

Diagnosing and managing diabetic gastroparesis

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Diabetic gastroparesis is a frequent and complex disorder with clinical consequences beyond upper gastrointestinal symptoms. Management may be demanding and is often refractory to first-line pharmacological therapies, dietary modification and optimisation of glycaemic control. A multidisciplinary approach with specialist input is often required.

Key points

- Delayed gastric emptying and upper gastrointestinal symptoms occur frequently but correlate poorly in people with longstanding type 1 and type 2 diabetes.
- The efficacy of current prokinetic and antiemetic therapies in treating symptoms of diabetic gastroparesis is limited.
- In insulin-treated patients, delayed gastric emptying may lead to a mismatch between the timing of insulin action and carbohydrate absorption, predisposing them to hypoglycaemia.
- Measurement of gastric emptying using either a stable isotope breath test or scintigraphy is needed to establish the diagnosis.
- Management of diabetic gastroparesis is often complex and specialist input is recommended.



Gastroparesis refers to a delay in gastric emptying in the absence of mechanical obstruction and occurs frequently in people with longstanding type 1 or type 2 diabetes (prevalence 30 to 50%).^{1,2} Risk factors for gastroparesis include having diabetes for more than 10 years, chronic suboptimal glycaemic control, as assessed by measurement of glycated haemoglobin level, autonomic neuropathy and, possibly, cigarette smoking.³ Evaluation for potential gastroparesis should be considered in people with type 1 or type 2 diabetes who experience recurrent symptoms, such as nausea, vomiting, postprandial fullness, bloating or abdominal discomfort. Such symptoms are often not volunteered, but occur frequently in people who have diabetes and adversely affect quality of life. This article outlines the assessment and management of this important condition.

Clinical considerations

Gastroparesis may have important clinical consequences, even in the absence of upper gastrointestinal symptoms. For example, in people with insulin-treated diabetes, it may be associated with recurrent postprandial hypoglycaemia.⁴ Individuals with type 1 or type 2

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diabetes are often instructed to administer short-acting insulin before or with a meal; however, a delay in gastric emptying increases the risk of insulin action occurring before the absorption of nutrients.⁴ Furthermore, patients with other comorbidities who require time-critical medications (e.g. levodopa for treatment of Parkinson's disease) may have a suboptimal response to these medications due to a delay in intestinal absorption.⁵

A common and longstanding misconception is that a delay in gastric emptying, particularly when marked, is closely associated with upper gastrointestinal symptoms, such as nausea and vomiting; however, symptoms and the rate of gastric emptying correlate only weakly.⁶ Accordingly, a marked delay in gastric emptying may occur in the absence of gastrointestinal symptoms while, conversely, bothersome upper gastrointestinal symptoms may not be associated with any delay in gastric emptying.⁶ Furthermore, gastric emptying is now recognised to often be accelerated, particularly in those with uncomplicated type 1 or type 2 diabetes.⁷ Abnormally slow gastric emptying cannot be discriminated from more rapid gastric emptying on the basis of symptoms. Therefore, it is essential to confirm the diagnosis of gastroparesis using a suitable method.

Recent data on full-thickness gastric biopsies from patients with severe refractory gastroparesis from the Gastroparesis Clinical Research Consortium showed that the pathophysiology of diabetic gastroparesis is complex and heterogeneous.⁸ As such, an empirical approach to treatment may not prove effective, which complicates the management of this condition.

Evaluation of suspected gastroparesis

In individuals with suspected gastroparesis and upper gastrointestinal symptoms, differential diagnoses to consider include gastric outlet obstruction, medication adverse effects (e.g. from opioids, glucagon-like peptide-1 agonists), cannabis hyperemesis syndrome and rumination syndrome. Gastroparesis should also be suspected in patients with diabetes experiencing frequent, unexplained postprandial hypoglycaemia, even without upper gastrointestinal symptoms. Physical examination is generally unremarkable. Individuals with gastroparesis are more frequently nutrient deficient than the general population, especially in iron (50%) and vitamins D (50%) and B12 (18%).⁹ Therefore, evaluation for nutritional deficiencies should be considered in those with suspected gastroparesis.

In patients with upper gastrointestinal symptoms, an endoscopy is required to exclude gastric outlet and proximal small intestinal obstruction. However, the presence of retained gastric food at endoscopy is not a strong indicator of gastroparesis, with a positive predictive value of only 55%.¹⁰

The standard test to confirm the diagnosis of gastroparesis is scintigraphy; however, the stable isotope breath test is an acceptable alternative if the former is not readily available.¹¹ The stable isotope breath test is also more simple to perform and is not associated with a radiation burden; however, it cannot discriminate changes in gastric emptying from those in small intestinal absorption or transit. Current US guidelines recommend a test meal of eggs, toast, jam and water

with only a solid component (eggs) radiolabelled.^{12,13} Although other meals are used, standardising the test meal and establishing a normal range for gastric emptying of that meal are essential. Blood glucose levels should be below 15 mmol/L during measurement, as acute hyperglycaemia slows gastric emptying.¹³

Management of gastroparesis

Management of diabetic gastroparesis often requires a multi-disciplinary team, including an endocrinologist, a gastroenterologist, a dietitian and a psychologist, in addition to the GP. Evaluation and management of common clinical presentations are summarised in the Table.

Dietary management

Patients with diabetic gastroparesis may be advised to consume a small particle diet to help alleviate symptoms. This may require mashing food (e.g. potato) into a small particle size using a fork and excluding foods that have peels, husks (e.g. corn, peas, tomato, cabbage) or membranes (e.g. oranges), as well as fibrous food (e.g. asparagus, leek), seeds, grains, pasta, rice, meat, cheese slices and white fresh bread. A small particle diet is, accordingly, highly restrictive. Moreover, there is little evidence that it improves symptoms of gastroparesis.¹⁴ Not surprisingly, such a diet is also often not sustainable for long-term management and may be associated with nutritional deficiencies. Other interventions that can potentially improve symptoms include minimising the fat content of meals and having more starchy, bland foods.¹⁵ However, dietary management alone does not typically lead to adequate symptom relief.

Optimising glycaemic control

Optimisation of glycaemic control is likely helpful in both the short- and long-term management of symptoms, although sound prospective data are lacking. The timing or type of insulin to be administered may need to be modified in individuals with markedly delayed gastric emptying or in those with frequent postprandial hypoglycaemia. This is often done with the support of an endocrinologist and the use of continuous glucose monitoring, with low glucose alarms. Current hybrid closed-loop insulin pump systems do not account for delayed gastric emptying; however, in a recent small case series (n=7), use of this technology in individuals with gastroparesis was associated with an improvement in time in euglycaemic range (3.9 to 10 mmol/L) from 26 to 58% without increasing the risk of hypoglycaemia.¹⁶

Mental health management

Diabetic gastroparesis is strongly associated with psychological distress and impaired quality of life.¹⁷ A mental health evaluation should be considered and psychological support may prove beneficial. There is little information to support the choice of pharmacotherapy, if indicated. Mirtazapine has been reported to improve symptoms of gastroparesis in an open-labelled, uncontrolled trial, but was poorly tolerated by participants.¹⁸

Table. Evaluation and management of diabetic gastroparesis

Clinical presentation	Evaluation	Management	Practice points
Frequent, unexplained postprandial hypoglycaemia without upper gastrointestinal symptoms in insulin-treated patients	Refer for scintigraphy (or stable isotope breath test)	<ul style="list-style-type: none"> Alter timing or type of insulin Consult an endocrinologist Consider insulin pump therapy in people with type 1 diabetes 	Consider use of continuous glucose monitoring to monitor treatment effectiveness
Upper gastrointestinal symptoms	<ul style="list-style-type: none"> Review drug history Refer for endoscopy Refer for scintigraphy (or stable isotope breath test) Check vitamin D, iron and vitamin B12 levels Evaluate mental health 	<ul style="list-style-type: none"> Stop drugs that may induce gastrointestinal symptoms where possible Encourage dietary modification Consider additional psychological support Consider metoclopramide or domperidone If refractory to dopamine-2 (D2) receptor antagonist: <ul style="list-style-type: none"> stop D2 receptor antagonist trial macrolide (e.g. erythromycin 50 to 100mg orally four times daily) refer to a gastroenterologist 	<ul style="list-style-type: none"> Counsel patients regarding risk of tardive dyskinesia with metoclopramide Check QT interval on ECG Exercise caution with other drugs that may prolong QT interval Review potential drug interactions with use of macrolides Manage patient expectations (counsel patients on the limited efficacy of drugs in symptom management)
Inability to tolerate oral intake	<ul style="list-style-type: none"> Review drug history Refer for endoscopy Refer for scintigraphy (or stable isotope breath test) Check vitamin D, iron and vitamin B12 levels Evaluate mental health 	<ul style="list-style-type: none"> Consider hospital admission for nutritional support, intravenous fluids, electrolyte replacement Refer for subcutaneous metoclopramide for symptom relief Refer to a gastroenterologist 	Consider risk for re-feeding syndrome

Pharmacological management

Dopamine-2 (D2) receptor antagonists (metoclopramide and domperidone) remain the first-line treatment for gastroparesis with upper gastrointestinal symptoms. Although these drugs accelerate gastric emptying, the relationship between improvement in symptoms and gastric emptying is weak at best. Individuals managed with metoclopramide should be counselled about the rare (0.1% per 1000 patient-years), but potentially irreversible, adverse effect of tardive dyskinesia.¹⁹ Domperidone improves symptoms of gastroparesis to a comparable extent to metoclopramide and is associated with a lower risk of tardive dyskinesia due to reduced permeability across the blood brain barrier.²⁰ Thus, domperidone may be a preferable option if available. As D2 receptor antagonists are associated with prolongation of the corrected QT interval on ECG, it is advisable to perform an ECG before and after initiating treatment.

Both metoclopramide and domperidone also have antiemetic properties. There is anecdotal evidence that self-administration of subcutaneous metoclopramide may be effective in the treatment of acute episodes of vomiting in patients with gastroparesis. Other antiemetic therapies (e.g. 5-HT3 antagonist, ondansetron) are used in the management of symptomatic gastroparesis, but evidence to support their efficacy is limited.

The macrolide antibiotics erythromycin, azithromycin and clarithromycin are also motilin-receptor agonists that accelerate gastric

emptying and are used ‘off-label’ for the treatment of diabetic gastroparesis.²¹ Although short-term use of these drugs accelerates gastric emptying, controlled trials are needed to determine their efficacy in improving upper gastrointestinal symptoms and accelerating gastric emptying in the longer term.²² Erythromycin is the best studied antibiotic for the management of gastroparesis; however, it has a high potential for drug interactions (e.g. with warfarin, atorvastatin, simvastatin) and should be used with caution in patients taking other medications.^{23,24}

Complementary and alternative medicines

Herbal therapies such as rikkunshito, iberogast or traditional Chinese medicines cannot currently be recommended for treatment of diabetic gastroparesis.^{21,25} Acupuncture is often used to manage gastrointestinal disorders and showed potential in alleviating symptoms of gastroparesis in initial trials. However, a subsequent meta-analysis was indicative of low-certainty evidence for acupuncture in improving symptoms of diabetic gastroparesis.²⁶

Invasive therapies

For individuals with gastroparesis refractory to pharmacological and nonpharmacological management, referral to a gastroenterologist is indicated. In a recent sham-controlled, randomised clinical trial of individuals with refractory gastroparesis, gastric peroral endoscopic pyloromyotomy (G-POEM) was associated with symptomatic

improvement in 71% of participants compared with 22% who underwent the sham procedure.²⁷ Gastric emptying is also accelerated following G-POEM.²⁸ Intrapyloric injection of botulinum toxin showed potential for improving symptoms associated with refractory gastroparesis in initial open-labelled clinical trials; however, two subsequent sham-controlled trials failed to demonstrate improvement in either symptoms or gastric emptying.^{29,30} The delivery of low-energy, high-frequency electrical pulses to the antrum (gastric electrical stimulation) can effectively treat vomiting in individuals with diabetes (irrespective of whether they have gastroparesis), but gastric emptying is not accelerated and overall quality of life may not be improved.³¹ Further studies are needed before gastric electrical stimulation is incorporated into routine clinical practice.

Conclusion

Management of diabetic gastroparesis is complex and usually necessitates a multidisciplinary team. It is now appreciated that the severity of delay in gastric emptying correlates poorly with symptoms. Delayed gastric emptying may impact glycaemic control and oral drug absorption adversely. Because of the heterogeneous nature of the underlying dysfunctions of diabetic gastroparesis, the efficacy of current empirical approaches to management is limited. Future therapy should ideally be more personalised and targeted at the relevant pathophysiology. **ET**

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Professor Horowitz is on the scientific and clinical advisory board for, and has stock options in, Glyscend.

Dr Jones has participated in the advisory board for Glyscend.