

GASTRO-INTESTINAL MANIFESTATIONS OF DIABETES MELLITUS

Abstract

With the increasing incidence of diabetes worldwide, the prevalence of gastrointestinal (GI) complications associated with diabetes is on the rise. These complications are often linked to poor glycemic control and are more prevalent in individuals with Type 1 diabetes mellitus. Gastrointestinal conditions caused by diabetes include esophageal involvement, gastroparesis, and diabetic enteropathy. Esophageal complications manifest as dyspepsia, heartburn, and difficulty in swallowing due to diabetic neuropathy affecting autonomic nerves. Gastroparesis, characterized by delayed gastric emptying, leads to symptoms such as abdominal fullness, nausea, and vomiting. Diabetic enteropathy results in intestinal abnormalities, causing diarrhea, constipation, or fecal incontinence, particularly in individuals with gastroparesis. The pathophysiology of these conditions involves impaired vagal control, loss of normal migrating motor complexes, and damage to the interstitial cells of Cajal. Diagnostic evaluations include patient history, physical examination, upper gastrointestinal endoscopy, and various tests such as antro-duodenal manometry and gastric emptying scintigraphy. Treatment strategies aim to rule out other causes, control weight, correct nutritional deficiencies, and alleviate symptoms. Gastrokinetic drugs, ghrelin agonists, and medications like erythromycin are employed in managing gastroparesis. Diabetic enteropathy treatment focuses on symptom relief, fluid correction, nutritional improvement, and glycemic control, with antimicrobial agents like rifaximin proving effective. Non-alcoholic fatty liver disease (NAFLD) is another common complication in individuals with Type 2 diabetes mellitus.

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and a high body mass index. It presents with elevated hepatic transaminase levels and can progress to non-alcoholic steatohepatitis (NASH) and cirrhosis. Diagnosis involves blood tests, imaging, and liver biopsy. Treatment includes gradual weight loss, blood glucose control, and pharmacologic interventions such as metformin and pioglitazone. The prevalence of diabetes is higher in individuals with hepatitis C infection, and certain oral hypoglycemics may pose hepatotoxic risks, especially in patients with liver disease. Additionally, diabetes is associated with a higher prevalence of idiopathic hemochromatosis, emphasizing the importance of screening for this condition in individuals with abnormal liver function tests or a family history of iron overload. Overall, understanding and addressing the gastro-intestinal manifestations of diabetes are crucial for comprehensive diabetes management.

Keywords: Diabetes, Gastroparesis, Hepatotoxic

I. INTRODUCTION

As the incidence of diabetes is increasing in the modern world, gastrointestinal (GI) complications of diabetes are becoming more common. Neuropathy and other gastrointestinal problems are associated with poor glycemic control, but not necessarily with chronicity of diabetes, mostly in people with Type 1 diabetes Mellitus. These problems and their symptoms are usually caused by abnormalities in gut motility due to diabetic autonomic neuropathy of the gut¹⁻³. These Gastrointestinal conditions caused by diabetes include gastroparesis, intestinal enteropathy (leading to diarrhoea, constipation, and faecal incontinence), and non-alcoholic fatty liver disease.

II. ESOPHAGEAL INVOLVEMENT

Muscle fibres in the oesophagus below the level of cervical oesophagus and in the lower oesophageal sphincter (LES) are composed of myenteric plexus. In individuals with longstanding diabetes, diabetic neuropathy affects these autonomic nerves. Consequently, this leads to irregularity in rhythm of normal peristaltic movement in the esophagus and a decrease in LES tone, structural remodelling of the musculature causing dyspepsia, heartburn and difficulty in deglutition⁴.

Other possible factors like obesity, hyperglycemia, and reduced bicarbonate secretion from parotid glands contribute to diabetes-related reflux. The management includes controlling blood sugar levels and using drugs for treating symptoms of reflux. The treatment of reflux disease includes the use of prokinetic drugs like metoclopramide and proton pump inhibitors. Studies show that taking erythromycin for two weeks can shorten the average time for esophageal and stomach emptying in people with type 2 diabetes⁵.

III. GASTROPARESIS

Gastroparesis refers to a condition where gastric emptying is delayed, affects 5 to 12 percent of diabetes patients, predominantly women. It is a frequent gastrointestinal complication seen in poor glycemic control patients and leads to symptoms of retention of gastric contents without any signs of obstruction⁶.

- 1. Clinical Features:** Symptoms include abdominal fullness, inability to finish normal sized meal, nausea, vomiting, bloating, postprandial fullness epigastric pain. Increase in mean transit time in stomach further leads to raised blood glucose level and poor control. This can be an early sign of gastroparesis⁷. Physicians should consider evaluating patients for diabetic gastroparesis where glycemic control is poor and patients experience frequent or unexplained changes in hyperglycemia and hypoglycemia due to the conflict between insulin action and carbohydrate absorption. Weight changes also occur, approximately 53% of patients lose weight and 18-24% gain weight⁸.
- 2. Pathophysiology:** The impaired gastric emptying in individuals suffering from diabetes mellitus with gastroparesis is thought to be basically resulting from impaired vagal control. Loss of the normal Migrating Motor Complexes, blunted antral contractions, spasm of the pylorus and small intestine and poor meal lodging inside the stomach are

all demonstrable in diabetes 7. Other factors contributing to these symptoms include the impairment of inhibitory nerves containing nitric oxide, underlying smooth muscle abnormality and damage to the interstitial cells of Cajal ⁹.

- 3. Evaluation:** While taking the patient's history, special attention should be paid to diabetes-related microvascular and macrovascular problems, although gastroparesis may occur independently. It is also important to exclude rumination syndrome.

In the **physical examination**, peripheral and autonomic neuropathy findings, epigastric distension and the presence of adverse effects in the postprandial period should be noted (noting succussion splash one hour after meals).

After that, an upper gastrointestinal endoscopy may be done to rule out any obstruction. The Physician alternatively performs an upper gastrointestinal series and magnetic resonance imaging of the small intestine. If patient experiences significant abdominal pain, an ultrasound examination of the abdomen is recommended to exclude biliary colic ¹⁰.

Other tests include **Antroduodenal manometry, Breath test and Elastogastrography.**

AGA recommends evaluating gastroparesis with patient history, physical exam, blood tests (CBC, TSH, metabolic panel, amylase if pain, pregnancy if applicable).

Gastric emptying scintigraphy is recommended for the diagnosis of gastroparesis. Technetium-labeled egg powder is consumed by patient and gastric emptying is measured by scanning at 15-minute intervals over a 4-hour period. More than 10% food residue after 4 hours indicates gastroparesis ¹¹.

4. Treatment

- Initial aim of treatment for diabetic gastroparesis is to rule out other causes, control weight, correct nutritional deficiencies, and lessen the symptoms.
- Eliminate drugs that induce gastroparesis like antidepressants, opioid pain relievers, and allergy medications wherever possible.
- Use of a grading system for severity assessment and treatment guidance:¹²
 - **Grade 1:** Symptoms are mild and easy to deal with. Potential to control body weight and maintain normal body nutrient levels via ordinary weight-reduction plan and lifestyle modification. Patients should maintain a good glycemic control
 - **Grade 2:** Symptoms are moderate and slightly controlled using antiemetic and gastroprokinetic drugs. Patients can take care of their nutrition through dietary and lifestyle modification.
 - **Grade 3:** Inability to control food intake by mouth; may require hospitalisation in Intensive Care Unit and management with fluid therapy and/or total enteral nutrition, insulin injections, and IV gastroprokinetic medications with antiemetics; long-term care may include endoscopic and/or surgical intervention or gastric pacemaker.

- Use Gastroprokinetic drugs:
 - Ondansetron 4-8 mg twice daily
 - Promethazine, prochlorperazine and chlorpromazine
 - Metoclopramide 10 mg 4 times/d
 - Domperidone 10 -20 mg 3 times/d
 - Erythromycin 50-250 mg thrice daily
- Ghrelin serves a crucial function in regulating the digestive system within the human body. Researchers have observed that TZP-101, a ghrelin agonist, demonstrates efficacy in alleviating nausea and vomiting among individuals diagnosed with diabetic gastroparesis when compared to a placebo 13.
- High blood sugar can cause peristaltic arrhythmias and a slow emptying rate, so blood sugar needs to be controlled.
- Correct nutritional deficiencies and alleviate symptoms to optimize management of diabetic gastroparesis.
- Trials have shown that Bethanechol (Urecholine) can strengthen contractions throughout the gastrointestinal (GI) tract. However, there is insufficient evidence on relieving gastroparesis symptoms when used alone or with other drugs¹⁴.
- Mosapride is a specific 5-HT₄ agonist known for its ability to accelerate gastric emptying. It has been seen in few studies that mosapride reduces symptoms in interferon-induced gastroparesis in hepatitis C patients 15-16.
- Other agents that have shown gastric stimulating effects in gastroparesis include prucalopride, velusetrag, naronapride (all 5-HT₄ agonists), and acotiamide (an acetylcholinesterase inhibitor), though further evidence is required to establish their benefits 6.

IV. ENTEROPATHY

Patients with long-term diabetes often experience Intestinal abnormalities, especially those suffering from gastroparesis. Diabetic enteropathy can cause diarrhea, constipation, or stool incontinence.

Advanced glycation end products (AGEs) have been implicated in causing cellular and tissue damage. Studies have shown elevated levels of AGEs in the ganglia, crypt, and brush border of the diabetic jejunum and ileum, as well as in the ganglia of the diabetic colon in animal models¹⁷. Autonomic neuropathy and fibrosis of intestinal muscular layers cause stasis of intestinal contents, resulting in reduced bowel motility, constipation, and potential overflow incontinence.

Intestinal stasis can cause **small intestinal bacterial overgrowth (SIBO)** and subsequent diarrhea.

Diabetic enteropathy presents with alternating **constipation** and painless diarrhea, often with fecal incontinence, more common at night.

This condition is commonly seen in uncontrolled diabetes mellitus with peripheral and autonomic neuropathy. Additionally, potential causes of abdominal pain encompass

pancreatic insufficiency, bile salt malabsorption, steatorrhea, and medications (e.g., metformin), which need to be ruled out to establish a diagnosis of enteropathy¹⁸.

1. Evaluation: Analyzing jejunal contents through aspiration and direct culture is regarded as the gold standard for diagnosing SIBO (Small Intestinal Bacterial Overgrowth). Nevertheless, these approaches have limitations, such as potential contamination from oropharyngeal bacteria during the process of Endotracheal Tube insertion and the possibility of not detecting patchy bacterial overgrowth with a single aspiration. Non-invasive diagnostic tests for SIBO predominantly involve measuring hydrogen exhaled in breath following luminal bacterial metabolism of carbohydrates¹⁹.

2. Treatment

- Diabetic diarrhea treatment focuses on symptom relief, fluid and electrolyte correction, nutrition improvement, and glycemic control, while addressing underlying causes.
- Caution should be exercised with anti-diarrheal agents as they can cause toxic megacolon.
- Rifaximin, an orally administered antimicrobial agent with limited absorption, has demonstrated efficacy in combating bacterial overgrowth in as many as 84% of patients²⁰.
- Anecdotal success has been observed in using somatostatin analogues to treat secretory diarrhea in diabetic patients with autonomic neuropathy.
- Additional antibiotics comprise amoxicillin-clavulanic acid, doxycycline, ciprofloxacin, metronidazole, neomycin, and norfloxacin.

V. NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

It is a liver condition resembling alcohol-induced injury, but occurring in individuals having a high body mass index (BMI) with Type 2 Diabetes Mellitus but no significant alcohol consumption history. There is a potential for progression to nonalcoholic steatohepatitis with inflammation and fibrosis, and in rare instances, it may result in cirrhosis.

Persistently raised hepatic transaminase levels aids diagnosis, and serologic testing excludes other liver conditions. Characteristic changes on ultrasonography or computed tomography, coupled with minimal alcohol consumption, confirm NAFLD diagnosis²¹.

1. Features and Clinical Course

- Nonalcoholic fatty liver disease (NAFLD) is frequently asymptomatic, though certain patients may encounter nonspecific symptoms such as malaise and right upper quadrant pain.
- The clinical presentation of NAFLD ranges from chronic liver enzyme elevation to fibrosis and nodular degeneration.
- NASH patients show reduced survival with more deaths from cardiovascular disease than liver-related causes
- Impaired fasting glucose and cirrhosis in NAFLD patients correlate with higher mortality, including liver-related deaths.

According to the guidelines of the American Association for the Study of Liver Diseases (AASLD), diagnosis of NAFLD requires hepatic steatosis, which is confirmed by blood tests or histology. In addition, excessive alcohol consumption, other competitive causes of steatosis, and chronic liver disease should not coexist²².

Liver biopsy is considered the most reliable method for detecting steatohepatitis and fibrosis in NAFLD patients. The presence of features related to metabolic syndrome can help predict steatohepatitis, leading to the recommendation of liver biopsy for NAFLD patients with metabolic syndrome. There is growing interest in non-invasive methods for identifying fibrosis in NAFLD.

The NAFLD Fibrosis Score is a valuable tool to identify patients with higher likelihood of bridging fibrosis or cirrhosis. Researchers have explored cytokeratin-18 fragments as a new biomarker to detect steatohepatitis in NAFLD patients²³. The sensitivity of this biomarker is 78%, while its specificity is 87%, making it effective in identifying steatohepatitis in individuals with NAFLD.

2. Treatment

- In the case of nonalcoholic steatohepatitis (NASH) patients, it is recommended to pursue gradual weight loss at a rate of approximately 1 to 2 lb (0.5 to 0.9 kg) per week and maintain proper blood glucose control (A1C less than 7 percent).
- Certain pharmacologic interventions, like metformin and gemfibrozil, have demonstrated positive effects in reducing hepatic transaminase levels and enhancing ultrasound findings in non-alcoholic fatty liver disease.
- Pioglitazone showed a statistically significant improvement in NASH histology in a small study (not yet approved by FDA for liver disease)²⁴.
- Maintaining optimal blood sugar levels with adopting weight loss approach should be focused upon.

VI. HEPATITIS C INFECTION WITH DIABETES

The prevalence of diabetes is higher in patients with hepatitis C compared to the general population (14.5% vs. 7.8%). Several factors, including older age, obesity, severe liver fibrosis, family history of diabetes, and interferon alfa treatment for hepatitis C, are linked to the development of diabetes in individuals with hepatitis C infection²⁵.

VII. ORAL HYPOGLYCEMICS AND HEPATOTOXICITY

FDA advises patients with liver disease to avoid thiazolidinediones. While uncommon, hepatotoxicity can occur with the use of sulfonylureas such as chlorpropamide and glipizide. On the other hand, acarbose may result in elevations of liver function tests²⁶.

VIII. IDIOPATHIC HEMOCHROMATOSIS

Patients with diabetes have a higher prevalence of **idiopathic hemochromatosis** (9.6 per 1,000) compared to the general population (4 per 1,000).

It is recommended to screen individuals with abnormal liver function tests, a history of arthritis, or a family history of iron overload for hemochromatosis by assessing transferrin saturation levels²⁷.

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