ORIGINAL ARTICLE

Diabetes mellitus affects various organs, including the gastrointestinal tract. The stomach is commonly affected, and symptoms related to the upper GI tract are frequently reported. Management of diabetic gastropathy involves dietary modifications, pharmacological agents, and occasionally, alternative feeding methods.

A Review of Diabetic Gastropathy

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Diabetes mellitus is a common disease, with substantial morbidity and considerable cost to the national health system.[1] Various organs are affected, chief among them are the kidneys, eyes, and the cardiovascular and cerebrovascular systems. Diabetes can affect the gastrointestinal (GI) tract throughout its length, the stomach in particular, and result in substantial morbidity.[2] We focus on gastric dysfunction in diabetes and review its pathophysiology, evaluation, and treatment.

PATHOPHYSIOLOGY

Diabetic gastropathy is a symptom complex with functional, contractile, electrical, and sensory dysfunction of the stomach.[2] The term gastropathy is more appropriate than gastroparesis, since gastric stasis of food is only one of a number of gastric disturbances observed in diabetes.

The effect of diabetes on the motor function of the stomach is multifactorial, the pathogenesis involving impairment of both autonomic and enteric nervous systems. Most data are derived from either streptozotocin-induced or spontaneously diabetic rats and showed significant abnormalities of both the sympathetic and parasympathetic elements innervating the gut.[3,4] Morphologic and immunohistochemical staining studies showed abnormalities of the myenteric nerves,[5-7] abnormal function of myenteric neurons,[8,9] and reduced nitric oxide synthase in the myenteric plexus.[9] However, whether these findings can be extrapolated to humans is not clear, particularly in the case of the streptozotocin-induced diabetic rat, since streptozotocin can be neurotoxic.[5] Morphological studies of the autonomic and enteric nervous systems in diabetic patients give conflicting results,[10-13] while vagal function is impaired.[14] It is likely that vagal dysfunction plays a major role in the pathogenesis of diabetic gastropathy. There is evidence of impaired vagal response to stimuli in

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insulin-dependent patients.[14] Gastric motor abnormalities in diabetics are comparable to those seen in patients following vagatomy.[15-16] Induced hyperglycemia, known to impair vagal function,[17] also impairs gastric motor function in healthy subjects, resembling the postvagotomy condition.[18] Thus, hyperglycemia in diabetics may further compromise gastric function by impairing vagal function. In the diabetic patient, hyperglycemia can aggravate gastroparesis.[19] This is an important finding since adequate glucose control is critical in the management of patients with diabetic gastropathy.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

The prevalence of diabetic gastropathy is unknown due to the lack of population-based studies. In selected diabetic patients, motor abnormalities throughout the GI tract can be detected in up to two-thirds of adult patients.[20] In an early study of unselected diabetic patients, nausea and vomiting was the third most common symptom complex (29% of patients).[21] More recently in a survey of patients visiting a diabetic clinic, upper GI symptoms were most frequent: heartburn (44.9%), bloating (34.2%), nausea (29.7%), early satiety (26.3%), and constipation (22.6%). Frequency was comparable between type 1 and 2 diabetics.[22] Nausea and vomiting are among the most disabling GI symptoms in diabetes. They are common during acute ketoacidosis, or present in a chronic pattern with fluctuating severity. A minority of patients present with intermittent severe episodes of nausea and vomiting requiring hospitalization and symptom free for periods in between. The pathophysiology is unclear, although periodic poor control of glucose may be a contributing factor.

The relationship between gastric emptying and glucose control is reciprocal. Gastric emptying can influence glucose homeostasis via a mismatch between the rate of nutrient delivery to the small bowel and the onset of insulin or oral hypoglycemic action. The role of the stomach in the regulation of glucose homeostasis is established.[23] In healthy individuals, the rate of gastric emptying is a determining factor in carbohydrate absorption and glucose homeostasis,[24] whereas impaired gastric emptying can delay the absorption of sulphonylurea drugs.

EVALUATION

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. Mechanical obstruction of the stomach or small bowel should be excluded by endoscopy, barium studies, and when necessary, abdominal computed tomography scan. Metabolic abnormalities, such as uremia and particularly hyperglycemia, should be evaluated. As with every patient with nausea and vomiting, factors not related to diabetes, such as side effects of drugs, central nervous system disorders and pregnancy should be considered. The evaluation is usually completed by quantitative tests of the rate of gastric emptying. The scintigraphic technique, which uses a radioisotope labeled test meal, is most commonly used. The addition of a liquid phase gastric emptying study may be helpful, as some diabetic patients may have an abnormally rapid rate of liquid emptying.[25] Conversely, upper gut symptoms may be present in the diabetic patient in the absence of documented gastroparesis, given the involvement of various segments of the stomach in diabetes. Finally, functional dyspepsia, which is common in the general population, and presents with comparable upper gut symptoms, could occur coincidentally in the diabetic patient.

TREATMENT

Management of diabetic gastropathy is aimed at improving symptoms and quality of life, and providing adequate nutrition to those most severely affected. In most patients management consists of dietary and pharmacologic manipulations. Every effort should be made to maintain adequate glucose control (a plasma glucose level < 200 mg/dL).

Diet. Small frequent meals should replace standard meals. Since the rate of emptying of liquids may be normal whereas solids are delayed, patients should be encouraged to replace solid food by liquid formulas whenever possible. Gastric emptying of nondigestible residue (such as found in fruits and vegetables) requires gastric motor functions that may be impaired in diabetic gastropathy, and hence, should be avoided to prevent gastric bezoars. High fat diets should also be discouraged.

Drug Therapy. Patients with nausea and vomiting should be treated with antiemetic and prokinetic drugs. Traditional antiemetics, such as the phenothiazines (promethazine and chlorpromazine) or newer, more potent, such as serotonin-3 antagonists (ondansetron) are available in various modes of administration. Parenteral route can be used for inpatients, while outpatient can use suppositories (phenergan) when nausea and vomiting impair oral use.

Prokinetic drugs include various medications that enhance gastric emptying.

*Cisapride.** Cisapride acts by stimulating serotonin type 4 receptors in the myenteric plexus. It has proved effective in the treatment of idiopathic gastroparesis, but has no antiemetic property.[26] It is also effective in the treatment of gastroesophageal reflux disease,[27] which can be aggravated by gastroparesis. Major side effects include abdominal cramping, diarrhea, and headache. The coadministration of azole antifungal drugs, macrolides (including erythromycin and clarithromycin), HIV protease inhibitors and some antidepressants is contraindicated for fear of increasing serum level of cisapride resulting in prolonged QT interval and torsade de pointes. However, its limited side effects and overall efficacy[27] make it an attractive option for the long-term treatment of gastroparesis. Standard dosage is 10 to 20 mg two to four times a day orally, 30 minutes before meals and at bedtime. If no effect is seen with the tablet, the suspension should be used.

Metoclopramide. Metoclopramide is a dopamine antagonist with a prokinetic and antiemetic properties. Major side effects such as tremors and Parkinson-like syndrome result from its antidopaminergic activity in the central nervous system, and limit its long-term use.[28] It is particularly useful when given intravenously (or subcutaneously in outpatient setting), for acute exacerbation of nausea and vomiting, with doses ranging from 5 to 20 mg, repeated up to four times. For chronic use, oral administration of the tablet or elixir is available at doses of 10 to 20 mg, 30 minutes before meals and at bedtime.

Domperidone. Like metoclopramide, domperidone is a dopamine receptor antagonist, with minimal penetration of the blood-brain barrier that accounts for absence of extrapyramidal side effects.[29] It also has prokinetic and antiemetic properties. Its fewer central nervous system side effects, greater efficacy, and better tolerance make it an attractive alternative to metoclopramide.[29] Standard dosage is 10 to 30 mg orally 30 before meals and at bedtime. It is available worldwide, and is expected to be approved in the US in the near future.

Erythromycin. Macrolide antibiotics and their nonantibacterial analogues enhance gastric and small bowel motor function by binding to motilin receptors in the gut.[30] Erythromycin, given intravenously, is a potent stimulant for gastric emptying in diabetic patients with gastroparesis. This effect is markedly diminished when given orally.[30] In addition, the overall therapeutic effect is also diminished over time when the drug is given orally.[31] Long-term intravenous administration in ambulatory setting (ranging from 1 to 19 months) was shown effective but associated with high frequency of line sepsis.[32] Currently, erythromycin is most useful in the short-term treatment of patients with gastroparesis, or in combination with other prokinetic agents, with the exception of cisapride.

Recommended doses are 125 to 250 mg orally, up to 4 times a day, 30 minutes before meals and at bedtime (tablets or suspension form) or 100 to 250 mg intravenous bolus over 20 to 60 minutes.

Combination therapy. Treatment with more than a single prokinetic may be necessary when monotherapy fails. When combination therapy is indicated, it is recommended that drugs with different mechanisms of action be considered. The addition of metoclopramide to cisapride is particularly effective,[33] though metoclopramide and erythromycin can also be used. When available, the combination of cisapride and domperidone may be particularly desirable.

Refractory patients. A limited number of options are available for patients who fail to respond to medical therapy, and particularly for those who sustain weight loss. The insertion of a feeding jejunostomy tube (endoscopic, laparoscopic, or open surgery) was shown to improve symptoms,[34] glucose control, and gastric emptying.[35] A gastrostomy is rarely indicated. Gastric surgery, such as subtotal gastrectomy, which may be effective in other types of gastroparesis, has not been successful in patients with diabetes.[36] More recently, a novel technique of pacing the stomach using electrodes attached to the surface of the stomach has been reported to improve gastric motility and symptoms in a few patients with refractory diabetic gastropathy.[37] The clinical role of this interesting approach requires further study. **CT**

*Since the submission of this manuscript, cisapride was removed from the US market because of cardiac arrhythmias.

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