Gastroparesis associated with diabetes: Symptoms, diagnosis and treatment

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Article points

1. Gastroparesis associated with diabetes is a severe form of autonomic neuropathy. Symptoms include a feeling of fullness when eating, vomiting weight loss, heartburn, erratic blood glucose levels and spasms of the stomach wall.
2. Diagnosis of gastroparesis is usually made on clinical history and confirmed with gastric emptying studies and a gastroscopy. Gastroparesis is diagnosed if more than 10% of the food is still in the stomach four hours after eating.
3. The aim of treatment for individuals with gastroparesis is to improve their symptoms. Enhanced glycaemic control is the only thing that consistently will have a positive impact on the symptom control of gastroparesis.

Key words

- Autonomic neuropathy
- Gastroparesis

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Gastroparesis associated with diabetes is a severe form of autonomic neuropathy. Symptoms include bloating, nausea and vomiting, and lead to variable absorption of glucose. Symptomatic gastroparesis is a rare complication of diabetes, but is a highly complex, multifaceted problem that is often difficult to manage and may even require periods of hospitalisation. The condition can have a significant impact on mental health, quality of life and ability to work. This article aims to explore the pathophysiology associated with gastroparesis and discusses some of the key therapy issues.

Gastroparesis associated with diabetes is a severe form of autonomic neuropathy, which has a profound negative effect on gastric function (Enck and Frieling, 1997). The associated symptoms of gastroparesis such as bloating, nausea and vomiting are extremely unpleasant and lead to variable absorption of glucose. For individuals treated with insulin, there is often a self-perpetuating cycle of symptomatic gastroparesis, which, in turn, is responsible for sub-optimal and erratic glycaemic control.

Symptomatic gastroparesis is a highly complex, multifaceted problem, which is difficult to manage and may even require periods of hospitalisation to stabilise (Sharma et al, 2011). Apart from the physical impact of gastroparesis, the personal costs of this condition to the individual are immense, given that it often has a substantial adverse effect on mental health, quality of life and ability to work (Talley et al, 2001). These factors, in turn, will have a negative impact on the individual's family unit as a whole.

Although the clinical evidence for the management of this condition is lacking, this article aims to explore the pathophysiology associated with gastroparesis and discusses some of the key therapy issues.

Prevalence

Approximately 30–50% of all individuals with diabetes are reported to have some form of gastric emptying delay (Horowitz et al, 1986; Horowitz et al, 1989). However, symptomatic gastroparesis is a rare complication of diabetes that most frequently occurs in those with long-standing sub-optimal glycaemic control (Feldman and Schiller, 1983). A rationale for this could be that there is an increased prevalence of autonomic neuropathy and other complications within this group of individuals (Kong et al, 1999a). Women have a much higher prevalence of gastroparesis than men, for reasons as yet unknown (Jones et al, 2001).

Common symptoms of gastroparesis

Signs and symptoms of gastroparesis, as described by NICE (2014) and Murray and Emmanuel (2005), include:

- Abdominal bloating.
- A feeling of fullness when eating.
- Nausea and vomiting.
- Weight loss.
- Heartburn.
- Erratic blood glucose levels.
- Spasms of the stomach wall.

All of the above signs and symptoms are unlikely to all be present at any one time in an individual with gastroparesis. The intensity of symptoms can also be influenced by a number of factors, which include degree of nerve damage, glycaemic control, diet and compliance with therapy.

Differential diagnosis

Kassander (1958) stated "gastroparesis diabeticorum" is a condition which "is more frequently overlooked than diagnosed". Unfortunately, even in more modern times, gastroparesis is a relatively rare condition and healthcare professionals often fail to make an accurate diagnosis, even when individuals present with the classical symptoms. Particularly in the early stages, it can be difficult to distinguish gastroparesis from irritable bowel syndrome, given that certain features such as bloating, colicky abdominal pain and periods of exacerbation and remission are common features of both conditions (NHS Choices, 2014). Equally, individuals who have classical indicators of gastroparesis are unlikely to relate them to a complication associated with their diabetes.

Pathology

Gastric emptying can be normal, accelerated or retarded in individuals with diabetes (Horowitz et al, 1996; Kong et al, 1996). However, people with gastroparesis will have multiple motor and sensory abnormalities of upper gut function. These anomalies include antral hypomotility, altered intragastric distribution of ingested food, abnormal intestinal contractions, increased fundic compliance and abnormal gastric sensation.

Gastroparesis impairs emptying of the stomach, which will lead to gastric dilatation and vomiting. Gastric stasis is a common feature of gastroparesis (Stacher, 2001; Stacher et al, 2003), and is thought to be due to vagal denervation of the stomach and smooth muscle loss (Jackson et al, 2004).

Studies have demonstrated that there is loss of myelinated and unmyelinated fibre in the vagus nerve in people with gastroparesis (Malagelada, 1980). Vagal nerve degeneration does not normally cause gut smooth muscle deterioration and is possibly related to glucose-mediated smooth muscle damage (Watkins, 1998).

Impact of blood glucose concentrations on gut function

Hyperglycaemia has a profound effect on gut function and has been found to slow gastric emptying, reduce post-prandial antral contractions and alter proximal stomach perception (Samson et al, 1997; Rayner et al 2000a).

All individuals with insulin-requiring diabetes need to co-ordinate the absorption of carbohydrate with insulin delivery. Yet, it is evident, both in healthy individuals and those with diabetes, that acute changes in blood glucose concentrations will have a substantial and reversible effect on gastric motility (Rayner et al, 2001).

Gastric emptying and postprandial antral contractions of the stomach are reduced during hyperglycaemia when compared to euglycaemia and increased during periods of hypoglycaemia (Samson et al, 1997). Even blood glucose variation within a normal postprandial range can impact gastric emptying and motility, with slower emptying occurring at blood glucose levels of 8 mmol/L, when compared to values of 4 mmol/L (Schvarcz et al, 1997).

Hyperglycaemia also seems to affect proximal stomach perception creating the sensation of "fullness", although, as yet, the mechanism by which this happens is unknown (Rayner et al, 2000a; Rayner et al, 2001). There is also some evidence to suggest that raised blood glucose levels may cause reversible vagal efferent dysfunction (De Boer et al, 1994).

Diagnosis

Diagnosis of gastroparesis is usually made

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1. Signs and symptoms are unlikely to all be present at once. The intensity of any symptom can also be influenced by a number of factors, including degree of nerve damage, glycaemic control, diet and compliance with therapy.
2. Gastroparesis is a relatively rare condition and healthcare professionals often fail to make an accurate diagnosis, even when individuals present with the classical symptoms.
3. Gastroparesis impairs emptying of the stomach, which will lead to gastric dilatation and vomiting.

Page points

1. Gastroparesis is diagnosed if more than 10% of the food is still in the stomach four hours after eating.
2. Gastric emptying studies measure the rate at which food leaves the stomach to pass into the small intestine and are considered the gold standard for measuring gastric motility.
3. Differential diagnoses include irritable bowel syndrome.

on clinical history and confirmed following the results of gastric emptying studies and a gastroscopy. Gastroparesis is diagnosed if more than 10% of the food is still in the stomach four hours after eating. A gastroscopy should also be performed to rule out any obstruction or other condition that may be impacting on the symptoms (Murray and Emmanuel, 2005). *Table 1* lists some common differential diagnoses.

Gastric emptying studies

Gastric emptying studies measure the rate at which food leaves the stomach to pass into

Table 1. Gastroparesis: Differential diagnoses.

Condition	Differentiating signs and symptoms	Differentiating tests
Irritable bowel syndrome (IBS) BMJ (2015)	Chronic condition characterised by abdominal discomfort, bloating and altered bowel movements (either constipation or diarrhoea, or both).	Normal gastric emptying studies and gastroscopy.
Gastric outlet obstruction BMJ (2015)	Obstruction in the distal stomach (pyloric stenosis and cancer). Symptoms similar to gastroparesis.	Retarded gastric emptying. Obstruction seen during gastroscopy
Cyclic vomiting syndrome (CVS) BMJ (2015)	Recurrent episodes of nausea and vomiting associated with severe epigastric pain. Nausea and vomiting occurs intermittently as opposed to chronically.	Normal gastric emptying studies
Functional dyspepsia BMJ (2015)	Chronic symptoms of postprandial nausea, vomiting, fullness, epigastric pain, and bloating. Symptoms similar to gastroparesis.	Normal gastric emptying studies
Rumination syndrome BMJ (2015)	Regurgitation of recently ingested food into the mouth. Food is regurgitated within minutes of eating in rumination as opposed to a slightly longer time phase between ingestion of food and vomiting, as found in gastroparesis.	Normal gastric emptying studies
Eating disorder Camilleri et al (2013)	Gastrointestinal symptoms are common and include lack of appetite, early satiety, epigastric fullness, abdominal bloating, nausea, and vomiting.	Re-alimentation and maintenance of normal body weight improve gastric emptying and gastrointestinal symptoms, but do not totally normalise them. (Geliebter et al, 1992)
Chronic use of cannabis Camilleri et al (2013)	Causes symptoms similar to CVS.	Normal gastric emptying studies.
Acute pancreatitis BMJ (2015)	Abdominal pain radiating to the back, epigastric tenderness, fever and tachycardia. Nausea, vomiting, history of gallstones or high alcohol intake is often present.	Elevated serum amylase. Arterial blood gas may show hypoxaemia and acid–base disturbances in severe cases. Abnormal abdominal X-ray

the small intestine and are considered the gold standard for measuring gastric motility (Maurer, 2008). The procedure involves the individual swallowing a small quantity of a radioactive substance that has been mixed with food. Then for a period of up to three hours, a radiation scanner is used to measure the level of radioactivity in the stomach. Review of the results of the gastric emptying study is compared with normal values so that the individual's rate of stomach emptying can be calculated.

There are some standardisation factors to consider when interpreting the results of the gastric emptying studies. These include any differences in the foods used during the test, the amount of food eaten, positioning and the use of pro-kinetic agents in the period leading up to the test (Abell et al, 2007; Maurer, 2008). Pro-kinetic agents should be discontinued at least 48 hours before gastric emptying studies (Camilleri et al 2013).

Although the levels of radioactivity during the procedure are very low and do not cause any side effects, women who are pregnant or breast-feeding should not participate, as there is a small risk of harm to the fetus or baby.

Prognosis

The long-term outlook for people with symptomatic gastroparesis and multiple complications relating to their diabetes is poor (Watkins et al, 2003). However, people with abnormal gastric emptying tests who do not necessarily have symptoms have a much better prognosis (Kong et al, 1999b).

General principles

A diagnosis of gastroparesis presents highly complex management problems for any healthcare professional to manage successfully in isolation. Support will be needed from a multidisciplinary team that can work in partnership with each other and the individual with gastroparesis. This seamless holistic approach will help to optimise outcomes.

Gastroparesis is a chronic condition associated with periods of exacerbation and remission, which will impact on the individual's general health (Dowling et al, 1985). Furthermore, as highlighted by Tally et al (2001), gastrointestinal dysfunction will probably have a profound negative impact on the person's life as a whole and this can be a contributor in the development of mental health issues, such as depression. A key treatment goal is that the symptoms associated with gastroparesis are minimised and adequate psychological support is provided by the professional team providing care.

In keeping with all people with diabetes, the individual with gastroparesis will require intensive education around their diagnosis and treatment plan so that informed choices regarding self-care management strategies can be made.

Glycaemic control

For individuals with gastroparesis, glycaemic control should be optimised as hyperglycaemia delays gastric emptying (Rayner et al, 2001). The absorption of glucose from food will be erratic due to the variability in gastric emptying. The usual outcome of this is glycaemic instability, including hypoglycaemia.

Pramming (1991) found that the vast majority of individuals with insulin-requiring diabetes fear hypoglycaemic episodes, and in an attempt to prevent these events, people with gastroparesis will omit insulin when they feel nauseous or are vomiting. Unfortunately, if this strategy is used, hyperglycaemia develops and this has a detrimental impact on gastric emptying and the symptoms associated with it (Schvarcz et al, 1997). Although this practice of omitting insulin is, to some extent, understandable, in the worst-case scenario, this practice of missing doses of insulin could cause the individual to develop the diabetic ketoacidosis. In addition in the long term, as illustrated by The Diabetes Control and Complications Trial (DCCT, 1993), ongoing suboptimal glycaemic control will increase the risk of exacerbating the individual's current complications and developing others.

Matching insulin to glucose release in individuals with gastroparesis is very difficult, despite the use of optimised insulin regimens. Clinicians often need to be "creative", given that

Page points

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2. A diagnosis of gastroparesis presents highly complex management problems for any healthcare professionals to manage successfully in isolation. Support will be needed from a multidisciplinary team that can work in partnership with each other and the individual with gastroparesis.
3. Gastroparesis is a chronic condition associated with periods of exacerbation and remission, which will impact on the individual's general health.

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1. Hypoglycaemia in people with gastroparesis can be prolonged and difficult to treat. If products such as fluids and starchy foods are used to treat hypoglycaemia, the release of glucose from these products is delayed due to abnormal gastric emptying.
2. In conjunction with pharmacological therapy, it is vitally important that nutrition health is maintained.
3. Pro-kinetic medication is used to improve gastric emptying by targeting a number of receptors.

the evidence base for insulin regimens aimed at individuals with gastroparesis is lacking. The action of the prandial insulin can be delayed to match the retarded glucose release, by taking it after eating. The time interval from ingestion to injection can be based on analysis of the gastric emptying studies and then be altered according to the response on glycaemic trends. Some clinicians advocate the use of soluble insulin taken with food to cover the postprandial rise in glucose. This is because soluble insulin is not active for approximately 20–30 minutes after injection and it will have a longer action time, when compared to a rapid-acting analogue. However, the prolonged action of soluble insulin can be responsible for episodes of hypoglycaemia due to its "tail" effect of 4–8 hours. There has also been significant success using continuous subcutaneous insulin infusions for selective individuals with severe gastroparesis in experienced insulin pump centres (Sharma et al, 2011).

Hypoglycaemia

Hypoglycaemia in people with gastroparesis can be prolonged and difficult to treat. If products such as fluids and starchy foods are used to treat hypoglycaemia, the release of glucose from these products is delayed due to abnormal gastric emptying. In addition, if carbonated products are used, these tend to make an individual with gastroparesis feel nauseous and cause them to vomit. In our clinical experience, these people should use dextrose tablets or glucose gel as a fast-acting carbohydrate, as these products can be absorbed buccally. Once the blood glucose has risen, a more complex product should be given in liquid or semi-solid form, such as milk or yogurt. As a back up, it is advisable for all individuals with gastroparesis to be prescribed glucagon injections and a family member should be taught how to inject.

Dietary issues

In conjunction with pharmacological therapy, it is vitally important that nutrition health is maintained (NHS Choices, 2014). Although there are currently no studies confirming the efficacy of dietary manipulation, it is intuitive that foods that slow gastric emptying will worsen gastroparesis in symptomatic periods (NHS Choices, 2014).

Any individual with gastroparesis needs to work closely with a dietitian who is familiar with the condition and they should be encouraged to follow the dietary principles as suggested by NHS Choices (2014) and detailed below:

- Eat little and often as smaller volumes will pass more quickly through the stomach.
- Eat soft and liquid foods, which will be easier to digest.
- Chew food well before swallowing.
- Drink non-carbonated liquids.
- Walk or sit for two hours following a meal, rather than lying down, to aid digestion.
- Avoid foods high in fibre and fat as they slow down digestion.

Should the individual with gastroparesis develop intractable vomiting then they may require feeding through a percutaneous endoscopic jejunostomy (PEJ) tube to maintain their nutritional state, which may alleviate the problem until a natural remission of vomiting occurs (Gentilcore et al, 2003). Initially, the feeds are administered over 24 hours so that a smaller hourly fluid volume can be tolerated (Murray and Emmanuel, 2005). The continuous feed rate encourages greater predictability of carbohydrate metabolism, which, in turn, leads to a reduction in glycaemic viability. These factors make it easier to match the individual's insulin requirements (Murray and Emmanuel, 2005). As the person's clinical condition improves, the hourly rate of the feed can be increased and rest periods off the feed can be incorporated into the feeding regimen. The individual would also be encouraged to slowly build up their oral intake of diet and fluids. Parenteral feeding would only be considered as a last resort due to the major associated risks, such as line sepsis (Murray and Emmanuel, 2005).

Pro-kinetic therapy

Pro-kinetic medication is used to improve gastric emptying by targeting a number of receptors. These pro-kinetic agents include the dopamine-2 antagonists, metoclopramide and domperidone, which enhance gastric tone and emptying

(Sturm et al, 1999). Erythromycin, a motilin analogue, can also be used as it has a substantial acceleration of gastric emptying (Janssens et al, 1990).

Due to potential side effects it is not advisable to take metoclopramide long term, due to the risk of extrapyramidal effect (Joint Formulary Committee, 2013). Indeed, recent guidance from the Medicines and Healthcare products Regulatory Agency (MHRA; 2013) recommends that the use of metoclopramide for adults should be restricted to a maximum of 5 days at a dose no higher than 10 mg three times per day. Another MHRA alert in 2012 highlighted that erythromycin should not be used in combination with domperidone, as there is a risk of causing a prolonged QT interval (MHRA, 2012).

The MHRA (2014) have recently recommended that domperidone should only be used to relieve nausea and vomiting, at the lowest effective dose, for the shortest possible duration of time due to the increased risk of cardiac arrhythmias. It could be argued that the MHRA (2012, 2013, 2014) recommendations are unrealistic for individuals with gastroparesis, given that long-term pro-kinetic therapy is usually required for this group of patients. A professional dilemma now exists; the prescriber must now decide, in partnership with the recipient, that the associated benefits of the drug outweigh any risks and so prescribe it "off licence".

At its best, pro-kinetic therapy has a variable effect on gastroparesis and is not effective at alleviating symptoms in the long term. With the issue of tachyphylaxis, the practitioner must be prepared to revise the treatment regimen as necessary.

A key part of any education programme for an individual with gastroparesis is information regarding their medication needs. Important components include the concept of pro-kinetic therapy, the issue of tachyphylaxis and the need to take medication on a regular basis to maximise its effect, rather than on an "as and when" basis.

In our practice, individuals prone to severe exacerbations of gastroparesis are taught to self-administer an intramuscular injection of metoclopramide, mainly for its pro-kinetic action rather than its antiemetic effect. This management plan gives the individual a degree of control, so that they have an opportunity to promptly intervene and self-manage their condition, without the need for hospital admission. If one injection of metoclopramide does not resolve the period of exacerbation, our guidelines instruct the individual to come to hospital.

If oral therapy does not sufficiently relieve the individual's symptoms then hospitalisation may be required so that intravenous pro-kinetic therapy can be delivered and glycaemic control maintained with intravenous insulin.

Efficacy of medication can also be detrimentally affected by gastric delay (Rayner et al, 2000b). All medication should be prescribed in suspension or dispersible formulation, given that there is some evidence of greater efficacy of drugs in this form for people with gastroparesis (Ehrenpresis et al, 1998).

Other treatment options

If pro-kinetic therapy alone fails to provide adequate relief from gastroparesis-related symptoms, then injections of botulinum toxin around the pylorus under endoscopic guidance can provide temporary relief of symptoms (Ezzeddine et al, 2002).

Despite optimised therapy, some individuals continue with intractable symptoms. In such individuals, gastric pacemakers have been used in specialist centres. These devices, which use neuro-stimulation to improve gastric emptying, have to be inserted surgically. Although gastric pacemakers are not considered standard practice, NICE (2014) have recently supported the use of gastric pacing in selected individuals attending specialist centres. However, the report also acknowledges the lack of solid evidence for gastric pacing, the potential side effects and the fact that many individuals do not get any benefit from it as evidence supporting positive outcomes is lacking (NICE, 2014). Indeed, as highlighted by Abell et al (2002), following insertion of a gastric pacemaker, there is often a poor correlation between gastric emptying and symptom improvement.

Conclusion

Gastroparesis is a difficult and complex problem that requires specialist management from diabetes

Page points

1. At its best, pro-kinetic therapy has a variable effect on gastroparesis and is not effective at alleviating symptoms in the long term.
2. If oral therapy does not sufficiently relieve the individual's symptoms then hospitalisation may be required so that intravenous pro-kinetic therapy can be delivered and glycaemic control maintained with intravenous insulin.
3. Despite optimised therapy, some individuals continue with intractable symptoms. In such individuals, gastric pacemakers have been used in specialist centres.

"Although gastric emptying will stay abnormal, enhanced glycaemic control is the only thing that consistently will have a positive impact on the symptom control of gastroparesis."

teams who are familiar with this condition, flexible in approach, and alert to the presence of other autonomic issues and complications associated with diabetes.

The aim of treatment for individuals with gastroparesis is to improve their symptoms. Although gastric emptying will stay abnormal, enhanced glycaemic control is the only thing that will consistently have a positive impact on the symptom control of gastroparesis. Unfortunately, to date, there is no specific therapy that totally addresses these goals.

In addition, education for the person with gastroparesis is essential. The more that an individual understands about their condition and its management, the more likely they are to be pro-active partner in its management. ■

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