Pathophysiology and Management of Diabetic Gastropathy

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I. INTRODUCTION

Diabetes mellitus, with an estimated prevalence of 3 percent to 10 percent of the population, is the fourth leading cause of death in the U.S. This disease complex can affect almost every organ system, including the gastrointestinal tract. Pathophysiologic changes involving the gut can be related to either acute hyperglycemia or chronic changes resulting from neuropathic or myopathic processes. This chapter will focus on the pathophysiology, diagnosis, and management of diabetic gastropathy.

The clinical presentation of diabetic gastropathy is not specific and may overlap with both structural disorders and functional dyspepsia. Nausea, vomiting, bloating, early satiety, postprandial fullness, and upper-abdominal discomfort are the most common presenting symptoms. Abdominal pain, which is likely due to gastric distension or retension, may be an important component of the overall symptomatology. Interestingly, symptoms do not correlate well with gastric-emptying rate; therefore, an improvement in the gastric-emptying rate does not always result in symptomatic improvement, or vice versa.

II. PHYSIOLOGICAL BASIS FOR GASTRIC SMOOTH-MUSCLE ACTIVITY

Gastrointestinal-contractile activity is regulated by smooth-muscle electromechanical properties. Gastric smooth muscle, similar to other smooth muscle, is characterized by a voltage-tension curve. In this relationship, depolarization of smooth-muscle cell membrane results in increased smooth-muscle tonic contraction. Slow waves, the basic gastric smooth-muscle electrical event, are periodic, regular depolarizations from the cell’s resting membrane potential. A slow wave follows a set sequence during changes in resting membrane potential: initially, a rapid upstroke depolarization, a partial repolarization, a sustained plateau potential, and then complete repolarization to the resting membrane potential. This chain of events is largely the result of activation and deactivation of calcium channels and calcium-dependent potassium channels. Only slow waves exceeding a threshold depolarization will result in an action potential leading to smooth-muscle contraction.

The basic rhythmic activity of gastric smooth-muscle cells is thought to originate from the interstitial cells of Cajal, which are located in the greater curvature at the junction of proximal and distal stomach. Interstitial cells of Cajal are found throughout the gastrointestinal tract. Both extrinsic nerves innervating the stomach and the intrinsic gastric nervous system are in constant interaction with the interstitial cells of Cajal, and thus may modulate relaxation and contraction of gastric smooth muscle. The regional variation of the relationship between electrical activity and tension development is the result of a proximal-to-distal gradient in cell resting-membrane potentials from –48 mV in the fundus to –75 mV in the pylorus. This difference is likely related to differences in the density of calcium-dependent potassium channels, since a chemical voltage clamp involving different concentrations of potassium chloride can change both the resting-membrane potential and the tonic contraction of smooth muscle obtained from different regions of the stomach.
relationship has been suggested to be the electrical basis for contraction and relaxation in canine gastric smooth muscle. This relationship may aid in understanding the varying mechanical functions of different gastric compartments, as well as the propagation of slow waves in an organized fashion from the proximal body to the pylorus.

In human stomach, gastric pacemakers generate rhythmic depolarizations at a frequency of three cycles per minute, resulting in circular muscle contractions. Abnormal rhythms of gastric myoelectrical activity, termed gastric dysrhythmias, originate from abnormal or ectopic gastric pacemakers. A suggested classification system includes a definition for tachygastria (> 6 cycles/min), bradygastria (< 3 cycles/min), bradytachyarrythmia, or absent activity.

### III. PATHOPHYSIOLOGY OF DIABETIC GASTROPATHY

In this chapter, we will address the pathophysiology, symptoms, and treatment options in patients with diabetic gastropathy. Potential pathophysiological abnormalities include: gastric dysrhythmias, antral hypomotility, pylorospasm, and gastroparesis.

There are several potential mechanisms to explain altered gastric physiology in patients with diabetes mellitus (Table 23.1). Almost 50 percent of diabetic patients have some form of neuropathy, such as peripheral, autonomic, proximal, or focal neuropathy, but gastrointestinal symptoms are not seen in all of these patients. Although the pathophysiology of diabetic neuropathy has not been clearly determined, the highest rates of diabetic neuropathy have been seen among patients with long-standing disease, especially in those patients with poor glycemic control. Although autonomic dysfunction, particularly vagal neuropathy, has been traditionally regarded as the likely origin for diabetic gastropathy, morphologic abnormalities of the vagus nerve or gastric myenteric plexus in patients with diabetes mellitus have not been routinely identified using conventional histology. Neuropathies, such as axonopathy in sympathetic nerves and ultrastructural and morphometric changes in parasympathetic nerves, have been described in animal models of diabetes mellitus. A decrease in the interstitial cells of Cajal, decreased inhibitory neurotransmitter systems containing neuronal nitric-oxide synthase, vasoactive intestinal peptide, or tyrosine hydroxylase immunopositive nerve fibers, and

<table>
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<th>TABLE 23.1</th>
<th>Potential Pathophysiologic Mechanisms for Diabetic Gastropathy</th>
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<td>1. Neuropathy</td>
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<td>2. Myopathy</td>
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<td>3. Glycemic Control</td>
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increased levels of excitatory neurochemical and substance P have been observed in the gut of long-standing diabetic patients. Further research examining the neuropathic aspects of diabetic gastropathy is needed to better define this potential pathophysiological feature.

There is a complex relationship between glycemic control and upper-gastrointestinal function. Postprandial glucose levels both determine and are determined by the delivery rate of nutrients from the stomach to the small intestine. Studies in both healthy individuals and diabetic individuals have revealed that hyperglycemia can affect gastrointestinal function (Table 23.2). It has been previously shown that hyperglycemia can induce: 1) delayed gastric emptying; 2) rapid gastric emptying; 3) gastric myoelectrical disturbances; 4) inhibition of migrating motor complexes; 5) inhibition of antral motility; 6) pyloric contractions; 7) inhibition of gallbladder contractions and small-intestinal transit; 8) altered esophageal motility; and 9) decreased lower esophageal sphincter pressure.

Normalization of blood-glucose levels in diabetic patients has been shown to improve gastric-emptying times. Previous studies have shown that secretion of the pancreatic hormone, human Pancreatic Polypeptide (hPP), is regulated by vagal-nerve input. Hyperglycemia can reduce hPP secretion, as well as gastric secretory and plasma hPP responses to modified sham feeding in humans; these findings support the notion of impaired vagal-cholinergic activity during hyperglycemia. Very low plasma levels of hPP have been reported in diabetic patients with cardiac autonomic neuropathy and delayed gastric emptying. In support of this concept, patients with poorly controlled diabetes mellitus have an increased perception of upper-gastrointestinal symptoms, such as nausea, fullness, early satiety, and upper-abdominal pain. The exact mechanisms by which hyperglycemia leads to disturbances in gastric motility has not been fully delineated.

Unfortunately, much of the available information on the effects of blood-glucose concentration on upper-gastrointestinal motor and sensory function has been observational. Available data on potential mechanisms that may mediate these effects are sparse. Major neurochemicals involved in the regulation of gastrointestinal motor function are summarized in Table 23.2.
function include nitric oxide (NO),\textsuperscript{48–50} vagally mediated cholinergic input, and vaso-vagal reflexes.\textsuperscript{51,52} In animal studies utilizing diabetic rats, there is evidence supporting the presence of impaired NO-synthase expression in the gastric myenteric plexus.\textsuperscript{53} Delayed gastric emptying can be reversed by restoration of neuronal NO-synthase expression through addition of insulin or addition of the phosphodiesterase inhibitor sildenafil, which increases NO signaling.\textsuperscript{54}

As an additional possible mechanism, impaired antioxidant status, which is associated with accelerated liquid gastric emptying,\textsuperscript{55} has been noted in individuals with impaired glucose tolerance and diabetes.\textsuperscript{56} However, a potential association with delayed gastric emptying has not yet been delineated.

Defective cholinergic neuromuscular transmission in the myenteric plexus,\textsuperscript{57} impaired release of vasoactive intestinal polypeptide and calcitonin gene-related peptide during stimulation of enteric nerves,\textsuperscript{58} and impaired NO-mediated relaxation of the duodenum\textsuperscript{59} have been observed in diabetic rats. Indomethacin, a prostaglandin-synthesis inhibitor, reverses gastric dysrhythmia induced by hyperglycemia.\textsuperscript{60} Additional studies are needed to examine the effects of neurohumoral and cellular mechanisms, and to elucidate the effects of abnormal glucose homeostasis on gastrointestinal motor and sensory function.

Although animal studies provide insight as to the mechanisms of diabetic gastropathy, we should be very careful in extrapolating this information into human disease. These observations suggest that the effect of glucose homeostasis on the gastrointestinal system is multifactorial, and more work is required to explore the pathophysiology of this common problem. In addition to the pathophysiological effects of glucose homeostasis on gastrointestinal motility, factors that modulate the rate of gastric emptying must be taken into consideration, such as volume, acidity, osmolarity, nutrient density, fat content, ileal fat, colonic/rectal distention, and use of medications.

**IV. SYMPTOMS OF DIABETIC GASTROPATHY**

Although gastrointestinal symptoms are common among diabetic patients seen in diabetic clinics,\textsuperscript{62} the prevalence of most gastrointestinal-tract symptoms is similar in persons in the community without diabetes mellitus.\textsuperscript{53} In subspecialty clinics, 76 percent of diabetic patients who participated in a survey had one or more gastrointestinal symptoms (Table 23.3), including constipation, diarrhea, fecal incontinence, and upper-abdominal symptoms, including nausea and vomiting.\textsuperscript{52} These patients are not immune to the presence of functional gastrointestinal symptoms, perhaps leading to an overestimation of symptom prevalence.

**V. PERSPECTIVES ON EVALUATION OF GASTRIC EMPTYING**

Beaumont made the earliest comments on the rates of gastric emptying in the early 19th century during his observations utilizing a patient with a traumatic gastric fistula.\textsuperscript{63} Von Luebe performed the first definitive gastric-emptying study by a single
gastric aspiration seven hours after liquid-meal ingestion. Rehfuss introduced repeated sampling of gastric contents at regular intervals. Hunt and Spurrell used an aspiration technique to measure the volume of a residual test solution and the concentration of a marker that was believed to estimate the amount emptied.

To overcome the need for repeated gastric intubation, George described a method using double-sampling of the stomach contents. A marker was administered following the initial sampling of a test meal. The marker concentration in the subsequent sampling allowed calculation of the remaining gastric volume, and the chloride concentration of the sample enabled determination of the rate of gastric secretion. Recovery of a gastric marker from the duodenum, with the help of duodenal and gastric intubation through a triple lumen assembly, allowed measurement of gastric emptying. In addition, distal-duodenal sampling allowed measurement of pancreatic and biliary secretions.

The first gastric x-ray studies concentrated on gastric motility rather than evaluation of gastric-emptying time. Subsequent x-ray contrast studies examined the emptying of liquid barium sulfate or a radiopaque meal. With these techniques, only complete gastric-emptying time of radiopaque material could be calculated, because the volume and density of gastric residual barium could not be determined radiographically. Dissociation of barium into liquid phase allowed assessment of only liquid emptying in tests using solid meals impregnated with barium granules. Comparison of a barium test meal with scintigraphic gastric emptying did not reveal a correlation between the magnitude of retained barium at six hours and the half-time, as well as percentage of gastric isotope remaining at six hours after ingestion of a test meal. Therefore, results from these two tests are not comparable.

VI. CONTEMPORARY METHODS FOR EVALUATION OF GASTRIC EMPTYING

The presence of multiple methods to evaluate gastric emptying is an indication of the absence of a precise and widely available technique (namely, a gold standard). Different techniques have limitations that need to be overcome. The following section critically analyzes and summarizes contemporary methods used for the assessment of gastric emptying of solids.
A. **Upper-Gastrointestinal X-Ray Series**

Since radiocontrast material is not a physiological meal and residual gastric barium can not be quantitatively measured, unless there is significant prolongation of gastric emptying, an upper-gastrointestinal X-ray series is not sufficiently sensitive to comment on gastric emptying. The primary role of these X-ray studies is to exclude a significant mucosal abnormality or a gastric-outlet obstruction.

B. **Scintigraphic Assessment of Gastric Emptying**

This test is sensitive, quantitative, noninvasive, easy to perform, and a physiologic method. Therefore, this test is currently considered to be the gold standard for the assessment of gastric emptying in research and clinical practice. The technique is based on the measurement of the disappearance of a radioisotope from the gastric region during scintigraphic scanning. Evaluation of gastric emptying of solids is a more sensitive technique, since gastric emptying of liquids is usually preserved even in the presence of abnormal solid gastric emptying. Gastric emptying of liquids can be clinically useful if the presence of rapid gastric emptying, termed dumping syndrome, is suspected.

There are important, basic points that alter the sensitivity and specificity of scintigraphic gastric-emptying studies. First, radioisotope marker should effectively bind to substrate, be nonabsorbable, be resistant to a wide range of pH, and be stable during the procedure. All studies should contain the same meal volume, composition, and caloric content. A standard patient position should be preserved to prevent variations due to the effect of posture. Appropriate corrections for radioisotope decay, three-dimensional motion of intragastric material, penetration, attenuation, and scattering must also be considered.

The use of a variety of radioisotopes, meals, and separate protocols by individual hospital centers impede the comparison of gastric-emptying studies from different institutions. Most major centers use either technetium-99m-labeled scrambled egg or chicken liver. Simplified standardized scintigraphic gastric-emptying protocols have been studied in order to establish normal gastric-emptying values, as well as to screen patients with suspected gastric dysmotility. In these studies, one-half emptying time of a gastric radioisotope (t1/2) is a commonly assessed parameter.

Unfortunately, scintigraphic gastric-emptying studies do not provide information with regards to the etiology and pathophysiology of gastric dysmotility. There is frequently no direct correlation between gastric-emptying time, patient symptoms, and their response to therapy.

C. **Tracer Methods**

These methods are based on the assumption that measurement of the appearance of a marker substance either in the blood or in expired air can serve as an indirect estimation of gastric emptying. Gastric emptying should be the rate-limiting step in the appearance of a marker substance either in the blood or in expired air. Specifically, the amount of gastric content that enters the duodenum should directly correlate with the amount that is absorbed and appeared in the blood or expired air. It is
assumed that the absorption, transport, and metabolism of a marker are constant both interindividually and intraindividually. Mucosal diseases that alter absorption, pancreatic diseases, hepatic diseases, and pulmonary diseases, as well as hemodynamic variations, can alter the accuracy of these studies.

Paracetamol,\textsuperscript{77} C$^{13}$-octanoic acid,\textsuperscript{78–82} and C$^{13}$-acetate have been used as markers in these tracer studies.\textsuperscript{83} In contrast to scintigraphic studies, the absence of ionizing radiation in C$^{13}$ breath tests enables the safe evaluation of children and pregnant women. Tracer methods can be used in centers without gamma camera, in physician’s offices, or at a patient’s hospital bedside. These tests are considered as test choice in certain centers in Europe, but are not widely used at this time in the U.S.

D. **Ultrasoundography**

Real-time ultrasonographic evaluation of gastric emptying is based upon the measurement of changes in the cross-sectional area of the antrum in response to a test meal.\textsuperscript{84–86} The return of antral area and volume to the fasting baseline are considered to mark the final emptying time. Gastric-contraction frequency can also be measured by ultrasonography.\textsuperscript{87} Ultrasoundography has been suggested to be equivalent to and a valid alternative to the use of scintigraphy.\textsuperscript{88,89} The main advantages of this method are that it is noninvasive, widely available, and there is absence of ionizing radiation. This makes ultrasonography suitable for repeated examinations. However, it is time-consuming, operator dependent, and difficult to perform in obese patients. It is also difficult to perform this test in the presence of excessive abdominal gas, it generally measures liquid gastric emptying, and it is not suitable for patients following partial gastrectomy.

E. **Magnetic Resonance Imaging (MRI)**

This noninvasive, radiation-free technique is very promising for providing information on gastric emptying, anatomical morphology, and gastric secretion.\textsuperscript{90,91} Improvements in MRI technology could allow the study of gastric motility.\textsuperscript{92,93} The cost and availability of MRI presently limit its clinical utility.

F. **Electrogastrography (EGG)**

EGG is a noninvasive method for the recording of gastric myoelectrical activity by placing electrodes on the anterior abdominal wall.\textsuperscript{95} The correlation between the cutaneous EGG recordings and myoelectrical activity recorded from gastric serosal electrodes has been previously validated.\textsuperscript{96–98} Important parameters that can be obtained with the use of EGG include different frequency components and relative power change.\textsuperscript{99} Normal gastric slow-wave frequency is considered to range between two and four cycles per minute. Conditions below this range are termed bradygastria, and above this range are termed tachygastria, or, as a general term, gastric arrhythmia. The relative power change corresponds to the gastric-contractile strength. Since gastric myoelectric activity is only one of many factors that alter gastric emptying, the correlation between EGG and gastric emptying is variable.\textsuperscript{100–103} According to a recent expert consensus opinion, the positive predictive value of an abnormal EGG
to predict delayed gastric emptying averages 65 percent, while the accuracy of a normal EGG to predict normal gastric emptying averages 75 percent. Gastric dysrhythmias rather than gastric retention may be a better prognosticator of upper-gastrointestinal symptoms. Therefore, EGG may be a complementary study rather than a replacement for standard gastric-emptying studies. Further studies are needed to clarify the potential role for and indications for performance of EGG.

VII. EVALUATION OF PATIENTS WITH SUSPECTED DIABETIC GASTROPATHY

Suggestions for the potential evaluation of patients with suspected diabetic gastropathy are outlined in Figure 23.1.

Major historical features can include a history of long-standing, insulin-dependent diabetes mellitus or a prior history of peptic-ulcer disease. The patient may have known diabetic nephropathy or diabetic retinopathy, which could support a diagnosis of gut autonomic neuropathy. A history of migraine headaches could support the presence of cyclical-vomiting syndrome. Suggestive gastrointestinal symptoms of diabetic gastropathy may include nausea, emesis, weight loss, history of dehydration, or early satiety. It is quite important to try to elicit the potential use of medications that can alter gastric emptying, including use of over-the-counter, nonsteroidal, antiinflammatory drugs or antihistamines, or prescription narcotics or anticholinergic compounds, such as antispasmodics. Nonsteroidal, antiinflammatory drug use may be detected by a serum platelet aggregation assay. Use of narcotics may be detected by urine screening. In young individuals, bulimia must be considered.
On physical examination, potential evidence for a peripheral neuropathy (stocking, glove) should be sought. Examination of the extremities includes looking for evidence of sclerodactyly. Upon examination of the abdomen, percussion in the upper abdomen or shaking the upper abdomen may confirm the presence of a succussion splash. It can be helpful to perform auscultation of the abdomen during percussion of the upper abdomen, which is designed to elicit a splashing sound due to the presence of air and fluid in the stomach. Normally, less than 200 ml of fluid is present in the stomach following an overnight fast.

Laboratory testing should include examination for potential thyroid dysfunction, hypokalemia, chronic renal failure, or hypercalcemia. Upper endoscopy is preferred in order to exclude ulcer disease or an obstruction at the pylorus or proximal duodenum. In the absence of obstruction, solid-meal gastric-emptying studies by scintigraphy are more readily available to look for evidence of delayed gastric emptying.

VIII. TREATMENT STRATEGIES IN DIABETIC GASTROPATHY

A. INTRODUCTION

The medical management of diabetic gastric disorders is challenging and may become frustrating for both clinicians and their patients. Present management principles include dietary and supportive care, optimizing care of an underlying etiology, and symptomatic relief. Medicines that alter gastrointestinal motility, such as anticholinergic medications and opiate agonists, should be avoided. Patients who do not respond to dietary and lifestyle modifications, improved glycemic control, and pharmacologic agents may be candidates for endoscopic or surgical intervention for symptomatic and supportive management.

B. DIETARY AND SUPPORTIVE THERAPY

Dietary modifications, such as use of low-residue, low-lipid, high-liquid-content meals in small but frequent portions may decrease bezoar formation, improve symptoms and prevent malnutrition, dehydration, and electrolyte imbalances. Some patients may benefit from a gastroparesis diet. Enteral feeding can permit adequate nutritional support and hydration in those patients who do not tolerate oral intake. Parenteral nutrition is reserved for patients in whom enteral feeding is not possible.

C. OPTIMIZING GLYCEMIC CONTROL

Hyperglycemia may cause antral hypomotility and pyloric contractions, affect gastric motility, and impair the efficacy of prokinetic agents. Gastric-emptying disorders may result in erratic glycemic control due to variability of glucose availability or absorption. Optimizing glycemic control may improve gastric dysmotility and patient symptoms. It is not presently clear whether improved nutrition alters patient symptoms via a mechanism that could include increased tissue levels of antioxidants.
**D. Metoclopramide**

Metoclopramide, the only Food and Drug Administration-approved agent for the treatment of gastroparesis, has both prokinetic and antiemetic effects through its antidopaminergic, 5-HT3 antagonist, and 5-HT4 agonist properties.\(^{106}\) Its prokinetic effects are limited to the upper-gastrointestinal tract. The usual oral dose ranges from 5 mg to 20 mg before meals and at bedtime, and is best provided in syrup form if gastroparesis is suspected. It can also be given to patients intravenously or subcutaneously if there is intolerance to oral intake. Although metoclopramide provides symptomatic relief and accelerates gastric emptying,\(^{111–113}\) its prokinetic effects are not sustained over a long period of time.\(^{114}\) It appears that its symptomatic relief may be due to its central antiemetic properties rather than being related to its prokinetic effects. Contrary to early studies, a more recent publication did not show any symptomatic, prokinetic benefit over use of a placebo.\(^{115}\)

Numerous adverse events affect up to 20 percent of patients, including development of acute dystonic reactions, extrapyramidal effects, drowsiness, fatigue, lassitude, restlessness, akathisia, irritability, elevation of serum prolactin level, Parkinson-like symptom profile, and tardive dyskinesia (which may be irreversible after the discontinuation of the drug).\(^{113,116–118}\) The poor side-effect profile and inconsistent efficacy on gastric emptying may limit the long-term use of metoclopramide in patients with diabetic gastropathy and gastric retention.

**E. Erythromycin**

Erythromycin is a macrolide antibiotic that has prokinetic properties through its presumed activation of motilin receptors.\(^{119}\) This agent may increase the amplitude and frequency of antral contractions, as well as initiation of gastric phase three contractions of the migrating motor complex.\(^{120–121}\) There is a motilin-receptor gradient in mammalian gastrointestinal tract, with the highest concentrations identified in the upper-gastrointestinal tract.\(^{122}\) Administration of erythromycin has been reported to improve solid and liquid gastric emptying in diabetic, postvagotomy, and idiopathic gastroparesis.\(^{123–127}\) Intravenous doses in acute treatment range between 1 to 3 mg/kg every eight hours. The commonly used oral doses are between 50 to 250 mg/kg every six to eight hours. Although the optimal dosing and route of administration has not yet been resolved, oral regimen does not appear to be as effective as intravenous administration.\(^{128}\) Unfortunately, the long-term efficacy of erythromycin has been unsatisfactory and may include the risks of long-term antibiotic use.\(^{129}\) Adverse events induced by erythromycin include abdominal pain, cramping, nausea, and vomiting.

**F. Cisapride**

Cisapride, a prokinetic agent with a mixed 5-HT3 antagonist and 5-HT4 agonist activity, has been extensively evaluated in those patients with gastrointestinal dysmotility and gastroesophageal-reflux disease. Its effects on gastric emptying are likely due to stimulation and coordination of antral-pyloro-duodenal motility and possibly due to changes in gastric-outlet resistance.\(^{130–135}\) Although cisapride has
been shown to accelerate gastric emptying in multiple studies, the correlation between improved gastric emptying and control of patient symptoms has remained less convincing.\textsuperscript{136–139} Reports of arrhythmias and sudden death related to prolongation of the QT interval resulted in significant restrictions on the routine use of cisapride in the United States.\textsuperscript{140–142} Most of these adverse events occurred in the context of concomitant systemic diseases or drugs that could prolong cisapride metabolism.

**G. Domperidone**

Domperidone, similar to metoclopramide, is an agent with both prokinetic and antiemetic properties related to its peripheral dopamine 2 receptor antagonist activity; this agent blocks dopamine’s inhibitory effects on smooth muscle.\textsuperscript{143} Domperidone is not available routinely in the United States, but it is available in Canada. Its antiemetic property is due to its antidopaminergic action on the central chemoreceptor trigger zone. Unlike metoclopramide, this agent does not cross the blood–brain barrier; therefore, adverse central nervous system side effects are less likely.\textsuperscript{144,145} Domperidone has been shown to improve liquid and solid gastric emptying and symptoms during the acute treatment of patients with diabetic gastroparesis.\textsuperscript{144,146} The long-term treatment effects on gastric emptying and symptoms have been variable.\textsuperscript{146–148} Side effects of domperidone are related to elevated serum prolactin levels, headache, diarrhea, somnolence, and abdominal pain.\textsuperscript{143}

**H. Tegaserod**

Tegaserod is a serotonergic (5-HT\textsubscript{4}) receptor partial agonist and has been approved by the FDA for treatment of women with constipation-predominant irritable-bowel syndrome.\textsuperscript{149} Although it increases orocecal transit time with preliminary promising results on gastric emptying, further studies are needed to determine its role in the management of gastroparesis.\textsuperscript{150–152} Use of tegaserod has been associated in routine medical care with the development of diarrhea, and possibly ischemic colitis.

**I. Refractory Gastropathy**

Some patients with refractory diabetic gastropathy undergo repeated hospitalizations for dehydration, develop protein-calorie malnutrition, or require frequent outpatient encounters. Frequent hospitalizations and outpatient encounters for refractory nausea, vomiting, and dehydration can be major burdens to health-care costs, as well as to the patient’s quality of life. Acceptable management of these difficult problems in refractory patients has been developed in medical centers that utilize a team approach. Management decisions can include input from an endocrinologist, a gastroenterologist, a nutritionist, a therapeutic radiologist, and a gastrointestinal surgeon.

Therapeutic options that utilize pharmacologic agents are limited for the treatment of refractory gastroparesis. Surgically or endoscopically placed gastro-jejunal or jejunal feeding tubes provide nutrition and rehydration by using a defined formula diet or elemental diet, and permit delivery of medications in a patient with a poorly emptying stomach. A gastrostomy or jejunostomy port allows simultaneous decompression of a dilated stomach or small intestine.\textsuperscript{153,154} Unfortunately, it is extremely
difficult and time-consuming to maintain gastrojejunostomy tubes that have been placed by therapeutic endoscopy. These devices are best managed in specialized centers that have extensive experience in their utilization and limitations. The use of total parenteral nutrition can be considered, especially in those patients with a generalized gastrointestinal motility disorder. Total parenteral nutrition should be reserved for those individuals who have not responded clinically during the use of an elemental diet. Data on the long-term effects of parenteral and enteral nutrition and micronutrients on diabetic gastroparesis is lacking.

Early data appears promising in specialty centers that have studied an external-stimulation device with temporary electrodes to pace the stomach.155–157 These studies have shown improvement in symptoms and gastric emptying. Although these devices are available in the United States, further controlled trials are needed to define their role in the management of refractory diabetic gastroparesis.

Select patients with refractory diabetic gastroparesis have been referred to surgery for total gastrectomy and formation of an esophago-jejunostomy. This extensive procedure should be reserved for those medical centers in which there is experience in the complex preoperative and postoperative evaluation and management of these patients.

IX. FUTURE STUDIES

Diabetes mellitus is a common medical problem that can result in gastrointestinal dysmotility secondary to acute hyperglycemic changes or chronic changes resulting in neuropathic or myopathic disorders. The most common presenting symptoms of patients with diabetic gastroparesis are nausea, vomiting, bloating, early satiety, postprandial fullness, and upper-abdominal discomfort and pain. Available clinical treatments are often unsatisfactory for refractory patients. Future research goals could include studies of micronutrient supplementation or studies of improved glycemic control by pancreas or islet-cell transplantation. It will be important to assess their effects on clinical symptoms, gastric emptying, and myopathic and neuropathic changes in the gut.

REFERENCES


