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Diabetic Gastroparesis: Perspectives From a Patient and Health Care Providers

Adam D. Farmer, PhD,^{1,2} Caroline Bruckner-Holt, MSc,³ Susanne Schwartz,⁴ Emma Sadler, RN,⁵ Sri Kadirkamanthan, PhD⁶

¹Institute of Applied Clinical Science, University of Keele, Keele, United Kingdom; ²Department of Gastroenterology, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, United Kingdom; ³Department of Palliative Medicine, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, United Kingdom; ⁴Gastroparesis & Intestinal Failure Trust, Stafford, United Kingdom; ⁵Department of Research and Development, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, United Kingdom; ⁶Department of Surgery, Broomfield Hospital NHS Trust, Chelmsford, United Kingdom

Abstract

Gastroparesis is defined as a delay in gastric emptying in the absence of mechanical obstruction in the stomach. Gastroparesis has a number of causes, including postsurgical, secondary to medications, postinfectious, idiopathic, and as a complication of diabetes mellitus, where it is underrecognized. The cardinal symptoms of diabetic gastroparesis are nausea, early satiety, bloating, and vomiting. Diabetic gastroparesis is more common in females and has a cumulative incidence of 5% in type 1 diabetes and 1% in type 2 diabetes. It is associated with a reduction in quality of life and exerts a significant burden on health care resources. The pathophysiology of this disorder is incompletely understood. Diagnosis is made based on typical symptoms associated with the demonstration of delayed gastric emptying in the absence of gastric outlet obstruction. Gastric emptying scintigraphy is the gold standard for demonstrating delayed gastric emptying, but other methods exist including breath testing and the wireless motility capsule. Diabetic gastroparesis should be managed within a specialist multidisciplinary team, and general aspects involve dietary manipulations/nutritional support, pharmacological therapy, and surgical/endoscopic interventions. Specific pharmacological therapies include prokinetics and antiemetics, with several new medications in the drug development pipeline. Surgical/endoscopic interventions include botulinum toxin injection into the pylorus, gastric peroral endoscopic myotomy and gastric electrical stimulation. This article provides a detailed review and summary of the epidemiology, pathophysiology, investigation, and management of diabetic gastroparesis, and also gives an individual patient's perspective of living with this disabling disorder. (*J Patient Cent Res Rev.* 2019;148-157.)

Keywords

diabetes; gastrointestinal dysmotility; gastroparesis; diagnosis; pathophysiology; patient perspective

Gastroparesis is defined as a delay in gastric emptying in the absence of mechanical obstruction in the stomach.^{1,2} Causes of gastroparesis can be postsurgical, secondary to medications (eg, opioids, anticholinergics, tricyclic antidepressants, beta-blockers, calcium channel blockers), postinfectious, idiopathic, or a complication

of diabetes mellitus. The differential diagnoses of gastroparesis include cyclic vomiting syndrome and cannabinoid-induced hyperemesis.³ The emergence of gastrointestinal (GI) complications of diabetes mellitus are a function of poor glycemic control rather than the longevity of the diagnosis.⁴ The most common complication is diabetic gastroparesis (DG) and is often underrecognized.⁵ The cardinal symptoms of DG are nausea, early satiety, vomiting, dyspepsia, and bloating. DG is associated with impaired glycemic control, marked psychological distress, and reduced quality of life.⁶ This review paper provides a dual perspective of DG: firstly, that of the health care

Correspondence: Adam D. Farmer, PhD, FRCP, Department of Gastroenterology, County Hospital, Weston Road, Stafford, Staffordshire, United Kingdom ST16 3RS (a.farmer@qmul.ac.uk)

professional, which will focus on the pathophysiology, clinical evaluation, and treatment of DG, and secondly, that of the patient, with regard to the experience of living with DG.

EPIDEMIOLOGY OF GASTROPARESIS

Population-based epidemiological DG data is sparse as the majority of studies are case series from single, usually specialized, centers. In a community-based study of DG in the United States, the cumulative incidence was higher in type 1 diabetes mellitus (5%) than type 2 diabetes mellitus (1%).⁷ Moreover, data suggest that hospital admissions related to gastroparesis have increased significantly between 1995 and 2004.⁸ The costs associated with inpatient management of gastroparesis have increased, after adjustment for inflation, from \$13,350 per patient in 1997 to \$34,585 per patient in 2013.⁹ There is a higher incidence in females of 4:1 compared to males, and the disorder most commonly presents between the ages of 30 and 40 years in type 1 diabetes mellitus.¹⁰ In general, females report more severe symptoms but have less hospital admissions in comparison to males.¹¹ While the absolute cause of the gender differences is not completely understood, possible explanations include the fact that males have generally faster gastric emptying than females¹² and, in female rodent models, the effect of diabetes on the enteric nervous system is higher.^{13,14}

CONTROL OF GASTRIC EMPTYING

The regulation of gastric motility represents a complex functional interplay between the vagus nerve, enteric nervous system, interstitial cells of Cajal (ICC, which act as pacemaker cells), and the smooth muscle of the stomach.¹⁵ With respect to food ingestion, the stomach can broadly be considered to consist of two complementary parts, namely the proximal and distal stomach. The proximal stomach, consisting of the fundus, relaxes to accommodate the ingested food, which in itself leads to further relaxation by activation of mechanosensitive receptors via the vagus nerve. Within the greater curve, at the junction between the fundus and the body of the stomach, ICC generate rhythmic slow-wave electrical activity, which induces peristalsis that transitions food from the proximal to the distal stomach, ie, the body and antrum. In the distal stomach, antral contractions, against a closed pylorus, serve to “grind” food into smaller particles.¹⁶

Following this, the pylorus relaxes and opens and the food is then ejected into the proximal small bowel through an antroduodenal reflex. The rate of emptying is highly regulated in order to optimize the delivery of nutrients to ensure maximal absorption and is modulated by a number of hormones, such as the incretins and glucagon.¹⁷ These hormones slow the rate of gastric emptying, thereby controlling postprandial glycemia. The gastric emptying of liquids is more rapid than solids (1–2 hours vs 3–4 hours), and those nutrients with a higher calorific value are emptied more slowly.¹⁸ These factors are schematically summarized in Figure 1.

PATHOPHYSIOLOGY OF DIABETIC GASTROPARESIS

While the exact pathophysiological mechanisms that lead to DG are incompletely understood, a number of factors have been implicated. These include vagus nerve dysfunction, the effect of glycemic excursions, diminution of expression neuronal nitric oxide synthase with the myenteric plexus on the enteric nervous system, disturbance of ICC networks, and a proinflammatory state that results in excessive oxidative stress.^{19,20}

CLINICAL EVALUATION AND INVESTIGATIONS

A careful and detailed history needs to be undertaken to establish the presence of cardinal symptoms (nausea, early satiety, vomiting, bloating), as the cornerstone of diagnosis is clinical in nature.²¹ It is important to establish the presence or absence of vomiting and also to exclude the rumination syndrome, which is characterized by effortless vomiting.²² It is also important to seek a full detailed history regarding the person's diabetes to include the presence of complications such as retinopathy or peripheral sensorimotor neuropathy.

Physical examination should focus on looking for stigmata of peripheral and autonomic neuropathy, abdominal distension with the presence or absence of a succussion splash being a useful clinical sign. Routine biochemical, hematologic, and hormonal parameters are useful. If DG is suspected, an upper GI endoscopy should be undertaken to exclude mechanical gastric outlet obstruction, the symptoms of which are virtually

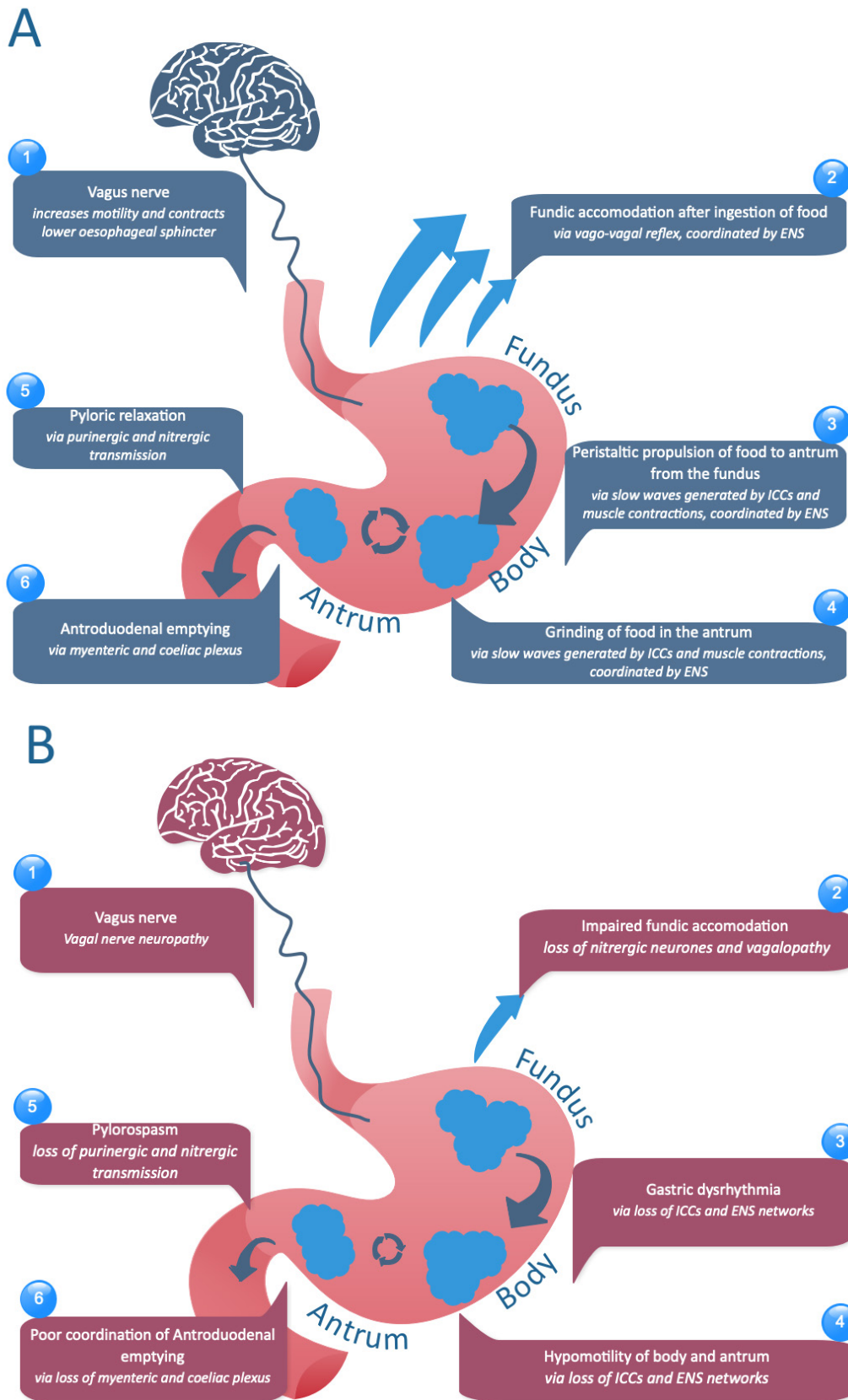


Figure 1. Gastric function in normal state (A) and in diabetic gastroparesis (B). A number of coordinated neuronal and myenteric processes are needed for normal coordinated gastric emptying. When these processes are disrupted at any level, then delayed gastric emptying may occur and symptoms may ensue.

identical. In the small proportion of patients who cannot tolerate/are unfit to undergo an upper GI endoscopy, a barium meal may be an alternative.

There are a number of techniques to measure gastric emptying, though scintigraphy is considered to be the gold standard.^{23,24} This is a noninvasive, quantitative method that involves the patient consuming a test meal consisting of 2 slices of bread with jam and 2 large eggs inoculated with 99-technetium. Scintigraphy scanning is performed at baseline and then after 30 minutes, 1 hour, 2 hours, and 4 hours postprandially.²⁵ The 1-hour scan is used to detect rapid gastric emptying, with a retention of less than 30% being consistent with this. The 2- and 4-hour scans are used to detect delayed gastric emptying, defined as a retention >60% or >10%, respectively.²⁵ As an alternative to percentage retention, gastric emptying time is sometimes reported. A half-emptying time greater than 80 minutes represents delayed gastric emptying.

The limitation of the test meal is that it is of small calorific value and often fails to reproduce symptoms.

Alternative test meals such as the Nottingham test meal, which consists of 400 mL liquid nutrient (0.75 kcal/mL), an optional solid component (12 solid agar beads), and recording of dyspeptic and filling sensations, also are available but require further validation in patient studies.²⁶ Filling and dyspeptic sensations are concomitantly recorded using a visual analogue scale.

Other methods of measuring gastric emptying include the wireless motility capsule and breath testing (Figures 2 and 3). The wireless motility capsule consists of an indigestible capsule, which detects luminal pH, temperature, and pressure as it passes through the GI tract, that wirelessly transmits high-frequency data to an external receiver.²⁷ Based on stereotypical changes in pH and temperature, gastric emptying, small-bowel transit time, colonic transit time, and whole-gut transit time. The wireless motility capsule compares well to scintigraphy and has robust normal values.²⁸⁻³⁰ The breath testing utilizes a nonradioactive ¹³C isotope bound to a digestible substance, most commonly octanoic acid or spirulina. ¹³C octanoic acid or spirulina is then mixed into an egg meal and ingested, where it

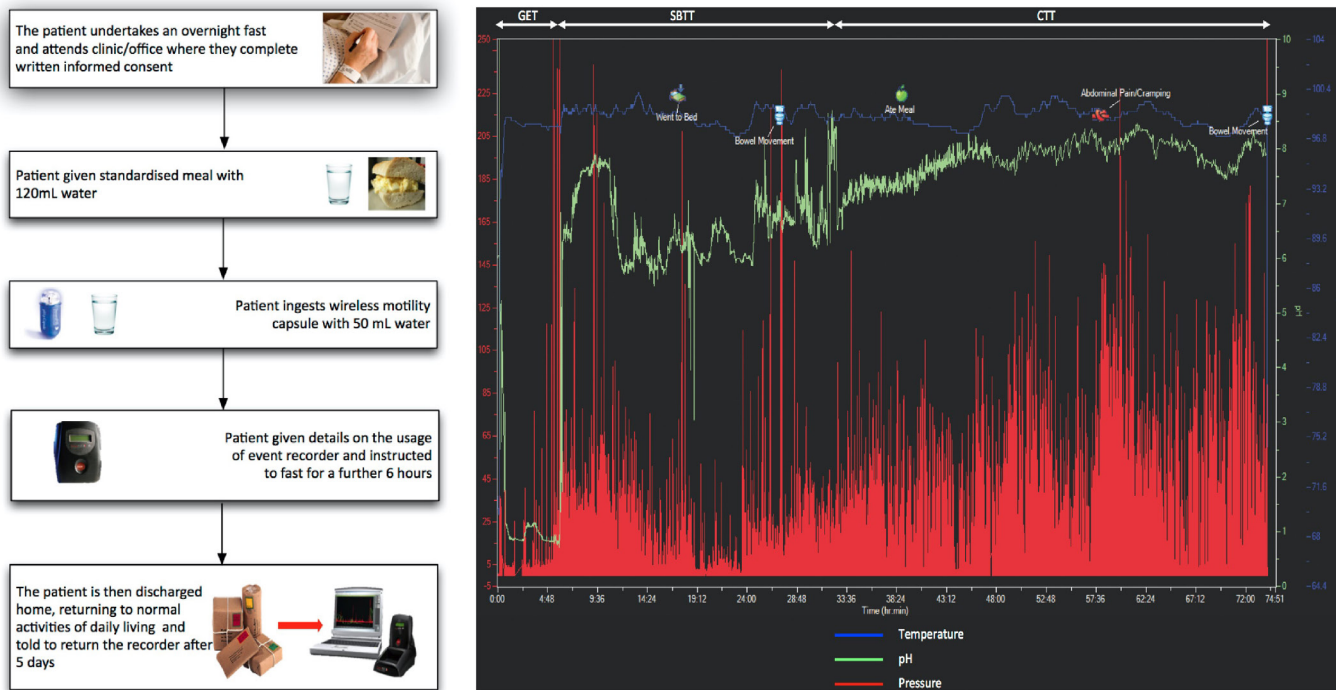


Figure 2. Standardized testing protocol for the wireless motility capsule and a typical trace demonstrating gastric emptying time (GET), small-bowel transit time (SBTT), and colonic transit time (CTT), from which the whole-gut transit time can be derived.

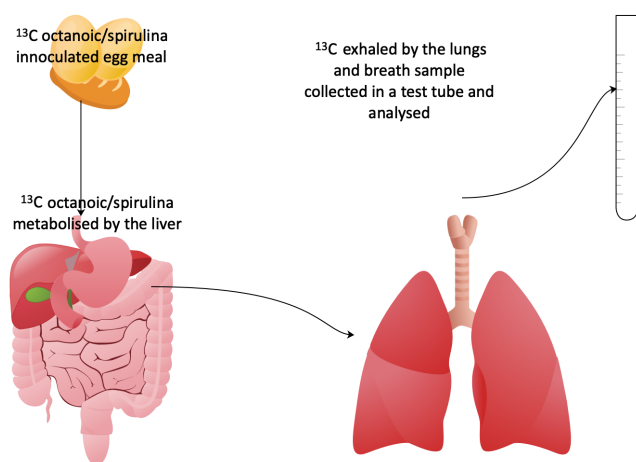


Figure 3. Schematic representation of the principles underpinning ¹³C octanoic acid breath testing to derive gastric emptying.

is absorbed from the small bowel and is subsequently metabolized by the liver to ¹³C-CO₂. It is then expelled from the lungs and measured in exhaled breath. The main advantages of these new technologies are that they limit radiation exposure to the patient, although their general availability at the current time is limited.

TREATMENT

DG is most effectively managed in the context of a wider multidisciplinary team that includes gastroenterologists, diabetologists, dieticians, and surgeons. The treatment of DG should adopt a stepwise approach that involves general aspects, dietary manipulations/nutritional support, pharmacological therapy, and surgical/endoscopic interventions.

General Aspects

General approaches include optimization of glycemic control, with correction of electrolyte imbalance if needed. A review of concomitant medications needs to be undertaken, as many classes of drug retard gastric emptying, including opioids, anticholinergics, and calcium channel blockers. When possible, such drugs should be discontinued if possible or at least minimized.

Dietary Manipulation and Nutritional Support

Given the symptoms of DG, patients often limit their oral intake, leading to dehydration, weight loss, and macronutrient/mineral/vitamin deficiencies.³¹ The overarching principle in the dietary management of

DG is to restore and preserve the patient's overall nutritional status. Clearly, dietary modifications are an important aspect of general diabetes management that will in themselves improve glycemic control.

Given the complexities of dietetic approaches to diabetic patients, modifications should be undertaken by a registered dietician with expertise in the area. A detailed clinical history establishing the types and consistencies of foods that are tolerated should be sought. In addition, the effect of content, timing, and size of meals and their relationship to symptoms should be established. Changing the frequency, size, and nutritional composition of meals can improve symptoms and is the cornerstone of initial management of DG.³² Patients should be encouraged to eat more liquid-based meals, given that liquids empty more rapidly than solids. Similarly, lower residue and lower fiber intake may be helpful. Lower fat/calorie-content meals also are advised, as these are emptied more rapidly.^{33,34}

Pharmacological Therapy

Current drug treatments in DG aim to promote gastric emptying or reduce nausea/vomiting. Prokinetic agents aim to accelerate the transit of food from the stomach to the small bowel. It is surmised that prokinetics reduce gastric dysrhythmias and improve antral contractility and antroduodenal coordination.³⁵

Antidopaminergics: Domperidone and metoclopramide are D₂ receptor blockers that exert their mechanism of action in the periphery and central areas, respectively. They have both prokinetic and antiemetic actions. While these drugs are generally well tolerated, both have been associated with potentially fatal cardiac arrhythmias through prolongation of QTc interval.³⁶ With domperidone, there are higher risks in certain circumstances: use in those >60 years old, a daily dose in excess of 30 mg, and use in those taking other concomitant medications that prolong the QT interval or inhibitors of CYP3A4. Domperidone is not available in the United States.

Given that metoclopramide crosses the blood brain barrier, it can cause extrapyramidal side effects and, rarely, irreversible tardive dyskinesia. Age 60 years and older, female gender, concomitant neuroleptics, and preexisting movement disorders confer a heightened

risk of this complication.³⁶ If physicians are considering commencing this medication, fully informed consent with a concomitant written contract needs to be executed. In February 2009, the Food and Drug Administration mandated a black box warning for metoclopramide, due to risks of tardive dyskinesia, and advocated that treatment periods should not exceed 3 months. Beyond this, treatment can be continued in rare/exceptional circumstances in which benefit outweighs risk.³⁷

Serotoninerigics: 5-HT₄ receptor agonists increase the release of acetylcholine from the efferent motor neurons in the enteric nervous system, which enhances contractions within the GI tract thereby accelerating motility. However, safety concerns regarding cardiac arrhythmias (cisapride) and ischemic colitis (tegaserod) have limited their availability.³⁸ Nevertheless, more selective 5-HT₄ receptor agonists, such as prucalopride, may offer an alternative.³⁹ A small study showed that prucalopride increases the rate of gastric emptying, though further studies are required to confirm this in clinical populations.⁴⁰

Antiemetics: In addition to the antidopaminergic agents, 5-HT₃ antagonists, antimuscarinic anticholinergics, H₁ antagonists, and NK₁ antagonists are established antiemetics. Although these drugs improve nausea, the utility is frequently limited by their anticholinergic side effects that slow gastric motility.

Ghrelin Agonists: Ghrelin is a gastric peptide that increases gastric activity in the postprandial and interdigestive periods and improves appetite. Relamorelin is a novel synthetic pentapeptide amide that is a potent ghrelin-receptor agonist.⁴¹ In comparison to endogenous ghrelin, it has increased potency, plasma stability, and a longer circulating half-life. Phase II trial data, at a twice daily subcutaneous dose of 10 mcg as compared to placebo, demonstrated that relamorelin improves gastric emptying and reduces vomiting episodes by 60%.⁴² Two large international multicenter studies evaluating relamorelin in DG are currently ongoing.

Invasive/Surgical Treatments

Endoscopic Therapies: A proportion of patients representing the severe end of the spectrum may need to be considered for escalation to nutritional

support. Clinical factors that may trigger this include unintentional loss of >10% of body weight over 6 months and refractory symptoms. In this context, a trial of feeding distal to the pylorus with a nasojejunal tube is of utility as a short-term measure in stabilizing and ultimately improving nutritional status. If successful, it may be followed by the placement of an endoscopically or surgically placed jejunostomy or gastrostomy with jejunal extension. Such enteral feeding strategies have been demonstrated to improve symptoms, reduce hospital admissions, and relieve symptoms.⁴³ In a small uncontrolled trial, venting gastrostomy was shown to reduce symptoms and improve functioning.⁴⁴

Intrapyloric injection of botulinum toxin, delivered at endoscopy, has been investigated as a management strategy in DG, albeit with unconvincing results.⁴⁵ It is postulated that the neurotoxin inhibits the release of acetylcholine at the neuromuscular junction, causing pyloric paralysis and allowing gastric contents to empty more readily into the duodenum.⁴⁶ The largest uncontrolled retrospective study of 179 patients (of which 81 had DG) reported an improvement in symptoms and body weight in the 4 months after intrapyloric botulinum toxin injection.⁴⁷ However, Friedenberget al reported that intrapyloric injection of botulinum toxin did not improve gastric emptying or symptoms over placebo at 1 month in a cohort of 32 patients.⁴⁸ Similarly, using a randomized crossover design, Arts et al demonstrated that intrapyloric injection of botulinum toxin was not superior to placebo in improving either the rate of gastric emptying or symptoms, although this study was performed in those with idiopathic gastroparesis.⁴⁹ Gastric peroral endoscopic myotomy (G-POEM) has been studied in DG and is associated with an improvement in symptoms and gastric emptying to at least 6 months, with an acceptable complication rate.^{50,51}

Surgical Interventions: Laparoscopically performed Heineke-Mikulicz pyloroplasty is considered to be an effective treatment for DG.⁵² The technique involves making a 5 cm full-thickness pyloromyotomy from the antrum to the duodenum, which is subsequently closed in a transverse fashion.⁵³ In a prospective cohort study of 177 patients, there was an improvement in the cardinal symptoms of gastroparesis at 3 months, and more than 75% had a normalization of gastric

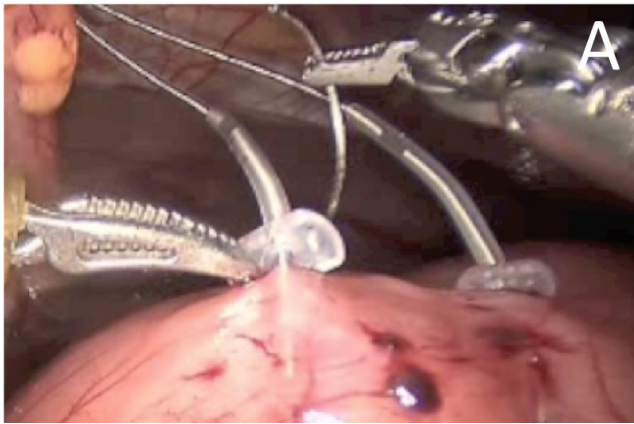


Figure 4. Surgical implantation of a gastric electrical stimulator. Panel A demonstrates suturing of the electrodes to the anterior wall of the antrum. Panel B shows the connection of the electrodes to the signal generator. Panel C depicts the insertion of the stimulator into a subcutaneous pocket.

emptying.⁵³ The overall morbidity rate was acceptable at 6.8%, though 10% required further interventions such as gastric electrical stimulator implantation. The weakness of this study was that it included patients whose gastric emptying was normal as measured by

scintigraphy, and it is not clear how many patients had DG. A small propensity-matched cohort study based on 30 patients with gastroparesis (of which 5 had DG) compared surgical laparoscopic pyloroplasty to endoscopic G-POEM and demonstrated a reduction in perioperative morbidity in the endoscopic group, with similar functional outcomes.⁵⁴

Patients with refractory DG can be offered implantable gastric electrical stimulation (GES), although availability varies between different health care economies. GES involves the surgical implantation of suturing of electrodes to the gastric antrum, which are then subsequently attached to a stimulus generator typically sited in a subcutaneous pocket in the left upper quadrant (Figure 4). Although improvement in symptoms is generally reported in open-label studies, a recent meta-analysis that included randomized placebo-controlled trials did not show any significant group differences in global or cardinal symptoms after GES, in the context of an overall complication rate of 1 in 10.⁵⁵ Nevertheless, patients with the most severe symptoms gained the largest therapeutic improvement. However, when considering the marked difference reported between open-label and placebo-controlled studies, it does suggest that there is a significant placebo response in what, by definition, is a group of patients with severe symptoms. Thus, the development of more objective and robust outcome measures that go beyond subjective reporting of symptoms is needed. In addition, the follow-up from the aforementioned studies is generally short, and longer-term outcomes in cohorts often display good improvement over time.

It is our experience that patients with recalcitrant symptoms do derive benefit from GES. Further work needs to be undertaken to identify objective patient factors that predict GES treatment response, such as relative loss of ICC.⁵⁶

PATIENT PERSPECTIVE

“Over the years I’ve seen a lot of doctors, and I’m exhausted. I have many health issues, with type 1 diabetes being the longest at play. My first gastric symptoms included bloating and nausea; I needed answers and quick. So, I went to a doctor, who sent me to another doctor — thankfully one who believed me and recognized my symptoms — who made a diagnosis then and there: DG.

“When I first received my DG diagnosis about 15 years ago, I was living in Canada and no tests were widely available for confirmation. After moving to England in 2013, my symptoms became disabling and I underwent some testing. A gastric emptying study came first. Result? Radioactive egg sat immobile in my stomach all day. I was told to return first thing the next morning for yet another nuclear medicine scan. Shock etched itself on the radiologist’s face. Nothing had moved. Rotting food in your stomach for days? It’s no picnic in the park.

“I tried many medications, including metoclopramide, cisapride, domperidone, erythromycin, to name a few, all to no avail. My surgeon thought my symptoms were so severe that I needed to have a gastric pacemaker implanted (given its trade name is Enterra, I dubbed it ‘Terry’). In my case, I can only describe the pacemaker in one word: disaster. The two years following were lost to indescribable pain. I did not get any benefit, and I lost weight and had back pain. My view was that ‘Terry’ had to go. Now that ‘Terry’ has been removed, I don’t feel the added pain, but the DG has not changed, and I still have to be very careful about what and how I eat.

“I’m one of the ‘lucky’ ones. I’ve been heard; I’ve been believed; I’ve been properly diagnosed. I have also connected to online patient groups, such as the Gastroparesis & Intestinal Failure Trust (GIFT), which is a ‘for patients by patients’ nonprofit support and research organization. I’ll be honest. This group is both encouraging and terrifying: so many questions answered; suggestions of what could help; acceptance; people who understand. No doctor could ever portray the brutalities of DG like other patients, as well as the courage and strength it takes to live with it. We, your patients, are people — broken, brave, resilient, shattered, strong. Yes, I’ve seen a lot of doctors, and I have hope. There is an urgent need for more research, more awareness, more compassion, and I hope, in time, the development of a cure.”

CONCLUSIONS

Although improvements in the understanding of the pathophysiology of diabetic gastroparesis have been made, to date there has been limited progress in the development of new treatments that translate to improved outcomes for patients. Given the burden

of disease and the associated morbidity, DG remains an area of significant unmet clinical need. Phase III clinical trials of novel agents, such as the ghrelin agonist relamorelin, are currently underway in patients with DG and, if efficacy is demonstrated, will represent welcome addition to the therapeutic armamentarium.

Patient-Friendly Recap

- Gastroparesis involves delayed emptying of the stomach, which can lead to recurrent nausea, bloating, and vomiting. Those living with this condition are at risk for dehydration and malnutrition.
- Gastroparesis in diabetics is common but often underrecognized, particularly in primary care.
- While pharmacological, endoscopic, and surgical approaches to treatment are available, results vary by individual and gains are limited.
- A frank account as told by one patient with diabetic gastroparesis exemplifies the challenges faced in battling this disease.

Author Contributions

Manuscript drafting: all authors. Critical revision: Farmer, Kadiramanthan.

Conflicts of Interest

None.

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