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REVIEW ARTICLE

Diabetic Gastropathy

Gastric Neuromuscular Dysfunction in Diabetes Mellitus A Review of Symptoms, Pathophysiology, and Treatment

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Diabetic gastropathy is a term that encompasses a number of neuromuscular dysfunctions of the stomach, including abnormalities of gastric contractility, tone, and myoelectrical activity in patients with diabetes. These abnormalities range from tachygastrias to antral hypomotility and frank gastroparesis. Diabetic gastropathies may be acutely produced during hyperglycemia. Symptoms of chronic diabetic gastropathy include chronic nausea, vague epigastric discomfort, postprandial fullness, early satiety, and vomiting. Because these symptoms are nonspecific, other disorders such as mechanical obstruction of the gastrointestinal tract, gastroesophageal reflux disease, cholecystitis, pancreatitis, mesenteric ischemia, and drug effects should be considered. Neuromuscular abnormalities of the stomach may be assessed noninvasively with gastric emptying tests, electrogastrography, and ultrasound. Gastrokinetic agents such as metoclopramide, cisapride, domperidone, and erythromycin increase fundic or antral contractions and/or eradicate gastric dysrhythmias. Diet and glucose control also are important in the management of diabetic gastropathy. As the pathophysiology of diabetic gastropathy is better understood, more specific and improved treatments will evolve.

KEY WORDS: diabetes mellitus; gastropathy; gastroparesis; gastric dysrhythmias; gastrokinetic agents; nausea and vomiting.

Upper gastrointestinal symptoms, particularly postprandial nausea, vomiting, and abdominal discomfort, occur in 30–60% of patients with type 1 diabetes mellitus (1, 2). In a survey of diabetic patients, 76% had chronic or recurrent gastrointestinal symptoms; 29% had nausea and vomiting, and 34% had abdominal pain (1). These are nonspecific symptoms and a broad differential diagnosis, including diabetic gastropathy, must be considered when evaluating these symptoms in diabetic patients. Early satiety, fullness, and bloating are also common symptoms associated with diabetic gastroparesis (1–4). As many as 50% of patients with type 1 diabetes have delayed gastric emptying or gastroparesis (4). In this review, upper gastrointestinal symptoms in diabetic patients and the relationships between symptoms and gastric motility dysfunction, ie, gastric neuromuscular dysfunction (diabetic gastropathies), will be addressed.

Diabetic gastropathy refers to a variety of neuromuscular abnormalities of the stomach that have been described in patients with diabetes. These abnormalities range from gastric dysrhythmias (5–7) to antral dilation (2), antral hypomotility (6, 8), and gastroparesis (5–9). The correlation between symptom severity and the rate of gastric emptying status has been poor. This poor correlation between symptoms and objective findings may be similar to the atypical presentations of cholecystitis or silent myocardial ischemia frequently seen in patients with diabetes mellitus. Generalized peripheral or autonomic neuropathy is not always a reliable predictor of the presence of diabetic gastroparesis (10). Furthermore, common

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diseases that cause the nonspecific symptoms that are associated with diabetic gastropathy must be excluded before gastric neuromuscular disorders can be diagnosed confidently and treated effectively with protrokinetic drug therapy and diet counseling (11).

In this review, the clinical presentation of diabetic gastropathy will be described, normal and abnormal gastric neuromuscular activity will be reviewed, and drug and dietary treatment options will be outlined.

NORMAL GASTRIC MOTILITY

Healthy individuals experience pleasant, satisfying sensations in the epigastrium after meals. These pleasant postprandial sensations occur while the stomach is performing the work of gastric emptying. In contrast, patients with diabetic gastropathy experience dyspepsia-like symptoms—nausea, unpleasant fullness, early satiety and vague epigastric discomfort—after meals. Before describing the gastric neuromuscular abnormalities in diabetic gastropathy, normal gastric neuromuscular function will be reviewed.

The essential neuromuscular functions of the stomach are to receive, mix, and empty nutrients from the stomach into the small bowel for absorption (12). Solid foods must be triturated, or broken down, into tiny particles, mixed with acid and pepsin, and then emptied from the stomach (12). The gastric myoelectrical and contractile activities that occur during these physiologic functions are controlled by extrinsic (parasympathetic and sympathetic) and intrinsic (enteric) nervous system activity. The autonomic nervous system links the activity of the central nervous system (CNS) and the enteric nervous system in order to modulate gastrointestinal motility (13, 14). The precise roles of various neurotransmitters, neuropeptides, and classic gut hormones such as gastrin and motilin in modulating gastric electrical and contractile functions are still not fully established.

During a meal, the fundus must relax to receive or accommodate the volume of ingested food. Relaxation of the proximal stomach is mediated by vagal efferent fibers and nitric oxide pathways. Receptive relaxation is the initial neuromuscular activity of the proximal stomach as a meal is ingested (Figure 1) (12).

After ingestion of the meal, regular gastric contractile activity begins in the body–antrum to mix and triturate the ingested food. Emptying of solids does not begin until particles are <1 mm in diameter in the nutrient suspension or chyme (Figure 1). The period

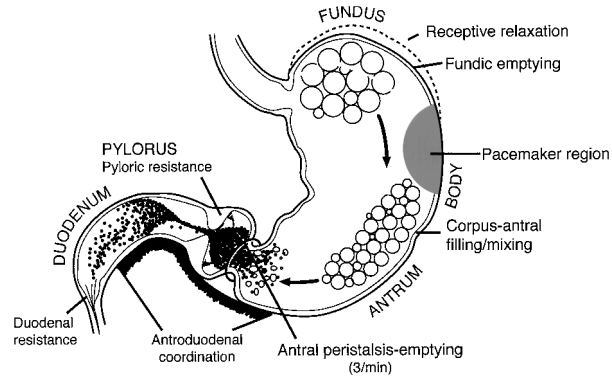

Fig 1. Postprandial gastric motility events include fundic receptive relaxation to accommodate the ingested food, and recurrent gastric peristaltic contractions in the corpus and antrum for mixing and emptying the chyme into the duodenum. Gastric peristalsis occurs at approximately 3/min. Antroduodenal coordination is necessary for efficient emptying. (See text for details). Reprinted with permission from KL Koch (12).

before emptying begins lasts about 30–40 min depending on caloric and physical characteristics of the food. This period is called the lag phase (9, 12, 13). Once emptying begins, nutrients are emptied in a linear fashion from the antrum into the duodenum. Undigestible fibers such as roughage are retained and emptied last or during phase III of the fasting or interdigestive period of gastric motility (12, 13).

Gastric peristalsis is controlled by the intrinsic electrical activity of gastric pacemaker cells, which is probably generated by interstitial cells of Cajal (15). The gastric pacemaker area is located in a region at the junction of the fundus and body on the greater curvature (Figure 2) (16, 17). Gastric pacesetter potentials or slow waves depolarize and repolarize at a frequency of approximately 3 cycles per minute (cpm) as recorded by sensal or cutaneous electrodes (16, 18). The slow waves are associated with very small contractions, but chiefly coordinate the frequency of circular muscle contractions in the body and antrum. The onset of circular muscle contraction also depends on actional potentials and plateau potentials, which are affected by ongoing neural and hormonal inputs as well as physical characteristics of the meal.

To summarize, in the normal postprandial situation, the stomach accomplishes the following neuromuscular activities: fundic relaxation, accommodation of the volume ingested, fundic emptying, peristaltic contractions of body–antrum for mixing, trituration and emptying of chyme, and coordination of peristaltic contractions from antrum to duodenum. These neuromuscular events are coordinated by gastric pacesetter waves, and the appropriate action and

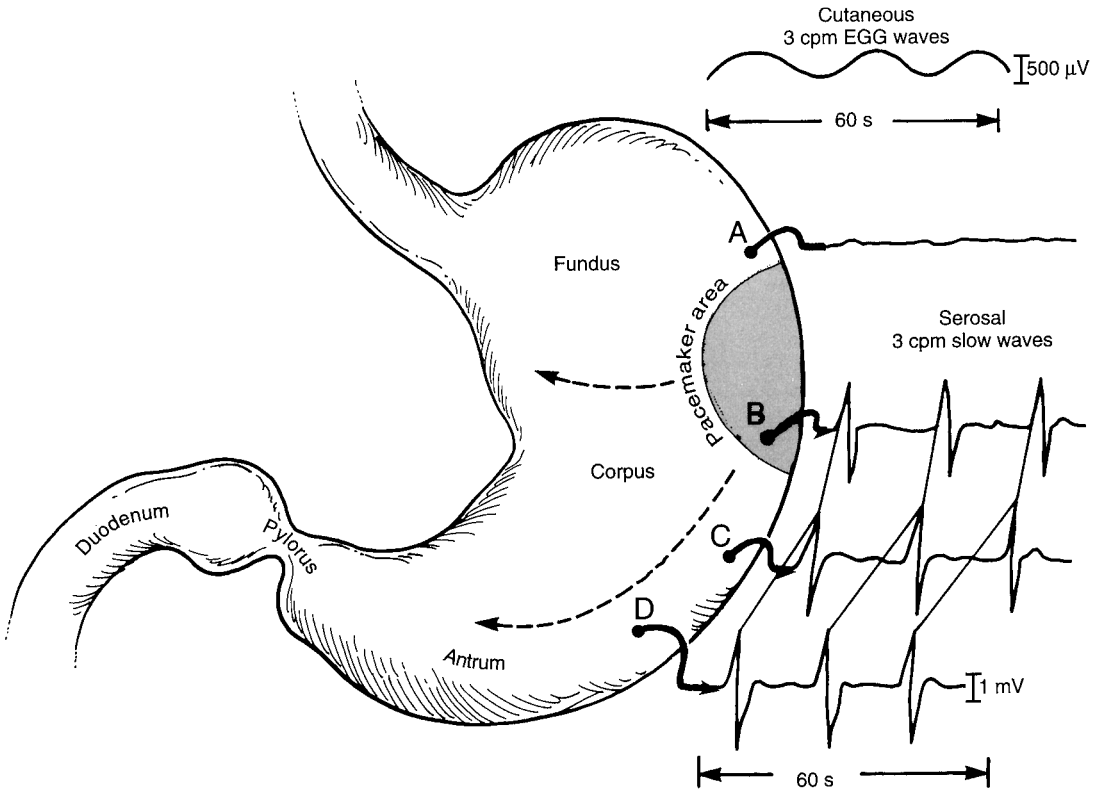

Fig 2. Gastric pacesetter potentials or slow waves originate from the pacemaker area. Pacesetter potentials travel in a circumferential and aboral direction at a rate of approximately 3 cpm. The cutaneously recorded electrogastrogram (EGG) shows a 3-cpm wave pattern. The fundus has no rhythmical electrical activity. Reprinted with permission from KL Koch (12).

plateau potentials that underlie circular muscle contractions (Figure 3).

DIABETIC GASTROPATHY—A SPECTRUM OF NEUROMUSCULAR ABNORMALITIES

Gastroparesis

As described above, diabetic gastropathy encompasses a variety of pathophysiologic neuromuscular events of the stomach in the patient with diabetes mellitus. The most severe neuromuscular abnormality is diabetic gastroparesis, which is diagnosed when delayed emptying of food from the stomach is documented (3, 5–7, 19). Gastroparesis has been found in up to 50% of patients with type 1 diabetes mellitus and 30% of patients with type 2 diabetes mellitus (4, 20). In the past, gastroparesis diabeticorum was considered to be an end-stage component of long-standing type 1 diabetes (21). Autonomic neuropathy rather than myopathy was believed to be the underlying cause of the gastroparesis (22). However, autonomic nervous system dysfunction does not necessarily predict gastroparesis in the type 1 diabetic patient (10).

Kassander suggested many years ago that diabetic patients had "autovagotomy" because of the similarity between radiographic findings of gastroparesis and the gastric atony observed after surgical vagotomy (19). However, Yoshida et al found no histologic or anatomic abnormalities in vagal nerve tissue obtained from diabetic patients (23). On the other hand, a recent study showed vagal nerve dysfunction as reflected in abnormal respiratory sinus arrhythmia in diabetic patients with gastroparesis (2). Thus, subtle and/or severe dysfunction of vagal afferent or efferent neurons is likely present in patients with a variety of diabetic gastropathies ranging from gastroparesis to gastric dysrhythmias.

Gastric Dysrhythmias

Gastric dysrhythmias have also been recorded in patients with diabetes mellitus and the meal-related symptoms described above (Figure 4) (5–7). Gastric dysrhythmias are defined as bradygastrias (1.0–2.4

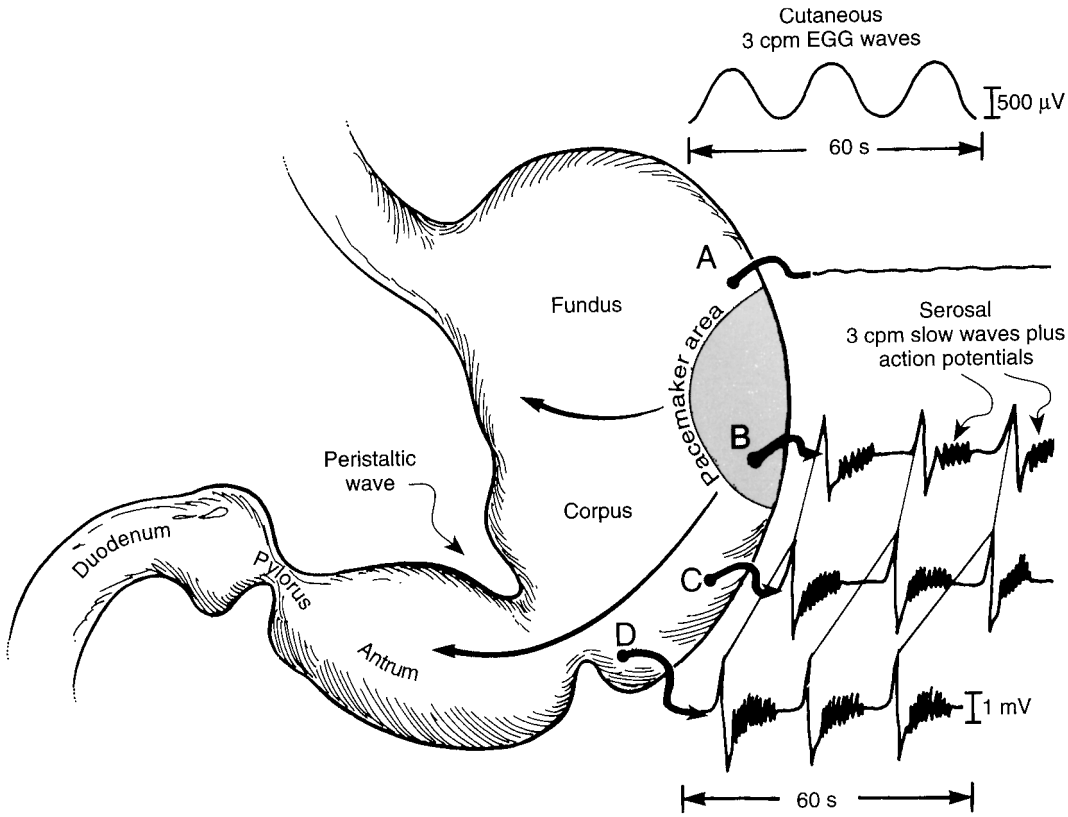

Fig 3. The electrical events that occur during a gastric peristaltic wave are shown. Action potentials occur in association with propagated pacesetter potentials during the myoelectrical and contractile events of gastric peristalsis. The amplitude of the EGG waves is increased. Reprinted with permission from KL Koch (12).

cpm activity), tachygastrias (3.6–9.9 cpm activity), or tachyarrhythmias, which are a combination of both bradygastrias and tachygastrias (24, 25). Gastric dysrhythmias interfere with the normal 3-per-minute gastric peristaltic contractions, which mix and empty food from the stomach. In patients with gastric dysrhythmias, abnormal gastric emptying is found 85–90% of the time (6). In some studies, gastric dysrhythmias have been found in 100% of diabetic patients with meal-related symptoms (5), but the incidence of gastric dysrhythmias probably depends on the predominant symptoms reported by the patient group studied (5–7, 26). The presence of gastric dysrhythmias is important because correction of the dysrhythmias is associated with improvement in nausea and upper abdominal symptoms (see treatment section below) (5, 7, 27). Figure 4 shows a bradygastria dysrhythmia in a symptomatic patient with diabetic gastroparesis before drug treatment and establishment of normal 3 cpm gastric myoelectrical activity after treatment with domperidone.

Antral Hypomotility

Antral hypomotility has been recorded with intraluminal pressure transducers in patients with diabetes mellitus (8). Poor antral contractility results in delayed emptying of food from the stomach and gastroparesis. Low amplitude or irregular contractions of the antrum also lead to poor antral–duodenal coordination in the function of providing the proper peristaltic waves to empty chyme into the duodenum (9, 13).

Antral Dilation

In studies using ultrasound to determine the diameter of the gastric antrum, symptomatic diabetic patients were found to have a significantly larger antral diameter in the postprandial condition compared with healthy controls (2). In patients with functional dyspepsia, increasing antral dilation correlated with the symptom of bloating (28), which is also very common in the diabetic patient population.

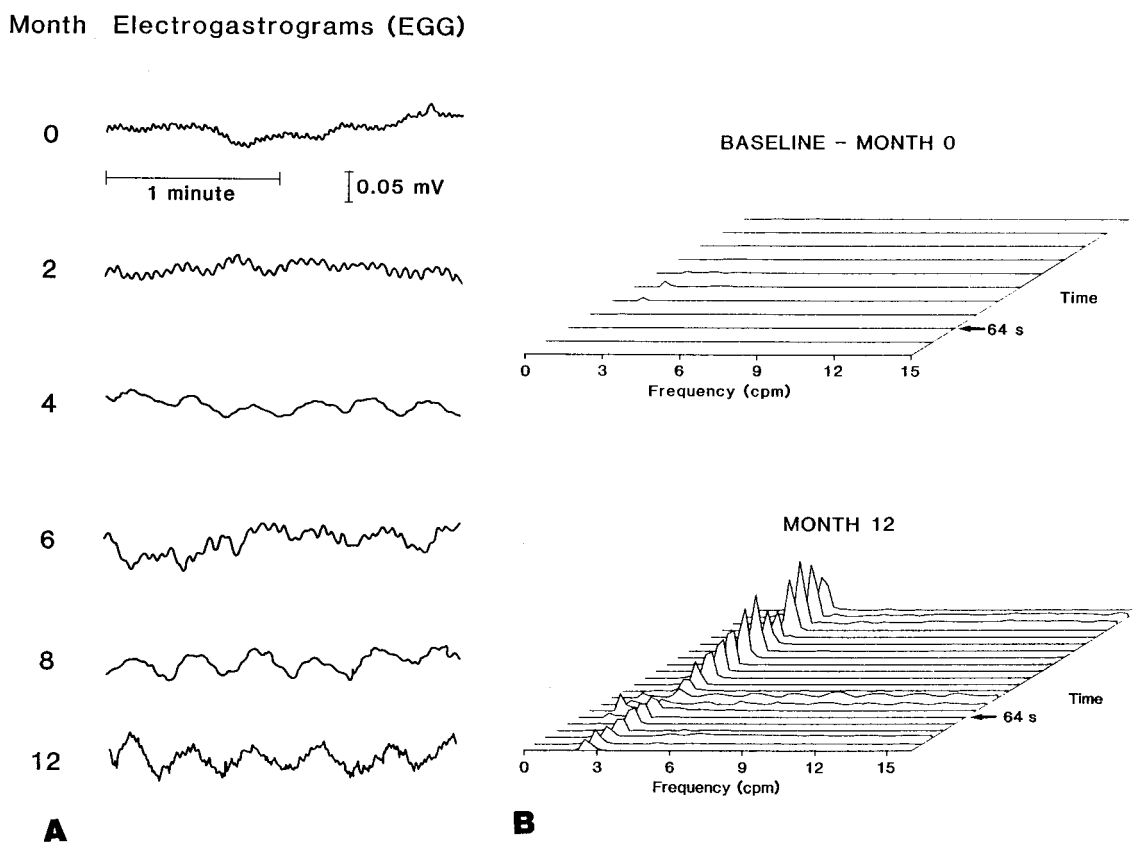

Fig 4. Gastric dysrhythmia (bradygastria) recorded from a symptomatic patient with type I diabetes mellitus and gastroparesis. (A) Flat-line bradygastria at month 0. During treatment with domperidone, the bradygastria disappeared and the EGG appeared normal (3 cpm). The patient's symptoms of nausea and vomiting also disappeared. (B) The running spectral analysis of the EGG signal recorded at month 0 and month 12. Note the change from no frequencies in the EGG signal at month 0 to clear peaks at 3 cpm at month 12.

Antroduodenal Coordination

The most efficient movement of chyme from the stomach to the duodenum requires antroduodenal coordination (9, 12). The pylorus and duodenum offer resistance to emptying of chyme from the antrum (29). Pylorospasm or uncoordinated pyloric contractions provide resistance to gastric emptying and has been reported as a cause of delayed gastric emptying in diabetic patients (29).

Gastric Tone

In diabetic patients the fundic tone does not relax normally in response to balloon distension when compared with control subjects (30). Fundic tone abnormalities may also have a role in dyspepsia-like symptoms experienced by diabetic patients.

To summarize, Figure 5 illustrates the various neuromuscular abnormalities that may afflict the stomach in patients with diabetes mellitus. In the patient at the extreme end of the spectrum, diabetic gastroparesis, gastric dysrhythmias, dilated antrum, and antral hypomotility may all be present and represent the underlying pathophysiology of symptoms. Pylorospasm and duodenal resistance may contribute to the delay in gastric emptying. Other patients may have predominantly dilated antrum or gastric dysrhythmias as the primary pathophysiologic event that correlates with meal-related symptoms. Most research has focused on the diabetic patient with severe symptoms. Studies of gastric neuromuscular function in a continuum of diabetic patients are needed.

Diabetic patients may have single or multiple elements of diabetic gastropathy described above and summarized in Figure 5. Because of the variable degree of vagal afferent and efferent dysfunction, the correlation between diabetic gastropathies and particular symptoms is not always straightforward. However, patients with diabetes mellitus may have upper gastrointestinal symptoms in the absence of frank gastroparesis, because the other gastric pathophysio-

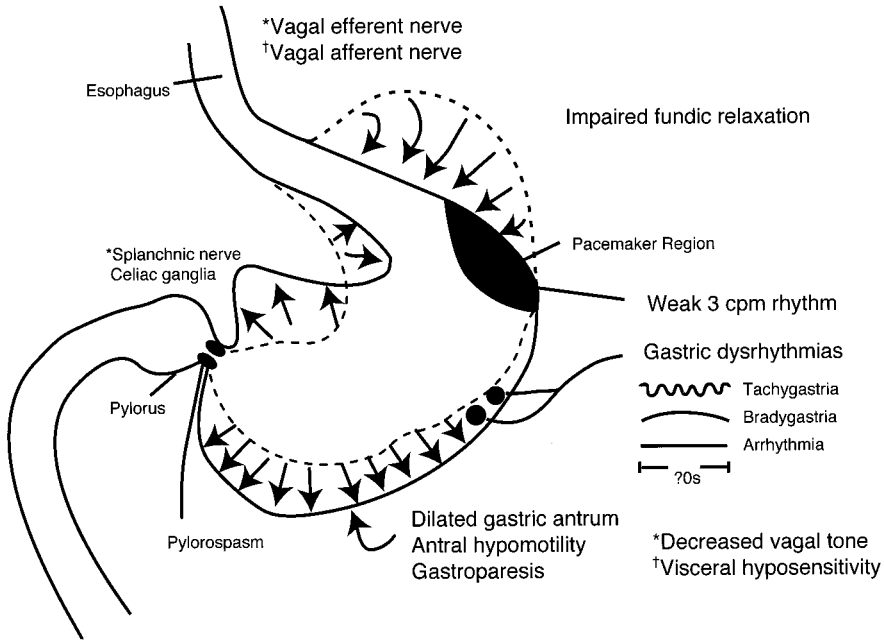

Fig 5. Summary illustration of the spectrum of gastric neuromuscular abnormalities that may occur in diabetic gastropathy. The abnormalities include impaired fundic relaxation, gastric dysrhythmias, dilated antrum, antral hypomotility and gastroparesis. Decreased vagal tone may be present as well as visceral hyposensitivity. Adapted from KL Koch (17).

logic mechanisms described above may be responsible for these symptoms.

MECHANISMS OF DIABETIC GASTROPATHY

The underlying mechanism(s) of the diabetic gastropathies are not precisely known. As with the other sequelae of diabetes mellitus, such as retinopathy, peripheral neuropathy, and nephropathy, there are several mechanisms of injury that may be responsible for the findings of diabetic gastropathy.

Autonomic neuropathies that involve the parasympathetic or sympathetic nervous system may be responsible for some of the gastric neuromuscular problems outlined above. Loss of vagal tone and increased sympathetic nervous system activity have been associated with gastric dysrhythmias (31, 32), and this may be a factor in the development of gastric dysrhythmias in some diabetic patients. Damage to enteric neurons or interstitial cell of Cajal or subtle dysfunction of these elements may also be mechanisms of diabetic gastropathy.

Microangiopathies contribute to retinal damage as well as peripheral neuropathies described in patients with diabetes mellitus. Microangiopathies may affect relevant nerve and muscle function of the stomach and may contribute to the evolution of diabetic gastropathy.

Postprandial hormone release of glucagon and pancreatic polypeptide, as well as the release of neurotransmitters, may be altered in the patient with diabetes mellitus. Hormonal responses are complex issues, particularly as the wide variety of foods ingested will evoke different gastric and neurohormonal responses.

Finally, glucose toxicity itself may play a role in the end-organ neuromuscular dysfunctions described above. Hyperglycemia affects both intracellular metabolic pathways as well as membrane function in neural cells. The acute effects of hyperglycemia have been studied in healthy subjects and in patients with diabetes mellitus. Antral contractions in the postprandial condition were significantly decreased during induced hyperglycemia (33). In this situation, pyloric contractions may be evoked while antral contractions are decreased, a situation that would lead to potential gastric stasis (34).

Hasler et al showed that increasing plasma glucose from normal levels to 230 mg/dl significantly decreased the antral motility index in healthy subjects (33). An equivalent level of insulin infusion did not suppress antral motility, indicating hyperinsulinemia was not the factor that affects antral motility. In similar studies, it was shown that the percentage of tachygastria activity increased significantly as plasma

glucose was increased from normal to 230 mg/dl using the glucose clamp technique (33). Figure 6 illustrates normal gastric electrical activity during euglycemia compared with tachygastrias evoked during hyperglycemia. The increase in tachygastria activity was blocked by pretreatment with indomethacin, suggesting a prostaglandin-sensitive pathway was related to the hyperglycemia-induced tachygastria. Taken together, these studies indicate that acute hyperglycemia in healthy subjects can evoke tachygastrias and suppress antral contractions, all of which may lead to decreased gastric emptying.

In diabetic patients, experimentally induced hyperglycemia resulted in a prolonged lag phase of gastric emptying after a standard meal (35). In the hyperglycemic setting, the amount of time required for 50% of the solid meal to be emptied was also significantly prolonged (35). A recent study by Schvarcz et al showed that even when glucose levels increase from low normal to the upper limits of the normal range of glycemia, an effect on gastric emptying can be measured in both healthy subjects and patients with type 1 diabetes mellitus (36). These studies showed that relatively subtle increases in plasma glucose delay the rate of gastric emptying. The mechanism of the delay in gastric emptying was not determined, but it is possible that gastric emptying was slowed by the glycemic effect on gastric myoelectrical rhythm and on the amplitude of antral contractions.

In summary, the mechanisms whereby diabetic gastropathy develops is a multifactorial and complex issue, much like the progressive neuropathy, retinopathy, and nephropathy conditions that are well appreciated. In terms of the diabetic stomach, there are no data regarding the timeline for the development and progression of the various pathophysiologic findings described above (Figure 7). Do multiple acute episodes of hyperglycemia that cause acute gastric dysrhythmias and antral hypomotility lead to chronic and persistent gastric dysrhythmias and antral hypomotility? Much more investigation is needed to clarify the natural history of the development of diabetic gastropathy.

CLINICAL PRESENTATION

Patients with insulin-dependent diabetes mellitus commonly have upper gastrointestinal symptoms. Almost 30% of diabetes patients reported nausea and vomiting (1). Typical upper gastrointestinal symptoms are early satiety, nausea and vomiting, abdominal discomfort, and postprandial fullness and bloating (1, 37). Bezoar formation may occur in patients with severe diabetic gastroparesis and exacerbate postprandial fullness and discomfort. Symptoms listed above are increased after the ingestion of meals, particularly by solid foods. The symptomatic patient may or may not have manifestations of peripheral and autonomic neuropathy, nephropathy, and retinopathy; however, these other complications of longstanding diabetes are not consistently found even in patients with frank gastroparesis (1, 4, 10, 38, 39).

Some diabetic patients with delayed gastric emptying may be asymptomatic (4, 19, 38). This should not be surprising, since more than 90% of ischemic ST-segment changes recorded on Holter monitor in patients with type 1 diabetes were not associated with reports of chest discomfort or pain (40). Furthermore, patients with meal-related symptoms may obtain temporary relief by making subtle changes in their diet.

The only clue that gastric neuromuscular dysfunction is present may be poor glycemic control (4, 41). Delayed gastric emptying in diabetic patients may also account for episodes of hypoglycemia, which occur as a result of the dyssynchrony of insulin administration and emptying of nutrients from the stomach to the small intestine (41). Infection and other causes of hyperglycemia also must be considered.

DIFFERENTIAL DIAGNOSIS OF DIABETIC GASTROPATHY

The symptoms associated with diabetic gastropathy are nonspecific dyspepsia-type symptoms: early satiety, abdominal discomfort, nausea, bloating, and postprandial fullness (1, 2, 4, 5, 41, 42). These symptoms may be caused by mechanical obstruction of the gastrointestinal tract, peptic ulcer disease, gastroesophageal reflux disease (GERD), chronic cholecystitis or pancreatitis, or metabolic abnormalities such as uremia, hypercalcemia, hypokalemia, hypocortisolemia, or hypothyroidism (9, 11, 43).

Several medications can also slow gastric emptying (Table 1) (9, 11, 41, 42) and contribute to gastroparesis. Eating disorders such as anorexia nervosa occur in adolescents, including adolescents with diabetes mellitus (44), and these patients may present with the nonspecific dyspepsia-like symptoms of diabetic gastropathy.

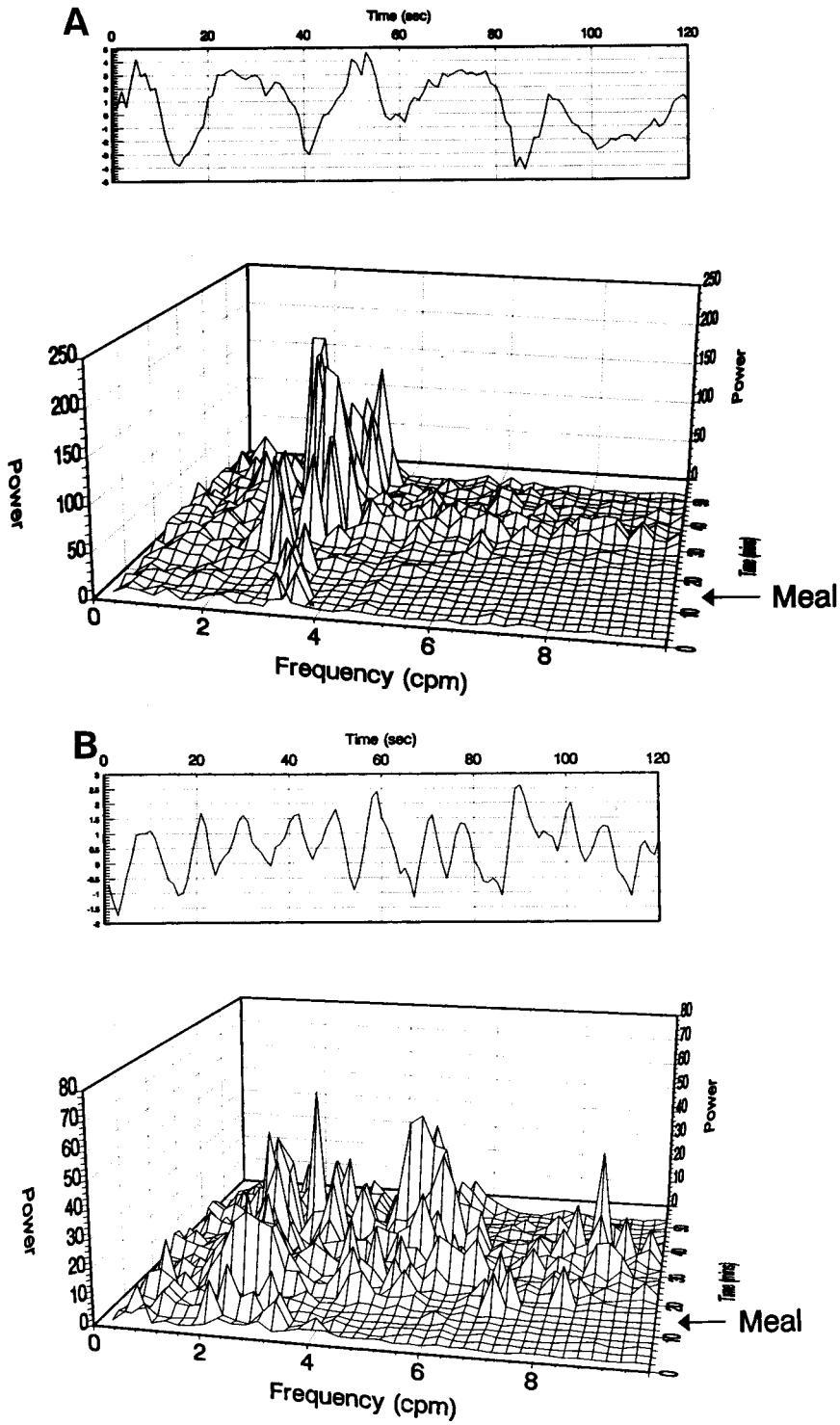

Fig 6. Hyperglycemia induces gastric dysrhythmias in healthy subjects. A: Normal 3-cpm gastric electrical rhythm in the EGG tracing and 3-cpm peaks before and after the meal in the running spectral analysis of the EGG signal. B: The effect of hyperglycemia (230 mg/dl) on gastric myoelectrical activity. The EGG tracing shows a tachygastria at 5–6 cpm and loss of the 3-cpm activity during hyperglycemia. The spectral analysis shows many peaks in the tachygastria ranging from 3.6 to 9 cpm. Reprinted with permission from WL Hasler et al (33).

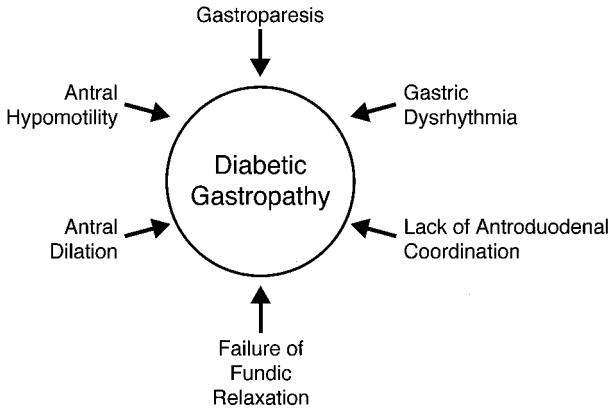

Fig 7. Elements of diabetic gastropathy are shown. Individual patients may have one, several, or all of these gastric neuromuscular abnormalities. The temporal development of these neuromuscular abnormalities in individual patients is unknown. From a neuromuscular viewpoint, gastroparesis indicates end-stage disease.

TABLE 1. MEDICATIONS THAT CAN SLOW GASTRIC EMPTYING

Anticholinergic agents
Antidepressants
β-Adrenergic agonists
Calcium channel blockers
Ganglion-blocking agents
Levodopa
Nicotine
Octreotide
Opiates
Tranquilizers
Vincristine

EVALUATION OF PATIENTS SUSPECTED OF HAVING DIABETIC GASTROPATHY

General Evaluation

Evaluation of patients with diabetes mellitus and the symptoms described above or with poor glycemic control should include a detailed history and physical examination. Insulin dosing, blood glucose patterns, and diet should be reviewed and adjusted as necessary. Basic diagnostic tests include routine laboratory tests (blood counts and chemistries), endoscopy or upper gastrointestinal series to exclude structural or mucosal abnormalities of the esophagus, stomach, and duodenum, and an ultrasound of the gallbladder and pancreas to exclude diseases of these organs that may also produce postprandial symptoms. If no abnormalities are found and symptoms and/or blood glucose levels remain difficult to control, then tests of gastric neuromuscular function should be considered.

Evaluation of Gastric Neuromuscular Abnormalities in Patients with Diabetic Gastropathy

Diagnostic tests that measure gastric myoelectrical activity and gastric emptying are indicated when the results of standard diagnostic tests are negative and symptoms persist. There are a number of methods available for assessing gastric myoelectrical and contractile events (Table 2). Some tests are invasive and are used primarily for research studies; others are noninvasive and available for clinical use.

Currently, gastric motility is generally assessed using gastric scintigraphy, a noninvasive means of mea-

TABLE 2. METHODS FOR EVALUATING GASTRIC MYOELECTRICAL AND CONTRACTILE EVENTS

Test	*Measures*	*Advantages*	*Disadvantages*
Gastric scintigraphy	Rate of stomach emptying	Noninvasive; solid- and liquid-phase studies; assesses global stomach neuromuscular activity	Wide normal range; radiation exposure; takes 2–4 hr
Electrogastrography	Gastric myoelectrical activity	Noninvasive; easily repeated	Movement artifact; difficult to interpret
Ultrasonography	Rate of emptying; antral diameter	Noninvasive	Requires expertise in imaging and interpretation; more accurate for liquid than solid emptying
Magnetic resonance imaging	Rate of emptying	Noninvasive	Time-consuming; expensive
Breath tests ^{13}C	Indirect measure of emptying	Noninvasive	Requires normal intestinal absorption, liver metabolism, lung function
Antroduodenal manometry	Assesses lumen-occluding contractions	Distinguishes fasting and postprandial contraction patterns	Invasive; radiation exposure; time-consuming (>4 hr); stressful for patient; recordings difficult to interpret

suring the rate of gastric emptying. These tests require ingestion of a meal (usually scrambled eggs or stew) labeled with radionuclides (9, 39). The test is performed in the morning after an overnight fast. Agents that can accelerate or delay gastric emptying must be discontinued 48–72 hr before the procedure. Diabetic patients are instructed to take one half of their normal morning insulin dose to avoid hyperglycemia, which can delay gastric emptying. Although both solid- and liquid-phase studies can be obtained, solid-phase studies are more sensitive for documenting gastroparesis (9). Gastric emptying is reported as the percentage of the meal emptied (or retained) after a specific period of time (usually 2 hr) or the time to emptying 50% of the meal (9, 39). The normal range of solid-phase gastric emptying is quite variable, and results can be affected to some degree by physiologic factors such as age, obesity, and menstrual cycle (9, 45). Emptying may be normal in patients with upper gastrointestinal symptoms, suggesting other more subtle abnormalities, such as gastric dysrhythmias, may be present (Figure 3).

Breath tests to measure gastric emptying are being developed. ^{13}C-labeled foods are ingested and the ^{13}C exhaled in breath is determined (46). For the ^{13}C to be present in the breath, it must be emptied from the stomach, absorbed from the intestine, metabolized by the liver, secreted into the blood, and finally expired from the lungs for measurement. The rate of emptying of the food from the stomach is then estimated from the ^{13}C values in the expired breath.

Electrogastrography (EGG) noninvasively measures fasting and postprandial gastric myoelectrical activity (24, 25). EGG records gastric myoelectric activity via electrodes placed on the skin in the epigastrium. EGG accurately reflects the normal 3 cpm electrical rhythm and abnormal gastric dysrhythmias termed tachygastrias (3.6–9.9 cpm) and bradygastrias (1.0–2.4 cpm) (24, 25). Care must be taken to keep the patient still, since artifacts in the EGG signal may be created by patient movement (25).

Ultrasonography is a noninvasive tool for evaluating gastric wall motion and gastric emptying of liquids, but considerable expertise in stomach imaging and interpretation is required (45, 47). The emptying of liquids from the stomach can be measured with this technique. Magnetic resonance imaging can accurately measure gastric emptying rates but is expensive, time-consuming, and facilities are limited (45, 48).

Antroduodenal manometry involves the positioning of a catheter in the antrum and duodenum with fluoroscopic guidance for intraluminal pressure measurements during fasting and postprandial periods (45). Small intestinal manometry can detect patterns reflecting disorders of neuropathic versus myopathic origin (45). Antroduodenal and intestinal motility tests are invasive, require fluoroscopy, are stressful for patients, and recordings can be difficult to interpret (45, 49). Table 3 lists motility test results and symptoms associated with abnormal test results.

TABLE 3. GASTRIC NEUROMUSCULAR TEST RESULTS AND ASSOCIATED SYMPTOM(S)

Test	*Result*	*Associated symptom(s)*
Gastric scintigraphy (solid-phase)	Delayed emptying (gastroparesis)	Early satiety, abdominal discomfort, fullness, vomiting
	Rapid emptying (dumping)	Abdominal discomfort, nausea, distention, diarrhea
Electrogastrography	Tachygastria, bradygastria	Nausea
Ultrasonography	Antral dilation	Bloating

Diabetic Gastropathies—A Practical Approach to Diagnosis

A practical approach to diagnosing diabetic gastropathies in patients with dyspepsia-type symptoms is to start with the noninvasive gastric motility tests and use invasive tests if further information is desired or necessary. The solid-phase gastric emptying test and the EGG will reveal abnormalities in overall emptying (a global reflection of gastric contractile function) and gastric myoelectrical abnormalities, respectively (50). If further insights into gastroduodenal function are needed, then ultrasound of the stomach, antroduodenal manometry, or barostat studies can be obtained.

TREATMENT OF DIABETIC GASTROPATHY

The treatment of diabetic gastropathies includes sustained attention to glycemic control, dietary modifications, and appropriate use of pharmaceutical agents. The goal of treatment is reduction in the upper gastrointestinal symptoms of nausea, vomiting, bloating, and early satiety or fullness; and improvement in glycemic control. In the most severe cases of diabetic gastroparesis, a gastrostomy may be indicated to vent the stomach to prevent recurrent vomiting, and a jejunostomy may be needed for enteral feeding if weight loss has occurred due to failure of the various treatment modalities (39, 42).

TABLE 4. NAUSEA AND VOMITING (GASTROPARESIS) DIET*

Diet	*Goal*	*Avoid*
Step 1: Gatorade and bouillon	1000–1500 cc/day in multiple servings (eg, 12 4-oz servings over 12–14 hr)	Citrus drinks of all kinds; highly sweetened drinks
For severe nausea and vomiting: • Small volumes of liquids such as Gatorade and bouillon (ie, salty, with some caloric content) to avoid dehydration • Multiple vitamin	Patient can sip 1–2 oz at a time to reach approximately 4 oz/hr	
Step 2: Soups	Approximately 1500 calories/day to avoid dehydration and maintain weight (often more realistic than weight gain)	Creamy, milk-based liquids
If Gatorade or bouillon tolerated: • Soup with noodles or rice and crackers • Peanut butter, cheese, and crackers in small amounts • Caramels or other chewy confections • Ingest above foods in at least 6 small-volume meals/day • Multiple vitamin		
Step 3: Starches, chicken, fish	Common foods that patient finds interesting and satisfying and that evoke 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
• 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/day • Multiple vitamin		

* Modified from Koch (11).

Dietary Modifications

Patients with symptoms of diabetic gastropathy may not tolerate standard American Diabetes Association diets. For example, patients with gastroparesis should have a diet that is low in fiber and digestible roughage, because these foods may be retained in the stomach and result in bezoar formation. A low-fat diet (<40 g/day) also is advised since lipids slow gastric emptying rates (9, 41). Patients should also be encouraged to eat small meals four to six times daily rather than consume three regular meals per day. The neuromuscular work of gastric emptying is reduced with the smaller individual meals, and some decrease in symptoms may also be experienced by the patient (11, 17). With the six smaller meals there may also be a slow but steadier rate of delivery of nutrients into the small bowel for absorption.

A three-step nausea and vomiting diet has helped patients with idiopathic gastroparesis and idiopathic nausea (Table 4) (11). This diet may be tried in the diabetic patient with upper gastrointestinal symptoms with or without frank gastroparesis. Total parenteral nutrition is rarely necessary, but some patients may require a jejunal feeding tube for enteral nutrition if gastroparesis and nausea and vomiting are severe and result in unexceptable weight loss. A venting gastrostomy may also be needed if uncontrolled vomiting is a problem.

As described above, studies in diabetic patients showed that increased blood glucose levels are associated with prolongation of the lag phase of gastric emptying (35, 36). Even if glucose levels are increased from low normal to the upper limits of normal ranges, this change in plasma glucose level slows the rate of gastric emptying (36). These studies suggest another reason to work diligently for good glucose control, since acute or chronic hyperglycemia alone has adverse effects on gastric emptying activity.

Drug Therapy

Diabetic patients with or without gastroparesis may develop the dyspepsia-like symptoms described above. Some of the patients with normal gastric emptying may have gastric dysrhythmias, altered fundic relaxation, or other subtle neuromuscular mechanisms that cause nausea and other symptoms. Gastrokinetic drugs used to treat diabetic gastropathy are metoclopramide, cisapride, erythromycin, and dom-

TABLE 5. GASTROKINETIC AGENTS USED TO TREAT SYMPTOMS ASSOCIATED WITH DIABETIC GASTROPATHIES

Drug	*Mechanisms of action*	*Oral dosage*	*Side effects*
Metoclopramide	Dopamine (D_2) receptor antagonist, 5-HT_3-receptor antagonist (central and peripheral)	5–20 mg before meals and at bedtime	Extrapyramidal symptoms, dystonic reactions, anxiety, drowsiness, hyperprolactinemia
Domperidone	D_2-receptor antagonist (peripheral)	10–20 mg before meals and at bedtime	Hyperprolactinemia
Cisapride	5-HT_4-receptor agonist (?)	5–20 mg before meals	Diarrhea, abdominal discomfort
Erythromycin	Motilin agonist	125–250 mg four times daily	Nausea, diarrhea, abdominal cramps, rash

peridone. These agents differ with respect to mechanism of action, efficacy, and side-effect profile (Table 5).

Metoclopramide. Metoclopramide has been in use as a gastrokinetic drug for many years, but therapy with this agent is limited by CNS side effects, which include extrapyramidal symptoms (11, 51). Metoclopramide is a central and peripheral dopamine (D_2) receptor antagonist, a 5-HT_4 agonist, a 5-HT_3 antagonist, and cholinesterase inhibitor (41, 42, 51). Metoclopramide improves gastric emptying by decreasing receptive relaxation in the upper stomach and increasing antral contractions (39). Metoclopramide also acts on dopamine receptors in the area postrema to produce an antiemetic effect, which may be as important as the drug's effects on the stomach in relieving the symptoms of gastropathy.

Domperidone. Domperidone, like metoclopramide, also antagonizes the peripheral D_2 receptor in the stomach, but domperidone does not readily penetrate the blood–brain barrier. Therefore, domperidone is a peripheral D_2-receptor antagonist with a low incidence of the CNS side effects that limit the use of metoclopramide (52). However, domperidone enters the pituitary and prolactin is released, resulting in prolactin-related symptoms. Domperidone improves gastrointestinal motility by inhibiting fundic receptive relaxation and enhancing antral contractions (52). Domperidone reaches the area postrema where its antiemetic action is produced.

The ability of domperidone to improve symptoms attributed to delayed emptying in diabetic patients is well documented (5, 52, 53). In a recent multicenter, double-blind, placebo-controlled trial, 77% of diabetic patients with symptoms of gastropathy experienced significant reductions in symptom severity following treatment with domperidone (54). Moreover, symptoms were alleviated regardless of the patient's gastric emptying status. Therefore, reduction in symptoms is not solely due to drug effects on the rate of gastric emptying. Domperidone also affects gastric myoelectrical activity by eradicating gastric dysrhythmias and reducing symptoms in patients with diabetic gastroparesis while modestly improving the rate of stomach emptying (5).

In a multicenter, double-blind comparison of domperidone and metoclopramide, the drugs were equally effective in relieving symptoms of nausea, vomiting, early satiety, and bloating/distension in 93 patients with insulin-requiring diabetes, but side-effect profiles were significantly different (55). The severity in elicited CNS side effects, including somnolence and reduced mental acuity, was greater during metoclopramide treatment. Open-label, long-term use of domperidone continued to control symptoms of diabetic gastropathy (56).

Cisapride. Cisapride improves gastric emptying through the release of acetylcholine in the myenteric plexus neurons of the stomach via 5-HT_4 receptors (57). Cisapride does not pass the blood–brain barrier and is thus free of CNS or prolactin-related side effects. Cisapride stimulates antral contractions and improves the emptying of both solids and liquids (58, 59). In the United States, cisapride is approved for the treatment of nocturnal heartburn, but this therapeutic benefit is achieved by improving lower esophageal sphincter pressure and enhancing gastric emptying. Thus, a therapeutic trial of cisapride (5–20 mg four times a day) is a reasonable option for the patient with symptomatic diabetic gastropathy.

Erythromycin. Erythromycin binds to the motilin receptor in the stomach, resulting in strong contractions of the antrum. Compared with placebo, intravenous erythromycin significantly improved the gastric emptying rates of solids and liquids in insulin-requiring diabetes patients with severe gastroparesis (60, 61). Long-term oral erythromycin also improved gastric emptying and reduced symptoms, but dose-dependent cramps and abdominal pain were common (61). Many patients are unable to tolerate erythromycin due to these side effects. New motilin-receptor agonists are based on the macrolide (lactone-ring)

structure. Other macrolide molecules are in development and will be available in the future to treat diabetic gastroparesis.

Other agents with possible gastrokinetic effects are under investigation. These include 5-HT_4-receptor agonists, cholecystokinin antagonists, and opiate receptor agents.

Nondrug Treatments

Nondrug treatment of nausea and vomiting related to gastroparesis or diabetic gastroparesis includes acustimulation at P6, a traditional Chinese acupuncture point (62), and gastric electrical stimulation using cardiac pacemaker technology (63). Acustimulation at P6 reduces nausea related to the first trimester of pregnancy (64), postoperative nausea and vomiting (65), and cancer chemotherapy treatments (66). Acustimulation treatment reduced idiopathic nausea approximately 40% in patients whose symptoms were refractory to drug therapy (62). The mechanism of action of acustimulation at P6 is unknown and further studies are needed.

For patients with drug-refractory gastroparesis who have also lost weight and require nutritional support, gastric electrical stimulation may have a role in the future. Preliminary studies have shown that electrodes positioned on the gastric corpus and stimulated at novel parameters reduce the incidence of vomiting and nausea episodes (63). Ongoing studies will clarify the patients for whom this is most suited as well as the efficacy of long-term gastric electrical stimulation.

CONCLUSIONS

Diabetic gastropathies encompass a spectrum of gastric neuromuscular dysfunctions, from gastric dysrhythmias to gastroparesis (Figure 7). The upper gastrointestinal symptoms described above that are associated with gastric neuromuscular dysfunction are common in patients with diabetes mellitus. Some diabetic patients have gastroparesis, but the symptoms of nausea and vomiting, abdominal discomfort, postprandial fullness and bloating, and early satiety do not always correlate with the presence of gastroparesis. Other gastric neuromuscular dysfunctions such as dysrhythmias or altered fundic or antral tone may be more relevant to symptoms.

Symptoms can be treated with dietary modifications, attention to glycemia and insulin dosing, and gastrokinetic therapies with metoclopramide, cisapride, and erythromycin. A fourth gastrokinetic drug—domperidone—is under review and should be available in the near future. Further studies are needed to assess the utility of acustimulation and gastric electrical stimulation in diabetic gastropathies. In addition, drug combinations should be studied in more detail before recommendations can be made; the combination of cisapride and erythromycin must be avoided. As the pathophysiology of the diabetic gastropathies are better understood, more specific and effective therapies can be developed.

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