Gastroparesis in people with diabetes

Philip Weston

Gastrointestinal symptoms are common in people with diabetes (Spångéus et al, 2002). Symptoms can arise from the whole of the gastrointestinal tract and disordered gut motility can have a profound effect on quality of life. The stomach seems to be particularly commonly affected in people with diabetes (Camilleri, 2007). Gastroparesis can lead to worsening glycaemic control, which in turn leads to further worsening of gastric dysmotility. This vicious spiral can lead to intractable symptoms, malnourishment and hospitalisation. It is important, therefore, that all physicians looking after people with diabetes are able to identify those suffering from gastroparesis and are able to investigate and treat this condition appropriately. This article outlines the epidemiology, pathophysiology, diagnosis and treatment of gastroparesis in people with diabetes.

Gastroparesis can be defined as delayed gastric emptying in the absence of mechanical gastric outflow obstruction. Cross-sectional studies show that delayed gastric emptying occurs in 30–50% of people with type 1 and type 2 diabetes, and symptoms of gastroparesis are reported in 12% of people with diabetes (Camilleri, 2007).

Why some people with evidence of delayed gastric emptying develop symptoms and some do not remains unclear. Delayed gastric emptying is not an "all or none" phenomenon and people who are symptomatic can become symptom-free when glycaemic control improves or intercurrent illnesses are treated. Symptomatic gastroparesis is frequently associated with other complications of diabetes such as retinopathy and nephropathy.

Pathophysiology

In a healthy individual, food is propelled from the oesophagus to the anus through coordinated muscular contractions in the gastrointestinal (GI) tract. The stomach can be functionally divided into two halves: the fundus and upper body acting as a reservoir for food, while the lower body and antrum grinds food, moving it on to the pylorus. Gastric contractility is controlled by neural networks located in the stomach wall and by the parasympathetic nervous system through the vagal nerve. When eating, the fundus relaxes to accommodate the food load and this process is vagally mediated. Contraction of the antrum is controlled by electrical signals that arise from interstitial cells of Cajal, found in the stomach's muscle layers. Cajal cells act as gastric pacemakers generating a "slow wave" of gastric contraction, mixing the food with gastric secretions and moving the food through the stomach (Read and Houghton, 1989).

In people with diabetes, gastroparesis is caused by a number of interrelated mechanisms. First, antral contraction and fundal relaxation is impaired by abnormalities of the autonomic nervous system, particularly the parasympathetic nervous system. In addition, other neural features such as reduced stomach wall inhibitory neurones and reduced Cajal cells, have been identified (He et al, 2001).

Second, high blood glucose levels, as indicated by high HbA_{1c} measurements, are directly

Article points

1. Gastroparesis is a common complication of diabetes and it is often symptomatic. Treatment involves dietary modification, prokinetics and anti-emetics. Tight glycaemic control is essential but difficult to achieve.
2. Symptoms of gastroparesis are reported in 12% of people with diabetes. Why some people with evidence of delayed gastric emptying develop symptoms and some do not remains unclear.
3. The initial steps of managing an individual with symptomatic gastroparesis are correcting exacerbating factors, such as intercurrent illness, and then the optimisation of blood glucose control.

Key words

- Delayed gastric emptying
- Gastroparesis
- Glycaemic control

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1. The most common symptoms of gastroparesis are nausea, vomiting, a feeling of fullness and abdominal bloating. These symptoms are, unsurprisingly, more common after meals but vomiting can occur many hours after eating.
2. With a suggestive history of gastroparesis, investigations should be done early rather that late. It must be remembered that diabetes is only one cause of delayed gastric emptying.
3. Urea and electrolytes also need monitoring to exclude electrolyte imbalances as a cause for gastroparesis. Hypokalaemia can result from persistent vomiting. Thyroid function tests should be performed, as vomiting due to thyrotoxicosis is well recognised.

linked to autonomic neuropathy. Furthermore, blood glucose has a direct effect on gastric emptying. As blood glucose levels rise beyond 15 mmol/L, gastric emptying slows by reduced fundal tone and impaired gastric coordination (Fraser et al, 1990; Hebbard et al, 1996).

Third, it appears that neurohormones, such as glucagon and incretins such as amylin and glucagon-like peptide-1 (GLP-1), which are released by the gut in response to food, have direct effects on the stomach and have been shown to delay gastric emptying (Rayner and Horowitz, 2006). It is unclear, however, whether the changes in these neurohormones seen in people with diabetes with gastroparesis are simply a consequence of poor glycaemic control resulting from the gastroparesis (Rayner and Horowitz, 2006).

The effect of these combined changes is to delay gastric emptying. Liquids often tend to empty from the stomach normally but solids can be significantly delayed.

Symptoms of gastroparesis

The most common symptoms of gastroparesis are nausea, vomiting, a feeling of fullness and abdominal bloating. These symptoms are, unsurprisingly, more common after meals, but vomiting can occur many hours after eating. Vomitus containing food eaten several hours previously is suggestive of gastroparesis. Abdominal fullness and postprandial bloating are said to be symptoms strongly suggestive of gastroparesis in people with diabetes. In addition, individuals may develop symptoms from hyper- or hypoglycaemia and in more severe cases can lose weight and become malnourished.

Physical examination is usually normal. Some individuals may have evidence of autonomic dysfunction, such as postural hypotension or gustatory sweating, while others may have an audible splash from the stomach when shaken. To illicit this sign the stethoscope is placed in the left upper quadrant of the abdomen while gently shaking the patient from side to side.

Diagnosis

With a suggestive history of gastroparesis, investigations should be done early rather that late. It must be remembered that diabetes is only one cause of delayed gastric emptying. Peptic ulcer disease and upper GI tract cancers can mimic the symptoms of gastroparesis and must be identified without delay.

With the recognised link between diabetes control and gastroparesis, HbA_{1c} levels should be checked. Urea and electrolytes also need monitoring to exclude electrolyte imbalances as a cause for gastroparesis. Hypokalaemia can result from persistent vomiting. Thyroid function tests should be performed, as vomiting due to thyrotoxicosis is well recognised.

All people with suspected gastroparesis should have an upper GI endoscopy to exclude mechanical gastric outflow obstruction. If the endoscopy shows food residue in the stomach despite fasting then this is suggestive of gastroparesis. Often people with severe gastroparesis will need to fast for prolonged periods of time to allow the stomach to empty so the endoscopist can confidently exclude obstructing lesions.

The current gold standard method for investigating gastric emptying is scintigraphy. For this the individual consumes a radiolabelled meal, such as scrambled eggs labelled with technetium, with toast and water. Images of the stomach are taken using a gamma camera over a period of time up to 4 hours. Reference values based on large controlled samples are available for comparison and allow the rate of stomach emptying of the test meal to be compared against a "normal value" (*Figures 1* and *2*).

Treatment

The initial steps of managing an individual with symptomatic gastroparesis are correcting exacerbating factors such as intercurrent illness and then the optimisation of blood glucose control. Some people with mild symptoms of gastroparesis may be able to manage with dietary changes alone. In particular, they should eat small regular meals (every 3–4 hours) and avoid fatty and fibre-rich foods that further delay gastric emptying. Support from a dietician is essential. Oral liquid nutritional supplements would normally be initiated at this stage.

If the person has significant symptoms, then medical therapy is required. This can be divided in to gastric prokinetics and anti-

emetics. When these are unsuccessful other non-pharmacological methods may be needed.

Prokinetics

The first-line therapy for people requiring prokinetic medication for gastroparesis would be domperidone or metoclopramide. Metoclopramide also acts as an anti-emetic but some people can develop extra-pyramidal side-effects (Abrahamsson, 2007).

Erythromycin is an agonist of motilin receptors. Motilin is a hormone released from the duodenum in response to food that stimulates gastric activity. Intravenous erythromycin is therefore a potent prokinetic. It can be administered intravenously when the individual is acutely unwell and remains first-line therapy in the acute setting. Erythromycin can also be used as maintenance therapy at a low oral dose of 250 mg four times daily, but some may develop tolerance and "wearing off" of the prokinetic effect (Abrahamsson, 2007).

In the first instance, the author recommends initiating domperidone at a dose of 10 mg four times daily as this seems to be the most effective in improving symptoms.

Anti-emetics

Anti-emetics can provide added symptomatic relief. In the author's experience, metoclopramide at a dose of 10 mg three times daily should be used first-line. This has the advantage of being prokinetic in addition to an anti-emetic. Those with established gastroparesis are often taught to self-administer this subcutaneously or intramuscularly when they have an exacerbation of their condition, to prevent the need for hospital admission. Second-line medication would be prochlorperazine. Other anti-emetics, such as ondansetron, are often tried but with little evidence of benefit.

Combination therapy is often required with many people needing domperidone and metoclopramide with erythromycin used intravenously for acute exacerbations.

Glycaemic control

Gastroparesis directly leads to poor glycaemic control and poor glycaemic control worsens the symptoms of gastroparesis. People with symptomatic, severe, gastroparesis invariably have poor glycaemic control. In those with type 1 diabetes it is important to ensure that insulin

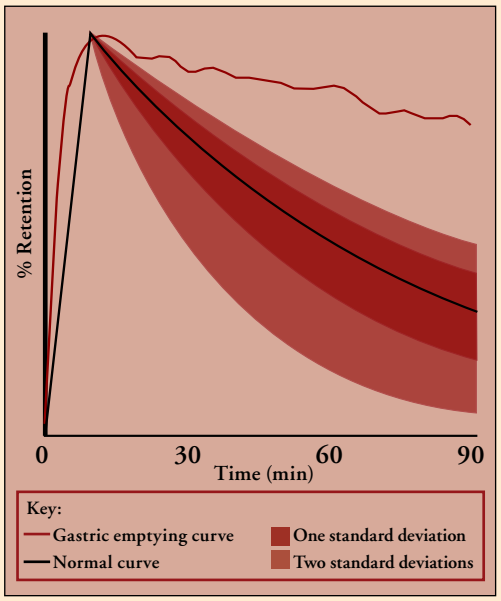

Figure 1. Gastric emptying study of a technetium-labelled test meal in a person with diabetes with gastroparesis. The red line on the graph represents the patient's clearance of isotope compared with the normal population (represented by the black line with coloured confidence intervals). Courtesy of Professor S Vinjamuri, Department of Nuclear Medicine, Royal Liverpool University Hospital, Liverpool.

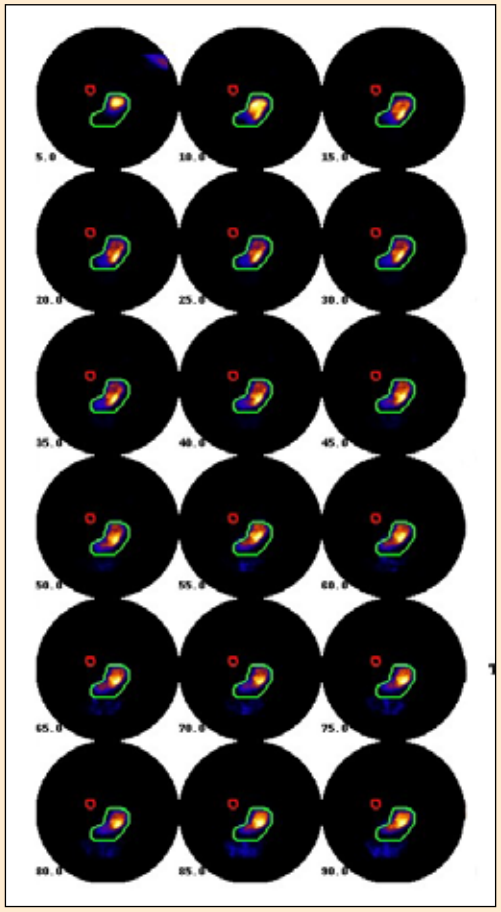

Figure 2. images of the stomach. The bright orange coloured mass in the fundus of the stomach is the technetium-labelled food, very little of which leaves the stomach over the duration of the test. Courtesy of Professor S Vinjamuri, Department of Nuclear Medicine, Royal Liverpool University Hospital, Liverpool.

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is available when the carbohydrate content of the food is released in the gut. In people with gastroparesis this is very difficult to manage and often they will experience hypoglycaemic episodes. It is not unusual for an individual to have omitted their rapid-acting insulin due to concerns about hypoglycaemia, and this further exacerbates the gastroparesis. The author has used insulin pump therapy in this situation with good effect (Morrison et al, 2006). With pump therapy it is possible to extend the bolus dose, often by several hours, to accommodate for the delayed release of food from the stomach.

For people with type 2 diabetes, delayed gastric emptying affects the pharmacokinetics of orally administered hypoglycaemic agents and often people with significant gastroparesis will need to convert to insulin therapy. Exenatide has a direct slowing effect on gastric emptying and should be stopped in people with symptomatic gastroparesis.

Non-pharmacological therapies

Despite the best medical therapy and intensive glycaemic control, some individuals with gastroparesis remain symptomatic. Non-pharmacological therapies have recently been developed, and may be of use in such people.

Botulinum toxin injected in to the pylorus during gastroscopy has been shown to result in a modest improvement in symptoms (Abrahamsson, 2007; Lacy et al, 2002). In some individual cases this improvement can be dramatic (Kong et al, 2009). Some small studies have shown benefits in the rate of gastric emptying as well as symptomatic improvement. However, one crossover randomised study in people with idiopathic gastroparesis showed no benefit for botulinum toxin over placebo (Abrahamsson, 2007). As with other indications for botulinum toxin therapy, any improvements seen are not permanent and the effect wears off after about 5 months. The author's experience of this therapy in people with diabetes has been disappointing with little benefit experienced.

Gastric electrical stimulation involves surgically implanting electrodes into the muscle wall of the stomach and these are connected to an electrical stimulator sitting in a surgically constructed pocket in the abdominal wall. Initial surgery involved a laparotomy but this technique can now be performed laparoscopically. Using a variety of different pacing strategies, evidence suggests that this device can improve symptoms although it seems to have little long-term effect on gastric emptying (Abell et al, 2002). Despite this, studies have shown a reduction in the numbers of prokinetics and anti-emetics taken after gastric pacing. NICE has said that this device should remain available but only for use in specialist centres (NICE, 2004).

In people with severe gastroparesis, especially those who start to lose weight and become malnourished, nutritional supplementation will be required. If oral supplementation is unsuccessful then a percutaneous jejunal (PEJ) feeding tube will be required. This is inserted via an upper GI endoscopy and allows people to be fed with liquid food that bypasses the stomach. These tubes are surprisingly well tolerated and can remain in place for a long time. Before inserting the PEJ tube a naso-jejunal tube is often inserted to ensure the patient can tolerate the volume of supplemental feed delivered in to the jejunum or duodenum.

Prognosis

Symptoms of gastroparesis usually wax and wane. Exacerbation of symptoms is often preceded by an intercurrent illness as well as worsening of glycaemic control.

The majority of people need long-term prokinetic therapy, although doses can be modified when the condition is in remission. Although the symptoms of gastroparesis are debilitating and hospitalization may be required, there does not appear to be an increase in mortality (Kong et al, 1999). Despite tight glycaemic control and maintenance, prokinetic therapy is essential to prevent relapses.

Conclusion

Gastroparesis is a common complication of diabetes and it is often symptomatic. Treatment involves dietary modification, prokinetics and anti-emetics. Tight glycaemic control is essential but difficult to achieve. For more resistant cases non-pharmacological treatments may be required. ■