REVIEW

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Diabetic gastropathy: A practical approach to a vexing problem

ABSTRACT

The clinical presentation of diabetic gastropathy varies, and a diagnosis usually must be confirmed with tests that evaluate the structure and function of the upper gut. Although glucose control, dietary changes, and drug therapy are the current mainstays of treatment, they may not be effective. Gastric pacing, a new technique that stimulates gastric motility, may give physicians another management tool.

KEY POINTS

Because high blood sugar levels can slow gastric emptying, adequate glucose control is a key factor in the treatment of diabetic gastropathy.

Common causes of nausea, vomiting, and abdominal pain need to be excluded before a diagnosis can be made because the clinical presentation of diabetic gastropathy is variable.

Although gastroparesis is a common cause of clinical symptoms, gastrointestinal symptoms may be present even when gastric motility is normal.

THE NAUSEA, VOMITING, AND OTHER gastrointestinal symptoms that commonly afflict patients with diabetes present a vexing set of diagnostic and treatment challenges to physicians.

Just agreeing on the *definition* is difficult. Many ascribe symptoms to diabetic gastroparesis, assuming that delayed gastric emptying is the culprit. However, diabetes can cause a wide variety of neuromuscular problems in the stomach and gastrointestinal tract—functional, contractile, electrical, and sensory—so the broader term diabetic gastropathy is more accurate.

Determining the *causes* of diabetic gastropathy is difficult as well. Often the gastrointestinal symptoms are intermittent, making it difficult to tell whether the cause is permanent neuropathy of autonomic and enteric nerves, transitory variations in glycemic control, or an interaction between the two.

Treatment can be difficult, too, because the relationship between high blood sugar and gastric emptying is reciprocal. Hyperglycemia can slow gastric motor function and delay emptying, which in turn can impair glucose control by producing a mismatch between the rate of nutrient delivery to the small bowel and the onset of insulin or oral hypoglycemic medications. Thus, adequate glucose control is vital, although difficult.

But even when patients have tight control over their blood sugar and have tried other treatments—mainly diet modification and drug therapy—there is no guarantee that their diabetic gastropathy will resolve. In the past, the physician has had little to offer such patients other than suggesting they undergo placement of a jejunostomy tube.

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TABLE 1

Stepwise diagnosis of diabetic gastropathy

Step 1	Detailed history and physical examination
Step 2	Exclude mechanical obstruction of stomach or small bowel with upper endoscopy, barium radiogram, or CT scan
Step 3	Exclude metabolic factors: poor glucose control, uremia Exclude adverse effects of drugs, central nervous system disorders, and pregnancy
Step 4	Perform scintigraphic studies of solid-phase and liquid-phase gastric emptying

IS THE CAUSE NEUROPATHY OR HYPERGLYCEMIA?

Most of what is known about diabetic gastropathy comes from studies that used rats with spontaneous and streptozotocin-induced diabetes. Two studies found structural abnormalities in the sympathetic and parasympathetic nerves that innervate the gut.[1,2] Histologic and immunohistochemical studies that have examined the myenteric nerves also have revealed structural abnormalities[3–6] as well as reduced nitric oxide synthase in the myenteric plexus.[7] Whether these findings can be generalized to humans is not clear, particularly the studies that used streptozotocin-induced diabetic rats, because this drug can be toxic to both nerves and islet cells.[3]

In mild cases, try simple dietary measures first

Human studies have provided no definitive answers about the pathogenesis either. Morphological studies on the autonomic and enteric nervous systems in human diabetic patients found no consistent abnormalities.[8–11]

Vagal nerve impairment has been detected in patients with diabetes,[12] and it likely plays a major role in the development of diabetic gastropathy. One study showed that patients with type 1 diabetes mellitus have an impaired vagal response to stimuli.[12] Also, gastric motor abnormalities in people with diabetes are comparable to those in patients who have had a vagotomy,[13,14] and induced hyperglycemia in healthy subjects can impair gastric motor function, which resembles the postvagotomy condition.[15] Hyperglycemia can also impair vagal function, as determined by its effect on gallbladder response to sham feeding.[16]

SYMPTOMS DO NOT ALWAYS CORRELATE WITH GI PATHOLOGY

The prevalence of diabetic gastropathy is not known, owing to the lack of population-based studies; however, many people with diabetes have gastrointestinal symptoms. In one study, motor abnormalities throughout the gastrointestinal tract were detected in up to two thirds of selected adults with diabetes.[17] In an early study of unselected patients with diabetes, nausea and vomiting were the most common symptoms, occurring in 29% of patients.[18] In a more recent survey of outpatients at a diabetes clinic,[19] upper gastrointestinal problems were the most common symptoms: heartburn (44.9%), bloating (34.2%), nausea (29.7%), early satiety (26.3%), and constipation (22.6%). The frequency of such gastrointestinal symptoms was comparable in patients with type 1 and 2 diabetes.[19]

Nausea and vomiting are among the most disabling symptoms in diabetic gastropathy. They commonly occur during acute episodes of ketoacidosis and may occur in a chronic pattern with fluctuating severity. A few diabetic patients experience intermittent, severe nausea and vomiting that require hospitalization, with symptom-free periods in between. Why this occurs is unclear, although periods of poor glucose control may be a factor.

Keep in mind that diabetic gastropathy symptoms may not correlate with gastric emptying abnormalities. Distressing upper gut symptoms may be present even when gastroparesis is not. But that should not come as a surprise given the involvement of various segments of the stomach or small bowel in diabetes that may not affect food emptying.

TABLE 2

Treatment of diabetic gastropathy

Step 1	Adequate glucose control Correct metabolic abnormalities such as ketosis, uremia, and hypokalemia Avoid drugs that can slow gastric emptying such as narcotics, anticholinergics, tricyclic antidepressants, and calcium-channel blockers
Step 2	Dietary modification Low-residue, low-fat diet Small, frequent meals Supplement with liquid formulas
Step 3	Monotherapy with antiemetic or prokinetic agents or both
Step 4	Combination pharmacotherapy (cisapride + metoclopramide, erythromycin + metoclopramide)
Step 5	Alternative feeding methods Jejunostomy tube Intravenous hyperalimentation

Symptoms may not be correlated with the degree of neurological damage caused by diabetes either. Patients with long-term peripheral and autonomic neuropathy, nephropathy, and retinopathy may or may not experience symptoms related to gastropathy. On the other hand, some patients with diabetic gastroparesis may have only minimal gastrointestinal symptoms.

EVALUATION AND DIAGNOSIS

A diagnosis of diabetic gastropathy is usually based on the clinical presentation and confirmed by tests that evaluate the structure and function of the upper gut (TABLE 1). Mechanical obstruction of the stomach or small bowel should be excluded by endoscopy, barium studies, and, when necessary, an abdominal CT scan. Metabolic abnormalities such as uremia and hypokalemia—and hyperglycemia, in particular—should be evaluated.

As with every patient with nausea and vomiting, it is important to consider causes that are not related to diabetes, such as drug side effects, central nervous system disorders, and pregnancy. Also, functional dyspepsia, which is common in the general population and causes similar upper gastrointestinal symptoms, can occur coincidentally in the patient with diabetes.

The evaluation usually ends with quantitative tests of the gastric emptying rate. Various techniques are available, including electrogastrography, ultrasonography, magnetic resonance imaging, antroduodenal manometry, and gastric scintigraphy. The last method is most commonly used. With this technique, patients consume a radioisotope-labeled meal. Counts of the radioisotope are then taken at intervals to evaluate the rate of gastric emptying. Both solid-phase and liquid-phase gastric emptying studies should be performed because some diabetic patients have an abnormally rapid rate of liquid-phase emptying.[20]

Try to keep plasma glucose levels below 200 mg/dL

TREATMENT

The goals of treatment are twofold: to improve symptoms and quality of life and to provide adequate nutrition to patients most severely affected. A stepwise approach (TABLE 2) can be followed.

Control glucose levels

Try to keep your patient's plasma glucose level less than 200 mg/dL—glucose levels higher than 150 mg/dL can delay gastric emptying in patients with type 1 diabetes.[21] Adequate glucose control can also improve gastric myoelectrical activity and autonomic function in patients with diabetic gastropathy.[22] Keep in

mind, though, that intensive glycemic control may not be possible in patients with advanced gastroparesis, and it may not make a difference in the severity of their symptoms.

Identify all medications the patient is taking

Obtain a complete list of all the medications your patient is taking because various drugs can aggravate diabetic gastropathy. These include tricyclic antidepressants such as amitriptyline, narcotics, anticholinergics/antispasmodics such as hyoscyamine, and calcium-channel blockers. If possible, avoid using these drugs in diabetic gastropathy patients, or consider decreasing the dose or replacing them altogether with alternative medications. Also, correct any metabolic abnormalities such as ketosis, uremia, and hypokalemia.

Dietary interventions

In mild cases, simple dietary measures should be tried first. Patients should eat small, frequent meals rather than a few large ones and avoid high-fat foods, which can delay gastric emptying. Because the stomach may empty liquids faster than solids, patients should be encouraged to replace solid foods with liquid replacement meals whenever possible. Patients who experience severe symptoms should substitute part or most of their solid food intake with liquid formula.

Encourage patients to replace solid food with liquid meals

Gastric bezoars can occur when patients with diabetic gastropathy eat high-residue foods such as fruits and vegetables, which are difficult to digest. To prevent this problem, they should be advised to peel fruits and cook vegetables such as carrots and cauliflower until they are very soft. Leafy vegetables such as lettuce that cannot be prepared in this way should be avoided altogether.

These dietary changes may enhance gastric emptying and result in higher levels of postprandial glucose. The patient may need to adjust his or her insulin therapy by taking higher doses of short-acting insulin before meals. This may be particularly relevant for patients who use frequent daily dosing of insulin for tight glucose control.

Treating nausea and vomiting

Nausea and vomiting should be treated with antiemetic and prokinetic agents. Traditional antiemetic agents such as phenothiazines and new, more potent classes of drugs such as serotonin 3 antagonists (ondansetron) are available in various dosage forms. The parenteral route may be appropriate for inpatients, while outpatients may take these drugs by mouth or use suppositories (such as promethazine) when nausea and vomiting impair oral use.

Prokinetic drugs

Prokinetic (promotility) agents are also used to treat diabetic gastropathy. However, the agent most commonly used for this condition, cisapride, is being withdrawn from general availability and will only be available through an investigational, limited-access program (see below). The following drugs may improve glycemic control by improving gastric emptying in patients with this condition:[23]

Metoclopramide (Reglan) is a dopamine antagonist that has prokinetic and antiemetic properties. It is particularly useful when given intravenously or subcutaneously in outpatients to treat acute exacerbation of nausea and vomiting. Major side effects include tremors and a Parkinson-like syndrome. These effects occur as a result of its antidopaminergic activity in the central nervous system, which limits its long-term use.[24] Metoclopramide should be discontinued as soon as any neurological problems are detected.

Doses range from 5 to 20 mg up to four times a day. When used to treat chronic disease, tablets or elixir are preferred. These are available at doses of 10 to 20 mg. Patients should take the tablets or elixir 30 minutes before meals and at bedtime.

Domperidone is another type of dopamine receptor antagonist. Like metoclopramide, it has prokinetic and antiemetic properties, but it penetrates the blood-brain barrier less and does not cause extrapyramidal side effects.[25] It also is more effective and better tolerated, making it an attractive alternative to metoclopramide.[25] However, it is not yet approved for use in the United States. It is available worldwide and is under consideration by the US Food and Drug Administration (FDA). The standard dose is 10 to 30 mg orally 30 minutes before meals and at bedtime.

Erythromycin is a macrolide antibiotic that, along with its nonantibacterial ana-

logues, enhances gastric and small bowel motor function by acting on motilin receptors in the gut.[26] When given intravenously to patients with diabetic gastropathy, erythromycin enhances gastric emptying. But the effect is markedly diminished when it is given orally.[26] Its overall therapeutic effect also diminishes with time when it is given orally.[27] When the drug was given intravenously in the long term (1 to 19 months) to outpatients in an ambulatory setting, it was effective but was associated with a high frequency of intravenous line sepsis.[28] Currently, erythromycin is most useful when used for short-term treatment of patients with gastroparesis or in combination with other prokinetic agents except cisapride.

Recommended doses are 125 to 250 mg orally, up to four times a day, 30 minutes before meals and at bedtime (tablets or suspension form) or 100 to 250 mg intravenous bolus for 20 to 60 minutes.

Cisapride (Propulsid) works by stimulating serotonin type 4 receptors in the myenteric plexus. Cisapride was recently withdrawn from general distribution and will only be available from Janssen Pharmaceutica through a limited- access program for patients for whom other drug treatments fail. This program will require that a gastroenterologist consultant be involved in the care of the patient, that the use of the drug have institutional review board approval, that physicians obtain a signed informed consent form from the patient, and perform baseline and serial laboratory tests and obtain an electrocardiagram.

Cisapride is an effective treatment for idiopathic gastroparesis that can be used on a long-term basis, but it has no antiemetic properties.[29] It can also be used to treat gastroesophageal reflux disease,[30] which can be aggravated by gastroparesis. The major adverse effects are abdominal cramping, diarrhea, and headache.

The co-administration of prokinetic drugs with azole antifungal agents, macrolides (including erythromycin and clarithromycin), anti-HIV protease inhibitors, and some antidepressants is contraindicated. These drugs may increase serum levels of cisapride, resulting in a prolonged QT interval and torsades de pointes. It is these complications that prompted the manufacturer to restrict its use. Prior to its withdrawal from general availability, FDA guidelines advised physicians to obtain an electrocardiogram and check blood levels of potassium, calcium, magnesium, and creatinine in each patient before starting cisapride treatment. Cisapride should not be prescribed if the patient's QT interval is longer than 450 msec.

The standard dose is 10 to 20 mg two to four times a day, 30 minutes before meals and at bedtime. If no improvement is seen with the standard tablet form, use the suspension form.

Combination therapies

A patient may require more than one prokinetic agent if monotherapy fails. Although combination therapy has not been extensively studied, it may be necessary in patients who are recalcitrant. When combination therapy is indicated, an agent with a different mechanism of action is added. The addition of metoclopramide to cisapride is helpful because of the antiemetic property of metoclopramide.[31] Combinations of metoclopramide and erythromycin can also be used.

There are a limited number of options available for patients whose condition does not respond to medical therapy and particularly for those who lose weight. A jejunostomy tube should be tried first. Research has shown that it can improve symptoms[32] as well as glucose control and gastric emptying.[33] A gastrostomy is rarely indicated.

Coadministration of cisapride and erythromycin is contraindicated

If adequate nutrition cannot be provided by the enteral route, intravenous hyperalimentation may ultimately be necessary. Gastric surgery, such as a subtotal gastrectomy, may be an effective treatment for other types of gastroparesis but has not been successfully used in patients with diabetes.[34]

Gastric pacing

More recently, a novel technique of pacing the stomach has been used to improve gastric motility and symptoms in nine patients with gastroparesis, five of whom had refractory diabetic gastropathy.[35] During surgery to place a jejunostomy tube, four pairs of temporary 28-gauge cardiac wires were implanted on the serosa. One pair of wires was used for pacing and the rest were used to record gastric myo-

electrical activity; the leads were attached to a portable pacemaker. The patients were instructed to use the pacemaker up to 1 hour before a meal and for up to 3 hours afterward. After a mean of 45 days, gastric emptying significantly improved—so much so that eight of the nine patients no longer had to rely on jejunostomy tube feedings. The FDA has approved the gastric pacing system as a humanitarian use device, which means that instituitional review board approval must be obtained prior to its use. Although promising, the clinical role of this interesting approach requires further study.

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