Diabetic Gastroparesis

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KEYWORDS

• Type 1 and type 2 diabetes mellitus • Gastroparesis • Gastric dysrhythmias
• Prokinetic and antinauseant drugs • Gastric electric stimulation • Nausea • Vomiting

KEY POINTS

- Gastroparesis is delayed gastric emptying in the absence of obstruction, a complication that affects patients with type 2 as well as type 1 diabetes mellitus.
- Symptoms associated with gastroparesis are nonspecific, and the diagnoses should be confirmed with gastric emptying tests.
- Patients are often overweight and have nutritional deficiencies.
- Obstructive gastroparesis, a subset of gastroparesis, is caused by pyloric dysfunction, and botulinum toxin A injections may be helpful.
- Trending postprandial glucose excursions with continuous glucose monitoring aids in the dosing and timing of insulin administration in diabetic patients with gastroparesis.

INTRODUCTION

When gastroparesis afflicts patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM), the consequences are particularly severe. Symptoms associated with gastroparesis, such as early satiety, prolonged fullness, nausea, and vomiting of undigested food, not only reduce the quality of life but also compound difficulties in controlling blood glucose levels.

Gastroparesis is defined as a delay in the emptying of ingested food in the absence of mechanical obstruction of the stomach or duodenum.[1] Many patients with diabetes (as well as their physicians) do not appreciate that gastroparesis has developed. In diabetic patients with gastroparesis, ingested food is not emptied in a predictable period of time; thus, the anticipated nutrient absorption is not the reality. Consequently, the selected dose and timing of insulin therapy to control postprandial glucose may be inappropriate.

In many patients with gastroparesis, erratic postcibal glucose levels result in swings from hypoglycemia to severe hyperglycemia and even ketoacidosis.[2,3] Hyperglycemia

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itself elicits gastric dysrhythmias and slows gastric emptying.[4,5] Patients frequently are seen in emergency rooms for low glucose levels, severe hyperglycemia, or ketoacidosis. Gastroparesis as an underlying condition needs to be considered in these cases.

In addition to antinauseant and prokinetic drug therapies, patients with diabetic gastroparesis also need to change their diet and the timing and dosing of insulin to better match the slow emptying of ingested food. The epidemiology, pathophysiology, clinical presentation, diagnostic testing, and treatments for diabetic gastroparesis are reviewed in this article.

EPIDEMIOLOGY

A recent update reported that there are more than 36 million individuals with diabetes in North America and the Caribbean[6] and most are cases of T2DM. The estimates of prevalence of gastroparesis in T1DM vary widely. Although in tertiary centers, up to 40% of patients with T1DM have gastroparesis,[7] surveys in Olmsted County, Minnesota, indicated a prevalence of 5%.[8]

Similarly, in specialized centers, 10% to 30% of patients with T2DM have gastroparesis[9]; in Olmsted County, the prevalence was 1%.[10] These differences likely reflect a selection bias, because more patients with diabetes and complications are seen in tertiary medical centers compared with surveys of patients in the community. Nevertheless, because of the increasing numbers of patients with T2DM, this population represents the largest group of patients with gastroparesis.

The number of patients with diabetes worldwide continues to increase. The World Health Organization estimated that in 2013 almost 350 million individuals had diabetes (mainly T2DM), and predicted mortality from diabetes will double by 2030 (http://www.who.int/mediacentre/factsheets/fs312/es/). Assuming a low estimate of gastroparesis incidence in T2DM of 1%, at least 5 million individuals with diabetes complicated with gastroparesis will require specialized diagnosis and care.

Gastroparesis evolves over time, presumably as acute and chronic hyperglycemia and reduced insulin and insulinlike growth factor 1 (IGF-1) signaling results in damage to the interstitial cells of Cajal (ICCs) and enteric neurons of the stomach.[11,12] Over a 10-year period, approximately 5.2% of patients with T1DM developed gastroparesis, whereas 5 times fewer (1%) patients with T2DM developed gastroparesis over that same period.[8] Although good control of glycemia prevents or delays many of the chronic complications of T1DM,[13] the effect of good glucose control on the onset or progression of gastroparesis in T1DM is unknown. Diabetic patients with gastroparesis often have many of the chronic complications of diabetes (retinopathy, nephropathy) and increased hospital use. In a few patients, gastroparesis is the first diabetic, neuropathic complication.

Compared with T2DM, patients with T1DM with gastroparesis are younger, thinner, and tend to have more severe delays in gastric emptying.[14] Mortality is increased in diabetic patients when they develop gastroparesis and is usually related to cardiovascular events[15] when compared with diabetic patients without gastroparesis.

NORMAL POSTPRANDIAL GASTRIC NEUROMUSCULAR ACTIVITY

The normal stomach performs a series of complex neuromuscular activities in response to the ingestion of solid foods.[16] First, the fundus relaxes to accommodate the volume of ingested food (**Fig. 1**). Normal fundic relaxation requires an intact vagus nerve and is mediated by enteric neurons containing nitric oxide. The relaxation of the fundus allows food to be accommodated without excess stretch on the fundic walls.

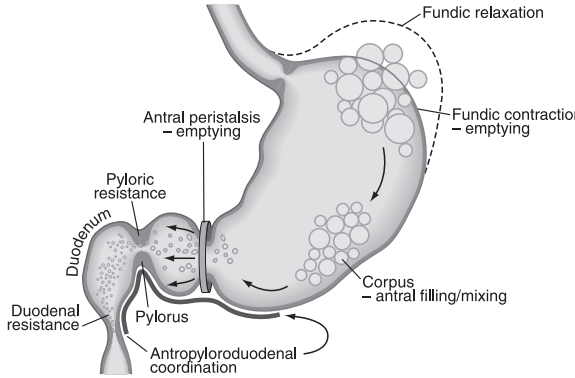

Fig. 1. Gastric neuromuscular responses to the ingestion of solid food. The fundus, corpus, antrum, pylorus, and duodenum are shown. The fundus relaxes to accommodate the ingested solid food. The fundus presses the food into the corpus-antrum, the mixing chambers of the stomach. Recurrent peristaltic waves triturate the solids into 1-mm to 2-mm particles (termed chyme), which are emptied from the antrum through the pylorus into the duodenum. The sequence requires antral-pyloroduodenal coordination. (*Adapted from* Koch KL. Gastric neuromuscular function and neuromuscular disorders. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Philadelphia: Elsevier; 2010. p. 789–815.)

Second, the corpus and antrum produce recurrent peristaltic waves that mix or triturate the ingested solids into fine particles termed chyme. The waves mix together the food particles, pepsin, and acid to prepare the ingested food for emptying. Peristaltic waves in the corpus-antrum occur at a frequency of 3 contractions per minute, a frequency that is dictated by the gastric pacemaker cells (the ICCs), which normally depolarize and repolarize at a rate of 3 cycles per minute (cpm) (see **Fig. 1**; **Fig. 2**).[17,18] The slow waves (pacesetter potentials) originate at the greater curvature of the stomach between the fundus and proximal corpus (see **Fig. 2**) and migrate in a circumferential and aboral direction at increasing velocity in the distal antrum.[16] The slow waves bring the circular muscle of the stomach to depolarization threshold and contractions, which occur in response to the release of acetylcholine. The action and plateau potentials are synchronized to the 3-cpm slow wave, thus resulting in the coordinated 3-per-minute peristaltic contractions.

Third, emptying of chyme contents begins when the ingested solid foods are sufficiently triturated. The peristaltic waves at 3 per minute empty aliquots of chyme through the pylorus into the duodenum (see **Fig. 1**). The pylorus acts as a sieve and can regulate the particle size as well as the volume of chyme that is emptied into the duodenum with each peristaltic wave. In the normal condition, the number of calories emptied per minute is consistent, at about 5 calories per minute in humans.[19] The emptying of food from the stomach is altered by the nature of the constituents (carbohydrate, protein, and fat) and the fiber and indigestible components. Carbohydrates are emptied faster than proteins, which are emptied faster than fats, which delay gastric emptying. Soluble and insoluble fibers are emptied after the nutrients.[20] Gastric emptying is also regulated by postpyloric influences. The release of cholecystokinin slows gastric emptying.[21] Intraluminal content with high concentration stimulates the release of peptide YY from the ileum to slow gastric emptying.[22] Normal postprandial neuromuscular activity is associated with a sense of comfortable fullness. In contrast, the ingestion of food elicits early satiety, nausea, and epigastric discomfort or pain in diabetic patients with gastroparesis.

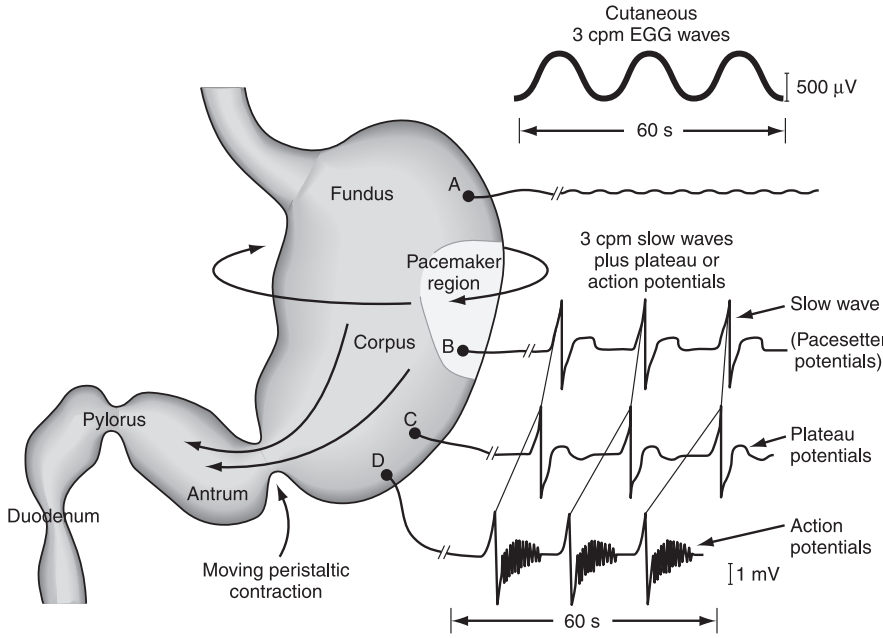

Fig. 2. Electrophysiology of gastric peristalsis. From the gastric pacemaker area on the greater curvature of the stomach to the pylorus, slow waves (pacesetter potentials) migrate circumferentially and distally as a myoelectric wave front. Electrodes placed on the fundus (A) show that there is little or no electric rhythmicity present. Electrodes B, C, and D record slow waves with plateau or spike potentials in the corpus-antrum. The plateau or spike potentials occur when enteric neurons release acetylcholine, resulting in circular muscle depolarization and contractions. The plateau and spike potentials, linked to the slow waves, result in 3 peristaltic contractions per minute controlled by the normal 3-cpm gastric slow wave. Gastric myoelectric activity recorded from cutaneous electrodes reflect the 3-cpm myoelectric events. (*Adapted from* Koch KL. Gastric neuromuscular function and neuromuscular disorders. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Philadelphia: Elsevier; 2010. p. 789–815.)

PATHOPHYSIOLOGY OF DIABETIC GASTROPARESIS

Gastric Neuropathy and Cajalopathy in Diabetic Gastroparesis

Full-thickness biopsies of the gastric corpus from patients with T1DM and T2DM and gastroparesis indicate that the disease is primarily a disease of gastric enteric neurons and ICCs.[11,12] We know that ICCs are depleted (<5/hpf compared with controls) in the diabetic gastroparesis stomach.[11,17] Gastric enteric neurons are decreased in numbers of cell bodies and processes are truncated. These neurons are surrounded by an immune infiltrate composed primarily of type 2 macrophages, suggesting a role for the immune system and carbon monoxide in the pathogenesis of diabetic gastroparesis.[23] The circular and longitudinal smooth muscle layers are normal or have very mild fibrosis. ICCs are depleted in diabetic mice with gastric emptying abnormalities.[24] Hyperglycemia in these animals is associated with dedifferentiation of ICCs into immature myoblasts, and intense insulin therapy restores ICC numbers to normal. It is postulated that platelet-derived growth factor (+) myoblasts have the potential to evolve into ICCs.[25]

Abnormalities of Fundic Relaxation

Relaxation of the fundus during ingestion of food requires normal vagus nerve function and the release of nitric oxide from inhibitory neurons.[26] In patients with diabetes, the fundus fails to relax normally (**Fig. 3**).[27] The ICCs function also as stretch receptors.[28] The loss of nitrergic neurons plus the absence of ICCs may account for the poor fundic relaxation and decreased gastric capacity seen in gastroparesis.[29]

Disorders of the Corpus-Antrum

The corpus and antrum perform the mixing and emptying activities of the stomach. In diabetic gastroparesis, corpus-antral contractions are ineffective, although the smooth muscle layers seem to be normal.[11,12] Thus, the depletion of ICCs and presence of abnormal enteric neurons are the mechanisms of gastric neuromuscular dysfunction. Loss of enteric neurons results in less acetylcholine release for contractions and less nitric oxide for relaxation of smooth muscle. Depletion of ICCs is associated with the presence of gastric dysrhythmias and loss of the normal 3-cpm myoelectric rhythm.[17,30] Gastric dysrhythmias range from tachygastrias to bradygastrias and a variety of aberrant conduction pathways in the corpus-antrum.[17] Gastric dysrhythmias reduce efficiency and the occurrence of normal gastric peristaltic waves and, thus, lead to slow gastric emptying and gastroparesis (see **Fig. 3**). Correction of gastric dysrhythmias with domperidone, a peripheral dopamine 2 antagonist, improved upper gastrointestinal (GI) symptoms, suggesting dysrhythmias correlate with symptoms.[31]

Disorders of Pyloric Relaxation

The pyloric sphincter also regulates gastric emptying.[16] The pylorus provides resistance to flow and a sieving function for particles as antral peristaltic waves propel

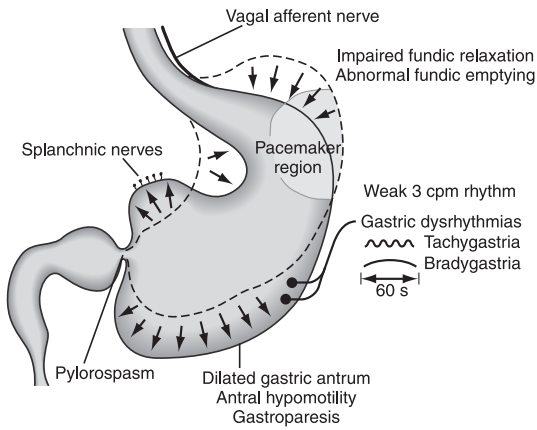

Fig. 3. Neuromuscular disorders of the stomach in diabetic gastroparesis. The fundus fails to relax normally to accommodate food. The gastric electric rhythm is abnormal because of the loss of ICCs, resulting in weak or absent 3-cpm activity and tachygastria and bradygastria. The antrum may dilate, and antral contractions are weak and uncoordinated, all of which lead to delayed gastric emptying. In a subset of patients with gastroparesis, 3-cpm myoelectric activity is present, but gastroparesis occurs because of pyloric dysfunction. Abnormalities of vagal afferent nerve or splanchnic nerve innervation may also be present in patients with diabetic gastroparesis. (*Adapted from* Koch KL. Gastric neuromuscular function and neuromuscular disorders. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management. Philadelphia: Elsevier; 2010. p. 789–815.)

chyme from the antrum into the duodenum (see Fig. 1). Relaxation of the pyloric sphincter to allow flow is mediated by nitric oxide released from enteric neurons.[16] In a subset of patients with idiopathic and diabetic gastroparesis, pylorospasm (failure of pyloric relaxation in coordination with antral peristaltic waves) results in gastroparesis (see Fig. 3).[32,33] Mechanical obstruction at the pylorus or post bulbar duodenum caused by ulcer disease or cancer must be excluded in patients with gastroparesis.[33]

Clinical Presentation

Symptoms associated with diabetic gastroparesis are early satiety, prolonged fullness, bloating, nausea and vomiting, and abdominal discomfort and pain. These symptoms are vague and nonspecific. Approximately 20% of patients develop these symptoms acutely and with a febrile illness.[34] A variety of diseases may cause these symptoms, and abdominal pain and causes of symptoms other than gastroparesis must be considered.

Nausea is the most bothersome and predominant symptom in diabetic patients with gastroparesis. Nevertheless, the nausea caused by gastroesophageal reflux disease (GERD) or constipation or gallbladder disease, common disorders in patients with diabetes, must be considered.[16] Nausea related to gastroparesis is typically located in the epigastrium and usually increases in severity after ingestion of meals. Vomitus contains chewed food. Prolonged stomach fullness and vague epigastric discomfort are common. Symptoms are similar in patients with T1DM and T2DM, although patients with T2DM tend to have more fullness and bloating.[34] Table 1 lists demographic parameters and symptoms in patients with T1DM and T2DM and

Table 1
Demographic and clinical differences in patients with gastroparesis and T1DM and T2DM from the gastroparesis clinical research consortium

	T1DM (n = 78)	T2DM (n = 59)	*P* Value
Female (%)	70	76	
Age (y)	39 ± 11	53 ± 11	*P*<.001
Married (%)	54	64	
Ever smoked (%)	29	39	
Time from diabetes mellitus onset to initial symptom (y)	14 ± 11	8.4 ± 8	*P*<.005
Symptom duration (y)	6.2 ± 6	4.1 ± 3	
BMI	26 ± 6	33 ± 8	*P*<.001
Normal BMI (%)	47	14	
HbA_{1c}	8.3 ± 2	7.4 ± 1.7	*P*<.003
Major depression (%)	28	32	
GCSI	2.8 ± 1.1	3.0 ± 1.0	
GET at 4 h (%)	47 ± 27	33 ± 24	*P*<.001
Severe GET (%)	54	32	*P*<.001
Number of hospitalizations in past year	5.1 ± 6.4	3.2 ± 6.6	*P*<.003

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; GCSI, Gastroparesis Clinical Severity Index; GET, gastric emptying test; HbA_{1c}, hemoglobin A_{1c}.

Adapted from Koch KL, Hasler WL, Yates KP, et al, for the Gastroparesis Clinical Research Consortium. Contrasting gastroparesis in type 1 (T1DM) vs. type 2 (T2DM) diabetes: clinical course after 48 weeks of follow-up and relation to comorbidities and health resource utilization. Gastroenterology 2013;144(5 Suppl):S926–7.

gastroparesis.[15] In contrast to patients with idiopathic gastroparesis, fewer diabetic patients with gastroparesis report pain as a predominant symptom.[34]

In some patients (20%) with gastroparesis, abdominal pain is the predominant symptom.[34] The pain should be evaluated separately from other symptoms associated with gastroparesis in an attempt to determine a specific cause for the pain. Chronic cholecystitis, peptic ulcer diseases, and the abdominal wall syndrome need to be excluded. Stomach pain can be caused by pylorospasm or gastric sensitivity to stretch in patients with gastroparesis. Mechanical obstruction at the pylorus caused by ulcer or cancer must be excluded in patients with gastroparesis.

Physical examination may be normal or show obesity or undernutrition, retinopathy, neuropathy, or vitamin deficiency (cheilosis). Obesity in patients with T2DM is a risk factor for gastroparesis.[35] Abdominal examination may show distension, a succession splash, or positive Carnett sign. A positive Carnett sign indicates that abdominal pain is from an abdominal wall syndrome secondary to nerve entrapment or inflammation, often located at a healed incision site.[36,37]

Standard laboratory studies are usually normal. Hemoglobin A_{1c} levels have a wide range. Thyroid-stimulating hormone levels and fasting cortisol should be measured to screen for Addison disease and hypothyroidism. Vitamin D levels are frequently low.

TESTS FOR GASTROPARESIS AND GASTRIC DYSRHYTHMIAS

Solid-Phase Gastric Emptying Test

Tests for gastroparesis and gastric dysrhythmias are nuclear medicine scintigraphy, wireless capsule endoscopy, and electrogastrography (EGG). These tests should be performed after upper endoscopy to rule out mechanical obstruction, which produces symptoms similar to gastroparesis. The most standardized test for gastric emptying is the technetium-labeled low-fat egg albumin-based meal.[38,39] The patient must stop prokinetic agents 7 days before the test, fast after midnight, and blood glucose level on the day of the test should be less than 270 mg/dL. Immediately after the patient ingests the 257-calorie meal, a 1-minute scintigram is obtained with the patient in a sitting position and then for 1 minute every hour for 4 hours. Normal gastric emptying is 39% or less of the meal retained at 2 hours and 9% or less retained at 4 hours. Thus, gastroparesis is diagnosed by a documented retention of 40% or more at 2 hours or 10% or more at 4 hours.

The solid-phase gastric emptying test is also important, because some patients who have the symptoms associated with gastroparesis have rapid gastric emptying or dumping syndrome. In dumping syndrome, less than 30% of the test meal is retained at 60 minutes.[38]

Wireless Capsule Motility Test

The wireless capsule motility test measures intraluminal pH and pressure.[40] The capsule is swallowed during ingestion of a nutrient bar that contains the same number of calories as the Egg Beaters test meal. No further food intake is allowed for 5 hours. If the capsule does not empty from the stomach into the duodenum in 5 hours, then delayed gastric emptying is diagnosed. Small bowel and colon transit time are also measured, and results may help in determining the underlying pathophysiology of other GI symptoms.

Electrogastrography

Electrogastrography is the method of recording gastric myoelectric activity with a noninvasive method.[41,42] Electrocardiography-type electrodes are placed on the

epigastrium, and the myoelectric signal is recorded before and after a water load or a nutrient load test. Normal gastric myoelectric activity (2.5–3.7 cpm) normally increases after the water load test.[42] Gastric dysrhythmias are defined as tachygastrias (3.5–10 cpm) or bradygastrias (1–2.5 cpm).[42] Tachygastrias and bradygastrias are associated with loss of ICCs; on the other hand, a normal 3-cpm rhythm is associated with the presence of normal numbers of ICCs.[21,34] A subset of patients with gastroparesis has normal or increased 3-cpm electric activity, a discordant finding that indicates the possibility of obstructive gastroparesis secondary to pyloric stenosis or pylorospasm (**Fig. 4**).[33,43]

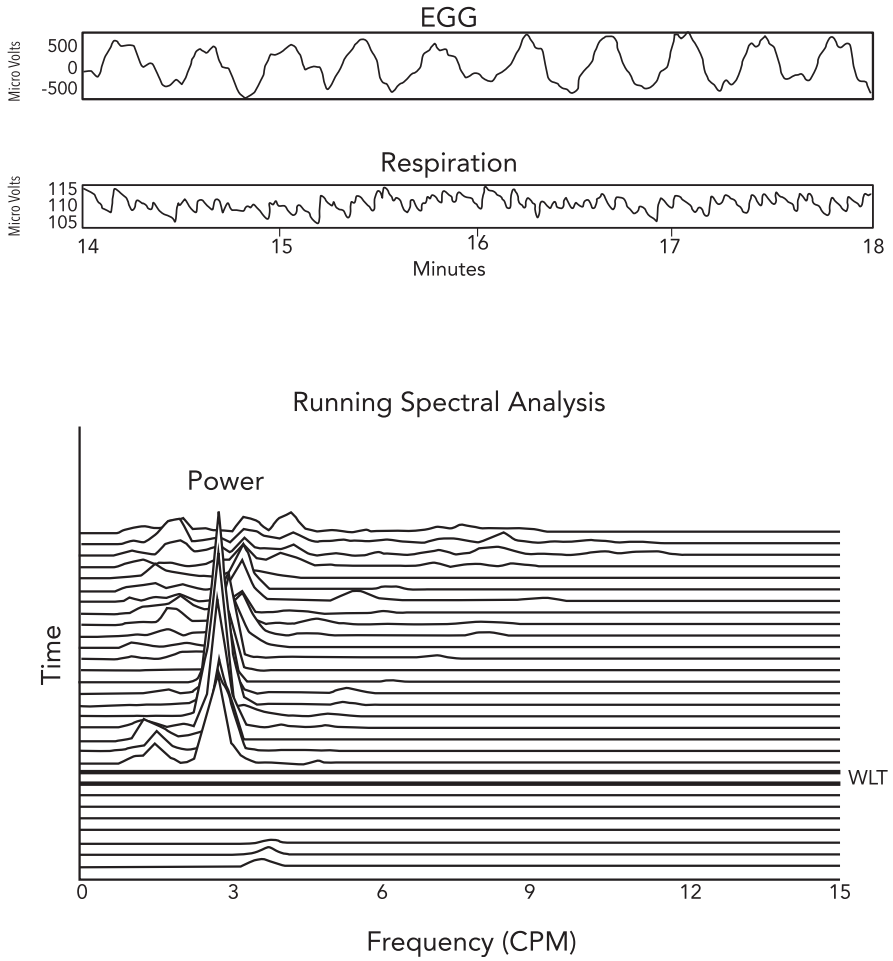

Fig. 4. Gastric myoelectric activity in diabetic gastroparesis and pyloric dysfunction. The upper tracings show an EGG rhythm strip and respiration rate signal. Time in minutes is shown. Clear 3-cpm EGG waves are present. The running spectral analysis shows frequency on the x-axis, time on the y-axis, and the power of the various frequencies in the EGG rhythm strip on the z-axis. After ingestion of the water load (WLT), most of the frequency peaks are in the normal range (2.5–3.5 cpm). This normal finding, in conjunction with delayed gastric emptying, suggests gastric outlet obstruction.

TREATMENTS

Diet for Diabetic Gastroparesis

Acute dietary management of exacerbation of symptoms associated with gastroparesis

Patients who have frequent vomiting episodes that may lead to dehydration are coached to sip small volumes (Step 1 of **Table 2**; eg, 56.6 g [2 oz] over 30–60 minutes every hour) of electrolyte-containing liquids and bouillonlike soup broths throughout the day; this may be accomplished with commercially available sports drinks. The purpose is to restore hydration with salt and water. Nausea and vomiting often improve with hydration, and the patient may then advance to steps 2 and 3, as outlined in **Table 2**.[16]

Chronic dietary management of symptoms associated with gastroparesis

One of the keys in the American Diabetes Association recommended medical nutrition therapy for patients with diabetes is an increase in consumption of complex carbohydrate-rich food items, such as salads, fresh raw fruits, and fresh raw vegetables.[44] These foods, although excellent for the diabetic patient with normal gastric emptying, are some of the most difficult foods for the weakened gastroparetic stomach to triturate and empty.

Table 2
Diet for nausea and vomiting in patients with diabetic gastroparesis

Diet	Goal	Avoid
Step 1: Sports Drinks and Bouillon		
For severe nausea and vomiting: Small volumes of salty liquids, with some caloric content to avoid volume depletion Chewable multiple vitamin each day	1000–1500 mL/d in multiple servings (eg, 12 120-mL servings over 12–14 h) Patient can sip 30–60 mL at a time to reach approximately 120 mL/h	Citrus drinks of all kinds; highly sweetened drinks
Step 2: Soups and Smoothies		
If step 1 is tolerated: Soup with noodles or rice and crackers Smoothies with low-fat dairy Peanut butter, cheese, and crackers in small amounts Caramels or other chewy confections Ingest above foods in at least 6 small-volume meals/d Chewable multiple vitamin each day	Approximately 1500 calories/d to avoid volume depletion and maintain weight (often more realistic than weight gain)	Creamy, milk-based liquids
Step 3: Starches, Chicken, Fish		
If step 2 is tolerated: Noodles, pastas, potatoes (mashed or baked), rice, baked chicken breast, fish (all easily mixed and emptied by the stomach) Ingest solids in at least 6 small-volume meals/d Chewable multiple vitamin each day	Common foods that patient finds interesting and satisfying and that provoke minimal nausea/vomiting symptoms	Fatty foods that delay gastric emptying; red meats and fresh vegetables that require considerable trituration; pulpy fibrous foods that promote formation of bezoars

Therefore, nutritious liquids, such as soups or smoothies, which require less gastric neuromuscular work to empty, are advised for patients with gastroparesis. Solid foods such as potatoes and pastas require less trituration and are emptied with less gastric neuromuscular work compared with red meats and fibrous foods. Starches are usually limited for the patient with diabetes, because of the high glycemic index, but these solid foods may be the only foods tolerated by patients with gastroparesis. The 3-step diet for patients with gastroparesis is a guide to help patients select foods that both limit postprandial GI symptoms and maintain hydration and nutrition (see **Table 2**).

These dietary changes require reeducation of the patient with diabetes and gastroparesis and their physicians. Less than 40% of diabetic patients with gastroparesis have had a dietary or nutrition consultation.[45] (See article elsewhere in this issue regarding diet counseling for patients with gastroparesis.) Consultation by a dietician who is knowledgeable in gastroparesis is invaluable. The goal is good nutrition and minimal postprandial symptoms, selecting foods appropriate for the severity of gastroparesis.

Glucose Control in the Diabetic Patient with Gastroparesis

Glucose control in the patient with diabetic gastroparesis can be difficult. The rate of gastric emptying of ingested nutrients is compromised by the severity of gastroparesis. Symptoms of nausea and vomiting affect appetite, and vomiting reduces absorption of anticipated calories. Liquid nutrients and solid foods may be retained in the stomach longer than expected by the patient or by the treating physician. Thus, postprandial hypoglycemia may develop if insulin is given in a preprandial time frame in patients with gastroparesis. A comprehensive approach to glucose control for patients with gastroparesis is reviewed later.

Patients with T1DM require insulin replacement, as do most (if not all) of the patients with T2DM and gastroparesis.[46] We do not recommend oral agents or noninsulin injectables for management of glycemia in patients with T2DM and gastroparesis. First, as a result of gastroparesis, oral medications may not empty from the stomach for hours, resulting in erratic pharmacokinetics and pharmocodynamics. The sulfonylureas are associated with hypoglycemia in these patients. The incretin mimetics slow stomach peristalsis and are associated with nausea and vomiting themselves and hence are not recommended.[47] Inhibitors of the enzyme dipeptidyl peptidase 4 depend on good insulin reserve, and most patients with T2DM and gastroparesis have had long duration of diabetes and likely have severely decreased capacity to secrete insulin. Besides the latter, no clinical trials have been published on the possible safety or efficacy of the use of these agents in patients with gastroparesis. The use of the peroxisome proliferator-activated receptor agonists in diabetes (without gastroparesis) is highly controversial and other agents (sodium-glucose cotransporter 2 inhibitors) have not been tested in these patients or may cause diarrhea and abdominal distension (disaccharidase inhibitors). Thus, we favor the use of insulin in the patient with T2DM and gastroparesis.

Basal and Meal Administration of Insulin by Injections

The current paradigm of insulin administration in the patient with T1DM or T2DM is based on the basal-bolus model, which is easier to model with pumps rather than multiple shots.[48] Basal is the amount of insulin estimated to be produced by the β cells to maintain glycemia in the postabsorptive state and hence independent of meal ingestion. Bolus is the insulin required to maintain postprandial glycemic excursion within an acceptable range. Basal insulin has to be administered via the subcutaneous route.

The boluses for meal insulin can be administered via the subcutaneous route or with the recently approved pulmonary route (via inhalation).

Basal and Meal Administration of Insulin by Pump

Insulin can be administered subcutaneously using a pump (continuous subcutaneous insulin infusion [CSII] delivery). CSII uses one type of insulin (fast acting), which is delivered continuously for the basal component. The pump can also deliver boluses of insulin in anticipation of or coincident with food ingestion.

A basic assumption (implicit and also explicit) of meal bolus is that gastric emptying of the ingested meal is completed within 4 hours and intestinal absorption of nutrients is completed within 4 to 6 hours. Thus, patients are recommended to use the new fast analogues of insulin, because they are absorbed from the subcutaneous tissue within 5 to 15 minutes after injection or delivery, peak in concentration in 1 to 2 hours, and decline in blood thereafter for a duration of 4 (kinetics) or 6 (pharmacodynamics) hours. Thus, these insulins are timed or administered to match anticipated nutrient absorption. This factor is problematic for patients with gastroparesis, because the onset and duration of the small intestinal absorption phase is critically dependent on the rate of gastric emptying, solid foods usually empty slowly, and the day-to-day variability in gastric emptying of common foods is unknown.

Sensor-Augmented Control of Glucose

Glucose sensors measure glucose continuously in the subcutaneous tissue, show the prevailing average results every 5 minutes, and allow patients to identify up or down trends and take preventive steps to avoid hypoglycemia or hyperglycemia.[49] This technique is now known as sensor-augmented management of glycemia.[50] The US Food and Drug Administration approved the first step in the evolution of technology toward an artificial pancreas, a software enhancement that allows for auto shut-off of insulin delivery by the pump if the glucose sensor detects hypoglycemia.[51]

Insulin Administration for the Patient with Gastroparesis

We recommend continuous insulin infusion for managing glycemia in patients with diabetes and gastroparesis, based not only on our experience but also on a small but positive trial that found improvement in glycemia and decreased hospitalizations.[52] If insurance coverage and patients' costs are an obstacle; then multiple shots are the next best option. In general terms, we do not favor the use of premixed insulin preparations. Monitoring of glycemia for insulin adjustment is preferably established with a system based on finger sticks augmented with continuous glucose monitoring.

Basal insulin administration

The estimated initial dose of basal insulin can be calculated using a formula of 0.2 to 0.3 units/kg/d for a patient with T2DM and 0.15 units/kg/d for someone with T1DM. Traditional adjustment of the basal is based on the glycemia measured before breakfast, which assumes postabsorptive state (some 11–14 hours after last meal). However, in patients with diabetic gastroparesis, the postabsorptive state is not so easy to define, because gastric emptying may be delayed all day, and an unknown amount of food (from accumulated breakfast, lunch, or dinner) is emptied during the night. Thus, the prebreakfast glycemia may not reflect real basal glycemia but ongoing postprandial glycemic excursions.

There are approaches to attempt to better estimate the postabsorptive glycemia in these patients. First, the patient may skip breakfast for 2 to 3 days and measure capillary glycemia every 1 to 2 hours after waking up until lunchtime to determine if

glycemia remains stable or decreases slightly, reflecting the postabsorptive state. Second, the patient may substitute dinner (or even skip it) and measure capillary glycemia frequently through the night. Third, a better approach is to use a glucose sensor to detect trends. Analysis of trends can determine if meals are being retained in the stomach until a large trigger distorts nighttime glucose excursions that extend into the next morning or if the glycemia reflects the need for more basal insulin. The identification of these trends is demanding, but patients may find it useful to avoid hypoglycemia and severe hyperglycemia.

Bolus insulin administration for meals

The challenges are more complex for the meal bolus than for the basal insulin, as discussed earlier and recently documented.[53] Instead of discrete postprandial peaks of increased and decreased of glucose level, patients with gastroparesis show almost constant hyperglycemia interrupted by unpredictable dips into normal or low glucose ranges. The day-to-day variations in food choices and in the gastric emptying rates of those foods (and thus time of nutrient absorption) are completely unknown in patients with gastroparesis. Despite these caveats, some general recommendations can be made regarding the insulin meal bolus for patients with gastroparesis.

If using injections, then we suggest:

1. Use regular insulin (rather than insulin analogues), which has a longer duration effect
2. Administer insulin after the meal (not before)
3. Give dose fractionated insulin in 2 to 3 minishots spaced within 4 to 6 hours after meal ingestion (ie, instead of a single shot of 9 units, use 3 shots of 3 units each)

If using pumps, then we suggest:

1. Start meal bolus approximately 15 minutes after meal ingestion
2. Encourage patient to use the dual-wave feature and program a small initial first wave (ie, 10% to 20%) and program second wave for the next 5 to 6 hours

We recommend that whenever feasible a glucose sensor should be used. The patterns of the 24-hour readings of preprandial and postprandial glycemia in the individual patient should be carefully examined. In our experience, patients who use CSII augmented with a glucose sensor attain better control of their glycemia compared with a regimen based on injections.

Prokinetic Agents for Gastroparesis

Drugs that increase the rate of gastric emptying (prokinetic agents) have been the goal for treatment of diabetic gastroparesis for many years. This approach has not proved to be fruitful. The only prokinetic drugs available to treat gastroparesis are metoclopramide (Reglan) and erythromycin (**Table 3**). Metoclopramide is a drug with effects on several receptors: dopamine 2 receptors, 5-HT_3 receptor antagonists, and acetylcholinesterase inhibitors.[54] Gastric emptying is increased by metoclopramide, but the drug also crosses the blood-brain barrier and causes a variety of central nervous system symptoms, ranging from nervousness to Parkinson disease to irreversible tardive dyskinesia.[55] Erythromycin is a macrolide antibiotic that stimulates motilin receptors and contractions in the corpus and antrum, which increases the rate of gastric emptying.[56]

Many drugs designed to improve the rate of gastric emptying have not improved the symptoms associated with gastroparesis. Studies of prokinetics and gastric stimulation have shown that the rate of gastric emptying does not correlate with the symptoms

Table 3
Drug and nondrug therapies used to treat upper GI symptoms in patients with diabetic gastroparesis

Therapy	Mechanisms and Sites of Action	Dosage	Adverse Effects
Prokinetic Therapy			
Macrolides			
Erythromycin	Motilin receptor agonist	125–250 mg 4 times daily	Nausea, diarrhea abdominal cramps, rash
Substituted Benzamides			
Metoclopramide	D_2 receptor antagonist; 5-HT_3-receptor antagonist; 5-HT_4 receptor agonist	5–20 mg before meals and at bedtime	Extrapyramidal symptoms, dystonic reactions, anxiety, depression, hyperprolactinemia, tardive dyskinesia
Domperidone[a]	D_2 receptor antagonist (peripheral)	10–20 mg before meals and at bedtime	Hyperprolactinemia, breast tenderness, galactorrhea
Antinauseant Therapy			
Serotonin Antagonists			
Ondansetron	5-HT_3 receptor antagonist	4–8 mg twice daily, either orally or intravenously	Headache, increased liver enzymes
Granisetron	5-HT_3 receptor antagonist	2 mg once daily or 3.1-mg patch	Headache, increased liver enzymes
Phenothiazines			
Prochlorperazine	CNS sites	5–10 mg 3 times daily	Hypotension, extrapyramidal symptoms
Antihistamines			
Promethazine	CNS, H_1 receptor antagonist	25 mg twice daily	Drowsiness
Dimenhydrinate	H_1 receptor antagonist	50 mg 4 times daily	Drowsiness
Cyclizine	H_1 receptor antagonist	50 mg 4 times daily	Drowsiness
Butyrophenones			
Droperidol	Central dopamine receptor antagonist	2.5–5 mg intravenously every 2 h	Sedation, hypotension
Antidepressants			
Mirtazapine	CNS sites	15 mg at bedtime	Weight gain
Benzodiazepines			
Lorazepam	CNS sites	0.5–1 mg 4 times daily	Drowsiness, lightheadedness
Alprazolam	CNS sites	0.25–0.5 mg 3 times daily	Drowsiness, lightheadedness
Dronabinol	CNS	5–10 mg 2 times daily	Sedation

(*continued on next page*)

Table 3
(*continued*)

Therapy	Mechanisms and Sites of Action	Dosage	Adverse Effects
Electric Therapies			
Gastric electric stimulation	?Vagal afferents	12 cpm, 330 μs, 5 mÅ	Pocket infection
Gastric pacing	Control dysrhythmias, improve gastric emptying	3 cpm, 300 μs, 4 mÅ	Pocket infection
Endoscopic Therapies			
Botulinum toxin A injection into pylorus	Relax pyloric muscle	25–50 units per quadrant of pylorus	None
Balloon dilation of pylorus	Stretch pyloric muscle	20-mm balloon, 2 min	None
Radiofrequency ablation at LES	Improve gastric emptying and gastric myoelectric activity	NA	Transient dysphagia
Diet Therapies			
Gastroparesis diet	Diet based on gastric emptying physiology	See Table 2	None
High-protein drinks	Decreases gastric dysrhythmias	Unknown	None
Gastrostomy	Venting paretic stomach	As needed	
Jejunostomy	Enteral nutritional support	As needed	
Total parenteral nutrition	Bypass paretic stomach	As needed	Sepsis, thrombosis of central veins

Abbreviations: ?, questionably; 5-HT, 5-hydroxytryptamine; CNS, central nervous system; D_2, dopamine 2; H_1, histamine 1; LES, lower esophageal sphincter; NA, not applicable.
[a] Compassionate clearance use only.

associated with gastroparesis.[57,58] Domperidone is a dopamine 2 receptor agonist that does not cross the blood-brain barrier, improves nausea and gastric dysrhythmias, and may improve the rate of gastric emptying in some patients with diabetic gastroparesis.[31] Pathophysiologic mechanisms, such as gastric dysrhythmias, gastric relaxation (or stretch), or pyloric dysfunction, may be more relevant to the postprandial nausea, early satiety, prolonged fullness, and discomfort than the rate of gastric emptying.

Antinauseant Drugs

Patients with diabetic gastroparesis often have daily nausea and vomiting. The quality of life during these times is poor. These symptoms may lead to dehydration, which requires frequent emergency room visits or hospitalizations. Table 3 lists several drugs that are used empirically to treat nausea for patients with gastroparesis. There is no way to predict which medication will decrease nausea in an individual patient. Each drug may be tried for 4 to 8 weeks to see if nausea and vomiting improve. These drugs have not been specifically approved for use in patients who have symptoms associated with diabetic gastroparesis. In unremitting nausea and vomiting, normal weight cannot be maintained. A jejunostomy tube may be required for enteral feedings if small bowel motility is normal. Total parenteral nutrition may be needed in a few patients to support nutrition.

Pyloric Therapies

An important subset of patients with gastroparesis has normal or more than normal 3-cpm (EGG) signals, as shown in **Fig. 4**. In these patients, pyloric dysfunction secondary to pyloric stenosis or pylorospasm should be suspected, because most patients with gastroparesis have gastric dysrhythmias rather than normal electric rhythm.[33] Fixed mechanical obstruction at the pylorus or postbulbar areas that may require surgery must be excluded. If no mechanical obstruction is present, then injection of botulinum toxin A (BTA) into the pylorus or balloon dilation of the pylorus often relieves the symptoms associated with gastroparesis.[43,59] Pyloroplasty improves gastric emptying and symptoms in highly selected patients with gastroparesis and normal 3-cpm EGG signals who have previously responded well to BTA or dilation.[60]

Gastric Electric Stimulation

Gastric electric stimulation (GES) refers to therapeutic stimulation of the stomach with electric pulses. The stomach is typically stimulated at 12 cpm, 5 mA, 330 microseconds, and 50 Hz to decrease symptoms associated with gastroparesis.[61] The incidence of vomiting in patients with diabetic gastroparesis is reduced with GES, with improvement in symptoms and emptying at 1 year.[61] The mechanisms of action of GES are not known, but increased fundic accommodation or vagal afferent nerve stimulation with central nervous system effects have been suggested. GES may help patients who have failed diet and drug therapies.

Future Directions

The number of patients with diabetes and, thus, the number of patients with gastroparesis, is increasing dramatically in the United States and around the world. Gastroparesis should be suspected in diabetic patients with glucose excursions that are difficult to control and early satiety, nausea and vomiting, and abdominal discomfort. Gastric emptying and gastric electric rhythm tests are needed to confirm gastroparesis and define the obstructive subgroup of gastroparesis. Novel approaches are needed for the treatment of gastric dysrhythmias and abnormalities of gastric compliance and for GES paradigms. Patients with gastroparesis secondary to pyloric dysfunction should be identified and treated with pyloric therapies.

The insightful and careful management of diet therapy and administration of insulin, based on detailed assessment of postprandial glucose excursions in patients with diabetic gastroparesis, are critical areas on which to focus. Understanding the rate of gastric emptying of nutrients and subsequent glucose excursions is key to better management of postprandial glucose and symptoms in patients with diabetic gastroparesis. Continuous glucose monitoring with insulin pump therapy, progress toward the artificial pancreas, and teams of dedicated gastroenterologists, diabetologists, and dieticians are needed to improve glycemia and symptoms for patients with diabetic gastroparesis.

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