Diabetic Gastroparesis: Evaluation and Management

Adewale B. Ajumobi, MD, MBA
Ronald A. Griffin, MD

Diabetic gastroparesis (DGP) is a clinical condition that affects many patients with diabetes mellitus. It is characterized by delayed gastric emptying and associated upper gastrointestinal (GI) symptoms in the absence of mechanical obstruction.[1] Delayed gastric emptying in diabetic patients may result in poor glycemic control, poor nutrition, and dehydration, which in turn may lead to poor quality of life, frequent hospitalizations, and loss of productivity. However, diagnosing DGP can be quite challenging, given the nonspecific nature of its symptoms and the associated large differential diagnosis. Likewise, managing DGP is challenging because the diagnosis is often made late, as many medical providers do not recognize DGP prior to the development of complications and refraction to therapy. In addition, randomized controlled studies of therapies currently used to treat DGP are lacking. However, new approaches to diagnosis and management represent a growing area of interest and hope for the many patients with DGP. This article provides a concise and pragmatic approach to the diagnosis and management of DGP.

TAKE HOME POINTS

- Diabetic gastroparesis (DGP) is a clinical condition characterized by delayed gastric emptying with associated upper gastrointestinal symptoms that occurs in the absence of mechanical obstruction in a diabetic patient.
- DGP is more common in women, patients with type 1 diabetes mellitus, or those with long-standing type 2 diabetes mellitus.
- Only fullness and bloating have some predictive value for delayed gastric emptying.
- Gastric emptying of a solid meal by scintigraphy is considered the gold standard for diagnosis, although there is lack of standardization in its technique and sensitivity varies.
- For patients with DGP, the goal of management is to maintain adequate glucose control, control upper gastrointestinal symptoms, ensure adequate hydration and nutrition, improve gastric emptying, and prevent complications.

DEFINITION

There is no clear consensus for the definition of DGP. The terms *diabetic gastroparesis* and *diabetic gastropathy* have been used interchangeably in the past. Bell et al[2] described DGP as neuropathy occurring in the GI system in people with diabetes. Talley[3] used the term *diabetic gastropathy* to refer to a clinical syndrome of upper GI tract symptoms suggestive of an upper motility disturbance in patients with diabetes whether or not there is delayed gastric emptying. However, most agree that delayed gastric emptying in DGP occurs in the absence of mechanical obstruction.[4–6] The American Gastroenterological Association (AGA) guidelines on the diagnosis and treatment of gastroparesis state that the diagnosis of gastroparesis should be based on the presence of appropriate symptoms and signs, delayed gastric emptying, and the absence of an obstructing structural lesion in the stomach or small intestine.[1] For the purpose of this review, DGP is defined as gastroparesis that occurs in a patient with diabetes mellitus, with gastroparesis being defined according to the AGA guidelines.

PREVALENCE AND CHARACTERISTICS OF PATIENTS

DGP affects 20% to 50% of the diabetic population, particularly those with type 1 diabetes mellitus or those with long-standing (≥ 10 yr) type 2 diabetes mellitus. DGP is usually associated with retinopathy, neuropathy and nephropathy as well as poor glycemic control.[7–10]

Dr. Ajumobi is an internal medicine resident, Loma Linda University Medical Center, Loma Linda, CA. Dr. Griffin is an assistant professor of medicine and chief, Gastroenterology Section, Jerry L. Pettis Memorial Veterans Affairs Medical Center, Loma Linda, CA.

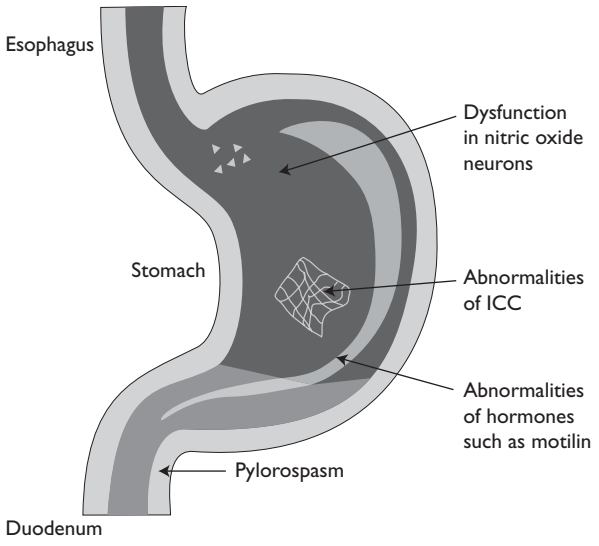

Figure 1. Pathogenesis of diabetic gastroparesis. Areas of the stomach affected by various etiologies of delayed gastric emptying are indicated (*arrows*). ICC = interstitial cells of Cajal.

The prevalence of DGP appears to be higher in women than in men for unknown reasons.[2,11,12] In a 1998 study, 1476 patients whose medical records indicated that they were hospitalized for DGP in North Carolina were mostly women (65.8%), aged 45 years or older (54.5%), had an average length of stay of 5.3 days per admission, and had Medicare as the primary payer (52.1%).[2] Another study on gastroparesis revealed similar results: 82% of the 146 patients with gastroparesis referred for consultation were women, with a mean age of 45 years.[12]

PATHOPHYSIOLOGY AND PATHOGENESIS

The precise cause of delayed gastric emptying is unknown. Normal gastric emptying results from the integration of tonic contractions of the fundus, phasic contractions of the antrum, and the inhibitory forces of pyloric and duodenal contractions,[13] which requires complex interactions between smooth muscle, enteric and autonomic nerves, and specialized pacemaker cells known as the interstitial cells of Cajal (ICC; **Figure 1**).[14] Neurotransmitters and neuroendocrine hormones also have roles in gastric motility. Nitric oxide (NO) is an important inhibitory nonadrenergic, noncholinergic neurotransmitter of the gut involved in gastric contractility. NO regulates the muscle tone of the lower esophageal sphincter and pylorus, the accommodation reflex of the fundus, and the peristaltic reflex of the intestine.[15,16] Dysfunction of NO neurons in the myenteric plexus may be responsible for many GI diseases, including DGP. Corticotrophin-releasing hormone has been shown to decrease gastric motility.[17] Normal gastric myoelectrical activity is initiated by the ICC, located in the muscular wall of the gastric antrum and corpus, at a rate of 3 cycles/min.[18] A disturbance in this pattern can lead to gastroparesis.[19,20] Other factors that may affect gastric emptying include autonomic neuropathy, enteric neuropathy, abnormalities of ICC, sudden fluctuations in blood glucose, and psychosomatic factors.[21–23] Gastric emptying is slower during hyperglycemia and accelerated during hypoglycemia.[24–26] Electrolyte abnormalities (eg, hypokalemia, hypomagnesemia) and GI hormones (eg, motilin, gastrin) may also have roles in the pathogenesis of DGP.[27,28]

CLINICAL FEATURES

The most common symptoms of DGP are nausea, vomiting, early satiety, postprandial fullness, belching, abdominal pains, bloating, anorexia, and weight loss,[12,29] which may lead to frequent hospitalizations and severe impairments in health-related quality of life.[30] Of these symptoms, only fullness and bloating seem to have some predictive value for delayed emptying.[11,31] On physical examination, neuropathy, abdominal distention, succession splash, foul breath, and orthostatic and postprandial hypotension may be present, but these findings are nonspecific for gastroparesis.[13] The nonspecific nature of these clinical features makes for a large differential diagnosis, which includes endocrine and metabolic disorders; autoimmune and collagen vascular diseases; central nervous system (CNS) lesions; and GI syndromes (**Table 1**).[12,13,32]

Revicki et al[33] devised a questionnaire called the Gastroparesis Cardinal Symptom Index (GCSI) to assess the severity of patients' symptoms. It consists of 3 subscales: postprandial fullness/early satiety, nausea/vomiting, and bloating. Patients are asked to rank symptoms (nausea, retching, vomiting, stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, loss of appetite, bloating, and the abdomen appearing visibly larger) using a scale of 0 to 5, with 0 being none and 5 being very severe. The GCSI can be used to assess severity of illness and response to treatment. However, the severity of symptoms does not always correlate with the objective evidence of the rate of gastric emptying.[11]

DIAGNOSTIC WORK-UP

DGP is diagnosed by the presence of upper GI symptoms suggestive of delayed gastric emptying in a diabetic patient, exclusion of mechanical obstruction that could cause upper GI symptoms, and demonstration of delayed gastric emptying (**Table 2**). Gastric and intestinal obstruc-

Table 1. Differential Diagnosis of Diabetic Gastroparesis

Autoimmune disorders	Gastrointestinal syndromes
Dermatomyositis	Achalasia
Myotonic dystrophy	Atrophic gastritis
Polymyositis	Functional dyspepsia
Progressive systemic sclerosis	Gastroesophageal reflux disorder
Raynaud's disease	Hiatus hernia
Scleroderma	Peptic strictures
Systemic lupus erythematosus	Pharyngeal pouch
Behavioral disorders	Pseudo-obstruction
Anorexia nervosa	Infections
Bulimia	Gastroenteritis
Psychogenic vomiting	HIV
Central nervous system disorders	Viral illnesses
Brain lesions	Medications
Migraine	Anticholinergic drugs
Parkinson's disease	Calcium channel blockers
Spinal cord lesion	Opioid analgesics
Electrolyte disorders	Tricyclic antidepressants
Hyperglycemia	Postsurgical complications
Hypokalemia	Adhesions
Hypomagnesemia	Gastrectomy
Endocrine disorders	Ileus
Addison's disease	Strictures
Hyperthyroidism	Vagotomy
Hypopituitarism	Others
Hypothyroidism	Idiopathic
	Liver disease
	Porphyria
	Postirradiation

Data from Soykan et al,[12] Park and Camilleri,[13] and Horowitz et al.[32]

tion caused by an intraabdominal mass may be excluded using abdominal radiography, computed tomography, and magnetic resonance imaging. An upper endoscopy is necessary to exclude the presence of stricture, mass, or ulcer. Tests that may be necessary to exclude infectious, metabolic, and immunologic causes of upper GI symptoms include a complete blood count; comprehensive metabolic panel consisting of electrolytes and liver function test; urinalysis; erythrocyte sedimentation rate; and assays for thyroid-stimulating hormone, rheumatoid factor, and antinuclear antibody. After excluding other potential etiologies of symptoms and obstruction with endoscopy and abdominal imaging, DGP is diagnosed by demonstrating delayed gastric emptying.[13] These studies are discussed in the following section.

Table 2. Diagnostic Tools for Diabetic Gastroparesis

Presence of symptoms	Abdominal imaging
Abdominal bloating*	Plain radiograph
Abdominal pain	Computed tomography scans
Anorexia	Magnetic resonance imaging
Early satiety	Endoscopy
Nausea	Esophagoduodenostomy
Postprandial fullness*	Gastric emptying studies
Vomiting	Scintigraphy
Weight loss	Breath tests
Laboratory studies	Ultrasound
Antinuclear antibody	Manometry
Complete blood count	Electrogastrography
Complete metabolic panel	
Erythrocyte sedimentation rate	
Rheumatoid factor	
Thyroid-stimulating hormone	
Urinalysis	

*Only abdominal bloating and postprandial fullness have predictive value for delayed gastric emptying.[11,31]

Gastric Emptying Studies

Different types of gastric emptying studies include scintigraphy with images taken at 1, 2, and 4 hours;[34] breath tests;[35–38] and ultrasonographic measurements.[39] Gastric emptying of a solid-phase meal by scintigraphy is considered the best accepted technique for diagnosing delayed gastric emptying because it quantifies the emptying of a physiologic caloric meal that can assess the motor function of the stomach.[13,34] The technique involves incorporating a radioisotope tracer in a standard meal and tracking its passage through the stomach using a gamma camera (**Figure 2**).[40] For a test that is considered the gold standard, it should be noted that there is lack of standardization of scintigraphic techniques, with substantial variations between different centers, and that the correlation between symptoms of DGP and rates of gastric emptying is poor.[32,34]

Breath hydrogen measurement 12 hours after the ingestion of a test meal containing potato starch and lactulose correlates with upper GI transit time and has been suggested as a screening tool for gastroparesis before using more expensive and definitive tests.[35] The breath test involves the ingestion of a standard meal containing carbon radioisotope–labeled octanoate (^{13}C-octanoate), a medium-chain triglyceride. After ingestion and stomach emptying, ^{13}C-octanoate is rapidly absorbed in the small intestine and metabolized to $^{13}CO_2$, which is expelled from the lungs during respiration. The rate at

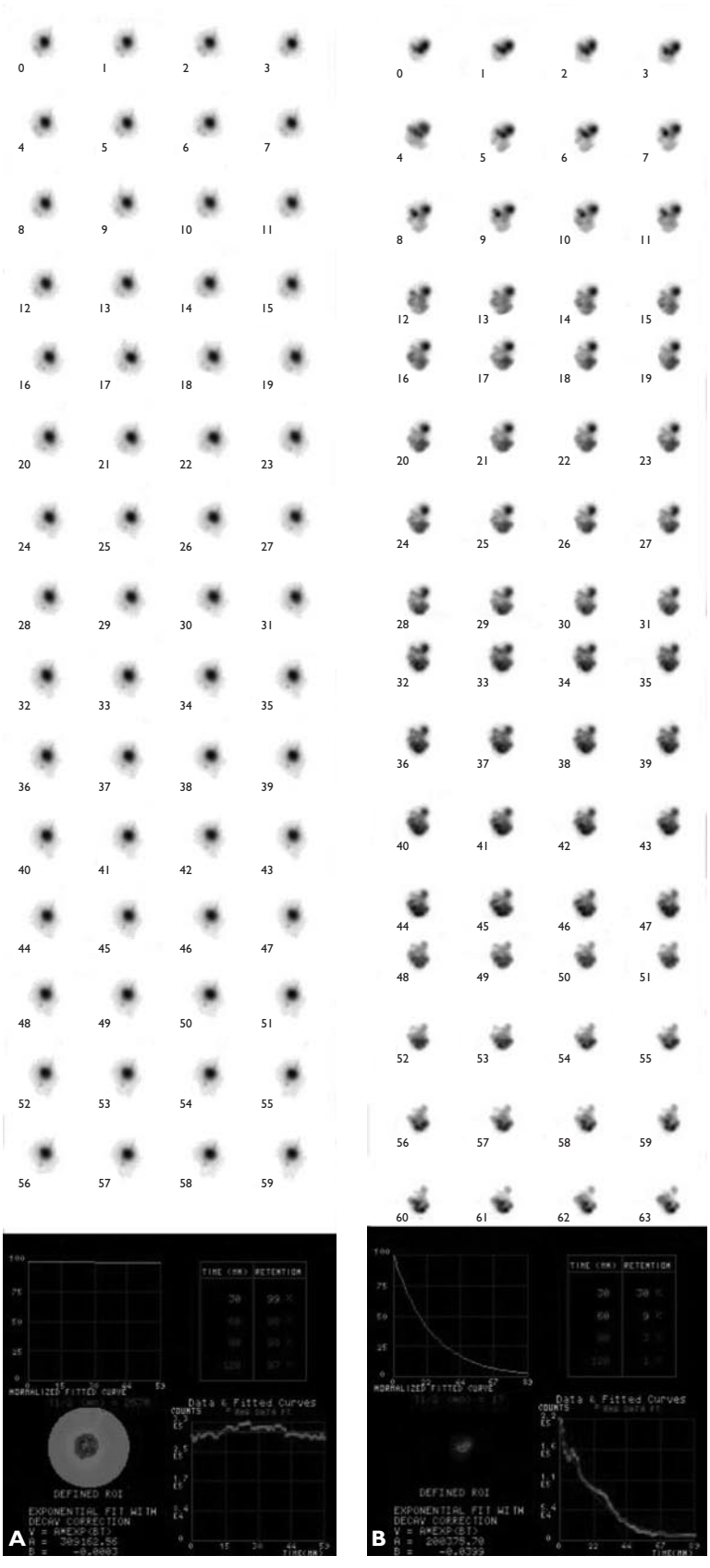

Figure 2. Results of normal (**A**) and abnormal (**B**) gastric emptying scintigraphy studies from 2 patients. Patients were fed a meal containing 1.1 mCi Tc-99m colloid. Serial 1-minute images were obtained afterwards. At 60 minutes, gastric retention is 98% for patient 1 (A) and 9% for patient 2 (B). Normal retention is 50% or less.

which $^{13}CO_2$ is detected in breath corresponds to gastric emptying rate, and the results correlate strongly with scintigraphy results.[36] However, this test assumes normal small bowel, pancreas, liver, and pulmonary function, which limits its use. Studies using breath tests in patients with diabetes are limited, and additional validation in patients with gastroparesis is required before their widespread use can be advocated.[32]

Ultrasonographic measurements of changes in the antral region of the stomach after ingestion of a liquid meal correlate closely with gastric emptying rates.[39] Ultrasound imaging of liquid gastric emptying is experimental and currently is not used in the clinical setting.

MANAGEMENT

The goal of managing patients with DGP is to maintain adequate glycemic control, control upper GI symptoms, ensure adequate hydration and nutrition, improve gastric emptying, and prevent complications such as dehydration, malnutrition, and frequent hospitalizations (**Table 3** and **Figure 3**). Medical management with prokinetic drugs, antiemetic agents, and occasionally analgesics may be required to control symptoms of DGP. Narcotics should be avoided in patients with DGP, as these agents (eg, morphine) can delay gastric emptying.[32] Novel nonpharmacologic approaches to managing refractory DGP include pyloric injection of botulinum toxin[41] and gastric electrical stimulation (GES).[42–44] Some of the symptoms and complications of severe, refractory DGP can be improved surgically through pyloroplasty and antrectomy.[5,45]

Glycemic Control

Glucose levels should be maintained below 180 mg/dL to avoid inhibiting gastric myoelectric control and motility.[42] Maintaining glycemic control is also important because hyperglycemia inhibits the action of prokinetic drugs such as erythromycin.[46] However, delayed gastric emptying of stomach contents, especially tablets and capsules which are not easily degraded by the stomach, may potentially lead to fluctuations in the serum concentrations of orally administered drugs.[32] This may be particularly important when a rapid onset of drug effect is desirable, as is the case with some oral hypoglycemic drugs.[32] Oral hyperglycemic agents, however, can be used in patients with type 2 diabetes and mild gastroparesis. Therefore, DGP may be an indication for insulin-pump therapy in patients with type 1 diabetes mellitus.[47]

Dietary Therapy

Adequate hydration and nutrition are essential, and the enteral route is preferred. Gastric emptying and the rate at which calories are delivered to the duodenum are functions of the caloric density.[48] Carbohydrates and substances with high osmolarity increase gastric emptying, whereas medium-chain triglycerides do not delay gastric emptying to the same extent as common fat.[49] Therefore, meals containing fats or that have a high-fiber content should be avoided. Instead, small meals at frequent intervals that consist of low-fat and complex carbohydrates are advised, and high-calorie liquid supplements may be required.[4] Parenteral nutrition may be needed to supply dietary requirements temporarily in severe cases. Enteral nutrition via jejunostomy may be indicated in patients who have failed medical therapy and who have severe malnutrition, nausea, and vomiting necessitating frequent hospitalization.[5] Gastrostomy can be used for gastric decompression.[50] Feeding gastrostomy is not advised because it does not bypass the primary dysmotility problem of gastroparesis experienced by these patients.

Table 3. Treatment Goals and Management Options for Patients with Diabetic Gastroparesis

Glucose control
Oral hypoglycemic agents*
Insulin therapy
Upper gastrointestinal symptom control
Prokinetic drugs
Antiemetic agents
Analgesic agents
Botulinum injection
Gastric electrical stimulation
Adequate nutrition
Small frequent meals
Liquid supplements
Enteral feeding
Percutaneous endoscopic jejunostomy
Total parenteral nutrition
Improve gastric emptying
Glucose control
Prokinetic drugs
Gastric surgery

*These drugs may not be suitable for use in patients with diabetic gastroparesis, as delayed gastric emptying may lead to fluctuations of orally administered drugs.[32]

Prokinetic Drugs

Several prokinetic drugs have been used successfully in managing the symptoms of gastroparesis. These agents include metoclopramide, domperidone, erythromycin, and cisapride.[3] Other agents that have been

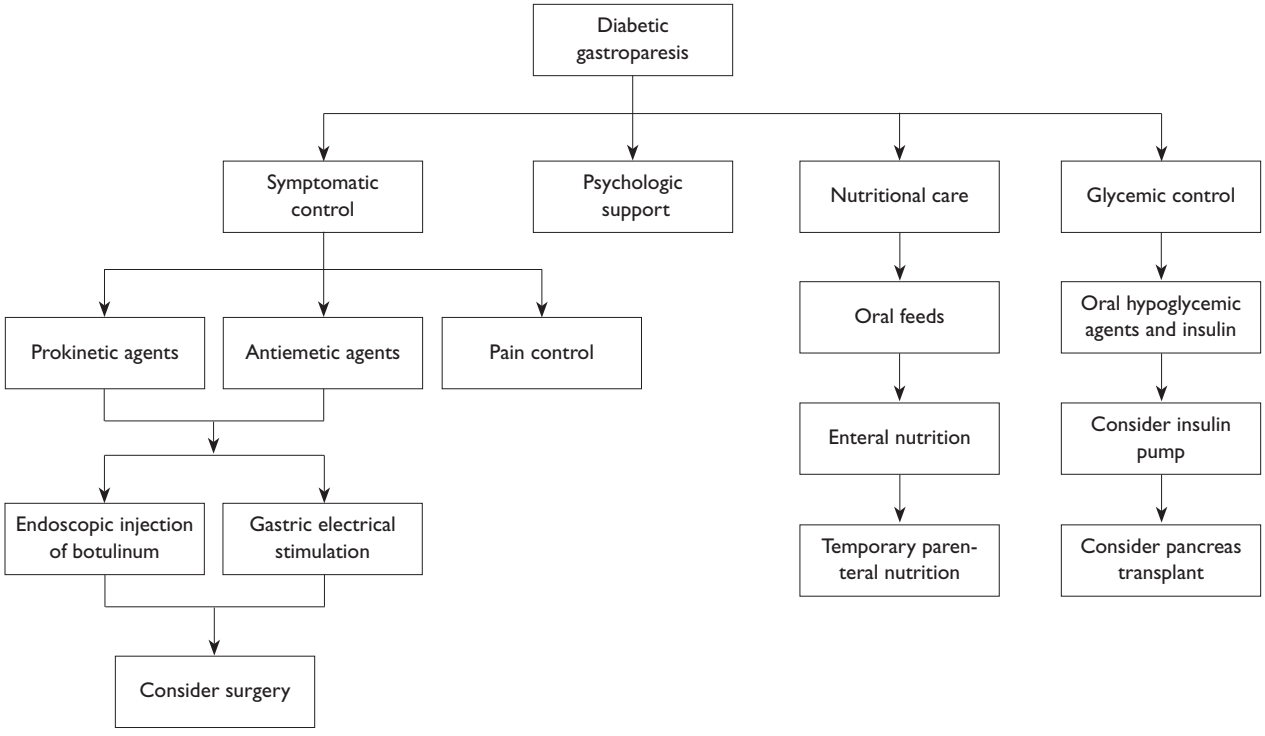

Figure 3. Treatment algorithm for diabetic gastroparesis.

tried include tegaserod, sildenafil, novel experimental motilides (eg, ABT-229 and GM-611 [mitemcinal], synthetic ghrelin, bethanechol, levosulpiride [unavailable in the United States]), and clonidine.

Metoclopramide is one of the oldest and most commonly used agents in the management of DGP. It is both a central and a peripheral dopamine-2 (D2)-receptor antagonist with antiemetic and prokinetic actions that increases antral contractions and coordinates antral-duodenal motility.[51] Metoclopramide can be administered parenterally when symptoms are severe; however, its use is limited by CNS side effects in as many as 40% of patients.[52] Restricting the total daily dose to 40 mg/day and using the liquid formulation to improve the pharmacokinetics of the drug tend to reduce the CNS side effects and provide some clinical efficacy.[13]

Domperidone is another D2-receptor antagonist with prokinetic actions. Unlike metoclopramide, it does not cross the blood-brain barrier and therefore has fewer CNS side effects.[53] Nonetheless, it can cause gynecomastia in men and breast enlargement and lactation in women due to treatment-related increases in prolactin levels. At doses between 10 and 30 mg taken orally a half hour before meals and at bedtime, domperidone has been shown to reduce GI symptoms and hospitalizations from gastroparesis, accelerate gastric emptying, and enhance quality of life.[54] This drug is not approved for use in the United States but can be obtained through the US Food and Drug Administration (FDA) investigational new drug process.

Erythromycin appears to be effective and well tolerated in DGP.[55] It stimulates motilin receptors and the cholinergic pathways[56] and increases gastric emptying in a dose-response fashion; 3 mg/kg of erythromycin administered intravenously seems to be the most effective dose.[57] Oral erythromycin between 50 and 100 mg taken 3 times daily in combination with a low-bulk diet was effective in controlling symptoms of gastroparesis in 83% of patients.[58] However, long-term improvement was less obvious, as only 67% experienced some improvement, which may be as a result of the known tachyphylaxis to erythromycin.[58] Erythromycin can also cause abdominal cramps and pain and has several drug interactions that can result in torsades de pointes.[59] Experimentally, transdermal passage of erythromycin has been demonstrated; however, therapeutic efficacy of patches has not been studied.[60] ABT-229, an analogue of erythromycin, is being studied and has been shown to be 7 to 40 times more powerful than erythromycin and may potentially have fewer side effects.[61]

Cisapride is a potent prokinetic drug that accelerates gastric emptying of solids and improves dyspeptic

symptoms in DGP.[62] It stimulates the stomach via 5-hydroxytryptamine (5-HT_4) receptors. This drug has been removed from the market due to a high rate of potentially fatal cardiac arrhythmias.

Antiemetic Therapy

There is limited literature on the use of antiemetic agents in the management of DGP. Prokinetic drugs such as metoclopramide and domperidone have antiemetic properties and are usually first-line agents for controlling the symptoms of DGP. Use of antiemetic medications without prokinetic activity may be beneficial in cases in which prokinetic drug therapy is ineffective or produces unacceptable toxicity.[63] In refractory cases of gastroparesis, both prokinetic and antiemetic drugs are often used in combination to control symptoms.

Endoscopic Therapy with Botulinum Injection

Pylorospasm is thought to contribute to the development of DGP.[21] Botulinum toxin, a potent inhibitor of neuromuscular transmission, has been reported to be efficacious in the management of gastroparesis.[41,64,65] In a study that involved 8 patients, mean symptom scores declined from 27 to 12.1, 4 patients noticed an increase in insulin use greater than 5 units/day, and 6 of 7 patients gained weight.[41] In another study, gastric emptying improved with botulinum injection, but symptoms were not different between the treatment and placebo groups at the end of the study.[64] Bromer et al[65] reported that 43% of patients had a response to botulinum treatment that lasted a mean of approximately 5 months. The limited clinical trials and inconsistent results with the use of botulinum toxin do not support its widespread use in the management of DGP at this time.

Gastric Electrical Stimulation

GES improves nausea, vomiting, quality of life, and nutritional status in patients with refractory DGP.[42,43] Three principal methods of GES have been described: gastric electrical pacing, high-frequency GES, and sequential neural electrical stimulation. Based on the number of stimulation electrodes, GES can be classified into single-channel GES and multichannel GES. Gastric pacing by high-energy, low-frequency GES (long pulses) attempts to restore the regular slow wave rhythm of 3 cycles/min of normal gastric myoelectrical activity and has been found to improve symptoms and gastric emptying;[66] however, it appears unsatisfactory in reestablishing efficient gastric contractions. Continuous low-energy, high-frequency stimulation (short pulses) via electrodes in the muscle wall of the antrum connect\ed to a neurostimulator in an abdominal wall pocket has been shown to significantly reduce symptoms and improve quality of life for up to 1 year.[42–44] This device also fails to achieve normal gastric emptying. The third method appears promising and involves microprocessor-controlled electrical activation of a series of annular electrodes that encircle the distal two thirds of the stomach.[67] Its effect is derived from a combination of 2 signals: continuous short pulses with a high frequency and a control signal to turn the pulses on and off. It should be noted that only high-frequency GES (short pulses) and sequential neural electrical stimulation GES are commercially available, and only high-frequency GES (Enterra [Medtronics, Minneapolis, MN], which has been approved by the FDA through a humanitarian device exemption) has been commercially applied for management of gastroparesis.

Surgical Management

Medical management is effective for managing symptoms in most cases of DGP. However, a small number of patients will have gastroparesis that is refractory to medical management.[68] There are limited controlled data in the surgical management of patients with DGP, and surgery is only used as a last resort due to the profound complications associated with these procedures.[5] The main role of surgery is in palliating symptoms, decompressing the stomach, providing access for enteral nutrition (*see* "Dietary Therapy"), and enhancing gastric emptying.[5,45,50,68] Major gastric resections, such as partial or total gastrectomies with Roux-en-Y reconstructions, could be helpful in palliating symptoms such as vomiting in patients with intractable DGP who have poor life expectancy.[69]

CONCLUSION

Because DGP can be a disabling condition, efforts should be made to recognize the condition early and treat it appropriately. Management of DGP consists of maintaining adequate glycemic control, hydration, and nutrition, and controlling symptoms of delayed gastric emptying. Effectively managing patients with DGP often requires an interdisciplinary approach with the involvement of a team of specialists, including the primary care physician, gastroenterologist, endocrinologist, dietician, psychologist, interventional radiologist, and surgeon.[63] However, few medications and interventions used to manage the symptoms of gastroparesis have been thoroughly studied. Therefore, well-designed randomized controlled trials are needed to determine the optimal management of this condition. **HP**

Corresponding author: Adewale B. Ajumobi, MD, MBA, Loma Linda University Medical Center, 11234 Anderson Street, Room 1556, Loma Linda, CA 92354; adewaleajums@yahoo.com.

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