# Diabetic gastroparesis: pathophysiology, evaluation and management

***As the incidence of diabetes mellitus inexorably rises, the burden of its complications is becoming increasingly problematic. Among the most bothersome, but often under-recognized, inadequately investigated and poorly managed, is diabetic gastroparesis.***

Diabetes mellitus is a group of metabolic disorders characterized by elevated blood sugar levels. Broadly speaking, there are three main types of diabetes: type 1, type 2 and gestational. The prevalence of diabetes is increasing, with the World Health Organization estimating that at least 171 million people suffer from it worldwide, with a doubling of prevalence estimated by 2030 (Wild et al, 2004). It has been hypothesized that this epidemic is a result of the increasing trend of urbanization and concomitant lifestyle and dietary changes.

The management of diabetes and its attendant complications uses considerable health-care resources, estimated to be in the order of $132 billion annually in the United States (Narayan et al, 2006). As the prevalence of diabetes increases, the incidence of complications is increasing. Among the most bothersome are sequelae of the impairment of gastrointestinal motility (Maleki et al, 2000). The development of gastrointestinal complications is associated with poor glucose control rather than the longevity of the diagnosis (Kim et al, 2010). This review focuses on the pathophysiology, clinical evaluation and treatment of diabetic gastroparesis, perhaps the most notable gastrointestinal complication of diabetes.

## Gastroparesis

The term 'gastroparesis' was initially coined in the mid-1940s, where a small cohort of diabetics with autonomic neuropathy were reported to suffer from severe upper gastrointestinal symptoms (Rundles, 1945). Towards the end of the 1950s, the term 'gastroparesis diabeticorum' was first used to describe diabetic patients with gastric aperistalsis in the absence of mechanical obstruction, characteristics that were similar to patients who had undergone truncal vagotomy (Kassander, 1958). Therefore diabetic gastroparesis can be defined as delayed gastric emptying in the absence of mechanical obstruction of the stomach. The most commonly reported symptoms are nausea, vomiting, early satiety and bloating. Up to 12% of patients with diabetes report symptoms consistent with gastroparesis and such symptoms may result in nutritional compromise, poor glycaemic control, psychological distress and a reduction in health-related quality of life (Talley et al, 2001).

Studies examining the natural history of diabetic gastroparesis have been limited by publication bias, relatively short follow up and small data sets. Nevertheless, it is broadly accepted that risk factors for the development of diabetic gastroparesis are date of diagnosis in excess of 10 years, elevated glycosylated haemoglobin level and ostensible macro- and microvascular complications. Indeed, poor glycaemic control may be the first indication that the patient is developing delayed gastric emptying.

## Pathophysiology of diabetic gastroparesis

In health, the proximal stomach serves as a reservoir while the distal portion 'grinds' food into particles of c.2 mm which are then emptied into the small bowel via the pylorus. The exact nature, and to a degree the absolute speed, of this process is determined by the nature of the food – large volume liquids empty rapidly whereas it may take up to 4 hours for solids to exit from the stomach. This process is influenced by a number of regulating hormones, such as glucagon and incretins, as the food arrives in different regions of the small bowel. These hormones decelerate the rate of gastric emptying thus allowing digestion and absorption to take place, in addition to controlling postprandial glycaemia.

In diabetes, there is often demonstrable dysregulation of many of these mechanisms. For example, neuropathy of the vagal and inhibitory neurons may result in motor incoordination of antral contractions and thereby delay gastric emptying. Acute hyperglycaemia may also contribute to this process with gastric emptying taking up to 15 minutes longer in subjects with blood glucose in excess of 10 mmol/litre in contrast to those with euglycaemia (Fraser et al, 1990). Extrinsic factors, such as medications, may also exacerbate gastric emptying and indeed this may necessitate their withdrawal. Concomitant dis-

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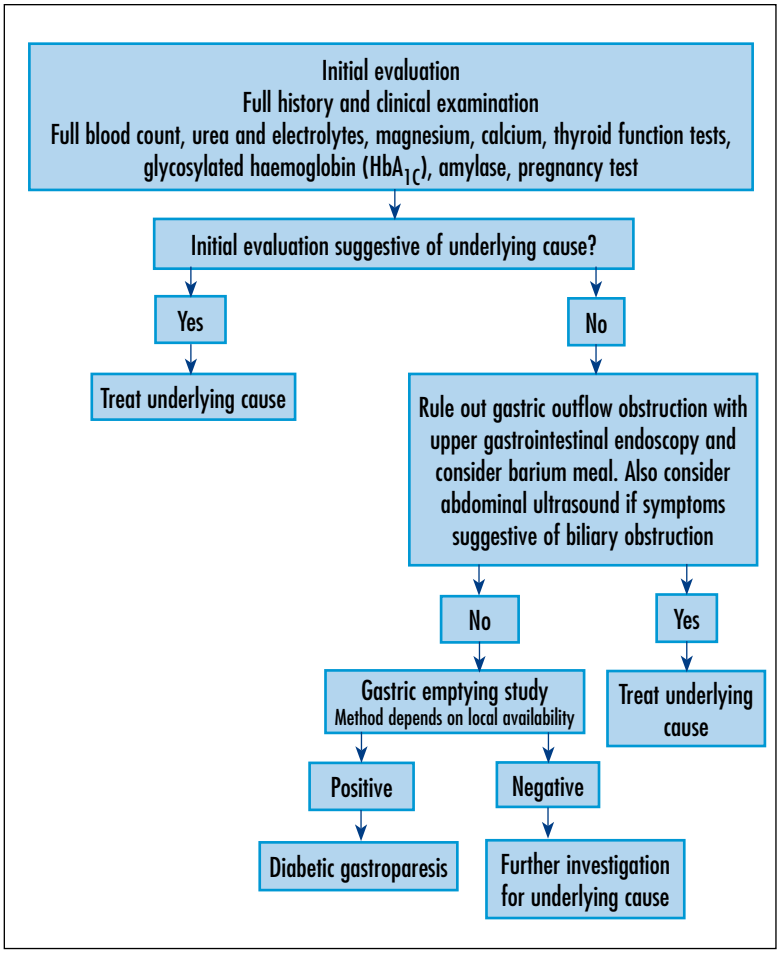
orders, such as anxiety and depression, also result in increased symptom reporting but the true relationship to the delay in gastric emptying remains unclear.

## Clinical evaluation

While there is a paucity of evidence-based UK guidelines, an American Gastroenterological Association technical review addressed the initial evaluation of the diabetic patient with suspected gastroparesis (Parkman et al, 2004). It is suggested that a careful history and physical examination should be completed by the measurements of routine biochemical, hormonal and haematological parameters, as detailed in *Figure 1*. In particular, a history of macro- and microvascular complications of diabetes should be sought, although gastroparesis may occur in their absence. A careful history must also be sought to exclude rumination syndrome, that is daily effortless regurgitation of food, which often occurs in the direct postprandial period.

Physical examination should focus on looking for evidence of peripheral and autonomic neuropathy, epigastric distension and the presence or absence of a sucussion splash. The absence of the latter 1 hour after eating suggests normal gastric emptying. Upper gastrointestinal endoscopy or a barium meal should be performed to exclude a mechanical cause for gastric outlet obstruction. If food is observed at endoscopy, following a 12-hour fast, then this is strongly suggestive of gastroparesis in the absence of gastric outlet obstruction. Abdominal ultrasonography should be undertaken in those with suspected biliary symptoms. Other investigations aimed at establishing the presence or absence of diabetic neuropathy, such as autonomic function tests or the novel non-invasive technology of corneal confocal microscopy, do not yet have a defined role in the investigation of diabetic gastroparesis (Tavakoli et al, 2010).

***Figure 1. A proposed algorithm for the clinical evaluation of suspected gastroparesis. Adapted from Shakil et al (2008).***




Scintigraphic measurement of gastric emptying is considered the gold standard for diagnosing gastroparesis. This is a non-invasive, quantitative method that involves the patient consuming a technetium-labelled meal with gastric emptying measured by scintigraphy. Although this method has long been used, there has been a disappointing lack of standardization between institutions. Particular differences include differences in test meal, patient positioning and duration or frequency of imaging. This places considerable limitations on interpreting such results between institutions and within the published literature. More recently, however, the American Neurogastroenterology and Motility Society recommended a test meal of two large eggs, two slices of bread with jam with the former labelled with technetium-99m sulphur colloid, with scintigraphy undertaken 0, 1, 2 and 4 hours postprandially (Abell et al, 2008). Delayed gastric emptying would be present if there is >90% retention at 1 hour, >60% at 2 hours and >10% at 4 hours.

Novel methods of evaluating gastric emptying include the wireless capsule (SmartPill GI Monitoring System, SmartPill Corporation, Buffalo, New York, USA) and breath testing. The SmartPill is a relatively recent technological advance facilitating the measurement of panenteric motility. Using a similar concept to wireless capsule endoscopy, the SmartPill is an indigestible capsule which senses luminal pH, temperature and pressure as it traverses the gastrointestinal tract. The capsule wirelessly relays data to a receiver unit worn by the patient until it is excreted. Gastric emptying is deduced by a sudden rise in pH from the acidity of the stomach to the relative alkaline environment of the duodenum. This technology compares favourably to scintigraphic measurements (Cassilly et al, 2008).

The breath testing method, providing an indirect estimate of gastric emptying, uses a non-radioactive 13C isotope bound to a digestible substance, most commonly octanoic acid. 13C octanoic acid is mixed into a solid meal and ingested, where it is absorbed from the small intestine and metabolized to $13CO_2$. It is then expelled from the lungs where it can be measured in exhaled breath. The main advantage of these new technologies is that they limit radiation exposure to the patient although their general availability is currently limited.

**Table 1. Proposed classification for assessing the severity of gastroparesis**

| | |
|---|---|
| Grade 1: mild | Symptoms easy to control |
| | Ability to maintain weight and nutritional status on regular diet or with minor dietary modifications |
| | Good glucose control minimizing hyperglycaemia |
| Grade 2: compensated | Moderate symptoms with partial control with pharmacological agents (such as prokinetics and anti-emetics) |
| | Ability to maintain nutrition |
| | Infrequent hospital admissions |
| Grade 3: gastric failure | Refractory symptoms despite maximal medial therapy |
| | Inability to maintain nutritional status orally |
| | Needing hospitalization for therapy and nutritional supplementation (either enteral or parenteral) |
| | May need surgical or endoscopic intervention |

From Abell et al (2006)

## Grading of severity

Abell et al (2006) have suggested a grading system to reflect the relative severity of diabetic gastroparesis (*Table 1*).

In addition to Abell's classification, a symptom-based tool known as the gastroparesis cardinal symptom index has been developed which assesses symptoms over the preceding fortnight (Revicki et al, 2004). The gastroparesis cardinal symptom index consists of nine subscales: nausea, retching, vomiting, stomach fullness, not being able to finish a normal size meal, feeling excessively full after a meal, loss of appetite, bloating and abdominal bloating. Patients self rate their symptoms on each of these subscales from none to very severe. In addition to the benefits to research studies of these two classification systems, practically they allow clinicians to stratify patients and thereby aid management and inform decisions regarding escalation of care or interventions.

## Treatment

Treatment of diabetic gastroparesis requires a logical stepwise approach that involves general measures, dietary modifications, pharmacological therapy (prokinetics and anti-emetics) and the consideration of more invasive surgical treatments (*Figure 2*).

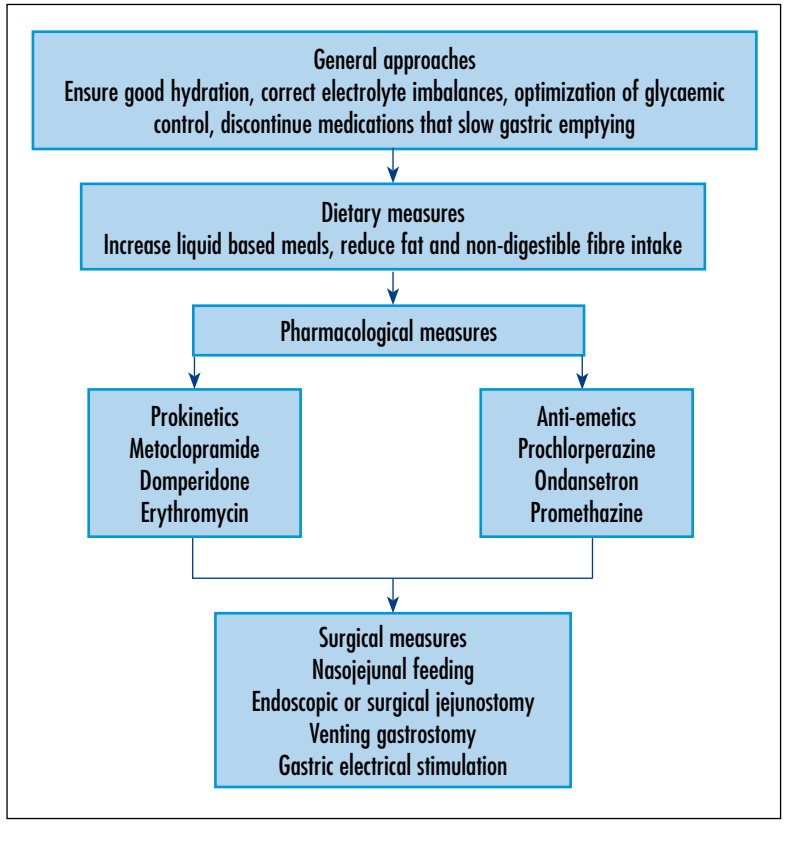
### General approaches

General approaches to managing diabetic gastroparesis include ensuring adequate hydration and correcting any electrolyte imbalances, optimization of diabetes management (including glycaemic control) and symptom reduction, often with pharmacotherapeutic agents. A detailed review of current medications history needs to be undertaken and medications that retard gastric emptying should be discontinued where possible. Such retardants include anticholinergic agents (e.g. tricyclic antidepressants, opioid analgesics), antihypertensives (e.g. calcium-channel blockers) and anti-secretory agents (e.g. $H_2$ receptor antagonists (ranitidine) and proton pump inhibitors).

### Dietary modifications

Dietary modifications mainly concern adjustments to timings of meals and their contents. Patients should be encouraged to eat more liquid-based meals, such as soups, since the gastric emptying of liquids is generally faster than that of solids. Intake of fat and non-digestible fibre should also be reduced, as the former is time dependent on gastric hormones to augment gastric emptying and the latter predisposes to phytobezoar formation as a consequence of reduced antral motility. Large meals, with high calorie content, have longer gastric emptying

***Figure 2. Treatment options in the management of diabetic gastroparesis.***



times, so smaller portioned meals spread throughout the day may help to overcome this. In a minority of patients, symptoms are severe enough for the clinician to consider nutritional support. Other indicators that nutritional support is required include unintentional loss of >10% of total body weight over 6 months, repeated admissions for refractory symptoms, interference in the delivery of therapeutics, and nausea or vomiting reducing quality of life. Further comments are made regarding the placement and utility of enteral feeding devices in the invasive treatment section.

## Prokinetics

Prokinetic agents promote the transit of stomach contents by enhancing antral contractility, improving gastric dysrhythmias and improving antroduodenal coordination. Randomized control trials of prokinetics have demonstrated a symptomatic benefit with this class of therapeutics, as summarized and reviewed by Talley (2003). At best, these medications only provide limited efficacy – there is often a discordance in demonstrable improvement in gastric emptying and symptom relief. Among the most commonly used prokinetic medications are metoclopramide, domperidone and erythromycin (*Table 2*). Metoclopramide and domperidone are considered to be of similar efficacy.

The 5-$HT_4$ receptor agonists have provided a helpful adjunct in the 'promotile' armamentarium. This class of medication facilitates the release of acetylcholine from the efferent gut motor neurons, thereby stimulating motility. However, safety concerns regarding an excess of cardiac arrhythmias (cisapride) and ischaemic events (tegaserod) have limited their utility. Nevertheless, new generation, selective 5-$HT_4$ receptor agonists such as prucalopride may offer another therapeutic option, particularly as prucalopride increases gastric emptying although further studies are warranted to evaluate its efficacy specifically in diabetic gastroparesis (Bouras et al, 2001). Other cholinergic and anticholinesterase agents such as bethanechol and pyridostigmine may accelerate gastric emptying but a paucity of data remains concerning their efficacy of the treatment of gastroparesis.

## Anti-emetics

The physiological mechanism by which diabetic gastroparesis is emetogenic remains incompletely understood. Nevertheless, antiemetic agents such as metoclopramide, ondansetron and promethazine are useful for symptomatic treatment. The mechanism of action of these drugs is via a multitude of central and peripheral pathways (*Table 3*).

## Invasive or surgical treatments

Refractory, grade 3 diabetic gastroparesis is seen in those who have failed medical therapy and who fail to meet nutritional requirements. A trial of feeding distal to the pylorus using a nasojejunal tube can be helpful as a short-term measure in improving nutrition and, if successful, may be followed by permanent percutaneous placement,

**Table 2. The most commonly prescribed prokinetics**

| Name | Mechanism of action | Dose | Notes | Adverse effects |
|---|---|---|---|---|
| Metoclopramide | Central and peripheral $D_2$ receptor antagonist | 10–20 mg oral three times daily | Anti-emetic action also contributes to symptom relief. As it has central effects patients are more prone to side effects. Blocks $D_2$ receptors, thus activating 5-$HT_4$ receptors augmenting acetylcholine release from the gut wall stimulating peristalsis | Extrapyramidal movements disorders, anxiety, depression, galactorrhoea |
| Domperidone | Peripheral $D_2$ receptor antagonist | 10–20 mg oral three times daily | Peripheral $D_2$ antagonism, thus central side effects are less common. Mechanism of action as above | Galactorrhoea |
| Erythromycin | Motilin receptor agonist | 125–500 mg oral four times daily | Macrolide antibiotic that has some activity at the motilin receptor. Motilin is a polypeptide that stimulates smooth muscle contraction in the gastrointestinal tract | Abdominal cramping, diarrhoea, loss of appetite. Multiple drug interactions – metabolized through cytochrome P450 3A4 pathway. May prolong QT interval |

**Table 3. The most commonly prescribed anti-emetics**

| Name | Mechanism of action | Dose | Notes | Adverse effects |
|---|---|---|---|---|
| Prochlorperazine | Phenothiazine derivative acting as an antagonist on the $D_2$ receptor | 5–10 mg oral three times daily | Specifically blocks the chemoreceptor trigger zone, in the area postrema, in the fourth ventricle | Sedation, extrapyramidal movements disorders and rarely drug-induced liver injury |
| Ondansetron | 5-$HT_3$ antagonist | 4–8 mg oral three times daily | Blocks the chemoreceptor trigger zone with additional effect on the afferent vagal nerve fibres | Constipation |
| Promethazine | $H_1$ receptor antagonist | 12.5–50 mg intramuscular daily | Anticholinergic that promotes acetylcholine activity, thereby stimulating gastrointestinal tract motility | Drowsiness, blurred vision, dry mouth and constipation. Contraindicated in glaucoma and urinary retention |

either surgically or endoscopically, of a jejunostomy. Jejunal enteral feeding maintains nutrition, relieves symptoms and reduces the frequency of hospital admissions (Fontana and Barnett, 1996).

The role of percutaneous endoscopic placement of a gastrostomy remains controversial – while not indicated for feeding, it does facilitate gastric decompression or venting and has been reported to improve symptoms, nutrition and functional status in a small uncontrolled trial of patients with idiopathic gastroparesis (Kim and Nelson, 1998). In addition, accumulating evidence suggests that gastrostomy insertion, thereby securing access to the gastric mucosa, and temporary placement of gastric electrical stimulating electrodes may represent a bridge to the placement of a more permanent system (Abell et al, 2011). Whether clinical response to such temporary systems will allow prediction of response to permanent gastric electrical stimulating systems remains unknown. Gastric electrical stimulation is discussed in more detail later.

It has been postulated that diabetic gastroparesis causes spasmodic contractions of the pylorus, further delaying gastric emptying (Mearin et al, 1986). Endoscopic pyloric injection of toxin from *Clostridium botulinum* has been used in the management of diabetic gastroparesis. This neurotoxin inhibits the release of acetylcholine at the neuromuscular junction and causing (a degree of) paralysis of the pylorus. The results of a number of non-randomized uncontrolled studies have suggested a degree of efficacy of intrapyloric injection of botulinum toxin. However, in a more recent randomized controlled trial, albeit performed in idiopathic gastroparesis, intrapyloric injection of botulinum toxin did not improve symptoms or gastric emptying over 1 month (Arts et al, 2007).

Gastric electrical stimulation involves the surgical, usually laparoscopic, placement of electrodes onto the muscle wall of the gastric antrum usually 10 cm proximal to the pylorus. These electrodes are then attached to a neurostimulator, which is implanted into a subcutaneous pouch in the left flank. This externally programmable neurostimulator sends continuous high frequency, low energy pulses to the electrodes on the antral wall.

Controversies exist as to the exact mechanism of action but it is suggested that the pulses enhance vagal autonomic function thereby improving gastric accommodation. In a double blind crossover study, gastric electrical stimulation reduces the frequency of episodes of vomiting in diabetic gastroparesis, while symptom severity and quality of life measures significantly improved at 6 and 12 months (Abell et al, 2003). Interestingly, gastric emptying was only modestly accelerated in this study, suggesting the mechanism of action is, to a degree, independent of this. In the longer term, an open label study with a mean follow-up period extending beyond 3 years, reported that gastric electrical stimulation decreased symptoms and reduced the need for nutritional support (Lin et al, 2006).

A meta-analysis of published literature by O'Grady et al (2009) suggested that gastric electrical stimulation significantly improved symptoms of gastroparesis such as nausea and vomiting and quality of life measured using SF-36 in patients with gastroparesis and reduced the requirement for assisted feeding via enteral or parenteral route. The optimum stimulation parameters, in terms of electrical frequency, duration and energy, remain uncertain but may improve efficacy. Further randomized controlled trials are needed to evaluate this therapeutic option.

## Conclusions

Major improvements have been made in our understanding of the pathophysiology of diabetic gastroparesis, yet significant knowledge gaps remain. Until these gaps are addressed, further advances in the treatment of this disorder, particularly in the most severely affected patients, will remain limited. Amid a global epidemic of diabetes, this presents a considerable, but not insurmountable, challenge. **BJHM**

Figure 1 *is reproduced from Shakil et al (2008) by kind permission of the American Academy of Family Physicians.*

*Conflict of interest: none.*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## KEY POINTS

- The incidence of diabetes is increasing.
- Diabetic gastroparesis is among the most bothersome complications and is defined as delayed gastric emptying in the absence of mechanical obstruction of the stomach.
- A gastric emptying study is the gold standard in establishing the diagnosis.
- Dietary advice and pharmacotherapy (anti-emetics and prokinetics) are the mainstay of therapy.
- Gastric electrical stimulation, while not widely available, represents an exciting new therapy.

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