharmacologic Agents

Prokinetics

Most patients with gastroparesis continue to experience symptoms despite optimal supportive care. The 2013 guideline from the American College of Gastroenterology recommends prokinetic agents as first-line therapy for gastroparesis.[34] Although the correlation between delay in gastric emptying and severity of symptoms remains controversial, clinical trials have shown the efficacy of prokinetic agents in enhancing gastric emptying and reducing gastroparesis symptoms.[35] In a systematic review of randomized, blinded, parallel, or crossover trials of 5-hydroxytryptamine 4 (5-HT_4) receptor agonists, dopamine D_2 receptor antagonists, or ghrelin receptor agonists, meta-regression revealed a positive association between improvement in gastric emptying (especially when time to one-half gastric emptying accelerated by 20.4 minutes) and upper gastrointestinal symptoms in studies with optimal gastric emptying tests.[35]

Metoclopramide is a central and peripheral dopamine receptor antagonist and the only FDA-approved medication for gastroparesis.[34] Metoclopramide crosses the blood-brain barrier and can cause anxiety, agitation, somnolence, extrapyramidal symptoms, and rarely irreversible tardive dyskinesia. Therefore, metoclopramide is approved only for a maximal duration of 12 weeks and carries a black box warning. The true risk of irreversible tardive dyskinesia caused by metoclopramide is low, estimated to be 0.1% per 1000 patient-years[36,37] and,

Table 1. Current and Investigational Prokinetic Drugs for Gastric Motility Disorders

Drug Name	Disease(s)	Effect(s) on Gastric Motor Function	GP Symptoms
5-HT$_4$ Receptor Agonists			
Prucalopride	IG and DG	↑ GE	Improved
Velusetrag	IG and DG	↑ GE	Improved
Felcisetrag	IG and DG	↑ GE	Not studied
Tegaserod	FD	↑ GA	Mixed effects
Dopamine D$_2$/D$_3$ Receptor Antagonist			
Trazpiroben	IG and DG	↑ volume to fullness, no change in GE	Improved
Ghrelin Receptor Agonist			
Relamorelin	DG	↑ GE, ↑ antral contractions	Improved
Motilin Receptor Agonists			
Erythromycin	IG and DG	↑ GE, ↑ fundic and antral contractions, ↓ pyloric contractions	Improved
Azithromycin	GP	↑ GE	Not studied
Clarithromycin	FD	↑ GE	Not studied
NK$_1$ Receptor Agonists			
Aprepitant	IG and DG	↑ GA, no change in GE	Improved
Tradipitant	IG and DG	Not studied	Improved
Opioid Antagonists (NS or PAMORA)			
Naloxone (NS)	FD and IG	No change in GE	Not studied
MNTX (PAMORA)	Opioid-induced gastric delay	No change in GE	Not studied
Naloxegol (PAMORA)	Opioid-induced gastric delay	No change in GE	Not studied
Phosphodiesterase-5 Inhibitor			
Sildenafil	GP with uremia	No change in GE	Not studied

DG, diabetic gastroparesis; FD, functional dyspepsia; GA, gastric accommodation; GE, gastric emptying; GP, gastroparesis; IG, idiopathic gastroparesis; MNTX, methylnaltrexone; NK_1, neurokinin-1; NS, nonselective; PAMORA, peripherally acting μ-opioid receptor antagonist; 5-HT_4, 5-hydroxytryptamine 4.

Marketed drugs are in bold. Reproduced from Camilleri M, Atieh J.[48]

more recently, 0.14 per 100,000 patient-years.[38] Metoclopramide is also available in liquid oral, nasal spray,[39] and parenteral (IV or subcutaneous) formulations.[40] Because gastroparesis is a chronic disease for which there are no approved alternative agents, experienced clinicians balance the FDA recommendation with the need to manage patients' symptoms, malnutrition, and other complications by using an effective dose (liquid formulation, 5-10 mg 3 times per day, 15 minutes before meals) over longer than 12 weeks, with 10-day interruptions every 3 months. During the drug holidays, patients are instructed to adhere strictly to a liquid or blenderized diet. Rescue antiemetic agents such as ondansetron (4-mg oral dissolving tablets) or short-term treatment with erythromycin (40-200 mg 3 times per day as tolerated) can be used as supportive therapy.[41]

Other marketed agents have been used off-label for the treatment of patients with gastroparesis, including

domperidone, macrolides, and 5-HT_4 receptor agonists such as prucalopride.

Domperidone is a peripherally acting dopamine D_2 receptor antagonist that is available through the FDA's program for expanded access to investigational drugs. Its efficacy for the treatment of gastroparesis is comparable to metoclopramide.[42,43] A systematic review of 28 trials showed symptomatic reduction in 64%, decreased hospitalization in 67%, and accelerated gastric emptying in 60% of patients with diabetic gastroparesis.[44] The risk of central nervous system side effects is much lower than with metoclopramide because domperidone does not cross the blood-brain barrier. However, domperidone was associated with corrected QT interval (QTc) prolongation,[44] limiting its use to small doses over less than 1 week in Europe. In clinical practice, the recommended dose of domperidone is 10 mg to 20 mg 3 times per day and at bedtime. Domperidone should be avoided in patients with prolonged QTc (>470 ms in males, >450 ms in females).

Among 5-HT_4 receptor agonists, cisapride was efficacious,[45] but it was withdrawn because of increased risk of cardiac arrhythmias.[46] Prucalopride is approved for the treatment of chronic constipation, but not for gastroparesis. In a randomized, placebo-controlled, crossover study of 28 patients with idiopathic gastroparesis and 6 with diabetic gastroparesis, prucalopride 2 mg once daily was superior to placebo at reducing symptoms based on total GCSI score and GCSI subscales of fullness/satiety, nausea/vomiting, and bloating/distention, as well as improving Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life score.[47] Velusetrag (Theravance), naronapride (Renexxion), and felcisetrag (Takeda/Theravance) are other investigational agents in the pipeline that are thought to be more selective for 5-HT_4 receptors in the gut (Table 1).[48]

Macrolides such as erythromycin, azithromycin, and clarithromycin are motilin receptor agonists with a prokinetic property. In a systematic review of 5 small-scale, short-term studies, erythromycin accelerated gastric emptying and improved symptoms in 43% of patients with gastroparesis.[49] When given orally, erythromycin was associated with tolerance within days to weeks.[50,51] Erythromycin may also prolong QTc and reduce gastric accommodation.[52] Azithromycin and clarithromycin have comparable efficacy and possibly better safety profiles than erythromycin,[53,54] but the concern for tolerance remains. In hospitalized patients, IV erythromycin (infused over 45 minutes) is widely used at 1.5 mg/kg to 3.0 mg/kg 3 times per day for the treatment of acute gastroparesis.

Long-term use of antibiotics may be associated with complications including antibiotic resistance and potential infections such as *Clostridioides difficile* toxin–induced colitis or antibiotic-induced diarrhea.

Antiemetics

Antiemetics acting on different mechanisms have been used for symptom relief in gastroparesis.

Dosed at 4 mg to 8 mg every 8 hours as needed, ondansetron is a 5-hydroxytryptamine 3 receptor antagonist that reduces nausea from stomach distension without affecting gastric compliance, volume, or accommodation.[55] Ondansetron causes QTc prolongation and in rare cases can lead to Torsades de pointes, a life-threatening cardiac arrhythmia. Baseline and continual monitoring of electrocardiogram is recommended. The sustained-release transdermal patch granisetron is a similar agent that was shown in an open-label study to reduce nausea and vomiting in gastroparesis.[56]

Prochlorperazine, promethazine, and scopolamine work on dopamine (D_2), histamine (H_1), and muscarinic (M_1) receptors, respectively. These antiemetics are available in orally dissolving, dermal, or rectal formulations for patients with gastroparesis. Sedation, dry mouth, and constipation are common side effects. Promethazine may be habit-forming and is reserved as a rescue agent.

The neurokinin-1 receptor antagonist aprepitant (approved for chemotherapy-induced emesis) affects the vomiting center in the brain stem and enhances gastric accommodation without retardation of gastric emptying.[57] In a randomized, double-blind, placebo-controlled trial of 126 patients with chronic nausea and vomiting of presumed gastric origin, aprepitant 125 mg daily significantly reduced the severity of nausea, vomiting, and overall symptoms.[58] Tradipitant (Vanda), a similar investigational agent, demonstrated decreased nausea score, increased nausea-free days, and improved GCSI score in patients with gastroparesis compared with placebo.[59]

Among 506 patients evaluated in the NIH Gastroparesis Consortium, 12% used medical or recreational marijuana for symptomatic relief,[60] although its main ingredient, tetrahydrocannabinol (THC), a nonselective cannabinoid receptor agonist, actually delayed gastric emptying of solids and may lead to cannabis-induced hyperemesis with chronic use. Dronabinol is a synthetic THC used as second-line therapy for patients with refractory nausea and is a potent appetite stimulant for those with weight loss. Dronabinol is limited to short-term use because of adverse effects such as marijuana-like highs and binge eating. Cannabidiol, a low-THC extract from *Cannabis sativa* approved for seizure disorders, is currently being studied as a potential therapy for gastroparesis (NCT03941288). Without the intoxicating adverse effects of marijuana, cannabidiol has gained popularity in recent years for its variety of therapeutic effects.

Table 2. Published Studies on G-POEM

Number of Pts	Types of Gastroparesis Pts	Changes in Gastric Emptying	Changes in Symptoms	Follow-Up Duration	Adverse Events
29	Diabetic=7 Idiopathic=15 Postsurgical=5 Scleroderma=2	70% normalized	79% at 3 months; 69% at 6 months. GCSI improved from 3.5 to 0.9 at 3 months	3 and 6 months	17% (2/12) with pneumoperitoneum requiring decompression
16	Diabetic=9 Idiopathic=5 Postsurgical=1 Postinfectious=1	75% normalized; 25% improved	81% improvement. GCSI improved from baseline of 3.4 to 1.46 after 12 months	12 months	None
47	Diabetic=12 Idiopathic=27 Postsurgical=8	4-hour retention improved from 37.2% to 20.4%	GCSI improved from 4.6 to 3.3	3 months (follow-up in 31/47)	1 death (unrelated)
30	Diabetic=11 Idiopathic=7 Postsurgical=12	47% normalized	No validated outcome measure available	6 months	2/30 (6%): 1 prepyloric ulcer and 1 capnoperitoneum
13	Diabetic=1 Idiopathic=4 Postsurgical=8	4/6 pts improved on post–G-POEM GES; % retention at 4 hours improved from 49% to 33%	In 11 pts, 4 improved considerably, 4 somewhat better, 1 no change, 2 worse	3 months	3 mucosotomies closed with clips; 1 pulmonary embolism
16	Diabetic=3 Postsurgical=13	Mean % retention (bread) at 2 hours improved from 69.3% to 33.4%	Mean total symptom score improved from 24.25 to 6.37; 13/16 improved	3 months	1 pyloric stenosis at day 45
20	Diabetic=10 Nondiabetic=10	% retention at 4 hours improved from 57.5% to 15%; 30% normalized	GCSI improved from 3.5 to 1.3; QOL improved	3 months	3 mild hemorrhages, 3 gastric perforations, 1 moderate dyspepsia
40	Diabetic=15 Nondiabetic=25 (of which 18= idiopathic)	% retention at 4 hours reduced by 41.7%	Improved GCSI and nausea/vomiting, but not improved bloating	Median of 15 months	1 tension capnoperitoneum, 1 exacerbation of COPD, 1 disrupted mucosotomy and ulcer
22	Diabetic=8 Idiopathic=14 (both groups with gastric electrical stimulation + diverse other procedures)	7/11 pts had normal GES post–G-POEM	GCSI improved (reduction of 1.63 points); improved all subscores	1 and 3 months	1 laparoscopy for pain due to capnoperitoneum and adhesions
38	All postsurgical; 29 with fundoplication or HH repair	% retention at 4 hours improved from 46.4% to 17.9%; 50% normalized	GCSI improved (mean reduction of 1.29 points); improved all subscores	1 month	2 readmissions: 1 melena, 1 dehydration
80	Idiopathic=33 Postsurgical=28 Diabetic=19	GES improved in 64.2% and normalized in 47.2% (of 53 cases with test) at 3 months	Decrease in total GCSI >1 and >25% decrease in at least 2 subscales in 66.6% at 12 months	3 months GES, 12 months clinical follow-up of symptoms	3 with symptomatic capnoperitoneum, 1 mucosotomy, 1 thermal mucosal injury

COPD, chronic obstructive pulmonary disease; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying scintigraphy; G-POEM, gastric peroral endoscopic myotomy; HH, hiatal hernia; pts, patients; QOL, quality of life.

The GCSI scores are mean values pre– or post–G-POEM. Reproduced from Camilleri M.[41]

Treatments for Pain Relief

Although abdominal pain is commonly experienced by patients with gastroparesis, those with predominant abdominal pain should be considered for an alternative diagnosis. Neuromodulators such as amitriptyline and nortriptyline are often considered first-line treatment for functional abdominal pain. However, in a randomized trial of 130 patients with idiopathic gastroparesis, nortriptyline was not superior to placebo at reducing symptoms based on GCSI score.[61] In a prospective, open-label study, mirtazapine was shown to improve nausea, vomiting, and appetite in patients with gastroparesis.[62]

Medications in Development

Investigational agents with different mechanisms are in the pipeline (Table 1).[48] Relamorelin (Allergan) is a pentapeptide ghrelin receptor agonist with preclinical evidence of strong prokinetic potency.[63] In diabetic patients with delayed gastric emptying, relamorelin significantly accelerated gastric emptying of solids.[64-66] Relamorelin also reduced core symptoms and composite score in patients with moderate to severe diabetic gastroparesis.[67,68] Elevated blood glucose has been reported with relamorelin, probably owing to enhanced emptying, and proactive management of hyperglycemia is advised.[69]

Trazpiroben (Takeda) is a dopamine D_2/D_3 receptor antagonist with minimal brain penetration. It has been shown to improve postprandial symptoms in response to a nutrient challenge meal in patients with idiopathic or diabetic gastroparesis,[70] with a lower risk of central nervous system or cardiovascular adverse effects than other dopamine D_2/D_3 receptor antagonists.[71]

Pyloric Interventions

In a subset of patients with gastroparesis, pyloric dysfunction characterized as unusually prolonged and intense tonic pyloric contractions was described.[72] This observation of pylorospasm paved the way for a variety of procedural interventions directed at the pylorus, including botulinum toxin injection, pyloric dilation and/or stenting, and surgical or endoscopic pyloromyotomy.

In patients with refractory gastroparesis despite pharmacotherapies, intrapyloric injection of botulinum toxin has been shown in multiple open-label studies to have short-term (<6 months) efficacy in accelerating gastric emptying and improving symptoms.[73] However, 2 small, randomized, placebo-controlled trials failed to replicate the efficacy of botulinum toxin injection in achieving symptom improvement, although 1 trial demonstrated accelerated gastric emptying with botulinum toxin compared with saline.[74,75] Acknowledging the discordant results, a large, open-label, retrospective analysis of 179 gastroparesis patients after botulinum toxin injection demonstrated dose-dependent, short-term (1-4 months) symptom improvement in 51.4% of patients, as well as factors for improved response, including female sex, age less than 50 years, and etiology not related to diabetes or surgery.[76] There is concern that repeated injection with high-dose botulinum toxin may induce pyloric fibrosis over time, thus reducing the feasibility of future interventions such as pyloromyotomy.

Surgical pyloroplasty has been advocated as a more robust pyloric intervention for gastroparesis. The most frequently performed type, Heineke-Mikulicz pyloroplasty, divides both longitudinal and circular muscle layers with a longitudinal incision across the pylorus, which is then closed transversely. In 177 patients with gastroparesis, laparoscopic pyloroplasty achieved improvement or normalization of gastric emptying in 90% of patients, as well as short-term improvement of nausea, vomiting, bloating, and abdominal pain.[77] However, the morbidity rate was relatively high (6.8%), with 4 patients requiring abdominal exploration and 2 confirmed leaks. Subsequent surgical interventions were required in 10.7% of patients (19/177), including implantation of gastric stimulator (12), jejunostomy (6), and subtotal gastrectomy (4).[77]

Gastric peroral endoscopic myotomy (G-POEM) is a novel pyloric intervention that has become increasingly popular as a promising treatment for refractory gastroparesis. Accessing the pyloric muscle from the gastric luminal side with an esophagogastroduodenoscopy, G-POEM cuts predominantly the circular muscle layer while leaving the longitudinal muscle intact to avoid perforation. G-POEM has been shown in multiple open-label studies, systemic reviews, and meta-analyses to be effective at improving gastric emptying, symptoms, and quality of life in the short- and mid-term.[78-81] Current evidence on the efficacy of G-POEM for gastroparesis is summarized in Table 2.[41] Overall, G-POEM is thought to be superior to gastric electrical stimulation for gastroparesis and equivalent to surgical pyloroplasty. Long-term results and randomized, sham-controlled trials are needed to assess the outcomes of G-POEM.

Gastric Electrical Stimulation and Other Experimental Devices

Using high-frequency electrical pulses delivered to the smooth muscles of the lower stomach, gastric electrical stimulation aims to modulate the afferent pathway and reduce gastroparesis symptoms. In a prospective cohort from the NIH Gastroparesis Consortium, 81 patients receiving gastric electrical stimulation had more improvement of 48-week GCSI scores greater than or equal to 1

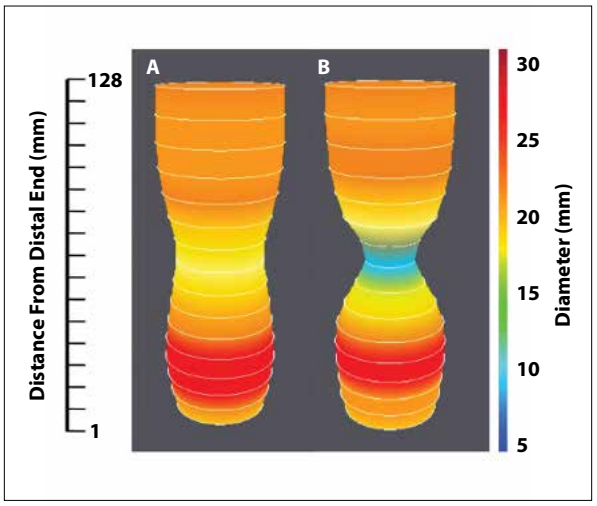

Figure 1. Representative EndoFLIP measurements at 40 mL of inflation from a healthy volunteer (**A**) and from a patient with diabetic gastroparesis and altered pyloric sphincter distensibility of 4 mm^2/mm Hg (**B**).

Reproduced from Desprez C et al.[93]

point compared with 238 patients not receiving gastric electrical stimulation. However, those receiving gastric electrical stimulation had more severe manifestations, and, when adjusted for characteristics, only improvement in nausea remained significant.[82] Similarly, in a large, multicenter, randomized, double-blind, crossover trial in France of 172 patients with refractory vomiting (133 with confirmed gastroparesis), gastric electrical stimulation improved vomiting scores but not gastric emptying or quality-of-life scores.[83]

In addition to gastric electrical stimulation, novel experimental devices have been developed to activate the antral muscles by directly stimulating the efferent vagal fibers or by centrally stimulating the afferent vagus nerve. In 2 small-scale, open-label, proof-of-concept studies, noninvasive self-administered stimulation devices (gammaCore, electroCore) applied to the vagus nerve in the neck were shown to improve gastroparesis symptom scores with no serious adverse events in 40% of patients.[84,85]

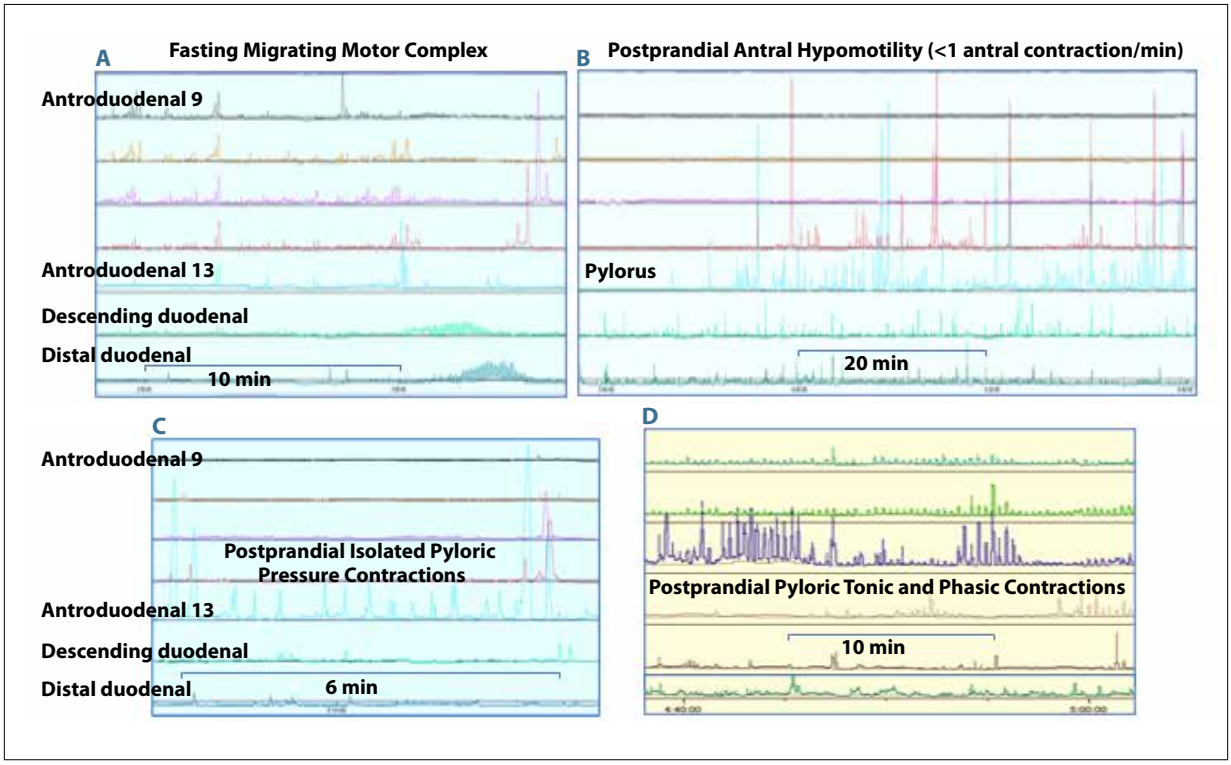

Figure 2. Examples of high-resolution antropyloroduodenal manometry in patients with delayed gastric emptying. Panel **A** shows normal fasting in the digestive migrating motor complex in the small intestine with a deficiency in the antral component of the migrating motor complex. Panel **B** shows the postprandial recording with the pylorus generally coordinated with antral phasic pressure activity, and a reduced frequency of distal antral contractions (less than 1 per minute). Panel **C** shows a short period with isolated pyloric pressure contractions unassociated with distal antral contractions in the postprandial period. Panel **D** shows a postprandial tracing consistent with pylorospasm from a separate patient, characterized by prominent pyloric contractility with tonic elevation of baseline pressure lasting several minutes together with superimposed phasic contractions over the elevated tone.

Alternative Therapy

Many patients with gastroparesis seek alternative therapy. Acupuncture is one of the most well-studied Eastern medicine therapies, and its efficacy in managing chronic pain is well supported in the literature.[86,87] A Cochrane analysis of 32 heterogeneous, low-quality studies with 2601 patients concluded that there was very low-certainty evidence for a short-term benefit with acupuncture alone or acupuncture combined with gastrokinetic drugs compared with the drugs alone in improving symptoms in diabetic gastroparesis.[88]

Gastrectomy

Patients with severe refractory gastroparesis may undergo near-total gastrectomy with Roux-en-Y reconstruction, or completion gastrectomy (for postsurgical gastroparesis) as a last resort. High morbidity (40%) and variable benefits (43%-90%) have been reported in a study of limited sample size.[89] Two recent studies (19 and 10 patients, respectively) showed that patients undergoing laparoscopic sleeve gastrectomy had significant improvement in symptoms and quality of life, and the morbidity rate was approximately 10%.[90,91] It is important to note that sleeve gastroplasty performed endoscopically slows gastric emptying and should not be applied alone in patients with gastroparesis.[92]

Future Directions

Gastroparesis is a motility disorder with multiple underlying pathophysiologic mechanisms. Individualized strategies based on the understanding of the mechanisms are pivotal in helping patients. For example, EndoFLIP (Medtronic) device measurements estimate the dimensions of the pylorus at baseline and the average increase of pyloric diameter or increased distensibility after G-POEM (Figure 1).[93] The change following G-POEM may determine success. It is also necessary to investigate the potential role of concurrent antral hypomotility or impaired gastric accommodation in appraising the outcome or concomitant treatment with a prokinetic agent. At this time, there is no sham-controlled study of G-POEM in which patients' baseline and posttreatment antropyloroduodenal motor functions are assessed by multilumen antropyloroduodenal manometry (Figure 2) and the pre– and post–G-POEM pyloric diameter and distensibility are assessed by transpyloric EndoFLIP. Defining and differentiating patients with predominant pylorospasm, antral hypomotility, or both are critical in identifying the optimal candidates for this promising treatment.

Conclusion

Gastroparesis is diagnosed by a well-validated gastric emptying study, such as scintigraphy or stable isotope GEBT, and robust cutoff values to differentiate normal vs delayed emptying. Management of gastroparesis takes on a multidisciplinary approach involving nutritional support, prokinetic agents, and antiemetics. Pyloric interventions such as G-POEM show promise, and future studies of patients with well-characterized pathophysiologic factors are needed.

Disclosures

Dr Zheng has no relevant conflicts of interest to disclose. Dr Camilleri has received research grants from Takeda (felcisetrag) and Vanda (tradipitant), and grant R01-DK122280 from the National Institutes of Health for the study of gastroparesis.

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