Both type 1 and type 2 diabetes mellitus can affect a patient’s entire gastrointestinal tract, from the esophagus to the anus. The symptoms that often accompany the GI effects of diabetes mellitus cause a great deal of misery for patients, as well as frustration for the physicians taking care of them. Because GI symptoms are common in the general population, physicians may have difficulty determining whether diabetes is the root problem.
In the past, physicians assumed that hyperglycemia leads to autonomic neuropathy, which leads to the GI abnormalities. In addition, physicians thought that patients must have diabetes for 10 years or more before GI symptoms occur. Recent findings, however, call both of these premises into question.

The most common GI problems encountered in clinical practice among patients with diabetes are constipation, diarrhea, abdominal pain, nausea and vomiting. Several other problems may be seen from time to time. In this article, I review the current knowledge regarding how diabetes affects the GI tract, how GI problems typically manifest themselves, and what treatment options are currently available.

**Symptoms and complications**

Gastrointestinal complications of diabetes include gastroparesis, small bowel enteropathy—which can cause diarrhea, constipation, and fecal incontinence—and nonalcoholic fatty liver disease.

In a review, J.H. Sellin and E. B. Chang examined the frequency and type of GI symptoms experienced by patients with diabetes and the underlying pathophysiologic mechanisms of these symptoms. According to Sellin and Chang, studies have had conflicting conclusions regarding which gastrointestinal symptoms are most common in patients with diabetes. Upper gastrointestinal tract complaints, such as nausea, vomiting and heartburn, are the most reported symptoms in many studies.

Some interesting findings and conflicts regarding GI symptoms can be found. For example, one study indicates that heartburn is decreased in patients with diabetes mellitus. Another study notes that women seem to be more affected with GI symptoms than are men.

Studies also indicate that there are likely to be multiple etiologic factors behind GI symptoms. For example, autonomic neuropathy was identified as being the cause of many GI symptoms. However, such symptoms may precede or at least not correlate with the presence of autonomic neuropathy. Thus, contrary to previous beliefs, the symptoms of diabetes affecting the GI tract may not correlate at all with the duration of a patient’s disease or degree of glycemic control.

The pathogenesis of diabetic autonomic neuropathy is related to hyperglycemia, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency. In patients with type 1 diabetes, enteric neurotransmission may be modulated by a functional immunoglobulin G autoantibody. Hypoglycemia, as well as hyperglycemia, can have a reversible effect on the metabolic and signaling pathways of enteric neurons, thereby altering intestinal function. There is also some evidence for enteric myopathy in patients with diabetes mellitus.

Causes of gastrointestinal problems in patients with diabetes can include certain metabolic insults that result in smooth muscle atrophy or in the transformation of one cell type to another: The pacemaker cells of the intestinal tract—the interstitial cells of Cajal (ICCs)—seem to be disrupted or altered in some way in diabetes.

Other potential causes of intestinal dysfunction include ischemia, hypoxia, and mitochondrial dysfunction.

Cumulatively, these metabolic and anatomic changes cause abnormalities in peristalsis, reflexive relaxation, sphincter tone, vascular flow and intestinal segmentation. These abnormalities manifest themselves clinically as dysphagia, gastroparesis, constipation, diarrhea, intestinal pseudo-obstruction and anal incontinence.

Because many pathologic conditions associated with GI complications of diabetes may become irreversible, efforts should be made early in the disease process to achieve the most consistent glucose control possible.
Esophageal disorders

Esophageal complaints among patients with diabetes include heartburn, dysphagia and odynophagia (ie, painful swallowing). As many as half of patients with diabetes have esophageal motility abnormalities or acid reflux problems—though many of these patients do not report symptoms.9 Autonomic neuropathy and motor neuropathy are likely causes of these complaints. Abnormal manometric findings in patients with diabetes include hypotensive lower esophageal sphincter pressure, diminished amplitude of peristaltic waves, prolonged esophageal transit time, and reduced rate of smooth muscle contraction.3

As a result of these pathologic conditions, gastroesophageal reflux disease (GERD) and dysphagia are more common in patients with diabetes than in other individuals. The presence of odynophagia should alert physicians to the possibility of Candida infection in the esophagus. Physiologic disturbances that increase risk for Candida infection include decreased candidal activity of neutrophils, reduced esophageal clearance for, and increased glucose content of, oral secretions.10

These various esophageal problems are manageable to some extent. Patients with GERD may respond to histamine-2 receptor antagonist therapy or to proton pump inhibitors. Candida infections can be cleared with an antifungal agent, such as fluconazole, and with improved glycemic control.

Dysphagia secondary to neuropathy may be more difficult than these other problems to manage, especially if the neuropathy is advanced. In patients older than 50 years who have been diagnosed as having new-onset progressive dysphagia, mechanical obstruction needs to be ruled out with the use of a barium swallow radiology test (ie, upper gastrointestinal series) or a gastroscopic inspection.

Diagnosis

Patients’ medical histories will often reveal the likely causes of GI abnormalities. The differential diagnosis should include any disease that typically has the symptoms of nausea, vomiting and early satiety.

Patients may also have pain, though it is usually not a prominent feature. If pain is prominent, however, peptic ulcer disease, cancer, gallbladder disease and pancreatic problems should be considered.

An upper GI radiographic or endoscopic examination should be performed to rule out any structural cause of the symptoms. Some patients will retain food in their stomachs even after an overnight fast. Physical examination may reveal epigastric fullness, succussion splash or both.

A definitive diagnosis of GI abnormalities can often be made with nuclear scintigraphic evaluation of solid-phase gastric emptying. Delayed emptying of a technetium-labeled solid meal in the absence of any anatomic abnormality is considered to be diagnostic of gastroparesis.

Although the patient’s symptoms may not correlate well with quantification of gastric emptying, therapy options can be evaluated to some extent based on the results of gastric emptying studies.

The cause of upper GI bleeding may be difficult to diagnose, even with the use of endoscopy. Causes include esophagitis and erosive gastritis. Bleeding may also be caused by a Mallory-Weiss tear, which can result from vomiting and retching.11 At the initial bleed, the use of endoscopy in the evaluation of the upper GI tract may be able to rule out other causes of bleeding.

(continued on the next page)

Figure 1

Gastric abnormalities

Gastric abnormalities in patients with diabetes usually involve either diabetic gastroparesis or upper GI bleeding.

Diabetic gastroparesis typically occurs in patients who have had long-standing type 1 diabetes. Symptoms may include nausea, vomiting, early satiety, bloating, epigastric pain and belching. These symptoms may wax and wane, or they may be constant. In patients with severe conditions, weight loss may result.11

Upper GI bleeding is common in patients with long-term diabetes, especially in the setting of diabetic ketoacidosis.

Normal gastric emptying is the result of a complex interplay among tonic contractions of the fundus, phasic contractions of the antrum, and inhibitory forces of pyloric and duodenal contractions. Coordination takes place among smooth muscle, enteric and autonomic nerves, and the ICCs.12

Physiologic mechanisms involved in gastric emptying are thought to cause many GI symptoms in patients with diabetes. Specifically, these mechanisms are hyperglycemia leading to delayed gastric emptying secondary to vagus autonomic nerve impairment, as well as damage to enteric nerves and the ICCs.

The results of these gastric abnormalities are changes in antroduodenal motility, failure of accommodation in the proximal stomach, pylorospasm, and gastric dysrhythmias. The precise role that these conditions play in causing the symptoms of gastroparesis in patients with diabetes is unclear.13

Treatment for patients with diabetic gastroparesis

- blood glucose control
- low-fat, low-fiber diet
- prokinetic drugs (eg, dopamine antagonists)
- antiemetic agents
- endoscopic therapies
- gastric pacemaker

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Treatment for patients with diabetic gastroparesis is multimodal (see Figure 1). It should begin with controlling blood glucose levels. Dietary changes to achieve control should include adopting a low-fat, low-fiber soft diet, with frequent small meals. Fat takes longer to leave the stomach in patients with diabetic gastroparesis, aggravating the symptoms of this condition. Under usual circumstances, liquid emptying is not impaired in diabetic gastroparesis. Thus, blended or liquid meals or nutritional supplements are generally well tolerated by patients.1

Beyond dietary changes, the management of diabetic gastroparesis consists of prokinetic drugs (e.g., dopamine antagonists), antiemetic agents, endoscopic treatments and gastric pacing.14

The dopaminergic antagonists metoclopramide and domperidone increase antral contractions and decrease receptive relaxation of the proximal stomach. Unfortunately, metoclopramide crosses the blood-brain barrier, and it has the potential for producing irreversible adverse neurologic effects, such as tardive dyskinesia.15 Some clinicians advocate obtaining informed consent from patients before prescribing metoclopramide, which can be administered as a tablet or liquid or parenterally.

Other adverse effects that can result from using metoclopramide include drowsiness, restlessness, fatigue and irritability. Rarely, acute dystonic reactions or Parkinsonian-like symptoms may occur with metoclopramide.15 Domperidone does not cross the blood-brain barrier, so it does not cause adverse neurologic effects. At present, domperidone is approved in several countries outside the United States to treat certain gastric disorders.

Another prokinetic drug that is available is erythromycin, which is administered either orally or parenterally. Erythromycin acts as a motilin receptor agonist that accelerates gastric emptying. Several studies have suggested that erythromycin can relieve symptoms for patients with diabetic gastroparesis,16-18 but the long-term efficacy of this drug is unproved. The adverse effects of nausea and cramping may limit erythromycin’s usefulness.

Cisapride has been shown to be as effective as erythromycin in patients with gastroparesis, but its use has been severely restricted by the FDA because of proarrhythmic effects.19

Antiemetic agents, such as promethazine and prochlorperazine, help relieve nausea and vomiting in patients with diabetic gastroparesis and can be administered either in oral form or as a suppository. However, these drugs do not alter gastric emptying or improve stomach function, and their long-term use is limited because of adverse effects.

When dietary and pharmacologic measures do not provide relief, other medicines that may help manage nausea and vomiting in these patients include ondansetron, dronabinol and the scopolamine transdermal patch.

Several endoscopic treatments are available for patients with diabetic gastroparesis. Research studies on intrapyloric injection of botulinum toxin type A (BTX-A, or Botox) suggest that about half of those patients treated with BTX-A responded with improved gastric emptying or symptom relief.1 As of mid-2008, however, no placebo-controlled, prospective study has clearly demonstrated the efficacy of BTX-A in managing diabetic gastroparesis.

Endoscopic or surgical treatments that have been tried for patients with diabetic gastroparesis include venting gastrostomy tubes and jejunal feeding tubes.1 Venting tubes help relieve symptoms, and feeding tubes allow for nutrition to be uninterrupted, yet little conclusive literature on these modalities exists.

One gastric pacemaker—Enterra™ Therapy—has been approved by the FDA for treating patients with
gastroparesis. When using this device, electrodes are placed surgically on the patient’s stomach and attached to a neurostimulator inserted subcutaneously in the abdominal wall. The stimulator device delivers high-frequency, low-energy gastric pacing, resulting in notable reduction in vomiting after 12 months. Infection is the most serious complication reported for this device. After five years of evaluation, the stimulator has been shown to improve glycemic control and nutrition parameters, to enhance quality of life and to decrease healthcare costs.

Managing upper GI bleeding in patients with diabetes may involve both endoscopic and pharmacologic treatments. Should active bleeding be visualized during an upper endoscopic examination, endoscopic therapy would be appropriate. Useful treatment modalities include endoscopic clips, injection of epinephrine around the bleeding vessel, and treatment with a thermal device, such as a heater probe.

After an upper endoscopic examination is performed, drug therapy with proton pump inhibitors or histamine-2 receptor antagonists is standard care for patients with upper GI bleeding and diabetes. These medicines can be administered either orally or parenterally.

**Diabetic diarrhea**

Although constipation is more common than diarrhea among patients with diabetes, diarrhea is the more troubling complication. According to one estimate, 3.7% of individuals with diabetes suffer from diarrhea.11 Diarrhea is most common in patients with type 1 diabetes mellitus and in men, and it may alternate with normal bowel function or constipation. It is seldom accompanied by bleeding or pain.

Several factors are likely to contribute to diabetic diarrhea. Autonomic neuropathy certainly plays a role in this condition by altering sympathetic function in the gut and by reducing input from alpha-2 adrenergic receptors. These changes lead to decreased fluid and electrolyte absorption.

Gastrointestinal dysmotility, which has been documented in patients with diabetes, can cause diarrhea if it slows small bowel transit time, leading to bacterial overgrowth. However, there is some evidence that bowel transit times may be faster in some individuals with diabetes.20 It is important that physicians evaluate patients’ bowel transit times. Antibiotics are more likely to benefit patients with slower transit times because bacterial overgrowth would be most likely in these patients. In contrast, antidiarrheal medications, such as loperamide and diphenoxylate, would be appropriate for patients with fast transit times.

Another cause of diarrhea to rule out in patients with diabetes is celiac disease, which occurs more commonly in patients with diabetes.21 Serologic testing and small bowel biopsy at the time of an esophagogastroduodenoscopy can be used to diagnose celiac disease.

Pancreatic disease, fecal incontinence, and various medications should also be considered. Fecal incontinence can be diagnosed by medical history, physical examination and—if available—manometric testing. A list of medications that can cause diarrhea can be found in Figure 2. Diarrhea caused by the diabetes medication metformin, a biguanide derivative with structural similarity to 5-HT3 receptor agonists, can be improved by switching to the extended-release form of this drug.

Other diabetes medications that may be responsible for diarrhea include acarbose and miglitol. Certain nondiabetes medications, including antibiotics and magnesium-containing antacids, may also cause diarrhea.

While the management of diabetic diarrhea may be unsatisfactory, it can be helpful in some cases. Improving glycemic control and using dietary fiber products may be of some benefit to patients with diabetic diarrhea.

Some patients will respond to clonidine, an alpha-2 adrenergic agonist, which may help reverse damage to alpha-2 adrenergic receptor function and improve fluid and electrolyte absorption. However, it is important to monitor a patient’s blood pressure during the use of clonidine.

Narcotics, such as codeine sulfate or tincture of opium, should be used only with caution.

**Unexplained abdominal pain**

Patients with neuropathy may be troubled by chronic abdominal pain that defies etiologic explanation. This pain is usually in the upper abdomen and generally occurs in a girdle distribution. Endoscopy, laboratory tests, and imaging techniques seldom reveal disease in these patients.

Research suggests that radiculopathy (ie, diabetic plexus neuropathy) or thoracic nerve roots may be the cause of this chronic abdominal pain.22 And, this pain may respond to amitriptyline or phenytoin.22
Colonic disease
Constipation, typically requiring laxative use, is the most common gastrointestinal complaint reported by patients with diabetes. Smooth muscle myopathy and loss of ICC function are the most likely causes of constipation among these patients. Autonomic neuropathy and neuroendocrine imbalances could also contribute to the problem. In severe cases, megacolon or, rarely, chronic intestinal pseudoobstruction can result.

Treatment of patients for diabetic constipation is not unlike that for idiopathic constipation—except that improved glycemic control is part of the regimen. Dietary fiber, increased fluid intake, stool softeners, and laxatives are the mainstays of treatment.

Lubiprostone, a selective type 2 chloride channel agonist, might be of benefit to patients with diabetic constipation because it has been shown to help patients with idiopathic constipation. Avoiding certain medications, such as aluminum-containing antacids, narcotics, and tricyclic antidepressants, may also be beneficial.

Fecal incontinence is sometimes the most troublesome problem of all for patients with diabetes. Thought to be a complication of autonomic neuropathy, fecal incontinence may coincide with the onset of diabetic diarrhea. Internal sphincter resting tone and relaxation are adversely affected in such cases.

Treatment options consist of increased dietary fiber; antidiarrheal medications, such as loperamide; and biofeedback. Patients with severe cases of fecal incontinence may benefit from surgery or sacral nerve stimulation.

Gastric abnormalities in patients with diabetes mellitus usually involve either diabetic gastroparesis or upper GI bleeding.

Final notes
This article reviews some of the most recent findings regarding the pathogenesis and management of GI complications of diabetes. Clearly, improving control of blood glucose levels with a balanced diet, adequate exercise and appropriate medications is the cornerstone of treatment. Because many pathologic conditions associated with GI complications of diabetes may become irreversible, effort should be taken early in the disease process to achieve the most consistent glucose control possible.

Through their thorough care of the entire person and not merely the management of symptoms, osteopathic primary care physicians are ideally positioned to help their patients minimize the destructive effects of diabetes.

References


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