Diabetic Gastroparesis: A Review

Clipper F. Young,[1] Marianne Moussa,[2] and Jay H. Shubrook[1]

[1]Primary Care Department, Touro University California College of Osteopathic Medicine, Vallejo, CA; [2]Graduate, Touro University California College of Pharmacy, Vallejo, CA

Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction. This complication is associated with uncontrolled diabetes, contributing to approximately one-third of all gastroparesis cases (1–3). Gastroparesis is more prevalent in patients with type 1 diabetes than in those with type 2 diabetes (4). The 10-year cumulative incidence of diabetic gastroparesis has been estimated to be 5.2% in patients with type 1 diabetes and 1% in those with type 2 diabetes (5,6). The prevalence of diabetes-associated gastrointestinal symptoms is 5–12% (7,8). In a study by Jung et al. (9) conducted in Olmsted County, MN, the prevalence of gastroparesis was about 5% in patients with type 1 diabetes and 1% in type 2 diabetes (9). In the same study, the age-adjusted incidence rate of gastroparesis was 2.4/100,000 person-years in men and 9.8/100,000 person-years in women (9).

Gastroparesis, a form of autonomic neuropathy, is most commonly seen in people who have had diabetes for >10 years and who have already developed other microvascular complications (10). Once the symptoms from gastroparesis begin, they typically persist and are stable over 12–25 years; this is true even when blood glucose levels have been controlled (11). The most common symptoms are early satiety, nausea, bloating, abdominal pain, and vomiting.

In terms of prognosis, a recent study published by Chang et al. (12) found no association between delayed gastric emptying and increased mortality over a 25-year period. Although there is no evidence to date that diabetic gastroparesis increases mortality, this complication substantially impairs all aspects of life (13).

Pathogenesis

Although still not fully elucidated, the suggested pathophysiology of diabetic gastroparesis includes poor glycemic control, sympathetic vagal neuropathy, Cajal interstitial cell abnormalities, and loss of neuronal nitric oxide synthase (nNOS) (3,14). The loss of interstitial cells of Cajal—the electrical pacemakers involved in stimulating motor function and neurotransmission in the stomach—may lead to the development of diabetic gastroparesis (15–17). The binding of advanced glycation products to myenteric neurons, which subsequently inhibits the expression of nNOS, has been observed in animal models (18). Although inhibited nNOS expression has been linked to diabetic gastroparesis, it is still uncertain whether delayed gastric emptying resulted from the loss of nNOS expression (6). In animal models with streptozotocin-induced diabetes, vagal neuropathy has been observed through vagal electrical stimulation to decrease gastric acid secretion (19,20). Hyperglycemia-induced reduced antral pressure waves, absence of antral motor activity, and increased frequency of pyloric pressure waves have been proposed to account, at least in part, for symptoms of gastroparesis in patients with diabetes (21,22).

Oxidative stress also has been associated with the pathogenesis of gastroparesis. Studies have revealed that upregulation of the enzyme heme oxygenase-1 (HO-1) in gastric macrophages will protect against oxidative stress in the stomach (23,24). In patients with diabetes, loss of HO-1 results in a subsequent loss of expression for the receptor tyrosine kinase (c-Kit), which is essential for maintaining gastric functioning (23,24). The combination of loss of HO-1 and suboptimal expression of c-Kit receptors has been postulated to explain delayed gastric emptying in individuals with diabetic gastroparesis (23).

A third theory explaining the pathogenesis of this condition focuses on hyperglycemia. Some studies have shown that acute elevations of serum glucose concentration, especially in patients with type 1 diabetes, may be involved in delayed gastric emptying via decreased gastric motility (25,26). This phenomenon can occur through various mechanisms, including apoptosis of enteric neurons, which may occur during hyperglycemic states (although it has only been

Corresponding author: Clipper F. Young, clipper.young@tu.edu

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observed in rodents) and lead to subsequently delayed gastric emptying and rapid intestinal transit (27,28).

Clinical Manifestations

Symptoms in diabetic gastroparesis can range from mild to severe and incapacitating. Diagnosing the condition is not always straightforward because of the extensive symptomatic presentations and because, conversely, patients may be asymptomatic, especially in the initial phase of the disease. The clinical presentation of diabetic gastroparesis includes early satiety, anorexia, abdominal pain, bloating, nausea, and vomiting (2). Pain is likely under-reported and significant for many patients; 72% of patients with gastroparesis have reported experiencing abdominal pain (29).

In a study conducted by Wang et al. (30) that looked at gastroparesis trends from 1995 to 2004, a 53% increased risk of diabetes-related hospitalizations was attributed to gastroparesis. The condition may also indicate a higher risk for other diabetes-related complications. For example, patients with diabetes who also experienced symptoms of gastroparesis were more likely than those without such symptoms to develop cardiovascular disease (19.2 vs. 6.4%, $P < 0.05$), hypertension (63 vs. 43%, $P = 0.005$), and retinopathy (33 vs. 11.7%, $P < 0.001$) (31).

Some patients with diabetes may not realize that they experience delayed gastric emptying but exhibit unpredictable responses to mealtime insulin. These responses result from a mismatch between food absorption (which is slowed) and insulin absorption (which is not slowed). This phenomenon may present as severe hypoglycemia soon after meals, leaving patients questioning their unpredictable postprandial glycemic control.

Other patients do not know they have diabetic gastroparesis until they are put on a glucagon-like peptide 1 (GLP-1) receptor agonist such as liraglutide, dulaglutide, semaglutide, lixisenatide, or exenatide to manage their blood glucose. This class of drugs can exacerbate the symptoms of diabetic gastroparesis. GLP-1 receptor agonists work by mimicking the human incretin hormone GLP-1, which reduces gastric emptying, appetite, and food intake and increases glucose-dependent insulin secretion (32). Thus, GLP-1 receptor agonist therapy is not recommended for people who experience symptoms of gastroparesis.

Diagnosis

The typical complaint associated with gastroparesis is a feeling of excessive fullness after eating, which can last for hours or even overnight. Furthermore, patients may report feeling full or satiated sooner than expected. When symptoms progress, some might vomit undigested food hours after eating. Although gastroesophageal reflux disease can be mistaken as gastroparesis, reflux is usually a less prominent symptom of gastroparesis than feelings of bloating and fullness. Symptoms can occur after any meal without regard to types of food consumed or time of the day. Finally, most people with diabetic gastroparesis have already developed other microvascular complications of diabetes.

Evaluation of those who exhibit symptoms of gastroparesis should include excluding other possible causes such as side effects from medications or other medical conditions. Some questions to keep in mind when taking patients' medical history are: *1*) Has this patient had previous abdominal surgery or a long history of constipation? and *2*) Is this patient on medications that are known to slow gastrointestinal motility such as GLP-1 receptor agonists or the amylin analog pramlintide?

Physical examination of patients with gastroparesis is only helpful sometimes because patients with this condition could have a normal abdominal exam, a distended abdomen, or epigastric tenderness. Patients with longstanding gastroparesis may appear to be too thin or malnourished. Thus, the diagnostic process can be aided by asking additional specific questions such as: *1*) What other diabetes-related complications are present? and *2*) What is this patient's nutritional status?

After reviewing a patient's medical history and performing a physical exam, the next step in evaluating for suspected gastroparesis is to rule out any mechanical obstructions. This step usually involves either an upper endoscopy or radiographic tests such as computed tomographic or magnetic resonance enterography (33). The appearance of food in the gut after a period of fasting would be highly suggestive of gastroparesis (33). A barium study of the stomach, which is an alternative method to measure any mucosal lesions or mechanical obstructions, may also be used; however, this method is not as sensitive as endoscopy (33).

Once mechanical obstructions have been ruled out, the next step to obtain a definitive diagnosis of gastroparesis is to assess gastric motility. According to the American Gastroenterological Association, the gold standard in diagnosing this condition is gastric emptying scintigraphy (33). Solid-phase meals are mainly used to assess delayed gastric emptying because liquid emptying might still be intact in the presence of abnormalities (33). However, liquid emptying may be used in patients who have suspected dumping disease or are unable to tolerate solid meals (33,34).

Approximately 48–72 hours before performing a diagnostic procedure, all motility-altering medications (e.g., anticholinergics, opiates, or prokinetics) should be withheld to ensure accurate results from the test. In addition, agents that are known for their effect in delaying gastric emptying should be stopped; antidiabetic agents with this effect include GLP-1 receptor agonists and pramlintide. Any other factors that can potentially slow gastroesophageal emptying such as smoking and alcohol consumption also should be avoided before and on the test day (35). All medications that induce delayed gastric motility (e.g., opiate analgesics and anticholinergics) also should be discontinued at least 48 hours before the procedure (33). Finally, because hyperglycemia can also delay gastric motility, glucose stability at a suggested level <270 mg/dL should be achieved before performing the test (33).

A standard low-fat, egg-white sandwich is used as a test meal, with images taken at 0, 1, 2, and 4 hours after food ingestion, varying in composition based on the patient's responses (36). At the end of the fourth hour, gastric retention >10% is considered delayed gastric emptying (37). Although the relationship between the rate of gastric motility and the severity of symptoms has not been established, a classification has been made that mild gastric emptying is characterized by 10–15% gastric retention after 4 hours of food ingestion, moderate has 16–35% retention, and severe has >35% retention (38). Gastroparesis can also be diagnosed when 35% of a standard low-fat meal remains in the stomach 4 hours after ingestion (14).

Treatment Approaches

Nonpharmacological Approaches

First-line treatments for diabetic gastroparesis include dietary modifications, glycemic control, and restoration of fluids and electrolytes (2). In patients experiencing mild gastroparesis, dietary modifications are considered the initial approach (2).

Foods that are spicy, acidic, and fatty should be avoided or minimized because they may worsen symptoms; with a similar impact, carbonated beverages can aggravate gastric distention (2,39). Smoking and consumption of alcohol may decrease gastric motility and should also be avoided (35,40). Dietitians, as part of a multidisciplinary approach to disease management, advise patients to eat smaller and more frequent meals (e.g., four to five meals per day featuring foods that are low in fat and soluble fiber; some examples to avoid are whole grains, beans, and legumes because they are high in fiber (2). Most recommended meal plans are low in fat, fiber, and residue to reduce the burden of digestion. More examples are summarized in Table 1.

In more severe cases, nutrition supplementation is needed. For patients who cannot ingest solid foods, homogenized or liquid meals are alternatives (2). If weight loss from malnutrition is predominant, enteral and parenteral feedings are also possible. Patients with gastroparesis may also develop electrolyte abnormalities and nutrient and vitamin deficiencies for which supplemental hydration and nutrition may be recommended (41). For mild cases of gastroparesis, oral intake is preferred, whereas in more severe cases, parenteral or enteral nutrition is recommended (2). When repeated attempts are inadequate via the oral route, enteral nutrition may be indicated via a jejunostomy tube (2).

Patients with diabetes and gastroparesis should aim to optimize their glycemic control, but this can pose a substantial challenge because food absorption is unreliable and may not match endogenous insulin secretion or exogenous insulin administration. For patients who take mealtime rapid- or short-acting insulin, dosing after meals rather than before meals may be necessary. Because people with gastroparesis have a slower postmeal rise in blood glucose levels resulting from delayed gastric emptying, administering prandial insulin after meals instead of before can better match the timing of the postprandial glucose excursion. Although achieving glycemic control lowers the risk of developing microvascular complications, there are limited data to demonstrate the benefits of long-term glycemic control on improving symptoms of gastroparesis or leading to the restoration of a normal gastric emptying rate (42,43).

Nutritional approaches are rarely enough to control symptoms of gastroparesis as the disease progresses. Many people will also need pharmaceutical or surgical solutions.

Pharmacological Approaches

Table 2 summarizes the pharmacological therapies available to treat gastroparesis (2,44–49). Pharmacological therapy should be considered for those who have experienced recurring symptoms despite dietary modifications and glycemic control (2).

Prokinetics, a class of drugs that increases the rate of gastric emptying, are recommended by the American College of Gastroenterology (ACG) to improve gastric emptying and symptoms of gastroparesis (2). Metoclopramide, a prokinetic drug with dopamine-2 receptor and 5-HT3 receptor antagonizing properties, is the first-line therapy often used because it is the only medication approved by the U.S. Food and Drug Administration (FDA) for managing gastroparesis, albeit for a maximum of 12 weeks and only in severe

TABLE 1 Sample Nutrition Recommendations for Diabetic Gastroparesis

Examples of Low-Fat Foods	Examples of Low-Fiber Foods
Dairy products, lean meat, poultry, fish, fruits, vegetables, grains, cereals, and pasta	Butter, margarine, oils, white bread, white rice, milk-containing foods, fish, eggs, and poultry

cases (2,50). This drug is recommended to be given at the lowest effective dose (no more than 40 mg/day in four divided doses) and as a liquid oral formulation to maximize absorption (2). Metoclopramide has a boxed warning for tardive dyskinesia (<0.1%), and its most common side effect is acute dystonia (2,51). In an observational study conducted by Bateman et al. (51) that included 479 cases of extrapyramidal side effects, younger adults and females were more likely to experience acute dystonia, whereas older adults were more likely to experience Parkinsonian side effects (51). Patients should be educated on these side effects, and clinicians should discontinue metoclopramide if a patient experiences involuntary movements or any similar side effects.

Domperidone, a type II dopamine antagonist, has effectiveness similar to that of metoclopramide in alleviating symptoms of gastroparesis but without extrapyramidal side effects, making it a suitable treatment option for gastroparesis (2). Although not readily available in the United States, domperidone can be prescribed to patients through an FDA investigational new drug application (2). However, this medication has been shown to have an increased risk of cardiac arrhythmias (52). Thus, the ACG recommends a baseline electrocardiogram (ECG) before initiation and during treatment with domperidone (2). ECG monitoring is recommended 1 week after therapy initiation in those who are at high risk for QT prolongation (53). Domperidone should be stopped when the corrected QT interval is >450 ms in men or >470 ms in women (2).

Erythromycin, a macrolide antibiotic and motilin agonist, is another treatment option for improving symptoms of gastroparesis and gastric emptying (2). Intravenous administration is recommended when this prokinetic agent is chosen for hospitalized patients (2). Oral administration of erythromycin is considered in patients who have failed treatment with metoclopramide and domperidone (2). Although oral treatment with erythromycin has been shown to be effective in improving gastric emptying, treatment duration should not exceed 4 weeks because of potential tachyphylaxis (2). Because of the decrease in clinical response over time and the common gastrointestinal side effects associated with erythromycin such as diarrhea and cramping, this agent has limited use in the treatment of gastroparesis.

Antiemetic drugs can be considered in patients with gastroparesis who are experiencing symptoms of nausea and vomiting (2). However, these agents do not improve gastric emptying and are used only for symptom management (2). The most common agents are phenothiazines (including prochlorperazine) and antihistamines (including promethazine).

Tricyclic antidepressants (TCAs) are also used in patients with refractory nausea and vomiting (2). Studies have shown that TCAs are effective in patients who have depression in addition to diabetes, and other open-label studies have shown TCAs' efficacy in reducing nausea and vomiting in those who suffer from diabetic gastroparesis (54–57). However, because some TCAs such as amitriptyline have anticholinergic properties, they can worsen gastric emptying. Thus, avoiding these agents in patients with gastroparesis would be the best practice (2).

Patients often complain of abdominal pain, so pain management should be considered when treating gastroparesis. Although avoiding TCAs is recommended in gastroparesis, these agents have been studied in patients with diabetes because of their effectiveness for depression in diabetes, associated with enhanced glycemic control, and reported to reduce symptoms of nausea, vomiting, and abdominal pain with low doses (55–57). The second-line approaches for pain management are the weak μ-opioid receptor agonist tramadol and the γ-aminobutyric acid analog gabapentin. The use of narcotics for pain associated with diabetic gastroparesis is not recommended because they can contribute to constipation and worsening of symptoms (2).

Botox injections have been used to manage gastroparesis, but data from clinical trials do not support its use for this purpose (58,59).

Surgical Approaches

Several surgical approaches have been tried for diabetes-related gastroparesis. These treatments have included surgical modification of the stomach, placement of a gastric electrical stimulator, and Roux-en-Y gastric bypass. For surgical treatments, gastrostomy for venting and jejunostomy for feeding may be done to alleviate symptoms (2). Those who are still having substantial symptoms may undergo a complete gastrectomy (2). Although refractory cases of gastroparesis have been treated with pyloroplasty

TABLE 2 Pharmacological Treatments for Gastroparesis

Treatment	Dosing for Adults	Maximum Dose	Warnings	Contraindications	Renal and Hepatic Adjustments	Special Populations
Metoclopramide (44)	Oral: 10 mg four times daily (30 minutes before each meal and at bedtime)	40 mg/day	Tardive dyskinesia (TD)	History of TD or dystonic reaction to metoclopramide When stimulation of gastrointestinal motility might be dangerous Pheochromocytoma, catecholamine-releasing paragangliomas Epilepsy Hypersensitivity to metoclopramide	Renal: with CCr ≤60 mL/minute, 5 mg four times daily (maximum 20 mg/day) In ESRD, hemodialysis, or continuous ambulatory peritoneal dialysis, 5 mg twice daily (maximum 10 mg/day) Hepatic: with moderate or severe impairment (Child-Pugh class B or C), 5 mg four times daily (maximum 20 mg/day)	Geriatric: use the lowest effective dose. Pregnancy: an increased risk of adverse pregnancy-related outcomes has not been reported.
Domperidone (45)	Oral: 10 mg three times daily	30 mg/day	Domperidone might be associated with an increased risk for serious ventricular arrhythmias or sudden cardiac death, especially in doses >30 mg or when used in patients >60 years of age	Known existing prolongation of cardiac conduction intervals, particularly QTc Significant electrolyte disturbances Underlying cardiac diseases such as congestive heart failure Coadministration with medications that prolong QTc interval Coadministration with potent CYP3A4 inhibitors Known hypersensitivity to domperidone or any of the excipients Prolactin-releasing pituitary tumor (prolactinoma) When stimulation of gastric motility might be dangerous Patients with moderate or severe impairment, use is contraindicated	–	Pregnancy: category B
Erythromycin	IV: 3 mg/kg administered over 45 minutes every 8 hours (2,46) Oral: 250–500 mg three times daily before meals (limit to 4 weeks because of potential tachyphylaxis) (2)	4 g/day (47)	–	Known hypersensitivity to erythromycin (47) When taking terfenadine or astemizole (47)	–	Pregnancy: category B (47)
Antiemetic (prochlorperazine) (48)	Oral: 5–10 mg three to four times per day	40 mg/day	Increased mortality in elderly patients with dementia-related psychosis	Known hypersensitivity to phenothiazines Coma or presence of large amounts of CNS depressants (e.g., alcohol, opioids, barbiturates) Pediatric surgery Infants and children <2 years of age or weighing <9 kg Pediatric conditions with no dosage established	–	Geriatric: initiate at the lower end of the dosage range; increase dose slowly and cautiously. Pregnancy: safety has not been established.
Antiemetic (promethazine) (49)	Oral, rectal: 12.5–25 mg every 4–6 hours, as needed	150 mg/day	In patients younger than 2 years of age because of potential fatal respiratory depression	In patients younger than 2 years of age because of potential fatal respiratory depression In comatose states In patients known to be hypersensitive In treating lower respiratory tract symptoms	–	Geriatric: start at the low end of the dosage range Pregnancy: category C

CCr, creatinine clearance; CNS, central nervous system; CYP3A4, cytochrome P450 3A4; ESRD, end-stage renal disease; IV, intravenous; QTc, corrected QT.

and gastrojejunostomy, more studies are warranted to validate their effectiveness as surgical treatment options (2).

In 2000, the FDA approved a gastric electrical stimulation device that delivers a high-frequency, low-energy electrical signal to the stomach to be used in refractory cases under a humanitarian device exemption (60). A meta-analysis showed benefit from such gastric electrical stimulation (61), although its exact mechanism with regard to management of gastroparesis symptoms is unknown. Alteration of the mechanisms through which nausea and vomiting are controlled, enhancement of vagal functioning, and reduction of sensitivity to distension have been proposed as possible mechanisms to explain the outcomes resulting from gastric electrical stimulation (62,63).

Clinical Implications

Diabetic gastroparesis has a wide spectrum of expression from asymptomatic to severe symptoms that may lead to dehydration and nutritional complications if left untreated. Early identification, normalization of blood glucose, and reduction of glucose variability can limit the consequences of this condition. Unfortunately, diabetic gastroparesis can cause great difficulty in controlling postmeal glucose excursions because food absorption can become unpredictable in these patients. A recent study by Calles-Escandón et al. (64) paired continuous subcutaneous insulin infusion (CSII) with continuous glucose monitoring (CGM) in patients with diabetic gastroparesis. This study showed that the combination of CSII and CGM helped to minimize hypoglycemic episodes, improve glycemic control, and enhance meal tolerance and quality of life (64).

Individual with gastropareses who take prandial insulin may need to delay their insulin doses after they eat to ensure that they have been able to keep the food down (not vomiting) before taking insulin. In some cases, patients may even inject their prandial insulin hours after a meal to try to make the insulin bolus match the late absorption of the food they consumed. Insulin pump therapy can sometimes be helpful in these patients because it allows for frequent small boluses, and the pump can be suspended if glucose levels trend toward low. Although safety features such as these can make it easier for patients, mealtime glucose management remains challenging.

Other complications from gastroparesis include dehydration and malnutrition from loss of vitamins and nutrients, especially in those who are experiencing vomiting. Over time, this can leave individuals malnourished and encourage the formation of bezoars, leading to abdominal obstruction (65). Current treatment options for bezoars include cellulase, acetylcysteine, and Coca-Cola via nasogastric lavage (66). Also, because of frequent changes in the amount and rate of food passing through the stomach, blood glucose levels may constantly be changing, making glycemic control even more difficult (37). Finally, these patients might have a poor quality of life because of the need to continually deal with flare-ups, symptoms that interfere with their daily lives, inability to eat solid foods, and frequent hospitalizations (65).

Summary

Diabetic gastroparesis is a severe complication resulting from uncontrolled diabetes that impairs quality of life and increases comorbid conditions and mortality. This complication is characterized by bloating, nausea, vomiting, weight loss, and early satiety but should be confirmed/diagnosed by scintigraphy. Initial management includes modifying the diet, restoring fluids and electrolytes, and controlling glycemic levels; those with persistent symptoms may require pharmacological or surgical therapy. Having a more thorough understanding of the pathogenesis and underlying mechanisms of diabetic gastroparesis encourages researchers and clinicians to further investigate this condition with the aim of advancing disease prevention and symptom management, as well as reducing the sequelae of diabetic gastroparesis.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

C.F.Y. researched data and wrote and edited the manuscript. M.M. researched data and contributed to the manuscript. J.H.S. reviewed/edited the manuscript. C.F.Y. is the guarantor of this work and, as such, takes responsibility for the integrity of the manuscript and the accuracy of the review.

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