The Complications of Diabetes in the Gastrointestinal Tract

Diabetes mellitus affects millions of people worldwide. With improved therapy, many patients are living longer, albeit with complications of the disease. Diabetes and hyperglycemia have immediate and long-term effects in the gastrointestinal (GI) tract. We comprehensively review the complications of diabetes in the gastrointestinal tract including oral and esophageal candidiasis, gastroesophageal reflux disease (GERD), esophageal dysmotility, gastroparesis, small intestinal bacterial overgrowth, diarrhea and nonalcoholic fatty liver disease (NAFLD). We also describe the increased risk of GI malignancies in these patients.

Diabetes mellitus (DM) affects 9.3% of the population of the United States (U.S.) and roughly 1.7 million new cases are diagnosed each year. Four percent of those diagnosed are type 1 diabetics. Diabetes currently affects 382 million people worldwide, and this is expected to increase to 592 million by 2035. With improved therapies, survival has increased and many patients live with long-term complications of the disease. Diabetes affects nearly every organ system including the gastrointestinal (GI) tract. The major gastrointestinal complications of diabetes are oral and periodontal infection, esophageal candidiasis, esophageal dysmotility, gastroesophageal reflux disease (GERD), gastroparesis, small intestinal bacterial overgrowth (SIBO), diabetic diarrhea, nonalcoholic fatty liver disease (NAFLD) and increased risk of GI malignancies. Here we comprehensively review the effects of diabetes on the gastrointestinal tract.

1. Oral Cavity
Candidiasis And Periodontal Disease

Epidemiology
Diabetes has several oral manifestations including fungal infections, periodontal disease, mucosal ulcerations, xerostomia and aguesia. The reported incidence of oral candidiasis is 11 to 30% and periodontal disease is 30
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Pathophysiology
Candida species normally colonize the oral cavity of healthy individuals, without causing infection. Hyperglycemia causes an increase in buccal mucin and glucose and decreased activity of salivary antimicrobial factors like lysozymes. This increases proliferation of buccal candida, the most common species being Candida albicans. Compromised neutrophil function from decreased adherence, chemotaxis and phagocytic function in the presence of uncontrolled hyperglycemia predispose to periodontal destruction and infection.

Diagnosis and Treatment
Symptoms usually include loss of taste and cotton-like sensation in the mouth. Oral candidiasis is diagnosed on inspection of the oral cavity; exam often reveals whitish, adherent plaques with erythematous and friable underlying mucosa.

Oropharyngeal candidiasis can initially be treated with topical antifungal agents such as nystatin 400,000 to 600,000 units daily in a swish and swallow manner. If topical agents are ineffective, oral "azoles", such as fluconazole or itraconazole are the mainstay of therapy. A loading dose of 200 mg followed by 100 to 200 mg daily for 7 - 10 days is recommended. Resistant cases may be treated with an oral suspension of amphotericin B.

2. Esophagus
Candidiasis

Epidemiology and Pathophysiology
Diabetes mellitus is associated with higher incidence of esophageal candidiasis, especially among elderly patients.

Pathophysiology
Esophageal dysmotility in diabetes is multifactorial with damage to interstitial cells of Cajal and vagal/autonomic neuropathy. This is characterized by smaller amplitude and velocity of lower esophageal contractions. As a result, there is impaired esophageal peristalsis with frequent retrograde waves, decreased lower esophageal sphincter (LES) tone and frequent transient LES relaxation causing heartburn, regurgitation and dysphagia.

Diagnosis
GERD is diagnosed clinically from typical symptoms of regurgitation and heartburn. Endoscopy may be performed for atypical, unresponsive or alarm symptoms. Ambulatory pH monitoring and esophageal manometry are recommended prior to surgical treatment.

Treatment
Lifestyle modifications such as weight loss, avoidance of meals two to three hours before bed time, elimination of foods triggering symptoms and elevation of the head of the bed are recommended. GERD is treated symptomatically with proton pump inhibitors (PPIs). If symptoms are unresponsive to PPIs, endoscopic or laparoscopic fundoplication surgery may be considered.

3. Stomach
Gastroparesis
Gastroparesis is a motility disorder characterized by
delayed gastric emptying in the absence of mechanical obstruction.

**Epidemiology**

Gastroparesis generally develops in long standing diabetes of more than 10 years duration with autonomic dysfunction. One third of gastroparesis is attributable to diabetes.\(^{21,22}\) The disorder is female predominant (4:1 compared to males), and a higher prevalence has been described in type 1 diabetes.\(^{23}\) Gastroparesis is characterized by nausea, vomiting, bloating, epigastric pain and early satiety.

Delayed gastric emptying was associated with other comorbid conditions such as hypertension, cardiovascular disease and retinopathy and may lead to more frequent hospitalizations among patients with diabetes.\(^{24}\)

**Pathophysiology**

Autonomic neuropathy, damage to the interstitial cells of Cajal by hyperglycemia and oxidative stress result in decreased gastric motility, impaired pyloric relaxation and increased post prandial resistance subsequently leading to delayed gastric emptying.\(^{25}\) Acute hyperglycemia (> 288 mg/dl) can be associated with increased gastric emptying time and worsening symptoms.\(^{26}\)

**Diagnosis**

The diagnosis is made by nuclear tests measuring the gastric emptying of solid phase meals. Evaluation is prompted by symptoms, poor glycemic control or in patients in whom oral hypoglycemic medications known to slow down gastric emptying time are being considered.\(^{27}\) The gold standard is gastric emptying scintigraphy or scinti scanning. A radionuclide labeled low fat, solid meal is ingested and the gastric emptying time is calculated by observing the fraction of the meal remaining in the stomach at baseline, 1, 2 and 4 hours after ingestion. Having patients observe an overnight fast and well controlled blood sugars (< 275 mg/dl fasting) ensure accuracy of the test.\(^{28}\) Modified scinti scanning, which measures the gastric emptying over a shorter time period, has lower sensitivity and specificity.

Gastric emptying breath test (GEBT), which measures gastric emptying by measuring the breath excretion of CO\(_2\) labeled with C\(^{13}\) radioisotope incorporated into a meal, has shown comparable sensitivity and specificity to scinti scanning in studies, but requires further validation.\(^{27,29}\) Upper endoscopy, performed after an overnight fast, that shows evidence of food retention in the stomach may also assist in making the diagnosis of gastroparesis.

Wireless capsules (“Smart Pill”) are used to measure the pH, temperature and pressure in the GI tract. A small capsule, with the ability to transmit data to a receiver worn around the patient’s neck, is ingested. It measures gastric emptying time by sensing the abrupt change in pH as the capsule passes from the stomach into the duodenum and thus is used to diagnose gastroparesis.\(^{30,31}\) Wireless capsule studies have a sensitivity and specificity of 83 % compared with gastric scintigraphy.\(^{29}\)

**Treatment**

Management strategies generally consist of optimizing glycemic control, improving hydration and nutritional status, controlling symptoms and managing complications.

Dietary factors play an important role in gastroparesis. Small, frequent low fat, low fiber meals are recommended with 55% to 60% of dietary calories from carbohydrates, 15% from protein and 25% to 30% from fat. Vitamins and minerals should be replaced through oral supplementation. If patients are unable to tolerate solid meals, more liquid calories are recommended since they empty more easily by gravity.\(^{32}\)

The mainstays of pharmacologic therapy are prokinetics such as metoclopramide, erythromycin and domperidone, which hasten gastric emptying. Erythromycin has the maximum effect on gastric emptying and is generally used for acute symptom management.\(^{32}\) Newer drugs such as 5HT4 receptor agonists (prucaloprid/velusetora)\(^{33}\) and muscarinic antagonists (acotiamide) are being studied for their efficacy in gastroparesis.\(^{34}\) Non pharmacologic methods such as intrapyloric botulinum toxin injection and gastric electrical stimulation are used to treat medically refractory gastroparesis.\(^{35}\) Anti-diabetic drugs, such as GLP1 analogs, that slow gastric emptying should be discontinued. Repeated hospitalizations in gastroparesis are usually for nausea, vomiting and pain management. Additional diagnostic testing rarely changes management and should be avoided to decrease prolonged hospitalizations and increased healthcare costs.\(^{36}\) Refractory nausea may be treated with (continued on page 62)
tricyclic antidepressants (TCA), phenothiazines and antihistamines such as meclizine. Selective serotonin reuptake inhibitors and low-dose TCAs may also help improve abdominal pain.²⁹

4. Small Intestine and Colon

Small Intestinal Bacterial Overgrowth

Definition and Epidemiology

Small Intestinal bacterial overgrowth (SIBO) refers to an increase in the number of bacteria or a change in the composition of the small bowel microbiome.

The incidence of SIBO in diabetic patients with autonomic neuropathy varies between 30 and 60%.³⁷,³⁸

Pathophysiology

Decreased intestinal motility, malabsorption and increased intestinal secretion cause SIBO in patients with diabetes. The disorder may present with abdominal pain, bloating, distention, flatulence and diarrhea and may result in nutritional deficiencies, chronic anemia, steatorrhea, and malnutrition.

Diagnosis

The gold standard for making the diagnosis of SIBO is a culture of jejunal aspirates. Noninvasive testing methods include hydrogen and methane breath testing after an oral glucose or lactulose load. An early peak in breath hydrogen or methane production is due to bacterial fermentation of glucose in the small bowel, indicating SIBO.³⁹ However, as a false positive early peak in the production of hydrogen and methane can occur with bacterial fermentation of glucose or lactulose in the cecum, this test has limited sensitivity, though good specificity.⁴⁰

Treatment

Glycemic control and cyclical antibiotics are the treatments of SIBO in patients with diabetes. Metronidazole (750 mg/day) or rifaximin (1200 mg/day) are the antibiotics of choice for SIBO.⁴¹,⁴² Prebiotics and probiotics may be used to modify the inflammatory response, however, they are contraindicated in patients who have lactobacilli overgrowth. Since SIBO is thought to be secondary to motility disorders, prokinetics such as metoclopramide or cyclic gut lavage with polyethylene glycol may be of benefit.

Diabetic Diarrhea

Definition and Epidemiology

Diarrhea in patients with diabetes may be caused by diabetes itself, coexisting conditions or by medications. It is often described as episodic, explosive diarrhea in the absence of an infectious or non-infectious cause.⁴³ The prevalence of diarrhea among diabetic patients is estimated at 15%.⁴⁴

Pathophysiology

Several mechanisms as to the etiology of diarrhea in diabetic patients have been postulated; these include autonomic dysfunction of the enteric neurons from autoantibodies as well as enteric inflammation with increased IL6 levels causing alteration of intestinal motility.⁴⁵ Exocrine pancreatic insufficiency, celiac disease, small intestinal bacterial overgrowth and microscopic colitis have an increased prevalence in patients with diabetes and may cause diarrhea.⁴⁶ Medications such as biguanides and acarbose inhibitors and dietary products like sorbitol based sweeteners may also contribute.⁴⁷ Poor glycemic control may also worsen the diarrhea.⁴⁶

Treatment

Strict glycemic control, eliminating possible food triggers and treatment of underlying causes form the basis of treatment. Pharmacotherapy is with anti-motility agents such as loperamide or tincture of opium. Topical or oral clonidine and somatostatin analogs may be used for severe symptoms.⁴⁷,⁴⁸

5. Liver

Non Alcoholic Fatty Liver Disease and Non Alcoholic Steato Hepatitis

Definition and Epidemiology

Nonalcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis in the absence of secondary causes. In the United States, NAFLD is the most common chronic liver disease. NAFLD is commonly associated with diabetes as part of the metabolic syndrome, which also includes central obesity, low levels of high density lipoprotein (HDL), hypertriglyceridemia and hyperglycemia.⁴⁹ Non-alcoholic steatohepatitis (NASH) is characterized by hepatocyte fat accumulation with concomitant hepatocyte injury and fibrosis. Studies have reported a
69 to 87% prevalence of NAFLD and 60% prevalence of NASH in patients with diabetes, compared with a roughly 20% prevalence of NAFLD and 3-5% prevalence of NASH in the general population.49,50

**Pathophysiology**

Development of NAFLD and NASH in DM is explained by a “two-hit” hypothesis. Accumulation of triglycerides in hepatocytes is considered to be the first step. The second hit is linked to the formation of advanced glycation end products that produce oxidative stress on hepatocytes and increase the fibrogenic potential of the stellate cells.51,52 Hyperinsulinemia and increased insulin resistance are associated with greater hepatic inflammation and fibrosis and patients with diabetes and NAFLD have a higher risk of progression to NASH.53

**Diagnosis**

Liver biopsy remains the gold standard for diagnosing NAFLD/NASH and should be performed in patients at high risk and in whom a competing etiology cannot be excluded. Imaging by ultrasound, computed tomography (CT) or magnetic resonance (MRI) may not accurately assess the degree of fibrosis and steatohepatitis. However, when coupled with non-invasive fibrosis markers like ultrasonic fibro-elastography and fibrosis prediction scores, they have excellent specificity and sensitivity and are gradually replacing liver biopsy for diagnosis of NASH.53,54

**Treatment**

Weight loss of 3 to 5% of total body weight will improve steatosis and greater than 10% weight loss improves steatohepatitis. Other lifestyle modifications reducing alcohol consumption and increasing exercise are also recommended. Over the years, several clinical trials, involving many medications and supplements have been undertaken in an effort to improve NASH and NAFLD. While some have shown promise, there is insufficient evidence to support the use of any drug as the sole treatment for NASH in diabetics.55

**6. Gastrointestinal Malignancies**

Diabetes mellitus is associated with an increased risk of various GI malignancies. Two mechanisms have been hypothesized.

1. Insulin receptor (IR) and insulin-like growth factor-1 receptor – (IGF-1R) pathway:

Chronic hyperinsulinemia leads to up regulation of IGF-1R, epidermal growth factor (EGF) and its downstream pathways. This results in cellular proliferation, angiogenesis and inhibition of apoptosis, which promote tumor development in the pancreas and pre-malignant advanced adenomatous polyp formation in the colon.56,57,58,59

Hyperinsulinemia also leads to increased pro-inflammatory cytokines like interleukin 6 (IL-6) and decreased anti-inflammatory compounds such as adiponectin subsequently causing hepatic inflammation and fibrosis, which are precursors to HCC.60

2. Receptor for advanced glycation end products (RAGE):

Advanced glycation end products accumulate at an accelerated rate in diabetes. In vitro studies show that up regulation of RAGE is associated with inflammation and tumorigenesis in colon and pancreatic cancer.61,62

**Pancreatic Adenocarcinoma**

**Epidemiology**

Several studies have shown an increased risk of pancreatic adenocarcinoma in diabetes and there is roughly around 70% prevalence of diabetes or impaired glucose tolerance in patients with pancreatic cancer.64,65 It is unclear whether diabetes is causal in the pathogenesis of pancreatic cancer or whether it is an effect of it.

New onset diabetes is peculiar to pancreatic cancer with a recent diagnosis of diabetes conferring a 50% greater risk of malignancy than long-standing (>5 years) diabetes65.66 Pannala et al. demonstrated that new onset diabetes associated with pancreatic cancer resolved after a curative resection.67

**Diagnosis**

Presenting symptoms are weight loss, epigastric pain, anorexia, painless jaundice and nausea. Several imaging modalities may be used to diagnose suspected pancreatic cancer. Diagnostic accuracy of CT varies between 73%-87% depending on the size of the mass.68 MRI is superior to CT with 90% sensitivity; this increases to 97% when combined with magnetic
resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) provides clear resolution images and allows for needle sampling of pancreatic cells. It has 98% sensitivity and is becoming the diagnostic modality of choice for pancreatic cancer. Tumor markers such as carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) are used more commonly as prognostic indicators and for assessing response to treatment.

Colorectal Cancer (CRC)

Epidemiology
Diabetes is associated with an increased risk for colon cancer in both men and women and increased risk of rectal cancer in men. Diabetic patients with colon cancer have increased perioperative mortality, disease recurrence, worse response to chemotherapy, more treatment complications and increased risk of hepatic decompensation.

Diagnosis
Presenting symptoms are usually hematochezia or melena, change in bowel habits, abdominal pain, unexplained iron deficiency anemia or weight loss. Rectal cancer may cause tenesmus and rectal pain.

Screening for colon cancer focuses on detecting pre-malignant polyps to prevent them developing into advanced disease. Colonoscopy is considered the test of choice as polyps can be removed and suspicious lesions can be biopsied. Other noninvasive screening methods include CT colonography and stool DNA testing. Assays to detect blood in stool such as fecal immunochemical testing (FIT) and guaiac occult blood testing (gOBT) have roughly 65%-80% sensitivity and 85%-95% specificity for CRC detection. However, sensitivity is lower for detecting advanced adenomas.

Hepatocellular Carcinoma

Epidemiology
Long standing NAFLD and NASH can lead to cirrhosis and the development of cirrhosis is the greatest risk factor for developing hepatocellular carcinoma (HCC). Diabetes confers a two to three times increased risk of HCC, especially in older, Caucasian patients. Prevalence of diabetes may be double among HCC patients compared with controls, which remained significant even after adjusting for confounding factors like alcohol use, hepatitis B or C infection, obesity and hemochromatosis. A longer duration of diabetes may increase the risk of developing HCC.

Diagnosis
Cirrhosis is the most important risk factor with 1% to 6% of cirrhotics developing HCC annually. Surveillance with ultrasound (US) at 6 months intervals has been associated with a reduction in mortality in these patients.AFP levels have historically been used for surveillance, but is no longer recommended.

Typical appearance on four phase (unenhanced, arterial, venous and delayed) CT scan and on MRI both have excellent sensitivity and specificity (> 90%) for lesions >2cm. Dual imaging with MRI and ultrasound has excellent positive predictive value for smaller lesions.

Management
While no specific recommendations exist for early screening of patients with diabetes for GI malignancies, knowledge of the increased risk warrants further investigation of gastrointestinal symptoms in these patients.

Metformin has been associated with decreased risk of pancreatic and hepatocellular carcinoma and is protective against colorectal cancer among patients with diabetes. Conversely, insulin and sulfonylureas have been associated with an increased risk of malignancy, supporting the hypothesis that hyperinsulinemia has tumorigenic effects.

CONCLUSION
Knowledge of the gastrointestinal complications of diabetes is important for physicians to make an appropriate diagnosis, manage symptoms and improve the quality of life of patients living with long-standing diabetes. Awareness of the increased risk of malignancies in this population may help in early referral and diagnosis.

References


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