Diabetes and the gastrointestinal tract

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Abstract

Gastrointestinal (GI) complications of diabetes mellitus are common and result in a significant diminution in health-related quality of life. Diabetes can affect almost every part of GI tract from the oesophagus to the rectum, and causes a variety of symptoms including reflux, heartburn, nausea, vomiting, abdominal pain, diarrhoea and constipation. Diabetes-induced GI complications are collectively referred to as diabetic enteropathy. Over recent years, the investigation of the underlying pathogenesis of diabetes-induced GI complications has provided objective evidence of abnormalities in the enteric nervous system, which is essential for normal motility within the GI tract. The diagnosis of diabetic enteropathy is complex, and other causes of GI symptoms should be excluded. There is currently no cure for diabetic enteropathy. Hence, the goals of treatment are to slow progression, relieve symptoms and manage complications. Key to this is tight glycaemic control, dietary advice and occasionally pharmacological treatment with, for example, prokinetics.

Keywords Diabetes complications; diabetes mellitus; diabetic neuropathies; enteric nervous system; gastrointestinal motility; gastrointestinal transit

Key points

- Gastrointestinal complications of diabetic neuropathy significantly reduce quality of life in individuals with diabetes mellitus
- Diabetes can cause dysmotility disorders in any part of gastrointestinal tract. Diabetes adversely impacts on several parts of enteric nervous system, including enteric neurones, interstitial cells of Cajal, glial cells, smooth muscle cells and enteric microvasculature
- The pathological mechanisms underlying diabetic enteropathy are complex and include glucose neurotoxicity, oxidative stress and inflammation, resulting in dysregulation of gastrointestinal function including altered secretion
- Management of diabetic enteropathy should ideally target both glycaemic control and symptom relief

Introduction

The prevalence of diabetes mellitus is increasing. Approximately 3.7 million people in the UK have been diagnosed with diabetes, and this number is expected to increase to 5 million by 2025. Worldwide, the burden of diabetes is expected to increase to 629 million people by 2045. Hence, the incidence of diabetes and its accompanying complications has become one of the most important current public health issues. The complications of diabetes have a direct negative impact on individual quality of life and increase socioeconomic expenditure. Among the diabetic complications that have the highest symptom burden but are frequently under-recognized and sub-optimally treated, are those associated with alterations in the enteric nervous system (ENS).

The enteric nervous system

The ENS comprises three pan-enteric, interconnected, juxtapositioned cellular networks — intrinsic autonomic neurones, interstitial cells of Cajal (ICCs) and enteric glial cells (EGCs) — which collectively govern gastrointestinal (GI) function, serving to maintain homeostasis. The ENS can be considered to be an independent network within the autonomic nervous system. In addition, however, extrinsic efferent input from the central nervous system via autonomic (sympathetic and parasympathetic) pathways, as well as afferent sensory neurones from the central nervous system following either vagal or spinal routes contribute to the regulation and coordination of GI function.

Intrinsic enteric neurones are localized in the myenteric and submucosal plexuses and are connected by inter-neurones. They can be categorized according to their connectivity and function, as reviewed elsewhere. The myenteric plexus is situated between the circular and longitudinal muscle layers and influences GI motility. The submucosal plexus is in close proximity to the muscularis mucosae, intrinsic vasculature and mucosa, and primarily regulates secretion and absorption.

ICCs, although not strictly neuronal, generate and convey electrical impulses to smooth muscle cells. This facilitates the slow-wave peristaltic movement of the GI wall; the cells are referred to as 'pacemaker' cells within the GI tract.

EGCs provide neurotrophic support and mediate bi-directional interactions between enteric neurones and other cell types such as immune effector cells, enteroendocrine cells, epithelial cells and blood vessels.

Diabetic enteropathy

It is widely accepted that autonomic neuropathy is the underlying mechanism that drives GI complications of diabetes. In diabetes, the microenvironment within the ENS is significantly altered because of the effect of, among others, hyperglycaemia, oxidative stress, neuroinflammation, reduced levels of neurotransmitters, enteric hormones, nerve growth factors and structural vascular changes. In addition, other factors such as increased levels of fatty acids, microRNA, endothelia dysfunction

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Symptoms reflecting dysmotility in different segments of the GI tract

Segment	Dysmotility	Symptom
Oesophagus	Oesophageal dysmotility	Dysphagia
	Lower oesophageal sphincter spasm	Heartburn/regurgitation
	Lower oesophageal sphincter relaxation	Gastro-oesophageal reflux disease
Stomach	Gastroparesis:	Delayed gastric emptying time Early satiety
	• Impaired fundic relaxation	Nausea
	• Reduced antral tone and motility	Bloating
	• Slow-wave dysrhythmias	Loss of appetite
	• Pylorospasm (intense, prolonged pyloric contractions)	Early satiety Postprandial vomiting
	• Impaired antropyloroduodenal coordination	Abdominal pain
Small intestine	Decreased transit time	Diarrhoea
	Small intestinal bacterial overgrowth	
	Increased transit time	
Large intestine and rectum	Decreased transit time	Constipation
	Altered microbiota	Diarrhoea
	Abnormal tone of the internal anal sphincter	Faecal incontinence
	Impaired rectal compliance and sensation	
	Increased transit time	

Table 1

and altered enteric microbiota have also been proposed to exert an influence. Several parts of ENS including enteric neurones, ICCs, EGCs and smooth muscle cells are affected by these changes. Enteric neurones and EGCs are particularly vulnerable to hyperglycaemia.

Hyperglycaemia in diabetes causes several fold increases in glucose levels; if this is persistent or repetitive, shifts in the intracellular glucose metabolism lead to the formation of advanced glycation end products, osmotic and oxidative stress. This leads to cellular damage and ultimately cell death; in

Commonly used questionnaires

Questionnaire	Assessment of	Comment
PAGI-SYM (Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index)	Severity of common upper GI symptoms: heartburn/regurgitation, postprandial fullness/early satiety, nausea/vomiting, bloating, upper/lower abdominal pain	Can be used for monitoring of outcomes in clinical practice/trials Reliable with respect to gastro-oesophageal reflux disease, dyspepsia and gastroparesis
GCSI (Gastroparesis Cardinal Symptom Index)	Severity of symptoms of gastroparesis: nausea/vomiting, postprandial fullness/early satiety and bloating	Based on a 2-week recall Reliable in assessing symptom severity related to gastroparesis Validated
GCSI-DD (Gastroparesis Cardinal Symptom Index-Daily Diary)	Severity of symptoms of gastroparesis/ responsiveness to treatment of gastroparesis	Based on a 2-week daily diary Otherwise as for the GCSI Validated
GSRS (Gastrointestinal Symptom Rating Scale)	Wide range of GI symptoms	Gives a broad perspective on patients' pan-enteric GI symptoms
PAC-SYM (Patient Assessment of Constipation-Symptoms)	Severity of symptoms of constipation: abdominal symptoms, stool symptoms and rectal symptoms	Reliable in assessing symptom severity related to constipation Validated
M-PAC-SYM (Modified Patient Assessment of Constipation-Symptoms)	Severity of symptoms of constipation	As for PAC-SYM, except for rectal symptoms May be more relevant in diabetes
PAC-QoL (Patient Assessment of Constipation Quality of Life)	Burden of constipation on patients' well-being and everyday functioning	

Table 2

neurones, this process is often referred to as glucose neurotoxicity. Hitherto, these mechanisms have primarily been described in the peripheral and central nervous system, but the same mechanisms are present in the ENS, as recently reviewed.[1]

Damage to neurones and ICCs leads to impaired control of GI function. Loss of EGCs contributes to the pathogenic process mainly because their neurotrophic support is diminished, which leads to neuronal neglect. Further contributing to the pathogenesis is a loss of the immunosuppressive and anti-inflammatory effects of EGCs. Inflammation is a key characteristic of neuropathy.

The diabetes-induced microenvironmental changes have a self-perpetuating effect with respect to cellular damage along the entire length of the GI tract. Consequently, diabetes leads to burdensome pan-enteric secretory and motility disorders.[2] Although the focus of this review centres on effects of diabetes specifically in the gut, it should be remembered that diabetes affects the entire nervous system, resulting in polyneuropathy. Central changes, such as microstructural changes in brain areas involved in visceral sensory processing, have been demonstrated. Changes in the insula in particular correlate to GI symptoms.[3] This may explain specific symptoms such as vomiting and nausea as these sensations are mainly controlled through gut–brain autonomic communication.

Methods for evaluating diabetes-induced dysmotility

Method	Evaluates	Principle	Comment
Traditional techniques			
Scintigraphy	Gastric emptying	Patient ingests a ^{99}technetium-radiolabelled standardized meal, after which gastric emptying is measured by gamma scanning	Gold standard for investigating gastroparesis Associations between scintigraphic results of gastric emptying and clinically experienced symptoms are poor, but associations have been shown between gastric emptying and fullness/early satiety and nausea/vomiting
Breath testing	Gastric emptying	Patient ingests a solid meal containing ^{13}C-octanoic acid. This is absorbed from the proximal small intestine and subsequently metabolized in the liver to $^{13}C\text{-}CO_2$, which is measured in exhaled breath	Less equipment is required; good receiver operating characteristics (sensitivity of 89%, specificity of 80%) in comparison to scintigraphy
Manometry (high-resolution)	Oesophageal motility or colonic motility	High-resolution manometry catheters allow for continuous pressure monitoring throughout the oesophagus/colon	Emerging technique; further studies are needed to assess associations with clinically experienced GI symptoms
Wireless motility capsule	Segmental and pan-enteric transit times, pH and motility	An indigestible capsule continuously measures pressure, temperature and pH as it traverses the GI tract Segmental and pan-enteric transit times can be derived based on stereotypical changes in temperature, pressure and pH	Data can be collected during patient's normal daily routine. pH changes across the ileocaecal junction can represent a surrogate marker for caecal fermentation, which can influence colonic transit times
Radio-opaque markers	Segmental and pan-enteric transit times	Patient ingests capsules containing plastic beads or rings, after which a plain abdominal radiograph is undertaken	Useful method to delineate the whole-gut transit time and proxy colonic transit time
Emerging techniques[a]			
Magnetic resonance imaging	Motility	Involves repeated T2-weighted images being recorded, and non-rigid image registration in regional areas of interest	Small and large bowel motor function can be elucidated
Three-dimensional transit system	Transit times and motility	Patient ingests an electromagnetic capsule Continuous tracking occurs relative to an external plate worn on the abdomen	Colonic retrograde movements can be elucidated
Video-capsule endoscopy	Transit times and motility	Patient ingests the video-capsule	Widely used clinically, e.g. to investigate occult GI bleeding Developments in automated software analysis have allowed systematic quantification of the motion and dynamics of the small bowel

[a] Normal values and the relation of findings to patient symptoms has not yet been established.

Table 3

Motility disorders

An overview of diabetes-induced alterations in the different GI segments and their related symptoms is provided in Table 1. The extension of damaged neurones and symptom severity are related to the duration of diabetes and to glycaemic control. However, the correlation between individual symptoms of dysmotility and objective pathophysiological measures, for example transit times, is rather poor, which is plausibly explained by high inter- and intra-individual variability. In addition, several studies have compared the prevalence of GI symptoms among adults with types 1 and 2 diabetes, along with transit times, but no consistent associations have been found.

Assessment of diabetes-induced dysmotility

Patients' experiences and perceptions are central to the clinical evaluation, and therefore patient-centred outcome measures, such as specific GI questionnaires, are helpful in both research and the longitudinal monitoring of response to interventions. Some of the most commonly used GI questionnaires for assessing gastroparesis and constipation are listed in Table 2, although there are not specifically validated for diabetes.

Furthermore, a number of complementary objective modalities exist for the detailed evaluation of diabetic enteropathy. These methods provide the clinician with the information necessary to elucidate the extent of the neuronal damage. Although few have been strictly validated, the most commonly used tests are listed in Table 3.

Clinical management

Diabetic enteropathy has no known cure. The goals of treatment are therefore to slow progression, relieve symptoms, manage complications and restore function.[4,5]

The key to preventing or delaying neuropathy is primarily tight glycaemic control. Such management, guided by age, disease duration and overall health, can even improve current symptoms. Dietary and lifestyle advice can provide individuals with diabetes with the tools for better glycaemic control in their everyday life. In persons with insulin-dependent diabetes, glycaemic control can also improve with use of an insulin pump. When gastroparesis is present, 'pre-prandial' insulin should therefore occasionally be administered after the meal, or in a reduced amount. Moreover, continuous glucose-monitoring devices that allow for glucose readings in real time have recently become available at a reasonable cost. Their use is recommended by national and international medical organizations and expert clinician consensus, both in combination with a pump and for those on multiple daily insulin injections. Both insulin pump and continuous glucose monitoring reduce the number of hyper- and hypoglycaemic events and are believed to have long-term neuroprotective effects.

Beyond optimizing glycaemic control, no available treatments targets the polyneuropathy underlying diabetic enteropathy. As a supplement to the initial treatment based on dietary consulting and improvement of glycaemic control, the specific treatment of GI symptoms arising from diabetic enteropathy is challenging. Some of the most frequently applied treatment possibilities are reviewed below.

Gastroparesis

Non-pharmacological management

To enhance emptying of the stomach, standard dietary modifications are recommended, for example low-soluble-fibre, low-fat and small-volume meals with protein supplementation as needed. If insufficient, a small particle size diet as well as liquid and homogenized nutritional supplementations can be initiated, with reservation of post-pyloric enteral tube feeding for the most severe cases.

Prokinetics for the treatment of diabetic gastroparesis*

Drug	Mode of action	Recommended daily dose (formulation)	Comment
Metoclopramide	$5HT_4$ receptor agonist D_2 receptor antagonist	10 mg tds (tablet)	Black box warnings for long-term use: • FDA <3 months • EMA ≤5 days
Domperidone	D_2 receptor antagonist	10 mg tds (tablet)	Should be avoided in the presence of a prolonged QT interval
Erythromycin	Motillin receptor agonist Cholinergic receptor agonist	250 mg tds (tablet)	Clinical efficacy often diminishes after 2–4 weeks because of tachyphylaxis Prokinetic action probably a drug class-effect, and other macrolides with less toxicity can be used (azithromycin, clarithromycin); however, evidence from controlled trials is lacking
Prucalopride	$5HT_4$ receptor agonist	2 mg (tablet)	Currently under investigation for diabetic gastroparesis in Phase III trials

bd, twice daily; tds, three times daily. *These drugs are not specifically licensed for the treatment of gastroparesis.
Source: Adapted from Meldgaard et al.[1]

Table 4

Prokinetics

Prokinetics are generally effective in the context of diabetic gastroparesis (Table 4). However, it must be made clear that there is no absolute association between symptom improvement and changes in gastric motility after treatment with prokinetics. Furthermore, most prokinetic drugs are limited to short-term use because of the risk of irreversible tardive dyskinesia (D_2-receptor antagonists) and are currently subjected to 'black box warnings' from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Relamorelin, a synthetic ghrelin analogue is currently being investigated in a clinical Phase III trial as it has shown promising results with respect to acceleration of GI motility.

Tricyclic antidepressants

Low-dose nortriptyline, amitriptyline and desipramine have been shown to reduce symptoms in patients with diabetes, chronic vomiting and inadequate response to prokinetics. However, more evidence is needed, as conflicting data exist: in idiopathic gastroparesis, 15 weeks of up to 75 mg nortriptyline daily showed no improvement in the overall symptom score in comparison to placebo.

Surgical procedures

Gastric electrical stimulation has been approved by the FDA as a humanitarian device exemption in patients with refractory symptoms of diabetic or idiopathic gastroparesis. It has been shown that it significantly reduces vomiting episodes and symptom severity. Other surgical options include total and subtotal gastrectomy. This should generally be a treatment of last resort in patients with severe treatment-refractory symptoms after thorough evaluation in a multidisciplinary setting. However, the surgical reports reporting favourable outcomes from these procedures have all been performed in uncontrolled settings, with relatively short follow-up. Taken together, more studies are needed to elucidate the underlying mechanisms and potentially identify the patients who could benefit from surgical intervention.

Abnormal bowel function

The treatment options available for intestinal dysfunction in patients with diabetic enteropathy follow the recommendations used for other functional GI disorders.

Diarrhoea

Patients should first be evaluated for secondary causes including infectious and inflammatory bowel diseases, coeliac disease, exocrine pancreatic insufficiency and small intestinal bacterial overgrowth. Fibre supplementation is helpful in some patients but can also worsen symptoms of gastroparesis and bloating. Loperamide is often an effective and safe treatment for chronic diarrhoea, although it has not been formally evaluated in the context of diabetic enteropathy.

Constipation

Treatment is based on conventional laxatives. For refractory cases, a more detailed work-up may be needed, which should ideally include biofeedback exercises, assessment of intestinal transit time, endoscopy, proctography and evaluation of anorectal physiology. In the presence of slow-transit constipation, osmotic laxatives are preferred over fibre supplementation and bulking agents because they stimulate the absorption of excessive amounts of fluid from the body into the intestines. Lactulose is generally best avoided as it can worsen bloating. Novel treatment options include prucalopride, which can also improve symptoms of gastroparesis, and linaclotide, which can be particularly helpful when concomitant symptoms of irritable bowel syndrome are present.

Abdominal pain

Treatment of abdominal pain secondary to diabetic enteropathy is complex and involves a multidisciplinary approach including specialists from diabetology, gastroenterology, pain management and psychology. Screening for psychiatric co-morbidity, including anxiety and depression, should be undertaken and treatment initiated if it is present. Studies investigating pharmacological therapies for pain associated with diabetic enteropathy are scarce. However, as the pain can be of neuropathic origin, drugs that have been evaluated for this indication in other diseases can be helpful. These include antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, selective serotonin–noradrenaline reuptake inhibitors) and gabapentinoids (gabapentin, pregabalin), which can be used alone or in combination. However, in many patients the pain is secondary to, for example, transit problems, bacterial overgrowth or constipation and should be treated accordingly. Furthermore, adverse effects to medications can also produce abdominal pain. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 64-year-old woman presented with a 3-week history of nausea, vomiting and weight loss of 6 kg. She had long-standing type 2 diabetes, chronic kidney disease, hypertension and diabetic retinopathy. Among her medications were aspirin, metformin and lisinopril.
Clinical examination was unremarkable.

Which is the most appropriate next investigation?

A. CT of the chest, abdomen and pelvis
B. HbA_{1c} measurement
C. Upper gastrointestinal endoscopy
D. Nuclear medicine gastric emptying test
E. Wireless motility capsule

Question 2

A 42-year-old man presented with a 2-week history of nausea and recurrent vomiting. He had long-standing type 1 diabetes. Clinical examination was normal.

Investigations

- Haemoglobin 162 g/litre (130–180)
- White cell count 5.6 × 10^9/litre (4.0–11.0)
- Urea 6.5 mmol/litre (2.5–7.0)
- Creatinine 68 micromol/litre (60–110)
- HbA_{1c} 60 mmol/mol (20–42); 9.6% (4–5.6%)
- Upper gastrointestinal endoscopy was normal
- CT of the thorax, abdomen and pelvis was normal.

Which of the following is the most likely diagnosis in this context?

A. Functional dyspepsia
B. Cannabinoid-induced hyperemesis
C. Cyclic vomiting syndrome
D. Gastroparesis
E. Gastro-oesophageal reflux disease

Question 3

A 52-year-old man presented with a 6-week history of change in bowel habit. He was opening his bowel three times per day in the absence of rectal bleeding or abdominal pain, but he had urgency. There was no history of weight loss. He had a 10-year history of type 2 diabetes, treated with metformin and insulin.

Investigations

- Haemoglobin 152 g/litre (130–180)
- White cell count 4.3 × 109/litre (4.0–11.0)
- Urea 3.9 mmol/litre (2.5–7.0)
- Creatinine 78 micromol/litre (60–110)
- HbA_{1c} 30 mmol/mol (20–42); 4.8% (4–5.6%)
- Faecal elastase 158 micrograms/g (>200)
- Stool microscopy and culture revealed no pathogens
- Coeliac serology was negative
- Colonoscopy with left- and right-sided biopsies was normal

What is the most likely diagnosis?

A. Irritable bowel syndrome with diarrhoea
B. Inflammatory bowel disease
C. Adverse effect of metformin
D. Adverse effect of insulin
E. Infectious gastroenteritis