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Gastroparesis and functional dyspepsia: spectrum of gastroduodenal neuromuscular disorders or unique entities?

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Conflict of interests

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Author Contributions

Dr. Sato: Study concept and design: Lead; Writing-Original Draft: Lead; Funding acquisition: Supporting

Dr. Grover: Study concept and design: Lead; Writing-Review & Editing: Lead; Funding acquisition: Lead; Study supervision: Lead

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Ethical Statement:

The study did not require the approval of an institutional review board.
Abstract

Gastroparesis is defined by delayed gastric emptying in the absence of mechanical obstruction of the stomach. Patients experience symptoms of nausea, vomiting, abdominal pain, fullness and early satiety. The recognition of the disorder has progressed due to availability of gastric emptying scintigraphy and advancements made in understanding its pathophysiology and treatment options. The clinical presentation and treatment of gastroparesis overlaps with a more commonly recognized disorder of gut-brain interaction, functional dyspepsia. Recent studies have reenergized the discussion whether these two are separate entities or perhaps reflect a spectrum of gastroduodenal neuromuscular disorders. The societal guidelines conflict on the utility of gastric emptying scintigraphy in assessment of patients with upper gastrointestinal symptoms. A better appraisal of similarities and differences between gastroparesis and functional dyspepsia will allow targeted treatment for these disorders. This is particularly important as specific pharmacological and endoscopic treatment options are being developed for gastroparesis which are unlikely to be helpful for functional dyspepsia. This review makes the case for considering these disorders in a spectrum where identification of both would most ideally position us towards providing the optimal clinical care.

Keywords:
diabetes mellitus; gastric emptying; gastric accomodation; Interstitial cells of Cajal; treatment
Introduction

Gastroparesis is a condition characterized by constellation of upper gastrointestinal (GI) symptoms and delayed gastric emptying (GE) in the absence of mechanical upper GI obstruction.\textsuperscript{1,2} It is rare but extremely morbid disorder which also associates with increased mortality. In contrast, functional dyspepsia (FD) is an extremely common disorder of gut-brain interaction that affects quality of life without an associated increase in mortality, but still with major unmet treatment needs.\textsuperscript{3,4} Studies have highlighted a role of impaired gastric accommodaion, duodenal inflammation, barrier dysfunction and chemosensitivity in pathophysiology of FD.\textsuperscript{5} Recent studies have highlighted a substantial overlap in the pathophysiology, symptoms, and clinical course of gastroparesis and FD. In this article, we primarily focus on the updates in epidemiology, clinical presentation, pathology, diagnosis, and treatment of gastroparesis. However, we highlight differentiation of gastroparesis from FD. Our goal is to appraise the pathophysiological and treatment concepts and make a case for appropriate recognition and diagnosis for both of these disorders.

1. Epidemiology

Two large-scale population-based epidemiological studies of gastroparesis were recently reported. In the United States, based on insurance claims database, standardized (to age, sex and geographical region) prevalence of gastroparesis was 267.7 per 100,000 adults, whereas prevalence of "definite" gastroparesis (individuals diagnosed within 3 months of GE scintigraphy with persistent symptoms for more than 3 months) was much lower at 21.5 per 100,000 persons.\textsuperscript{6} On the other hand, in the United Kingdom, standardized prevalence of gastroparesis, as documented in general practice records, was 13.8 per
100,000 persons, and standardized incidence of gastroparesis rose from 1.5 per 100,000 person-years in 2004 to 1.9 per 100,000 person-years in 2016. Among these studies, the most common etiologies were diabetic mellitus (37.5%-57.4%), idiopathic (11.3%-39.4%), followed by drug-induced (11.8%-19.6%) and postsurgical (1.1%-15.0%). These prevalence estimates should be considered with caution considering the study designs and a relative under testing for gastroparesis in the UK compared to the US. The risk of type I and II diabetes for gastroparesis are considered relatively similar although gastroparesis due to type II diabetes is more prevalent than that with type I due to a greater number of patients with type II diabetes. The medications that may induce gastroparesis includes opioids, calcium-channel blocker, anticholinergic agents, and glucagon-like peptide-1 receptor agonists like exenatide (often used to treat diabetes). Post-surgical gastroparesis is associated with fundoplication (due to vagal injury), Roux-en-Y gastric bypass, partial gastrectomy (due to extrinsic denervation of the gastric remnant or abnormal motility in the anastomosed jejunal loop). Partial gastrectomy and bariatric procedures like sleeve gastrectomy can cause rapid GE (discussed later). Rare etiologies include connective tissue disorders like scleroderma, collagen storage disorders and neurodegenerative diseases. In gastroparesis, female: male prevalence is nearly 2:1, and peak prevalence was reported in late 50 to 60 years of age in the latest insurance claims-based study from the U.S.

In addition, ethnic and racial differences in prevalence of gastroparesis have also been noted from tertiary care cohort studies from the U.S. A significantly higher proportion of non-Hispanic blacks were found to have gastroparesis of diabetic etiology than of non-Hispanic whites (60% vs 28%); non-Hispanic blacks also had more severe retching,
vomiting and a higher percentage were hospitalized in the past year. Hispanics had less-severe nausea, and less early satiety. With expected increase in the prevalence of diabetes worldwide (5.1 billion in 2021 to 6.4 billion in 2045\textsuperscript{10}), it becomes important to recognize gastroparesis among other end-organ complications of diabetes mellitus.

FD is a gastroduodenal disorder with a recent study showing 7.2\% average global prevalence\textsuperscript{4}, making it one of the common GI disorder. In a recent internet based survey of adults from U.S., U.K., and Canada, approximately 10\% of the adult population fulfilled the Rome IV criteria for FD and these patients incurred greater healthcare utilization.\textsuperscript{11} Although it is difficult to compare due to the considerable racial, ethnic, dietary and environment variability, the prevalence of FD in Asia and western countries is relatively similar.\textsuperscript{12} Similar to gastroparesis, FD is more prevalent in females (1.3-1.5 female/male), but was found to peak in 20’s-30’s and decreased with age.\textsuperscript{4} FD is also reported to be highly concomitant with irritable bowel syndrome with these patients having greater symptom severity.\textsuperscript{13}

2. Clinical presentation

Symptoms attributed to gastroparesis include postprandial fullness, early satiety, nausea, vomiting and abdominal pain. Nausea was reported by 96\% of the patients with gastroparesis (predominant symptom in 29\%), while 65\% experienced vomiting.\textsuperscript{14} Abdominal pain as a common symptom, especially in cases of idiopathic gastroparesis, but is often overlooked.\textsuperscript{15} In one study, vomiting more often prompted evaluation for diabetic gastroparesis. In contrast, abdominal pain, early satiety and postprandial fullness
were more common in idiopathic gastroparesis. A number of studies do not find a robust association between the severity of symptoms and the magnitude of GE delay. This often happens when non-validated or insufficient GE testing protocols are used. A meta-analysis concluded that when appropriate testing protocols are used, the symptoms associated with GE and additionally, improvement in GE with prokinetics associated with improvement in symptoms. In comparison with idiopathic gastroparesis, gastric retention was greater in patients with type 1 diabetes associated gastroparesis. Psychological co-morbidities such as depression and anxiety are associated with symptom severity, although psychological dysfunction does not vary by the etiology of gastroparesis or the degree of GE delay.

Gastroparesis Cardinal Symptom Index (GCSI) is a validated questionnaire, and had been used to identify the predominant or most bothersome symptoms (nausea/vomiting, fullness/early satiety, bloating/distension) and decide the treatment choices. It is more practical to classify disease based on required treatment, (1) mild: symptoms are easily controlled and patients are able to maintain their weight with minor dietary modifications; (2) moderate: symptoms are frequent, although not present every day, and can be controlled with antiemetic and promotility agents along with diet, and in diabetic gastroparesis, glucose control (3) severe: symptoms persist at a daily level despite maximum medical treatment, and there is accompanying malnutrition along with weight loss requiring frequent emergency room visits and multiple hospitalizations.

Symptoms of FD such as postprandial fullness, early satiety, epigastric pain, and epigastric burning overlap considerably with gastroparesis. The Rome IV criteria distinguishes FD into epigastric pain syndrome (EPS) and postprandial distress syndrome.
Studies, including from Asia, demonstrate that 65% FD patients suffer from PDS. There is a suggestion that presence of vomiting is one of the distinguishing features of gastroparesis since less than a third of FD patients (without delayed GE) report vomiting. In fact, the European guidelines suggest using presence of nausea and/or vomiting as a distinguishing feature of gastroparesis from FD. However, other studies suggest a significant overlap and lack of symptoms specific for the two disorders (Fig. 1). Frequency and severity of psychological co-morbidities like depression and anxiety are also not different between gastroparesis and FD. Recent analysis from a cohort of idiopathic gastroparesis patients also demonstrates that ~30% were obese and only 10% underweight. Furthermore, over 48 weeks of follow-up, 53% patients stayed at stable weight, 30% gained weight, and 17% lost weight. This is in contrast to conventional description where gastroparesis patients often reported weight loss. It is unclear if FD patients demonstrate similar weight distribution patterns. Conventionally, presence of weight loss would be treated as an alarm symptom for excluding an alternative cause for the dyspepsia.

3. Pathology

Loss of pacemaker interstitial cells of Cajal (ICC), possibly due to macrophage-based immune dysregulation is the leading explanation for the pathology of gastroparesis. In gastroparesis, full-thickness biopsies of the stomach showed loss of ICCs and anti-inflammatory (CD206 positive) macrophages that normally play a homeostatic and tissue protective role. Additionally, electron microscopy showed poor ICC-nerve and ICC-smooth muscle contacts. The molecular landscape of stomach in diabetic and idiopathic
Gastroparesis was investigated using proteomics analysis, and “role of macrophages, fibroblasts and endothelial cells” has been reported to be the most altered signaling pathway in both disorders.\(^{31}\) Generally, gastroparesis develops after having 5 years of diabetes and often accompanies microvascular and other end-organ complications from diabetes \(^{32}\), however, which diabetic patient may develop gastroparesis is unclear. In animal models, a role of oxidative stress is suggested in loss of ICC and delayed GE.\(^{33}\) One of the mechanisms for suppression of oxidative stress is the pathway including hemeoxygenase-1 (HO-1) which is produced by CD206 positive anti-inflammatory macrophages. miR-10b-5p is indicated to be a key regulator in diabetes and GI dysmotility via the Krüppel-like factor 11 (KLF11)-receptor tyrosine kinase (KIT) pathway.\(^{34}\) Other than ICCs, a potential mechanistic link between mucosal 5-HT deficiency in gastric antrum and delayed GE was also recently reported \(^{35}\) which may support the use of 5-HT4 agonists for the treatment of gastroparesis. Other studies have shown reduced gastric mucosal innervation \(^{36}\), changes in duodenal mucosal mitochondrial gene expression \(^{37}\) and neurohormonal influences on gastric emptying.\(^{38}\)

In normal gastric physiology proximal stomach (fundus) generates tone that is actively regulated to accommodate ingested food. In contrast, the distal stomach (corpus and antrum), triturate and processes food before emptying; and the pyloric sphincter, regulates the rate of GE.\(^{39}\) The mechanisms that may result in delayed GE include impaired fundic accommodation, insufficient antral contractions (antral hypomotility) or pyloric relaxation (pylorospasm).

On the other hand, the pathology of FD is complex and multifactorial and best understood as a disorder of gut-brain axis.\(^{5}\) A predominant physiological characteristic of FD is
impaired gastric accommodation, particularly in the setting of post-prandial symptomatology and early satiety.\textsuperscript{40} Other mechanisms include gastroduodenal hypersensitivity, low-grade duodenal inflammation, increased mucosal permeability, and central sensitization. In FD, increase of lymphocyte populations, including B- and T-lymphocyte numbers and activation status were reported in conjunction with duodenal eosinophilia \textsuperscript{41}, and association between activation of small bowel homing T-cells and delayed GE was reported.\textsuperscript{42} Further, a positive correlation between duodenal permeability and GE time was indicated.\textsuperscript{43} Impaired gastric accommodation can happen as a result of gastroduodenal motor and sensory dysfunction as well as due to imbalance of gut-brain interactions \textsuperscript{5}, although the precise mechanisms are still unclear. In a study examining patients with diabetes referred to a tertiary care medical center for evaluation of upper GI symptoms, 56% had abnormal GE (37% rapid GE, 19% slow) with or without delayed accommodation, 16% had reduced gastric accommodation (but normal GE), while 28% had neither of those abnormalities.\textsuperscript{44} The overlap of these physiological abnormalities between gastroparesis and FD reflects that these disorders should be treated as belonging to a spectrum of upper GI neuromuscular disorders.

4. Diagnosis

An upper endoscopy within the previous 1-2 years is important to rule out gastric outlet obstruction when entertaining the diagnosis of gastroparesis. GE scintigraphy or breath testing are the most validated and frequently used modalities for diagnosis of gastroparesis.\textsuperscript{2} GE scintigraphy is performed with an \textsuperscript{99m}Tc sulfur colloid labelled egg white meal (~300 kcal, 30% fat) to assess emptying of solids. A 4h scan is used to detect delayed GE (4h>20%, respectively) (Fig. 2).\textsuperscript{45} It is to be noted that some protocols use
255 kcal, 2% fat meal and in Asian countries a steamed rice-based meal is sometimes preferred. The lower fat content-based study uses >10% retention at 4 hrs for defining delayed GE as emptying of fat is slower than other nutrients. The 1h or 2h scan is used to detect rapid GE (1 hr emptying >30% in women or >40% in men; 2 hr emptying >70% in women or >80% in men) which is mainly observed in diabetic or post-surgical (gastric) patients. The clinical utility of GE scintigraphy depends on complete consumption of adequate test meals and adequate duration of imaging (at least 3 hrs). It also relies on having normative data from a large cohort of healthy volunteers considering the significant variability in the physiological measurement. A stable isotope (\(^{13}\)C) spirulina (algae) or octanoic acid breath testing is an alternative option approved by the U.S. Food and Drug Administration. Considering lack of radiation, it is a particularly appealing choice for pregnant and breast-feeding women as well as children. Wireless motility capsule (WMC, SmartPill, Medtronic) can be used to assess full GI transit, however the correlation of scintigraphic gastric retention and retention of WMC at 2 hr was found to be 0.95 but declined to 0.73 by 4 hr. Overall agreement in results between the 2 methods was 75.7% (kappa = 0.42). In non-diabetic subjects, the WMC detected a higher proportion of subjects with delayed GE than scintigraphy. A higher proportion of subjects with diabetes had delayed GE detected by scintigraphy compared with non-diabetic subjects. The emptying of a solid capsule from stomach most likely happens in the phase III of antral migrating motor complex (interdigestive phase) when indigestible material is being cleared, thus not ideally reflective of the gastric meal emptying. In one study, 62% of gastroparesis subjects were found to have regional and generalized transit abnormalities. Additionally, a study from gastroparesis clinical research consortium found that gastroparesis patients have high prevalence of constipation; and WMC thus
having the added advantage of providing broader assessment of the GI motility. Dynamic magnetic resonance imaging can measure GI responses to meal ingestion, although it is still used mostly for research purposes. Nutrient drink testing to determine maximum tolerated volume and symptoms can be utilized to measure complex mechanisms of gastric accommodation, emptying and visceral sensitivity. Single photon emission computed tomography (SPECT) method was also developed and validated for gastric accommodation. Moreover, considering the recent advancements in pyloric therapies (discussed later), pyloric function can be assessed using a high-resolution, multi-sensor antroduodenal manometry or endoFLIP. However, many of these tests are only available in specialized centers.

In contrast, FD is diagnosed based on the symptoms using Rome criteria and differentiated as PDS and EPS. Although a subset of patients with FD can have mild GE delay, most have a normal or accelerated GE. For simplification, it is best to conceptualize FD as having upper GI symptoms in the absence of delayed GE, with latter meeting the criteria for gastroparesis. Additionally, the definition of FD requires absence of any organic, systemic or metabolic disorders that may explain the chronic symptoms (that have lasted at least 3 months with symptom onset 6 months or more before diagnosis). The PDS subset is characterized by meal-induced dyspepsia symptoms of early satiety and postprandial fullness, whereas EPS patients have epigastric pain and burning unrelated to the meals. These subsets have some unique aspects to their pathophysiology with impaired gastric accommodation likely be the predominant mechanism driving PDS. In contrast, visceral hypersensitivity in response to nutrients or gastrointestinal secretions is more prevalent in patients with symptoms of EPS. In a multi-national population-based study, 61% had PDS, 18% EPS, and 21% were
overlapping.\textsuperscript{11} There are specific indications for performing upper endoscopy in the work-up for FD which are reviewed in recently published guidelines.\textsuperscript{55}

Over time, the GE may fluctuate but the nature or severity of symptoms may remain unchanged. Pasricha et al. reported nearly 40\% patients diagnosed with gastroparesis and FD based on GE may switch to the other diagnosis during a 48 week follow-up period.\textsuperscript{26} It is plausible that once disease establishes, the underlying physiology at any given time becomes a poor predictor of the symptoms or the severity. It is also possible that measuring the composite endpoint of GE is too simplistic and more specific pathophysiological mechanisms like regional alterations in gastric function, dynamic changes in post-prandial accommodation and antropyloric coordination would provide better associations with clinical symptoms. In a cohort of patients undergoing GE, rapid GE was reported in 8\% of the patients and interestingly, upper GI symptoms were common and similar in both rapid and delayed GE, whereas, constipation was more common in delayed GE patients.\textsuperscript{47}

5. Treatment

Nutrition and pharmacological interventions

Although it has not been rigorously validated, dietary adjustment is often the primary modality for management of gastroparesis patients. Dietary counselling includes eating frequent smaller-size meals and replacing solid food with blended or liquid diet. Limited literature is available rigorously assessing the impact of dietary manipulation in gastroparesis. In a trial, a frequent dietary counselling of small particle diet was shown to improve the key symptoms in diabetic gastroparesis patients.\textsuperscript{57}
Further, prokinetics are suggested for clinical symptoms of gastroparesis, which include dopamine (D2) receptor antagonists, serotonin (5-HT4) receptor agonists, cholinesterase inhibitors, motilin-like agents, ghrelin receptor agonists.\textsuperscript{56} Metoclopramide is the only medication approved for the treatment of gastroparesis in the US for up to 12 weeks. It has multiple mechanisms of action as Dopamine-2 antagonism and 5-HT4 agonism that exerts both prokinetic and antiemetic effects. However, metoclopramide can cross the blood-brain barrier resulting in neurological side effects as well as involuntary orofacial and extremity movements such as tardive dyskinesia (estimated risk < 1\%). Domperidone has a similar mechanism of action and does not pass through the blood-brain barrier, however, it still can exert the antiemetic effects. Clinicians need to take into account a potential risk of cardiac arrhythmias and even sudden death, due to inhibition of human Ether-a-go-go Related Gene channel activity and relative prolongation of the QTc interval, typical of other pharmacological agents with non-selective 5-HT4 receptor agonistic activity.\textsuperscript{58} In a recent metanalysis, domperidone was associated with an increased risk of composite endpoint of sudden cardiac death or ventricular arrhythmia compared to nonuse (adjusted odds ratio 1.7).\textsuperscript{59} Mosapride is a commonly used 5-HT4 receptor agonist in Asia, effective for treatment of gastroparesis similar to a newer agent prucalopride which is approved for the treatment of chronic idiopathic constipation in the US but was also shown to accelerate GE without significant cardiac adverse events. This is likely due to the greater sensitivity for 5 HT4 receptors as well as greater intrinsic activity and specificity for the GI receptor. Prucalopride and velusetrag have GI prokinetic effects inducing both symptom relief and acceleration of GE.\textsuperscript{60,61} Acotiamide was developed as a cholinesterase inhibitor that also exerts a presynaptic muscarinic autoreceptor inhibitory activity. It was shown to enhance both contractile and
accommodation activities of the stomach and improved FD symptoms. It is usually well tolerated and approved for treatment of FD in Japan. Motilin receptor agonists (Erythromycin, Azithromycin) have been tried in gastroparesis with some benefit. Erythromycin improved GE as well as fundic/antral contracts, however, tachyphylaxis results in a loss of long-term benefit. One study showed that intravenous azithromycin was equivalent to erythromycin in accelerating GE in adults with gastroparesis. A more detailed interrogation comparing the two demonstrated more frequent migrating motor complexes in the gastric antrum as well as longer activity fronts with azithromycin. Ghrelin receptor agonist had mixed results on improvement in clinical symptoms of gastroparesis. Neurokinin antagonists as aprepitant are approved for the treatment of chemotherapy-induced emesis. The APRON trial did not show positive result on the primary endpoint of nausea, but revealed positive effects on multiple secondary endpoints. Recently in a Phase II study, Tradipitant was shown to meet primary endpoint of improvement in nausea scores as well as nausea free days in a female predominant population of gastroparesis patients (60% idiopathic, 40% diabetic) with moderate to severe nausea. Treatment for rapid GE includes dietary modifications (smaller portions, avoidance of fluids within 30 min after meals, avoiding rapidly absorbable carbohydrates and eating foods high in fibre and protein), dietary supplements (guar gum, pectin), alpha-glycosidase inhibitors (acarbose), and somatostatin analogues.

In contrast, for patients with FD, 1st step is lifestyle and dietary modification, acid suppressants, prokinetics, and herbal medicine rikkunshito. In addition to the elimination diets removing trigger foods, gluten-free and low FODMAPs diet have been tried in FD with some success. However, improvement in symptoms with those dietary changes may be due to concomitant IBS. Kampo medicine like rikkunshito is one
of the major herbal medicine in Asia, and clinical evidence for FD was reported.\(^77\) If *Helicobacter pylori* infection is detected, it should be eradicated. Second-line therapy includes dopamine receptor antagonist, HT-4 receptor agonists, other herbal medicines, and anxiolytic/anti-depressants. Itopride (a combined D2 receptor antagonist and acetylcholinesterase inhibitor) has an evidence of efficacy for FD symptoms\(^74\), and mainly used in Asia. The efficacy of tandospirone citrate (a 5-HT1A agonist) in improving symptoms of patients with FD was revealed in RCT \(^78\), and meta-analyses show the efficacy of antidepressants and anxiolytics.\(^79\) Based on the results of two RCTs \(^80,81\), anti-depressants (Nortriptyline, Amitriptyline, and Escitalopram) do not improve the symptoms in gastroparesis. In contrast, tricyclic anti-depressants can be helpful as a neuromodulatory strategy for FD. Amitriptyline was shown to improve FD symptoms with some improvement in gastric accommodation but no negative effects on GE.\(^82\) In a larger trial of FD patients, amitriptyline but not escitalopram benefitted FD patients, particularly with pain predominant symptoms.\(^83\) Additionally, mirtazapine, a dual adrenergic and serotonergic blocker improved the symptoms of FD in an RCT.\(^84\) Therefore, dyspepsia patients who are non-responders to such antidepressants should undergo GE testing to assess for gastroparesis.

In a study done by the gastroparesis consortium, 64% of gastroparesis patients reported caloric-deficient diets and often lacked nutritional counselling.\(^85\) In a subset of patients with refractory gastroparesis with associated malnutrition (usually defined by \(\geq10\%\) weight loss over 6 months), nutritional support often becomes necessary. It is best delivered using post-pyloric feeding such as a nasojejunal feeding tube (for 4-6 weeks) with an eventual plan to use a percutaneous jejunostomy or gastrojejunostomy tube (where the gastric tube can be used for gastric decompression).
Surgical and endoscopic interventions

These approaches are typically reserved for patients with severe symptoms associated with frequent ER visits, hospitalizations and/or inability to maintain nutrition via oral route. Gastric electrical stimulation is one of the choices for gastroparesis patients with refractory/intractable nausea and vomiting who have failed standard therapy.\(^{86,87}\) However, clinicians need to consider the unknown mechanism of action, lack of validated methodology for the stimulator settings, and potential complications including infection that may necessitate removal. In a recent double-blind trial of patients with refractory vomiting, gastric electrical stimulation reduced the frequency of vomiting in patients with and without diabetes but did not affect GE or quality of life.\(^{87}\) Inclusion of severe and refractory subset of patients may have influenced the efficacy outcomes in studies assessing electrical stimulation. Partial or subtotal gastrectomy is considered as the last resort for refractory gastroparesis and is often not clinically beneficial.\(^{1,2}\) Two RCTs of intrapyloric botulinum toxin injections (to treat pylorospasm) failed to show the improvement.\(^{88,89}\) In these two RCTs, participants did not receive any investigations for pyloric dysfunction before treatment.

Targeting specific physiological changes driving delayed GE and associated symptoms has been of interest. An example is treating pyloric spasm with balloon dilations or Botulinum toxin. More recently, gastric peroral endoscopic myotomy (G-POEM) is a novel, third-space endoscopic treatment using the POEM technique developed for esophageal achalasia. This minimally invasive pyloric-directed procedure has been gaining significant interest among physicians and patients; although most of the data is driven by short-term and uncontrolled studies.\(^{90}\) A recent multicenter prospective study
showed 56% responder rate at 12 months and normalization of GE in 47% at 3 months. Baseline GCSI >2.6 (1-5 scale), 4 h gastric retention >20% and success at 1 m predicted 12 m success. In another recent study of G-POEM vs. sham for severe gastroparesis, 71% responded to G-POEM (as defined by 50% decrease in GCSI at 6 months) compared with 22% with sham. The response was particularly promising in diabetic patients with 89% showing treatment success. Moreover, in order to predict the responder, testing for pyloric dysfunction and excluding antral hypomotility is recommended before the G-POEM.

6. Clinical course of gastroparesis

Less than one-thirds of patients treated for gastroparesis are reported to have reduction in GCSI scores of ≥1 regardless of the etiology over a median follow-up period of 2.1 years. Overweight status, a history of smoking, use of pain modulators, moderate to severe abdominal pain, a severe gastroesophageal reflex, and depression are reported to be the risk factors for long-term persistence of symptoms. Post-infection or post-viral gastroparesis has a more favorable outcome with resolution of symptoms over time and less morbidity associated with the disease. Regarding the long-term outcomes in UK, patients with diabetic gastroparesis had an almost two-fold mortality compared with idiopathic gastroparesis, and probability of 5-year survival in diabetic gastroparesis is about 80% 7, although the disease specific mortality is unknown. In Minnesota, US, probability of survival of definitive, probable, and possible gastroparesis is estimated to 0.80, 0.76, and 0.67 at 5 years, respectively.

The long-term prognosis is favorable in the majority of patients with FD and the life expectancy is similar to the general population. On the other hand, the natural course of
FD includes high turnover in symptom status (Table 1). 96,97

Conclusion

We summarized several key points in epidemiology, clinical presentation, diagnosis and treatment of gastroparesis and FD with an emphasis on differentiating features of these disorders. Although significant advancements have been made in understanding pathophysiology of gastroparesis, FD remains a less well understood and heterogenous disorder. There is a significant overlap of symptoms between these two disorders and transition in diagnosis over time. Assessment of GE serves several important roles such as differentiating rapid from delayed GE (especially in the setting of diabetes and post-surgery), guiding treatment options like tricyclic antidepressants, neurokinin-1 antagonists, and G-POEM. The recognition of gastroparesis and utilization of GE will allow significant improvement in therapeutic targeting, particularly in the patients with severe symptoms and associated malnutrition.
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Table 1: Gastroparesis and functional dyspepsia -Highlighting similarities and differences

<table>
<thead>
<tr>
<th></th>
<th>Gastroparesis (Gp)</th>
<th>Functional dyspepsia (FD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>• 0.27% and 0.01% in U.S. and U.K.</td>
<td>• 7.2% average global prevalence</td>
</tr>
<tr>
<td></td>
<td>• Female: male prevalence 2:1</td>
<td>• Female: male prevalence 1.3-1.5: 1</td>
</tr>
<tr>
<td></td>
<td>• Peak prevalence (population studies) 50-60 years of age</td>
<td>• Peak prevalence 20-30 years of age</td>
</tr>
<tr>
<td></td>
<td>• Common etiologies diabetic mellitus (37%-57%) and idiopathic (11%-39%)</td>
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<tr>
<td>Clinical presentation</td>
<td>• Gastroparesis Cardinal Symptom Index primary symptom index consists of 3 subscales: post-prandial fullness/early satiety, nausea/vomiting and bloating</td>
<td>• Postprandial distress syndrome: Predominantly meal-induced symptoms of early satiety and postprandial fullness</td>
</tr>
<tr>
<td></td>
<td>• Abdominal pain is common</td>
<td>• Epigastric pain syndrome: Predominantly epigastric pain and burning unrelated to the meals</td>
</tr>
<tr>
<td>Pathology</td>
<td>• Loss of pacemaker interstitial cells of Cajal, possibly due to macrophage-driven immune dysregulation.</td>
<td>• A disorder gut-brain interaction with complex pathophysiology</td>
</tr>
<tr>
<td></td>
<td>• A subset of patients also has loss or damage to enteric nerves/neurons and changes in the smooth muscle cells</td>
<td>• Impaired gastric accommodation, gastroduodenal hypersensitivity, low-grade duodenal inflammation, increased mucosal permeability, and central sensitization</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>• Diagnosed based on the delay of gastric emptying of solids</td>
<td>• Diagnosed based on the Rome IV criteria that require symptoms for the last 3</td>
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Gastroparesis and Functional Dyspepsia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months with symptom onset at least 6 months before diagnosis</th>
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<tbody>
<tr>
<td>A) Diet &amp; lifestyle</td>
<td>• Dietary counselling of frequent, small particle diet, and avoidance of larger, high-caloric, fatty meals can be helpful. Nutritional deficiencies are common</td>
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<td>B) Pharmacotherapy</td>
<td>Metoclopramide, Domperidone (multiple action as Dopamine-2 antagonism and 5-HT4 agonism). Mosapride, Velusetrag (5-HT4 agonist).</td>
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<td>Some evidence of efficacy</td>
<td>Mirtazapine improved the symptoms of FD (Anti-depressants (Nortriptyline, Amitriptyline, and Escitalopram) may improve FD symptoms but do not improve the symptoms in Gp).</td>
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<td>Under investigation</td>
<td>Relamorelin (Ghrelin receptor agonist). Prucalopride (a 5-HT4 agonist).</td>
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<td>C) Intervention</td>
<td>Gastric electrical stimulation†. Intrapyloric botulinum toxin injection†. G-POEM 91,92.</td>
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<td>Clinical course</td>
<td>Probability of 5-year survival in diabetic Gp is about 80%.</td>
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GE may normalize over time, but symptoms persist in more than two-thirds patients\(^93\).

High turnover in changeable symptom\(^{72-74}\).

\(^{†}\)FD management exclude GERD & H\(_{pylori}\) associated dyspepsia, \(^{*}\)Potential efficacy in selected cases.
Figure legends

**Figure 1:** Overlap and differences in symptoms and pathophysiology of gastroparesis and functional dyspepsia. Nausea and vomiting are more prominent in gastroparesis whereas post-prandial abdominal pain or discomfort are more classical for functional dyspepsia. Overtime, the characteristics and severity of symptoms may change in both gastroparesis and functional dyspepsia. Additionally, the influence of local factors, physiology and molecular changes overlaps between gastroparesis and functional dyspepsia.

**Figure 2:** Gastric emptying scintigraphy (A) An example of normal gastric emptying where expected amount of the test meal is emptied at 1, 2 and 4 hrs. (B) A case of gastroparesis with increased retention of the test meal at 2 and 4 hrs (clinically relevant delayed GE is defined as a percentage retention >60% at 2 h and/or >20% at 4 h). (C) An example of a symptomatic, diabetic patient with rapid GE. (gastric emptying 85% at 2 h).