Gastro-intestinal complications of Diabetes Mellitus

# **Introduction:**

Gastrointestinal (GI) complications of diabetes have become more common as the rate of diabetes has increased. These complications and their symptoms are often caused by abnormal GI motility, a consequence of diabetic autonomic neuropathy in the GI tract. The Diabetes Control and Complications Trial suggested that, at least in persons with type 1 diabetes, neuropathy and other GI complications are associated with poor blood glucose control and not necessarily the duration of diabetes1-3. These GI conditions caused by diabetes include gastroparesis, intestinal enteropathy (leading to diarrhoea, constipation, and faecal incontinence), and non-alcoholic fatty liver disease.

## **Esophageal Involvement:**

The thoracic oesophagus and the lower oesophageal sphincter (LES) consist of smooth muscle fibres that are innervated by the myenteric plexus. In individuals with longstanding diabetes, diabetic neuropathy can affect these autonomic nerves. This can lead to abnormal peristalsis, spontaneous contractions, and a decrease in LES tone due to autonomic neuropathy and structural remodelling of the oesophageal musculature in diabetes causing heartburn and dysphagia 4.

Other possible factors like obesity, hyperglycemia, and reduced bicarbonate secretion from parotid glands contribute to diabetes-related reflux. Treatment involves controlling blood glucose levels and using medication for reflux management. The treatment of reflux disease includes the use of prokinetic drugs like metoclopramide and proton pump inhibitors. Studies have demonstrated that a two-week administration of erythromycin can decrease the mean oesophageal transit time and gastric emptying time in individuals with type 2 diabetes5.

## **Gastroparesis:**

Gastroparesis, a condition where gastric emptying is delayed, affects 5 to 12 percent of diabetes patients, predominantly women. Gastroparesis, one of the most frequent gastrointestinal complications of diabetes mellitus, gastroparesis leads to symptoms of gastric retention in the absence of any physical obstruction6.

### Clinical Features:

Symptoms include early satiety, nausea, vomiting, bloating, postprandial fullness, or upper abdominal pain. Delayed gastric emptying impacts blood glucose control and can be an early sign of gastroparesis 7. When glycemic control worsens, and patients experience frequent hypoglycemic episodes or unexplained alternating hyper- and hypoglycemia due to insulin action and carbohydrate absorption mismatch, clinicians should consider evaluating them for diabetic gastroparesis. Weight changes are also common, with approximately 53% of patients experiencing weight loss and 18%-24% experiencing weight gain 8.

### Pathophysiology:

### The delayed gastric emptying in patients with gastroparesis is believed to be primarily caused by impaired vagal control. Additional factors contributing to this condition include the dysfunction of inhibitory nerves containing nitric oxide, damage to the interstitial cells of Cajal, and underlying smooth muscle dysfunction 9. Loss of the normal Migrating Motor Complexes, blunted antral contractions, spasm of the pylorus and small intestine and poor meal accommodation in the stomach are all demonstrable in diabetes 7.

### Evaluation:

When taking a patient's **medical history**, special attention should be given to both macro- and micro-vascular complications associated with diabetes, even though gastroparesis may manifest independently. It is essential to exclude rumination syndrome as well.

During the **physical examination**, particular focus should be placed on identifying signs of peripheral and autonomic neuropathy, epigastric distension, and the presence of succussion splash one hour after meals.

Subsequently, upper **gastrointestinal endoscopy** can be conducted to rule out any mechanical obstructions. Alternatively, medical professionals may opt for an upper gastrointestinal series with small bowel follow-through or **small bowel magnetic resonance imaging**. If significant abdominal pain is present, an abdominal ultrasound scan is recommended to rule out biliary colic 10.

Other tests for evaluation of Diabetic Gastroparesis 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). To rule out obstruction or GI conditions, consider endoscopy or upper GI series with small bowel follow-through. Ultrasonography is advised for biliary symptoms or significant abdominal pain.

For diagnosing gastroparesis, gastric emptying scintigraphy is recommended. Technetium-labelled egg meal is ingested, and gastric emptying is measured via scintiscanning at 15-minute intervals over four hours 11. Simplified scanning with four images has comparable results to 13 images. Retention of over 10% of the meal after 4 hours indicates gastroparesis.

Treatment:

1. Focus on excluding other causes, assessing severity, correcting nutritional deficiencies, and reducing symptoms in managing diabetic gastroparesis.
2. Utilize a grading system for severity assessment and treatment guidance 12.
   1. Grade 1: Mild symptoms relatively easy to control. Ability to maintain weight and nutrition on a regular diet or with minor dietary modifications. Patients with diabetes should strive for optimal blood glucose control to minimize effects of hyperglycemia on gastric function.
   2. Grade 2: Compensated moderate symptoms with partial control using pharmacologic agents (typically involving a combination of antiemetic and prokinetic medications given at regularly scheduled intervals) Ability to maintain nutrition with dietary and lifestyle adjustments; Rare hospital admissions.
   3. Grade 3: Gastric failure; Refractory symptoms despite medical therapy. In-ability to maintain nutrition orally; Aggressive treatments, including hospitalization for intravenous hydration, insulin administration, and intravenous antiemetic and prokinetic agents, are considered; Chronic care may include total enteral or parenteral nutrition with endoscopic and/or surgical intervention or gastric "pacemaker".
3. Eliminate medications and substances that worsen underlying dysmotility. Medications delaying gastric emptying include aluminium hydroxide antacids, anticholinergic agents, beta-adrenergic receptor agonists, calcium channel blockers, diphenhydramine, histamine H2 antagonists, interferon alfa, levodopa, opioid analgesics, proton pump inhibitors, sucralfate, and tricyclic antidepressants 13.
4. Medications accelerating gastric emptying include beta-adrenergic receptor antagonists and prokinetic agents 13.
5. **Prokinetics** are medications that augment gastrointestinal motility. In general, these increase gastric motility and enhance stomach emptying:

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| Drug/drug group | Mechanism of action | Common side effects | Efficacy |
| Metoclopramide 10 mg 4 times/d | Anti-emetic, reduces nausea and post-prandial fullness, increases gastro-esophageal sphincter tone and improves antro-pyloro-duodenal coordination | Tardive dyskinesia, drowsiness, irritability, extrapyramidal symptoms and dystonic reactions | Symptom control in 1/3 to 2/3 of patients |
| Domperidone 10 -20 mg 3 times/d | Similar to metoclopramide with fewer CNS side effects due to a predominant peripheral mechanism of action | May prolong QTc interval in ECG; in turn may provoke cardiac arrhythmia | Effective in up to 60% of cases; tachyphylaxis develops in a few weeks requiring discontinuation |
| Erythromycin 50-250 mg thrice daily | Motilin receptor agonist. Reduces gastric emptying time | Nausea and vomiting at high doses | Modest symptom control Intravenous form can be useful in refractory vomiting |
| Promethazine, prochlorperazine and chlorpromazine | Mechanism of antiemesis poorly understood | Drowsiness, liver injury and extrapyramidal effects | Marginal improvement of symptoms Intramuscular chlorpromazine is very effective in refractory vomiting |
| Ondansetron | Central serotonin receptor (5-HT3) antagonist Inhibits vagus nerve | Extrapyramidal effect | Modest efficacy |

Originated from Hasler 6. CNS: Central nervous system; ECG: Electrocardiogram; QTc: Corrected QT interval.

1. High blood glucose levels contribute to gastric dysrhythmias and delayed emptying, necessitating blood glucose control.
2. Correct nutritional deficiencies and alleviate symptoms to optimize management of diabetic gastroparesis.
3. Bethanechol (Urecholine) has been observed to increase the strength of contractions in the entire gastrointestinal (GI) tract. However, there is insufficient evidence regarding its impact on gastroparesis symptoms when used in isolation or in combination with other medications 14.
4. Mosapride is a specific 5-HT4 agonist known for its ability to accelerate gastric emptying. Studies with orally administered mosapride citrate in ob/ob obese mice have shown a significant increase in food intake, along with a tendency to decrease fasting blood glucose and fructosamine concentrations when compared to control groups. Recent research has also reported symptom reductions in interferon-induced gastroparesis in hepatitis C patients who were treated with mosapride. 15-16.
5. 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.

## **ENTEROPATHY**

Patients with longstanding diabetes commonly experience small intestinal and colorectal dysfunctions, especially in the presence of gastroparesis. Diabetes-related enteropathy can lead to diarrhea, constipation, or fecal incontinence, similar to upper GI complications in diabetes.

Advanced glycation end products (AGEs) contribute to cellular and tissue damage, found increased in the ganglia, crypt, and brush border of diabetic jejunum and ileum, as well as in the diabetic colon's ganglia in animal models 17. 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** may also lead to **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. It is typical in poorly controlled diabetes with peripheral and autonomic neuropathy 18. Other causes of diabetic diarrhea include pancreatic insufficiency, bile salt malabsorption, steatorrhea, and drugs (e.g., Metformin), which should be excluded through investigations before diagnosing enteropathy.

Evaluation:

Examination of jejunal contents through aspiration and direct culture is considered a gold standard for SIBO diagnosis 19. However, these methods have limitations, including possible contamination from oropharyngeal bacteria during intubation and the potential to miss patchy bacterial overgrowth with a single aspiration. Non-invasive diagnostic tests for SIBO mainly rely on measuring hydrogen excretion in breath after luminal bacterial carbohydrate metabolism.

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 due to the risk of toxic megacolon.
* Rifaximin, a minimally absorbed oral antimicrobial agent, is effective against bacterial overgrowth in up to 84% of patients 20.
* Other antibiotics include amoxicillin-clavulanic acid, doxycycline, ciprofloxacin, metronidazole, neomycin, and norfloxacin.
* Somatostatin analogues have shown anecdotal success in treating intractable secretory diarrhea in diabetic patients with autonomic neuropathy.

## NONALCOHOLIC FATTY LIVER DISEASE:

Nonalcoholic fatty liver disease (NAFLD) is a liver condition resembling alcohol-induced injury, but occurring in individuals with no significant alcohol consumption history. It is often associated with type 2 diabetes and obesity. Progression to nonalcoholic steatohepatitis with inflammation and fibrosis is possible, and in rare cases, it may lead to cirrhosis.

Persistent elevation in 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 diagnosis 21.

Features and Clinical Course:

* Nonalcoholic fatty liver disease (NAFLD) is often asymptomatic, but some patients may experience nonspecific symptoms like malaise and right upper quadrant pain.
* NAFLD's clinical spectrum ranges from mild liver enzyme elevation to severe fibrosis and nodular degeneration.
* About 30% of NAFLD cases with isolated steatosis progress to NASH, of which 20% may develop cirrhosis, and 40% of cirrhotic patients experience decompensated liver disease.
* 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.

As per the American Association for the Study of Liver Diseases (AASLD) guidelines, diagnosing NAFLD necessitates the presence of hepatic steatosis through imaging or histology, with no significant alcohol overconsumption, no competing etiologies for hepatic steatosis, and no co-existing causes for chronic liver disease.

Liver biopsy is the most reliable method to detect steatohepatitis and fibrosis in NAFLD patients. Features of metabolic syndrome can predict steato-hepatitis, thus liver biopsy is recommended for NAFLD patients with metabolic syndrome. Non-invasive methods for identifying fibrosis in NAFLD have gained interest.

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

Treatment:

* Gradual weight loss (approximately 1 to 2 lb [0.5 to 0.9 kg] per week) and good blood glucose control (A1C less than 7 percent) are recommended for nonalcoholic steatohepatitis (NASH) patients.
* Pharmacologic interventions like metformin and gemfibrozil (Lopid) have shown benefits in lowering hepatic transaminase levels and improving ultrasound findings in nonalcoholic fatty liver disease or NASH.
* Pioglitazone (Actos) showed a statistically significant improvement in NASH histology in a small study, but it is not FDA-approved for liver disease use 24.
* Routine use of these drugs solely to normalize hepatic transaminase levels is not recommended due to a lack of sufficient evidence.
* Overall, effective NASH management should focus on weight loss and good control of blood glucose levels

## Association Between Diabetes and Other GI Diseases:

**Diabetes and Hepatitis C infection:**

Diabetes is more prevalent in patients with hepatitis C compared to the general population (14.5% vs. 7.8%). Factors such as older age, obesity, severe liver fibrosis, family history of diabetes, and interferon alfa treatment for hepatitis C are associated with diabetes development in patients with hepatitis C infection 25.

**Oral Hypoglycemics and Hepatotoxicity:**

The FDA recommends avoiding thiazolidinediones in patients with liver disease. Although rare, sulfonylureas like chlorpropamide, glyburide, glipizide, and tolbutamide can cause hepatotoxicity, while acarbose (Precose) may lead to mild liver function test elevations 26. Due to hepatotoxicity concerns, troglitazone (Rezulin), a thiazolidinedione, was withdrawn from the market.

Patients with diabetes have a higher prevalence of **idiopathic hemochromatosis** (9.6 per 1,000) compared to the general population (4 per 1,000); those with abnormal liver function tests, arthritis, or a family history of iron overload should be screened for hemochromatosis by checking transferrin saturation levels 27.

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