Gastrointestinal Disturbances in Diabetes

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Gastrointestinal disorders are common in patients with diabetes mellitus. As many as 75% of patients visiting diabetes clinics will report significant gastrointestinal (GI) symptoms. The symptom complex experienced may vary widely. Many patients go undiagnosed and undertreated. Patients with a history of retinopathy, nephropathy, or neuropathy should be presumed to have GI abnormalities until proven otherwise. The workup should start with a thorough patient history and appropriate laboratory, radiographic, and GI testing. In addition to pharmacologic therapy, glycemic control and dietary manipulation play an important role in managing GI disorders in people with diabetes.

Introduction

Gastrointestinal (GI) disorders have long been observed in diabetic patients. It is relatively common in clinical practice to encounter diabetic patients who complain of GI symptoms. Common symptoms associated with impaired gastrointestinal motility include the following: dysphagia, early satiety, anorexia, reflux, constipation, abdominal pain, abdominal distention or bloating, nausea, vomiting, diarrhea, regurgitation, dyspepsia or indigestion, straining, urgency, anal blockage, and fecal incontinence.

There has been much uncertainty as to whether these GI symptoms are truly increased in patients with diabetes when compared to those without the disease. Recently, a study published by Bytzer *et al.* [1••] proved that all upper and lower GI symptoms that were evaluated were more common in diabetic patients than in control subjects. Earlier studies had revealed conflicting results. Studies by Feldman and Schiller [2] and Clouse and Lustman [3] had found that 76% of patients referred to a diabetes clinic in the United States had at least one GI tract symptom ,and 20% of patients with diabetes from the registry of a General Clinical Research Center had nausea, abdominal pain, and diarrhea, respectively. However, in the Rochester Diabetic Neuropathy Study, only 1% of the patients had symptoms of gastroparesis and only 0.6% had nocturnal diarrhea [4]. Similarly, in the Pittsburgh Epidemiology of Complications Study, autonomic symptoms and GI tract manifestations were rare [5]. These were studies done in tertiary settings. Another study looking at the prevalence of GI disturbances in diabetes in the community showed that GI tract symptoms were similar in persons with or without diabetes [6•]. The pathogenesis underlying GI symptoms in diabetes is poorly defined and controversial. Some of the factors implicated include autonomic neuropathy [2], hyperglycemia [7•], psychiatric comorbidity [8•], and duration of diabetes [9].

In a cross-sectional study of 1101 subjects with diabetes recruited from outpatient clinics, 57% reported at least one GI complication [7•]. These complications were independently associated with both symptom complexity (*ie,* number of symptoms) and self-reported symptoms of peripheral neuropathy. Poor glycemic control assessed by hemoglobin A_{1c} and self-reported fingerstick blood glucose measurements were an independent risk factor for upper GI symptoms. Increased levels of anxiety and depression have been found to be associated with GI symptoms such as abdominal pain, postprandial fullness, nausea, dysphagia, and loose watery stools [8•]. It is uncertain whether psychological distress is causally linked to symptoms or whether GI symptoms increase anxiety and depression. The entire GI tract can be affected by diabetes, from the oral cavity and esophagus to the large bowel and anorectal region. This article reviews the common GI disorders seen in diabetic patients, their pathophysiology, and the current management recommendations.

Esophageal Abnormalities

Esophageal dysmotility in diabetes is mostly due to autonomic dysfunction [10]. Most patients with motility abnormalities also have other evidence of peripheral and autonomic neuropathy. Symptoms are also more common with coexisting gastroparesis [10]. The symptoms of esophageal abnormalities may be heartburn, dysphagia, or even chest pain. Twenty-four-hour pH studies have shown that gastroesophageal reflux is more prevalent in diabetic patients [11]. However, reflux does not seem to occur more frequently in diabetic patients with neuropathies versus those without evidence of neuropathic changes. The esophageal manometric abnormalities that have been described in patients with diabetes mellitus include hypotensive lower

esophageal sphincter pressure, decreased amplitude and frequency of esophageal contractions, and prolonged or aperistaltic contractions in the body of the esophagus [12]. The treatment of esophageal symptoms in diabetes should follow the same guidelines as those used in patients without diabetes. Use of conservative measures, antacids, antisecretory agents, and possibly a prokinetic agent for gastric stasis may be necessary.

Odynophagia is another symptom that is often reported. In the setting of diabetes, this must be carefully evaluated and should be considered *Candida esophagitis* until proven otherwise [13]. Endoscopy with biopsy and brushings is the most sensitive and specific diagnostic test. The preferred treatment is with fluconazole 200 mg on day 1, then 100 mg/d for at least 3 weeks. Refractory cases may need treatment with intravenous amphotericin.

Gastric Abnormalities

Gastroparesis is one of the most common motility disturbances seen in diabetes mellitus; it affects 58% of diabetic patients [14]. It was first described as a complication of diabetes in 1945 [15]. It is associated with retinopathy, nephropathy, peripheral neuropathy, and other forms of autonomic dysfunction. Symptoms include early satiety, weight loss, anorexia, postprandial nausea, vomiting, bloating, and epigastric distress. Rarely, patients can also present with retrosternal or epigastric pain and symptoms suggestive of cardiac, biliary, or pancreatic disease. The pathogenesis of gastroparesis is related to lack of antral motor function and coordination, hyperglycemia, and other factors such as hypokalemia or acidosis [10].

Diabetic gastroparesis affects several aspects of the normal and fed patterns in the stomach [16]. Receptive relaxation of the stomach may be affected and may contribute to accelerated emptying of liquids and an abnormal gastroduodenal pressure gradient. During the fasting state, phase III activity, which is responsible for the emptying of indigestible solid food from the stomach, is reduced or absent [17]. As a result of delayed emptying of indigestible solids, bezoars are often found in diabetic gastroparesis. Postprandial antral contractions may also be diminished in frequency and amplitude in diabetic gastroparesis. Diabetic patients may also have pyloric dysfunction or spasm, which may explain recurrent nausea and vomiting [18].

Acute hyperglycemia (blood glucose level > 200 mg/dL) may lead to delayed gastric emptying in both healthy individuals and in those with diabetes [19,20]. In healthy individuals, the induction of hyperglycemia results in antral hypomotility, stimulates isolated pyloric pressure waves, and increases the compliance of the gastric fundus, all of which retard gastric emptying [21]. Even physiologic changes in blood glucose within the normal postprandial range can impair gastric emptying. For example, in one study, intragastric retention of a solid meal at 100 minutes in eight normal subjects was 55% at a blood glucose level of 144 mg/dL compared with 37% at a blood glucose level of 72 mg/dL. The values in nine type 1 diabetic patients were 44% and 36%, respectively. The differences between normal subjects and those with diabetes were not significant, showing that gastric emptying during physiologic hyperglycemia was not mediated by changes in plasma insulin [22]. These findings show that acute elevations of glucose result in delayed gastric emptying. The role of chronic hyperglycemia is less clear. There are also no studies that show that improvement in glycemia improves gastric emptying.

Hormonal imbalances may also play a role in diabetic gastroparesis. Diabetic patients have elevated basal levels of motilin [23]. These elevated levels may be a compensatory reaction as a result of decreased frequency of migrating motor complexes seen in gastroparesis. When gastroparesis is treated with metoclopramide, the levels of motilin decrease [24].

The diagnosis and treatment of gastroparesis is crucial because, if clinically significant, it can compromise adequate glycemic control or impair absorption of orally administered drugs. The diagnosis requires demonstration of a delay in gastric emptying. Barium studies and scintigraphy using labeled liquid meals are of limited use because the gastric emptying of liquids and semisolids is frequently normal even in the presence of moderately severe symptoms. Assessment of the emptying of solids is a more sensitive test. Initial studies can include esophagogastroduodenoscopy to rule out peptic ulcer disease and esophagitis [13]. This can then be followed by radiolabeled scintigraphy after ingestion of a solid meal to document gastric emptying and quantify response to prokinetic agents [16]. Scans taken immediately after meal ingestion and 2 and 4 hours later showing the proportion of radioisotope retained in the stomach are sufficient in most cases to make the diagnosis.

Treatment

Several modalities of therapy may be required to relieve symptoms effectively (Table 1). The mainstay of treatment should revolve around tight management of blood glucose levels. Treatment should include diet modification, such as eating small frequent meals and use of liquid supplements. A low-residue diet to avoid bezoar formation should be recommended. Enteral nutrition via a jejunostomy tube may be required occasionally, but parenteral nutrition should be restricted to cases with severe gastric and small intestine dysmotility. If symptoms do not respond adequately to dietary modification, the use of drugs that increase gastric emptying should be considered. Medications that enhance the transit of material through the gastrointestinal tract are called prokinetic agents. These agents act through one or more of the following pathways: 1) directly or indirectly promoting cholinergic tone; 2) antagonizing inhibitory neurotransmitters like serotonin, dopamine, and so forth; and 3) mimicking noncholinergic, nonadrenergic compounds that increase motility (*eg,* motilin) [25]. Metoclopramide,

Table 1. Management of diabetic gastroparesis

Blood glucose control
Diet modification
Small meals
Low-residue diet
Liquid supplements
Medications
Antihistamines and antiemetics
Prokinetic agents
Metoclopramide
Domperidone
Erythromycin
Cisapride
Total parenteral nutrition and feeding jejunostomy
Experimental
Pancreas-kidney transplantation
Gastric pacing

domperidone, cisapride, and erythromycin have all been used to treat diabetic gastroparesis.

Metoclopramide is a peripheral cholinergic and antidopaminergic agent. It acts by coordinating pyloric relaxation and duodenal peristalsis and stimulating gastric smooth muscle contractions, which hasten gastric emptying. It may act in part by central antiemetic effects, because improvement in symptoms can occur without apparent enhancement of gastric emptying [25]. The starting dose is 10 mg orally 30 minutes before each meal and at bedtime. If tolerated, the dose can be increased to 20 mg four times a day. It can cause drowsiness and restlessness; this can occur in about 20% to 30% of patients. Because it is a dopamine antagonist, extrapyramidal effects, parkinsonism, lowering of seizure threshold, and irreversible tardive dyskinesia may occur; therefore, its use should be limited to short courses.

Domperidone is a peripherally acting dopamine antagonist without cholinergic activity. Central nervous system side effects are observed less frequently with domperidone than with metoclopramide, because it does not cross the blood-brain barrier to the extent that the latter does. The usual dose is 20 mg orally four times a day. Domperidone has not yet been approved for use in diabetic gastroparesis in the United States.

Erythromycin mimics the effect of motilin and stimulates smooth muscle motilin receptors, which are located in several regions of the mammalian GI tract. It is a powerful gastroprokinetic agent. It stimulates fasting and postprandial antral contractile activity, enhances antroduodenal coordination, and induces a phase III–like pattern during fed motor activity [26]. Despite its efficacy in the acute management of symptomatic patients with gastroparesis, there is little evidence to show that it improves symptoms over the long term. The dose in acute exacerbations of gastroparesis is an intravenous infusion of 250 mg over 20 minutes every 8 hours. Side effects include flushing, salivation, urge to urinate, blurred vision, GI toxicity, ototoxicity pseudomembranous colitis, and induction of resistant bacterial strains. Oral erythromycin is less effective secondary to problems with drug absorption. Other erythromycin analogues being developed without antibiotic properties are currently under investigation and hold considerable promise [27].

Cisapride acts as a partial agonist on 5-hydroxytryptamine 4 (5-HT4) receptors. It appears to have a sustained action, improving gastric emptying of nondigestible solids, and may be more potent than equivalent doses of metoclopramide. It also seems to have beneficial effects on small bowel motility. However, cisapride has been associated with a number of drug interactions and fatal cardiac arrhythmias, promoting severe restrictions on its availability in the United States. Since August 2000, prescriptions for the drug can only be filled directly through the manufacturer after providing documentation as to the need for the drug and assessment of risk factors for cardiac arrhythmias in the individual patient.

The addition of centrally acting antiemetics may be useful in refractory cases. Antihistamines (H_1) and phenothiazines such as prochlorperazine may be used. Side effects include sedation and orthostatic hypotension. Some patients may continue to have symptoms even after maximal therapy. These patients may benefit from total parenteral nutrition or feeding jejunostomy to bypass an atonic stomach. In patients with diabetic nephropathy, combined pancreas-kidney transplantation has been shown to improve autonomic gastric function at 1-year follow-up [28]. A few other reports have shown improvement of GI symptoms and gastric emptying using high frequency gastric electric pacing [29]; however, this modality warrants further investigation.

Other gastric abnormalities

Hematemesis occurs frequently, especially during diabetic ketoacidosis, and may be secondary to hemorrhagic gastritis. It can effectively be treated with conservative medical management. Chronic gastritis may be severe in diabetic ketoacidosis. Upper endoscopy is recommended as an initial diagnostic tool in diabetic patients who are being evaluated for gastritis symptoms [13]. Although gastritis is common, ulcer disease has a low incidence in diabetes probably because of the inhibitory effects of hyperglycemia on acid production, increased glucagon levels, which also suppress acid secretion, decreased vagal tone secondary to autonomic neuropathy, decreased sensitivity to gastric stimulation, and chronic gastritis [10]. Patients with longstanding diabetes are also at risk for pernicious anemia secondary to antibodies to parietal cells. Vitamin B_{12} deficiency should be evaluated for and treated promptly.

Small bowel dysfunction

Patients with diabetic gastroparesis may also have altered intestinal motility. There could be either a delay in transit of a liquid meal or hastened intestinal transit with rapid emptying into the colon. This hastened transit and rapid emptying may be a partial explanation for the diarrhea, which is seen

in a subset of diabetic patients. Delayed emptying and stagnation of fluids in the small intestine may lead to bacterial overgrowth syndromes. An empiric trial of antibiotic drugs is often the most efficient means of diagnosing and treating this condition. At times, enteric neuropathy may lead to a chronic abdominal pain syndrome. This condition may be very difficult to treat, but will sometimes respond to tricyclic antidepressants such as amitriptyline.

Biliary Tract Abnormalities

Diabetes mellitus is associated with an increased incidence of cholelithiasis, cholecystitis, and ascending cholangitis. The impaired gall bladder motility may be due to autonomic neuropathy or lower plasma levels of cholecystokinin [30]. In the past, prophylactic cholecystectomy was recommended for all diabetic patients with cholelithiasis. The justification for this was based on the belief that diabetic patients present more frequently with complications such as perforation and emphysematous cholecystitis. Currently, however, prophylactic cholecystectomy is not recommended in diabetic patients with asymptomatic cholelithiasis.

Liver disease

Up to 80% of diabetic patients may have nonalcoholic liver steatosis; this could be related to hypertriglyceridemia, poor glucose control, or both [10]. Fatty infiltration of the liver may lead to tender hepatomegaly, elevated liver function tests, and abdominal pain. The diagnosis is usually suspected on the basis of the clinical presentation but can be confirmed with abdominal ultrasonography. Therapy is geared toward improving glycemic control and instituting a low-calorie, low-fat diet.

Pancreatic disease

Pancreatic exocrine dysfunction may be seen in both type 1 and type 2 diabetes but is rarely clinically significant. Individuals who have secondary diabetes because of severe pancreatitis or surgical removal of the pancreas usually have more severe symptoms of pancreatic exocrine insufficiency. Treatment with pancreatic enzyme replacement therapy is usually effective.

There has been considerable controversy about whether diabetes mellitus is a risk factor for pancreatic cancer. Diabetic patients who consume large quantities of alcohol have been reported to have a two to four times increased incidence of adenocarcinoma of the pancreas [31]. A recent study, which summarized the literature on this phenomenon, concluded that diabetes of at least 5 years' duration increased the risk of subsequently developing pancreatic cancer [32••].

Diarrhea

Diarrhea is seen in up to 20% of diabetic patients [10]. It seems to be more common in middle-aged diabetic patients who are insulin dependent and have long-standing poorly controlled diabetes [33]. The causes are usually multifactorial and include neuropathic motility disturbances and bacterial overgrowth, pancreatic exocrine insufficiency, electrolyte imbalances, and altered gut hormone production [34]. Several motility abnormalities have been described in the stomach and small intestine of diabetic patients. Phase II activity and phase III activity (migrating motor complex) have been shown to be abnormal in both the stomach and small bowel of diabetic patients [16]. Another potential mechanism is sympathetic denervation of the gut. If adrenergic nerves are damaged in diabetes, the intestinal reabsorption of fluid may be impaired and may lead to diarrhea [10].

Small bowel bacterial overgrowth is an infrequent finding among diabetic patients with chronic diarrhea. Interdigestive migrating motor complexes that are normally responsible for decreased bacterial gut content may be absent in diabetic patients. The common pathogens include *Escherichia coli*, enterococci, *Aerobacter*, and staphylococci [33]. An additional factor that may mediate or exacerbate diabetic diarrhea is bile acid malabsorption due to a decreased bile salt pool. Exocrine pancreatic dysfunction causing decreased secretion of amylase, bicarbonate, and proteases can also cause diarrhea. Hypokalemia, hyperkalemia, as well as hypoglycemia and hyperglycemia resulting from poor diabetes control, may induce diarrhea by altering the intestinal transport of water and electrolytes.

Diabetic diarrhea is more common in men than in women, with a ratio of 3:2. It is episodic and can alternate with periods of normal bowel movements or constipation. The episodes can last from days to weeks. The diarrhea is characterized by intermittent brown watery, voluminous stools and is occasionally accompanied by tenesmus. It can occur at any time of the day but is often nocturnal [34]. Surprisingly, patients do not have weight loss, cachexia, or other biochemical abnormalities observed in malabsorptive disorders. Steatorrhea is also common; it may occur in as many as 75% of diabetic patients with diarrhea.

Evaluation of diarrhea

A careful history has to be obtained to rule out sorbitol use, laxative ingestion, or heavy alcohol consumption. A detailed physical examination should be done, and an anorectal examination should be performed to assess the resting and squeeze anal sphincter pressures. Lack of sensation in the rectum and perianal area may indicate neuropathy. Absence of the cutaneous anal "wink" reflex indicates sacral root dysfunction. Estimation of stool volume or weight may be helpful. A 72-hour stool collection for weight and fecal fat determination, stool analysis, culture for ova, parasites, cysts, bacteria such as salmonella, *Shigella*, and *Campylobacter*, can all be performed. An upper GI series, and barium roentgenograms of the small intestine and colon to exclude a specific GI process, are other ancillary tests that can be performed.

Diabetes and diarrhea are cardinal features of three major types of tumors: glucagonoma, vipoma, and somatostatinoma. Thus, they should be considered in the differential diagnosis of diabetic diarrhea. If the patient has evidence of

normocytic normochromic anemia, glossitis, cheilosis, venous thrombosis, or neurologic changes, the possibility of glucagonoma should be considered and fasting plasma glucagon levels should be measured. Somatostatinomas should be considered in the differential in any patient who has had diabetes for a short duration and, if the diarrhea is associated with weight loss, cholelithiasis or postprandial fullness. Immunoreactive somatostatin levels are usually high. Salt and water transport in the gut is affected in vipomas leading to secretory diarrhea. Other features include glucose intolerance, increased calcium, weight loss, acidosis, hypokalemia, and basal achlorhydria. Checking a vasoactive intestinal peptide level by radioimmunoassay may be helpful in this situation. Celiac sprue has been shown to be more common in type 1 diabetic patients [35]. Both type 1 diabetes and sprue have the histocompatibility antigens HLA- B8 and HLA-D3 in common.

Treatment of diarrhea

Treatment is empiric and mostly directed to relieving symptoms. General measures should include maintenance of oral fluid intake of 2 to 3 qt/d. Caffeinated drinks, fat-containing foods, and dairy products should be avoided as much as possible because they can worsen the diarrhea. Fiber supplementation with bran, Citrucel (GlaxoSmithKline, Philadelphia, PA), Metamucil (Proctor & Gamble Pharmaceuticals, Cincinnati, OH), or high-fiber foods may help in thickening the consistency of the bowel movement and decrease watery diarrhea. The two most commonly used antidiarrheal drugs are diphenoxylate hydrochloride with atropine sulfate (Lomotil; Searle, G.D. & Co., Chicago, IL) and kaolin pectate (Kaopectate; Pharmacia Corp., Kalamazoo, MI).

Pancreatic enzyme supplements may help those with steatorrhea and pancreatic insufficiency. A small number of patients have had benefit from a 2-week course of broad spectrum antibiotics, such as 500 to 1000 mg/d of tetracycline hydrochloride or ampicillin 250 mg four times a day for 1 week in each month. The use of clonidine, an α_2-adrenergic agonist (1 mg/d), may also help decrease the frequency and volume of diarrheal episodes. Clonidine can cause orthostatic hypotension and worsening of gastric emptying, which may limit its use. If the oral form produces undesirable side effects, the patch form may be tried. The somatostatin analogue, octreotide acetate (Sandostatin; Novartis Pharmaceuticals Corp., East Hanover, NJ) administered subcutaneously 50 to 75 µg twice a day has been shown to be effective in refractory cases [36]. It acts by inhibiting stimulated water secretion and increasing gut absorptive capacity. The diarrhea of celiac sprue in general responds to a gluten-free diet.

Constipation

Constipation is seen in up to 18% of diabetic patients [2]. It is thought to be secondary to autonomic neuropathy. Treatment includes good blood sugar control and the use of bulk or osmotic laxatives. In patients in whom colonic transit time is abnormally prolonged, stimulants of colonic motility such as bisacodyl or glycerin suppositories may be helpful [37].

Anorectal Abnormalities

Fecal incontinence can occur as a result of decreased internal anal sphincter tone; it is seen in 40% of diabetic patients with diarrhea [38]. External anal sphincter function is not affected in diabetes. Therapy of fecal incontinence includes symptomatic treatment with loperamide or psyllium. Some patients may benefit from biofeedback therapy aimed at increasing anal sphincter tone [39].

Conclusions

The GI problems associated with diabetes are protean and may have diverse pathophysiologies. Patients may present with a spectrum of manifestations, from severe GI symptoms to mild, subclinical disease. Motility disturbances are common in diabetic patients; however, they do not correlate well with the presence or severity of symptoms. A complete evaluation should be done to uncover other potentially reversible diseases before ascribing the cause to diabetes. Many treatment options are now available for the diabetic patient with GI disorders; therefore, it is important for both the physician and the patient to be educated about the symptoms and the therapeutic options.

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