46 Gastrointestinal Manifestations of Diabetes

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Keypoints

- Gastrointestinal manifestations are frequent in diabetes.
- Diabetes may not be the cause of gastrointestinal symptoms.
- Glycemia influences development of neuropathy and acutely changes gastric emptying.
- Extrinsic and enteric neuropathies are key mechanisms in diabetic gastroenteropathy.
- Motor dysfunctions may affect any region of the gastrointestinal tract in diabetes and cause fast or slow transit.
- Incontinence, a frequently unvoiced symptom, may reflect sphincter or sensation deficits.
- Assessments of hydration, nutrition and metabolic status are essential.
- Measurements of regional transit and anorectal motor and sensory functions are key to management of diabetic gastroenteropathy.
- For management of gastroparesis and dyspepsia, correct hydration, nutrition and metabolic status; exclude any iatrogenic factor, such as GLP-1 analog, and "gastroparesis"; and treat the pathophysiologic process.

Introduction

Although most attention has traditionally focused on the stomach, diabetes can affect the entire gastrointestinal tract. The term diabetic enteropathy refers to all the gastrointestinal complications of diabetes. Gastrointestinal involvement may be asymptomatic or manifest as symptoms (i.e. dysphagia, heartburn, nausea and vomiting, abdominal pain, constipation, diarrhea and fecal incontinence). These manifestations may affect quality of life, impair nutrition, and affect glycemic control.

Epidemiology

Studies in selected patient groups, often from tertiary referral centers, suggest that gastrointestinal symptoms are common in diabetes mellitus [1,2]; however, these studies are prone to selection and other biases, which are avoided by studies conducted among people with diabetes in the community, where the prevalence of gastrointestinal symptoms is either not different, or only slightly higher than people without diabetes. Thus, in the Rochester Diabetic Neuropathy Study, only 1% of patients had symptoms of gastroparesis and only 0.6% had nocturnal diarrhea [3]. In another study from Olmsted County, Minnesota, the prevalence of gastrointestinal symptoms (i.e. nausea and/or vomiting, dyspepsia, heartburn, irritable bowel syndrome, constipation and fecal incontinence) was not significantly different between individuals with either type 1 (T1DM) or type 2 diabetes mellitus (T2DM) and age-matched controls [4]; however, people with T2DM and men with T1DM used laxatives more frequently than in controls. Moreover, that study and a Finnish population-based study reported that people with T1DM had a lower prevalence of heartburn [5].

In contrast to these studies, a study from Australia found that the prevalence of several upper and lower gastrointestinal symptoms was higher in 423 patients with predominantly (95%) T2DM than in controls [6]. Taken together, these data suggest that gastrointestinal manifestations are not uncommon among patients with diabetes presenting for care. In the general population, however, the prevalence of gastrointestinal manifestations is not substantially higher among people with diabetes and matched controls, perhaps partly because the prevalence of gastrointestinal symptoms, mostly attributable to functional gastrointestinal disorders (e.g. irritable bowel syndrome), among people without diabetes in the community is relatively high, and approaches 20%. In Olmsted County, Minnesota, the age-adjusted incidence per 100,000 person-years of definite gastroparesis for the years 1996–2006 was 2.4 (95% confidence interval [CI] 1.2–3.8) for men and 9.8 (95% CI 7.5–12.1) for women. The age-adjusted prevalence of definite gastroparesis per 100 000 persons on January 1, 2007, was 9.6 (95% CI 1.8–17.4) for men and 37.8 (95% CI 23.3–52.4) for women [7].

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein. © 2010 Blackwell Publishing.

Diabetic gastroparesis may cause severe symptoms and result in nutritional compromise, impaired glucose control and a poor quality of life, independently of other factors such as age, tobacco use, alcohol use or type of diabetes [8]. Studies of the natural history of gastroparesis have been limited by relatively small numbers of patients, potential referral bias or short follow-up periods. The data suggest that gastric emptying and its symptoms are generally stable during 12 years of follow-up or more [9]. In a study of 86 patients with diabetes who were followed for at least 9 years, gastroparesis was not associated with mortality after adjustment for other disorders [10]. Among patients with gastroparesis, overall survival was significantly lower than the age- and sex-specific expected survival computed from the Minnesota white population [7]; the most common causes of death were cardiovascular disease (24.6%), respiratory failure (23.2%), malignancy (15.9%), chronic renal failure in 11 (15.9%), cerebrovascular accident (10.1%) and other causes (10.1%).

Pathophysiology

Gastrointestinal dysmotility in diabetes is caused by extrinsic (i.e. sympathetic and parasympathetic) neural dysfunction, hyperglycemia and hormonal disturbances. More recently, a role for intrinsic (i.e. enteric) neuronal dysfunctions, resulting from loss of excitatory and inhibitory neurons and interstitial cells of Cajal, has also been implicated [11]. Neural dysfunction has been attributed to several mechanisms (e.g. oxidative stress) described below and detailed elsewhere [12].

Normal gastrointestinal motor functions

Gastrointestinal motor function is primarily controlled by the intrinsic or enteric nervous system (i.e. the "little brain" in the digestive tract) and modulated by the extrinsic (i.e. parasympathetic and sympathetic) nervous system (Figure 46.1) [13]. While intrinsic and extrinsic controls are independent, the prevertebral ganglia integrate afferent impulses between the gut and the central nervous system and provide additional reflex control of the abdominal viscera. The parasympathetic arm is excitatory to non-sphincteric muscle and inhibits sphincters. The sympathetic component has opposite effects. The enteric nervous system consists of 100 million neurons that are organized in distinct ganglionated plexi including the submucous plexus, which is primarily involved in absorption and secretion, and the myenteric plexus, which regulates motility. The interstitial cells of Cajal serve as pacemakers and also convey messages from nerve to smooth muscle. As with the somatic and autonomic nerves elsewhere, the gut's autonomic and enteric nervous system can be affected in diabetes. Derangements of the extrinsic nerves at any level may alter gastrointestinal motility and secretion [14].

Gastrointestinal digestion and absorption require gastrointestinal motility, gastric and pancreatic secretion, and gastrointestinal hormonal release, which in turn, modulate motor, secretory and absorptive functions in the upper gut [15]. Traditionally, these processes are considered in three phases (cephalic, gastric and intestinal), which are integrated and overlap. Normally, liquids, particularly non-caloric liquids, empty rapidly from the stomach in a linear fashion. In contrast, gastric emptying of solids follows an exponential pattern. During the first 45 minute postprandial period (i.e. the lag phase), the gastric antrum grinds

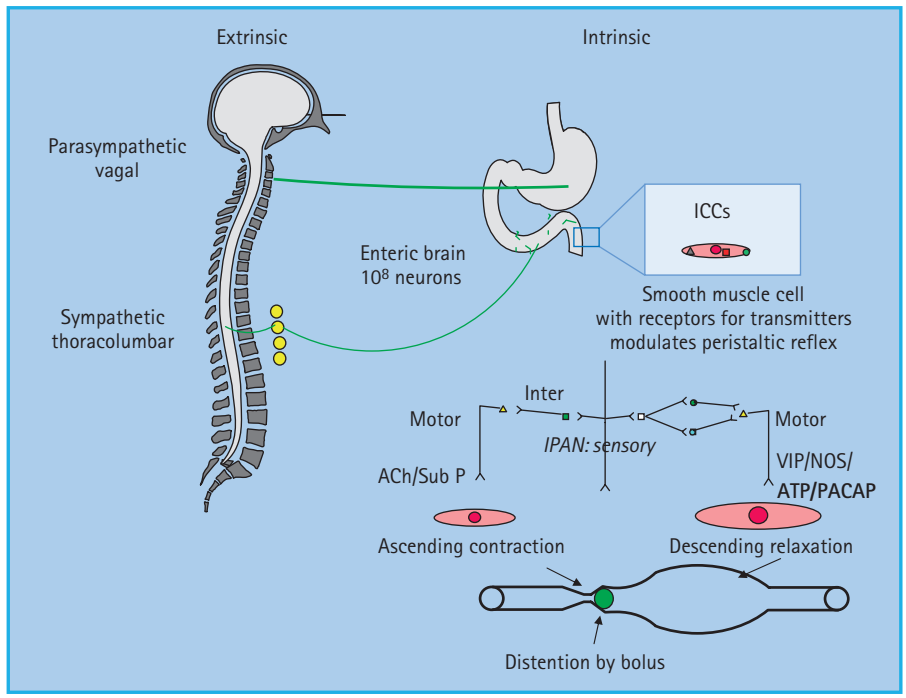
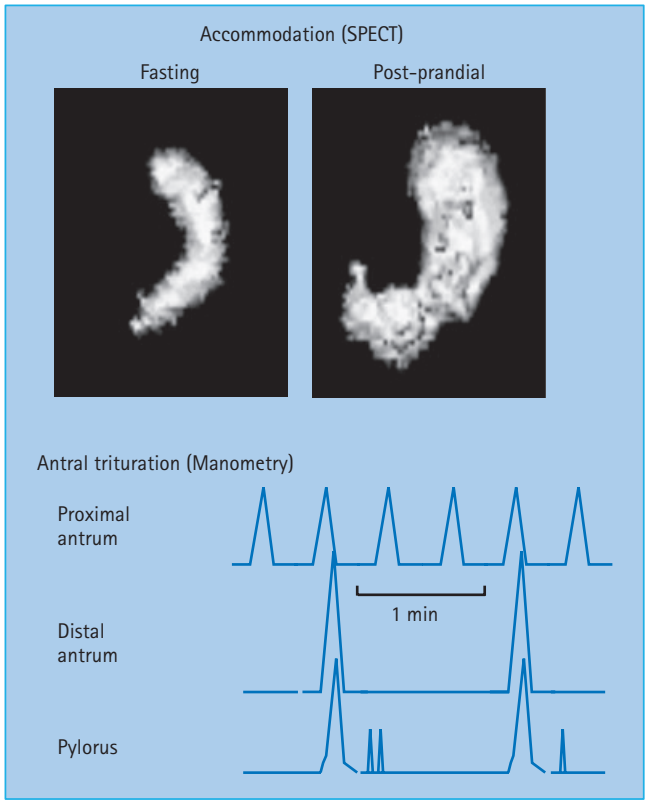


Figure 46.1 Control of gastrointestinal motility. Note the extrinsic or autonomic nervous system modulates the function of the enteric nervous system, which controls smooth muscle cells through excitatory (i.e. acetylcholine [Ach], substance P [Sub P]) or inhibitory (nitric oxide [NO], vasoactive intestinal peptide [VIP], pituitary adenylate cyclase activating peptide [PACAP]) neurotransmitters. ICC, interstitial cells of Cajal; IPAN, intrinsic primary afferent neuron. Adapted from Camilleri M, Phillips SF. Disorders of small intestinal motility. *Gastroenterol Clin North Am* 1989; **18**:405–424.



solids into particles smaller than 2 mm in size, so they can be emptied through the pylorus. During the lag phase, the stomach relaxes or accommodates, providing room for digestion to occur (Figures 46.2 & 46.3). Thereafter, solids are emptied in a linear fashion, with approximately 50% emptying in 2 hours and 100% emptying in 4 hours.

Pancreatobiliary secretions and mechanical processes ensure small intestinal digestion, which precedes absorption. The small intestine transports solids and liquids at approximately the same rate; the head of the column of liquid chyme may reach the cecum as early as 30 minutes after ingestion. As a result of the lag phase for the transport of solids from the stomach, liquids typically arrive in the colon before solids. It takes about 150 minutes for half the solid and liquid chyme of similar caloric density (assuming solids are presented in a triturated form to the small bowel) to traverse the small bowel. Complex carbohydrates or fat in the

Figure 46.2 Assessment of gastric motor functions. Gastric accommodation can be assessed by measuring the post-prandial change in gastric volume using single photo emission computed tomography (SPECT). (top panel) The stomach wall is labeled with intravenous ^{99m}Tc pertechnetate. Food is subsequently transferred to the antrum. Manometry (bottom panel) demonstrates that the distal antrum and pylorus contract synchronously to grind food into smaller particles. Only particles 2 mm or smaller can be emptied through the pylorus.

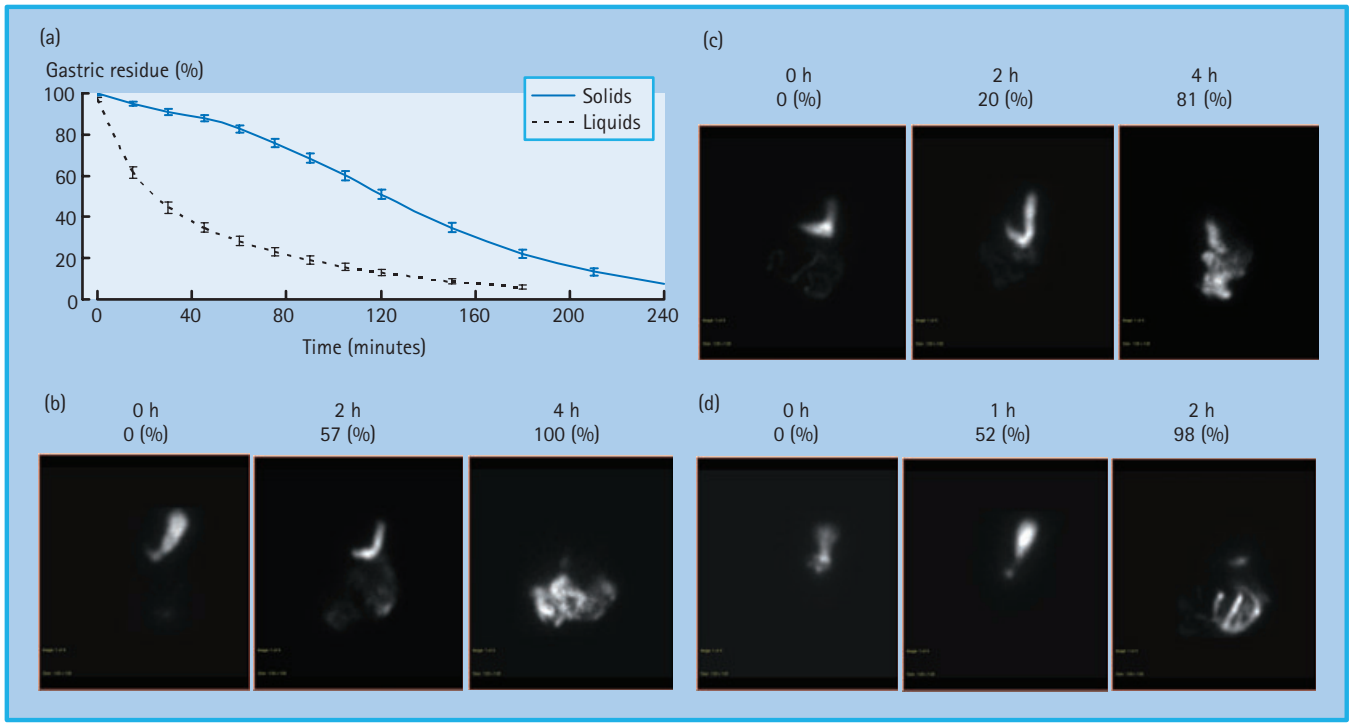


Figure 46.3 Assessment of gastric emptying by scintigraphy. Normally liquids are emptied in a linear manner while solid emptying has an exponential profile, characterized by an initial lag phase, followed by a more rapid, linear emptying (a). The lag phase corresponds to the time required for antral trituration and gastric accommodation, during which approximately 10% of solids are emptied. (b, c, and d) Representative examples of normal, delayed and accelerated gastric emptying respectively of an egg meal, labeled with ^{99m}Tc, in patients with diabetes. At time 0 (i.e. first image in each panel), the entire meal was in the stomach. Thereafter, the normal ranges for gastric emptying are 11–39% at 1 hour, 40–76% at 2 hours and 84–98% at 4 hours.

distal small intestine exert feedback control of proximal small intestinal motility, a process known as the small intestinal brake. Chyme is transferred from the ileum to colon in intermittent boluses. On average, it takes 36 hours, with an upper limit of 65 hours, to transfer contents from the cecum to the rectum. Compared to the stomach and small intestine, colonic transit is relatively prolonged, permitting digestion of fiber and absorption of water and electrolytes to be completed.

Pathophysiology of diabetic enteropathy: insights from animal studies

In animal models, extrinsic neural dysfunction has been primarily implicated to a loss of myelinated and unmyelinated fibers without much neuronal loss [16,17]. The loss of nerve fibers is often multifocal, suggestive of ischemic injury. Within the enteric nervous system, reduced neuronal staining, and to a lesser extent neuronal loss, particularly inhibitory neurons expressing nitric oxide synthase (NOS) have been described in several animal models of diabetes [12]. In theory, this reduction in nitrergic inhibitory functions may contribute to impaired gastric accommodation and accelerated intestinal transit in diabetes. Reduced sympathetic inhibition may also contribute to accelerated intestinal transit. Because nitric oxide (NO) is a mediator of pyloric relaxation, loss of NOS may impair pyloric relaxation and thereby retard gastric emptying. Loss of intestinal cells of Cajal (ICC), documented in several animal models and case reports of diabetes, may also contribute to gut dysmotility [11,18].

Several mechanisms, including apoptosis, oxidative stress, advanced glycation end products and neuroimmune mechanisms may be responsible for neuronal loss and gut dysmotility [12]. The loss of ICC has been attributed to a reduction in heme-oxygenase (HO-1) and other protective mechanisms against hyperglycemia [11]. The effects of diabetes on neuronal morphology and functions are reversible. Insulin or pancreas transplantation improved glycemic control and the axonopathy affecting autonomic nerves in rats with diabetic autonomic neuropathy [19]. Insulin also restored expression of NOS and gastric emptying in animal models of diabetes while insulin and insulin-like growth factors prevented the loss of ICC in cultures [20,21]. Because ICC do not express receptors for either hormone, these effects are perhaps mediated by smooth muscle secretion of stem cell factor, which is the most important growth factor for ICC rather than directly by insulin and insulin-like growth factors [11]. Overexpression of glial cell line-derived neurotrophic factor, a trophic factor for enteric neurons, in transgenic mice reversed hyperglycemia-induced apoptosis of enteric neurons, improved gastric emptying and intestinal transit [22].

Pathophysiology of diabetic enteropathy in humans

Gastric dysfunctions

Neuropathy

Diabetes is associated with accelerated or delayed gastric emptying, increased and reduced gastric sensation, and impaired gastric accommodation (Figure 46.4). A vagal neuropathy can cause antral hypomotility and/or pylorospasm, which may delay gastric emptying [23]. The pathophysiology of rapid gastric emptying in diabetes is less well understood. Conceivably, impaired gastric accommodation resulting from a vagal neuropathy [24] may increase gastric pressure and thereby accelerate gastric emptying of liquids. However, the relationship between rapid gastric emptying and impaired gastric accommodation has not been substan-

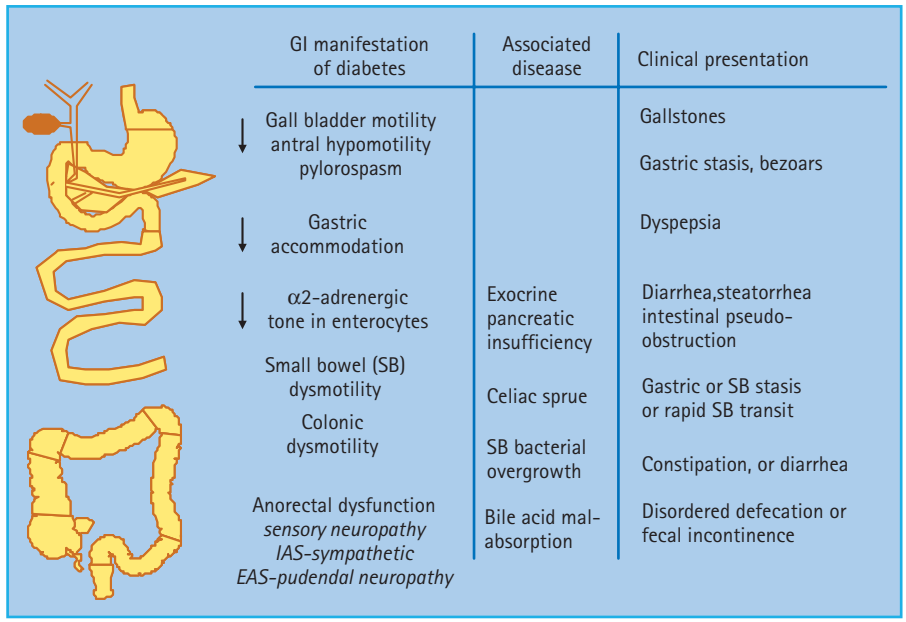


Figure 46.4 Pathophysiology of diabetes enteropathy in humans. Adapted from Camilleri M. Gastrointestinal problems in diabetes. *Endocrinol Metab Clin North Am* 1996; **25**:361–378.

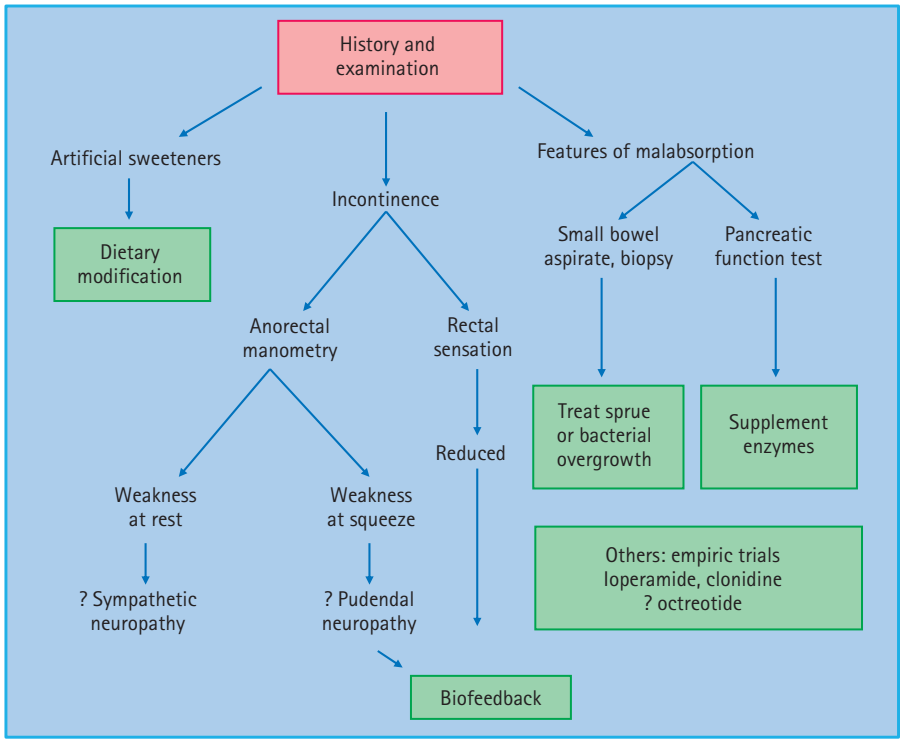


Figure 46.5 Management of diarrhea in diabetes mellitus. Adapted from Camilleri M. Gastrointestinal problems in diabetes. *Endocrinol Metab Clin North Am* 1996; **25**:361–378.

tiated. The relationship between vagal neuropathy and impaired post-prandial accommodation is unclear because accommodation may be preserved even in people with diabetes and vagal neuropathy [25], perhaps reflecting non-vagal adaptive mechanisms involving enteric neurons [26]. Some patients with diabetes and gastroparesis also have small intestinal dysmotility, more frequently characterized by reduced than by increased motility [27]. Small bowel dysmotility may also contribute to gastric stasis.

Hyperglycemia

Acute hyperglycemia delays gastric emptying in healthy subjects and in T1DM [28–31]. These effects may be explained by hyperglycemia-induced suppression of antral motility and migrating motor activity, the so-called intestinal "housekeeper" [32–34]. The effects of acute hyperglycemia on gastric emptying are modest. Indeed, even in T1DM, severe acute hyperglycemia (i.e. 16–20 mmol/L vs 4–8 mmol/L) prolonged the gastric emptying half-time by only 17 minutes from 124 to 141 minutes. Acute modulation of blood glucose within the physiologic post-prandial range (4–8 mmol/L) can also delay gastric emptying, to a lesser degree [31]. Cross-sectional studies suggest that higher glycated hemoglobin concentrations are associated with a higher prevalence of gastrointestinal symptoms and slower gastric emptying among people with diabetes in the community [6,35]. While strict glycemic control improves neural, renal and retinal functions in diabetes, the impact on gastric emptying is unclear [36]. Indeed, in the only study that assessed this question, improved glycemic control did not improve gastric emptying 1 week later in 10 patients with T2DM [37]. In addition to hyperglycemia, electrolyte imbalances caused by diabetic ketoacidosis (e.g. hypokalemia) and uremia may also aggravate impaired motor function in patients with diabetes. Iatrogenic gastroparesis may result from treatment with amylin or GLP-1 analogs.

Diabetic diarrhea

It is useful to categorize the pathophysiology of diabetic diarrhea into conditions that are associated with malabsorption and those that are not (Figure 46.5). Involvement of sympathetic fibers, which normally inhibit motility and facilitate absorption via α_2-adrenergic receptors, can result in accelerated small intestinal transit and cause diarrhea [38]. Artificial sweeteners such as sorbitol may also contribute to diarrhea. Patients with rapid ileal transit may have bile acid malabsorption [39,40] and deconjugated bile acids induce colonic secretion.

Features suggestive of malabsorption such as anemia, macrocytosis or steatorrhea should prompt consideration of bacterial overgrowth, small bowel mucosal disease or pancreatic insufficiency. Small intestinal dysmotility predisposes to bacterial overgrowth, which can cause bile salt deconjugation, fat malabsorption and diarrhea. Although T1DM is associated with celiac disease, most patients with celiac disease and T1DM in the community are asymptomatic [41]. Chronic pancreatic insufficiency may result from pancreatic atrophy, disruption of cholinergic enteropancreatic reflexes, or elevated serum hormonal levels of glucagon, somatostatin and pancreatic polypeptide, which reduce pancreatic enzyme secretion [42]. Nevertheless, the association between chronic pancreatic insufficiency and diabetes is uncommon. Moreover, because there is sufficient pancreatic reserve,

only 10% of pancreatic function is sufficient for normal digestion.

Fecal incontinence

Loose stools and anorectal dysfunctions contribute to fecal incontinence in diabetic diarrhea. Compared to continent people with diabetes and healthy controls, patients with diabetes and fecal incontinence have a higher threshold for rectal perception of balloon distention, a marker of reduced sensation [43,44]. A sympathetic neuropathy may impair internal anal sphincter function and anal resting pressures while a pudendal neuropathy may result in reduced anal squeeze pressure.

Constipation

The mechanisms of constipation in diabetes have not been carefully studied and are poorly understood. Clinical observations suggest that, similar to idiopathic chronic constipation, both colonic dysmotility and anorectal dysfunctions, such as impaired anal sphincteric relaxation during defecation, may contribute to constipation in diabetes [45]. Patients with colonic dysmotility have an impaired colonic contractile response to a meal and delayed colonic transit [46]. Patients with reduced rectal sensation may not perceive the desire to defecate. Compared to euglycemia, acute hyperglyemia inhibits the colonic contractile response to gastric distention and proximal colonic contraction elicited by colonic distention in healthy subjects [47]. By contrast, acute hyperglycemia did not significantly affect fasting or post-prandial colonic tone, motility, compliance and sensation, or rectal compliance and sensation in healthy people [48].

In addition to these factors, it is also important to consider the role of psychologic factors in the perception of gastrointestinal symptoms. Indeed, psychosomatic symptoms are significantly associated with the reporting of gastrointestinal tract symptoms [4]. Several medications have gastrointestinal side effects; for example, metformin can cause diarrhea while among other medications, verapamil and anticholinergic agents, can cause constipation.

Clinical manifestations

Dysphagia and heartburn

Esophageal dysmotility, typically characterized by impaired peristalsis with simultaneous contractions, is common, may cause dysphagia, and may be related to cardiovascular autonomic neuropathy in diabetic mellitus [49]. The amplitude of peristaltic contractions and basal lower esophageal sphincter pressures are generally normal. Symptoms of gastroesophageal reflux are also common, particularly in patients with impaired gastric emptying who have vomiting. Rarely, recurrent vomiting may lead to Mallory–Weiss tears and bleeding.

Dysphagia and heartburn should prompt upper gastrointestinal endoscopy to exclude reflux and other incidental mucosal diseases, such as candidiasis and neoplasms. While manometry may reveal esophageal peristaltic disturbances in patients with significant dysphagia that is not explained by a structural lesion, it is unlikely to alter management, except for rare patients in whom another disorder, such as achalasia, is responsible for dysphagia. Because of the high prevalence of coronary atherosclerosis in diabetes, testing for coronary artery disease should be considered when necessary in patients with chest pain.

Dyspepsia and gastroparesis

Although gastroparesis refers to a syndrome characterized by symptoms of nausea, vomiting, early satiation after meals and impaired nutrition and objective evidence of markedly delayed gastric emptying, gastric retention may be asymptomatic [50], perhaps because of the afferent dysfunction associated with vagal denervation [51]. Nausea and vomiting often occur in episodes lasting days to months or in cycles. Nausea and vomiting may be associated with impaired glycemic control and often cause hypoglycemia, perhaps because delivery of food into the small bowel for absorption is not sufficient to match the effects of exogenous insulin.

Consistent with the concept of a paralyzed stomach, the term gastroparesis should be restricted to patients with markedly delayed gastric emptying. When the delay in gastric emptying is not severe, the term diabetic dyspepsia is perhaps more appropriate. Dypepsia is characterized by one or more, generally post-prandial, upper gastrointestinal symptoms, including bloating, post-prandial fullness and upper abdominal pain. Typically, vomiting is not severe but significant weight loss secondary to reduced caloric intake is not unusual. In addition to delayed gastric emptying, impaired gastric accommodation and abnormal, either increased or decreased, gastric sensation may also contribute to symptoms in diabetes [52,53]. Nonetheless, the distinction of dyspepsia from gastroparesis is challenging because there is no official distinction between moderately and severely delayed gastric emptying. Perhaps, gastric emptying of less than 65% at 4 hours reflects a significant delay as it is often associated with nutritional consequences, the need for nutritional supplementation, jejunal feeding or gastric decompression [54].

Patients with diabetic gastroparesis frequently have long-standing T1DM with other microvascular complications, including retinopathy, nephropathy, peripheral neuropathy and other forms of autonomic dysfunction. These can present as abnormal pupillary responses, anhidrosis, gustatory sweating, orthostatic hypotension, impotence, retrograde ejaculation and dysfunction of the urinary bladder) (Table 46.1). In contrast, it has been suggested that rapid gastric emptying of liquids is a relatively early manifestation of T2DM [55–59]. Clinicians have relied on these manifestations, and on certain symptoms, such as vomiting of undigested food eaten several hours previously and weight loss, and signs (e.g. a gastric succussion splash or features of an autonomic neuropathy) to predict delayed gastric emptying in patients with diabetes who present with upper and gastrointestinal symptoms. Several studies have shown, however, that symptoms are of limited utility for predicting delayed gastric emptying in diabetes

[60–66]. Similarly, the type and duration of diabetes, glycated hemoglobin levels and extraintestinal complications were, in general, not useful for discriminating normal from delayed or rapid gastric emptying; however, significant weight loss and a neuropathy were risk factors for delayed and rapid gastric emptying, respectively [67].

In patients with upper gastrointestinal symptoms, an upper gastrointestinal endoscopy is necessary to exclude peptic ulcer disease and neoplasms, either of which can cause gastric outlet obstruction. Upper endoscopy may reveal gastric bezoars, which suggest antral hypomotility. Metabolic derangements, such as diabetic ketoacidosis or uremia, and medications, particularly opiates, calcium-channel blockers and anticholinergic agents, may contribute to dysmotility. Rarely, patients with gastroparesis present with retrosternal or epigastric pain and cardiac, biliary or pancreatic disease may be considered.

Table 46.1 Symptoms and signs of autonomic dysfunction. Reproduced from Camilleri M. Disorders of gastrointestinal motility in neurologic disease. *Mayo Clin Proc* 1990; **65**:825–846, with permission.

Sympathetic	Parasympathetic
Failure of pupils to dilate in the dark	Fixed dilated pupils
Fainting, orthostatic dizziness	Lack of pupillary accommodation
Constant heart rate with orthostatic hypotension	Sweating during mastication of certain foods
Absent piloerection	Decreased gut motility
Absent sweating	Dry eyes and mouth
Impaired ejaculation	Dry vagina
Paralysis of dartos muscle	Impaired erection
	Difficulty emptying urinary bladder; recurrent urinary tract infections

Barium X-rays of the small intestine or enterography with computed tomography should be considered only when the clinical features raise the possibility of small intestinal obstruction. Gastric emptying of solids should be quantified by scintigraphy and antroduodenal manometry should be considered in selected circumstances. Measurement of pressure profiles in the stomach and small bowel can confirm the motor disturbance and may facilitate the selection of patients for enteral feeding (Figure 46.6). Patients with selective antral hypomotility may tolerate feeding delivered directly into the small bowel while those with a more generalized motility disorder may not.

Diarrhea and constipation

The term diabetic diarrhea was first coined in 1936 by Bargen at the Mayo Clinic to describe unexplained diarrhea associated with severe diabetes [68]. Diabetic diarrhea is typically chronic, may be episodic and can be severe. Diarrhea can occur at any time but is often nocturnal and may be associated with anal incontinence,

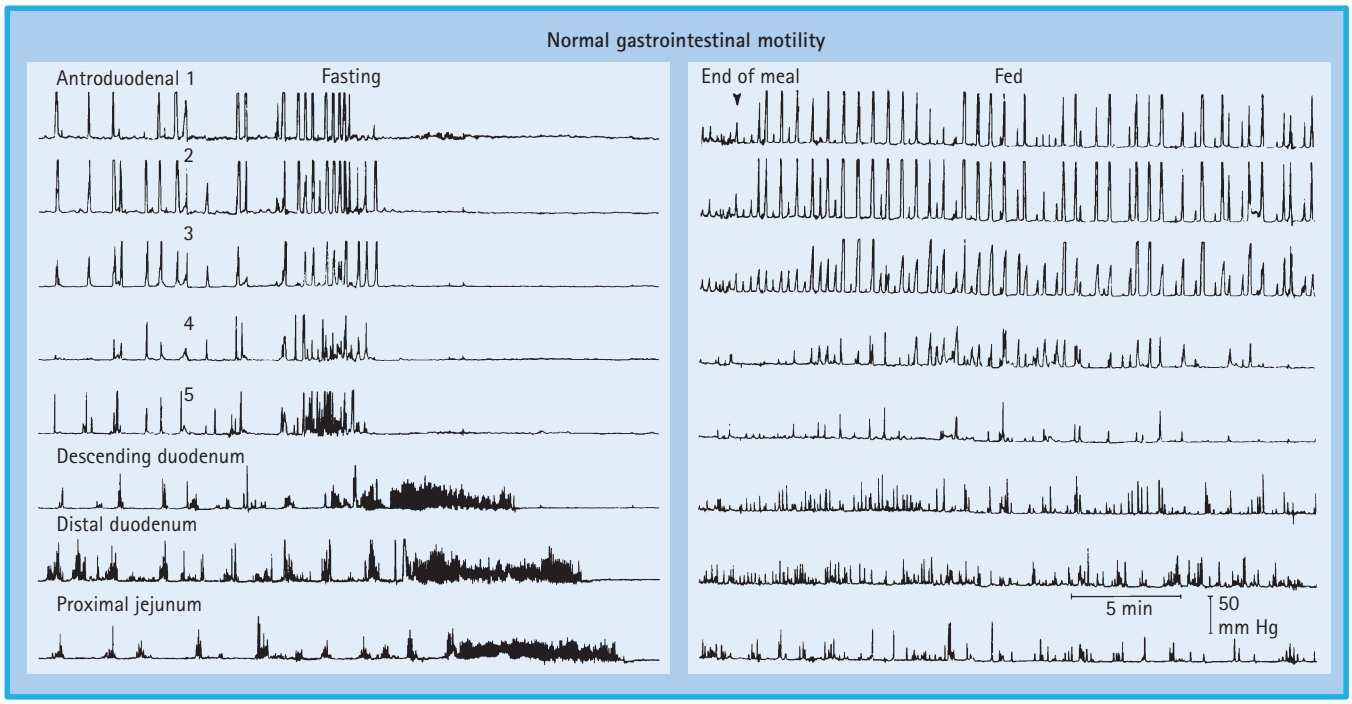


Figure 46.6 Normal manometric profile (fasting and post-prandial). The migrating motor complex characteristic of fasting state is demonstrated by the presence of quiescence (phase I), intermittent activity (phase II) and an activity front (phase III). Post-prandial profile shows high amplitude, irregular but persistent phasic pressure activity at all levels. Reproduced from Malagelada J-R, Camilleri M, Stanghellini V. *Manometric Diagnosis of Gastrointestinal Motility Disorders.* New York: Thieme Publishers, 1986, by permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

which may indicate internal anal sphincter dysfunction. Patients with diarrhea often have symptoms of delayed gastric emptying such as early satiety, nausea and vomiting.

Constipation may occur in isolation or alternate with episodes of diarrhea. Many physicians regard constipation to be synonymous with infrequent bowel movements. It is important to characterize symptoms because many people have misconceptions about normal bowel habits. For example, it is not necessary to have a bowel movement daily – the normal range varies from three bowel movements every week to three every day. Moreover, by constipation, patients refer to one or more of a variety of symptoms including infrequent stools, hard stools, excessive straining during defecation, a sense of anorectal blockage during defecation, the need for anal digitation during defecation and a sense of incomplete evacuation after defecation [69]. Some of these symptoms, such as a sense of anorectal blockage during defecation, may suggest disordered evacuation. A careful rectal examination during relaxation and straining is needed to exclude rectal mucosal lesions and to detect the presence of rectal prolapse, rectocele and disordered defecation. Normally, voluntary contraction is accompanied by upward and anterior motion of the palpating finger toward the umbilicus as the puborectalis contracts. Conversely, the puborectalis should relax and the perineum should descend (by 2–4 cm) during simulated evacuation. The rectal examination may suggest features or defecatory disorders such as reduced or increased perineal descent and paradoxical contraction of puborectalis.

Abdominal pain

Patients with diabetes are obviously susceptible to the usual causes of abdominal pain seen in the general population. There is an increased prevalence of gallstones because of altered gallbladder contractility and of mesenteric ischemia caused by generalized atherosclerosis; however, there is little evidence that altered gallbladder contractility per se (i.e. in the absence of gallstones) causes symptoms. Thoracolumbar radiculopathy may result in pain in a girdle-like distribution which does not cross the midline. Specific tests are indicated in the clinical features of pain suggest these disorders. It is essential to elicit a careful history.

Diagnostic tests

Typically, diagnostic testing is primarily guided by symptom pattern and severity; however, because patients with delayed gastric emptying are often asymptomatic, gastric emptying assessments should also be considered in patients with unexplained hypoglycemia. After initial testing to identify disturbances of transit, more detailed testing with intraluminal techniques, such as manometry and/or a barostat, may be useful for characterizing motor dysfunctions and guiding therapy (Table 46.2). Autonomic function testing is also useful [70]. Delayed gastric emptying can be documented by scintigraphy or the presence of a large amount of retained food in the stomach. Barium studies and scintigraphy using labeled liquid meals are of limited value for identifying dysmotility because the gastric emptying of liquids and semisolids (e.g. mashed potatoes) frequently is normal, even in the presence of moderately severe symptoms. Assessment of solid emptying by means of a radiolabel that tags the solid phase of the meal is a more sensitive test with a well-defined normal range. The proportion of radioisotope retained in the stomach at 2 and 4 hours distinguishes normal function from delayed gastric emptying with a sensitivity of 90% and a specificity of 70% [71]. The importance of obtaining scans for 4 hours after a meal cannot be overemphasized. Because gastric emptying is slow initially, it is not accurate to extrapolate emptying from scans taken for a shorter duration. Another useful test for measuring solid phase gastric emptying utilizes a standardized meal with biscuit enriched with ^{13}C, a substrate containing the stable isotope. When metabolized, the proteins, carbohydrates and lipids of the *S. platensis* or the medium chain triglyceride octanoate give rise to respiratory CO_2 that is enriched in ^{13}C. Measurement of $^{13}CO_2$ breath content (a reflection of the amount of biscuit remaining in the stomach) by isotope ratio mass spectrometry allows an estimation of gastric emptying $t_{1/2}$ [72]. Further validation of this technique is necessary in patients with bacterial overgrowth and small bowel mucosal disease.

For patients with severe upper gastrointestinal symptoms, antropyloroduodenal manometry is a specialized technique that assesses pressure profiles in the stomach and small bowel and also guides management. Manometry may also reveal hypomotility of the gastric antrum and/or an intestinal neuropathy (Figures 46.6 & 46.7). Patients with selective abnormalities of gastric function may be able to tolerate enteral feeding (delivered directly into the small bowel) whereas patients with a more generalized motility disorder may not.

Gastric accommodation in response to meal ingestion may be impaired in diabetes [73]. This may contribute to the gastrointestinal symptoms of nausea, bloating and early satiety. Imaging of the stomach wall using ^{99m}Tc pertechnetate allows measurement of gastric volume after meal ingestion.

For patients with constipation, colonic transit, anorectal manometry and rectal balloon expulsion tests provide a useful start. Anorectal manometry and the rectal balloon expulsion test generally suffice to diagnose or exclude defecation disorders; magnetic resonance imaging (MRI) or barium proctography are only required in selected patients. Colonic transit is often delayed in patients with defecatory disorders. Therefore, in patients with slow colonic transit, slow transit constipation can only be diagnosed after excluding defecatory disorders. Intraluminal assessments of colonic phasic motility (by manometry) and tone (by barostat) often reveal other dysfunctions (e.g. impaired contractile responses to a meal and/or pharmacologic stimuli (e.g. bisacodyl or neostigmine) in patient with slow transit constipation. Colonic transit can be characterized by radiopaque markers, which, depending on the technique, takes 5–7 days, or by scintigraphy, which takes 24–48 hours. Both techniques are equally accurate for identifying slow or rapid colonic transit.

Table 46.2 Commonly performed autonomic tests. Reproduced from Camilleri M, Ford MJ. Functional gastrointestinal disease and the autonomic nervous system: a way ahead? *Gastroenterology* 1994; **106**:1114–1118, with permission.

Test	Physiologic functions tested	Rationale	Comments/pitfalls
Sympathetic Function			
1. Thermoregulatory sweat test (% surface area of anhidrosis)	Preganglionic and postganglionic cholinergic	Stimulation of hypothalamic temp. control centers	Cumbersome, whole body test
2. Quantitative sudomotor axon reflex test (sweat output, latency)	Postganglionic cholinergic	Antidromic stimulation of peripheral fiber by axonal reflex	Needs specialized facilities
3. Heart rate and blood pressure responses			
Orthostatic tilt test	Adrenergic	Baroreceptor reflex	Impaired responses if intra-vascular volume is reduced
Postural adjustment ratio	Adrenergic	Baroreceptor reflex	Impaired responses if intra-vascular volume is reduced
Cold pressor test	Adrenergic	Baroreceptor reflex	Impaired responses if intra-vascular volume is reduced
Sustained hand grip	Adrenergic	Baroreceptor reflex	Impaired responses if intra-vascular volume is reduced
4. Plasma norepinephrine response to:			
Postural changes	Postganglionic adrenergic	Baroreceptor stimulation	Moderate sensitivity, impaired response if intravascular volume is reduced
Intravenous edrophonium	Postganglionic adrenergic	Anticholinesterase "stimulates" postganglionic fiber at prevertebral ganglia	False-negatives caused by contributions to plasma norepinephrine from many organs
Parasympathetic Function			
1. Heart rate (RR) variation with deep breathing	Parasympathetic	Vagal afferents stimulated by lung stretch	Best cardiovagal test available, but not a test of abdominal vagus
2. Supine/erect heart rate	Parasympathetic	Vagal stimulation by change in central blood volume	Cardiovagal test
3. Valsalva ratio (heart rate, max./min.)	Parasympathetic	Vagal stimulation by change in central blood volume	Cardiovagal test
4. Gastric acid secretory or plasma pancreatic polypeptide response to modified sham feeding or hypoglycemia	Parasympathetic	Stimulation of vagal nuclei by sham feeding or hypoglycaemia	Abdominal vagal test, critically dependent on avoidance of swallowing food during test
5. Nocturnal penile tumescence	Pelvic parasympathetic	Integrity of S2-4	Plethysmographic technique requiring special facilities
6. Cystometrographic response to bethanechol	Pelvic parasympathetic	Increase in intra-vesical pressure suggests denervation supersensitivity	Tests parasympathetic supply to bladder, not bowel

Small intestinal dysmotility may manifest as one or more of the following features: abnormal migrating motor complexes; failure to convert from fasting to post-prandial motor pattern and/or features of a vagal neuropathy such as excessive number of fasting migrating motor complexes or persistent post-prandial migrating motor complexes). Assessment of stool fat provides a useful differentiation point for diabetic diarrhea, as it indicates malabsorption as the pathophysiology leading to diarrhea. An upper endoscopy provides an opportunity to obtain duodenal aspirates for bacterial overgrowth and small bowel biopsy to exclude celiac disease. Lactose or glucose hydrogen breath tests rely on substrate metabolism by bacterial overgrowth in the small intestine with hydrogen release and breath excretion; however, studies have shown that the early peak is frequently caused by rapid delivery of the substrate to the colon with bacterial metabolism by normal colonic flora rather than small bowel bacterial overgrowth [74]. To reduce the potential impact of this confounding factor (i.e. rapid intestinal transit), a more restricted definition to diagnose small intestinal overgrowth may be preferable. An early hydrogen peak (20 ppm), caused by small intestinal bacteria, may be seen at least 15 minutes before the later prolonged peak, which corresponds to the passage of the remaining lactulose into the colon. Even with more restricted definitions, the sensitivity and specificity of the lactulose hydrogen breath test in detecting small bowel bacterial overgrowth have been reported to be only 68% and 44% and for the glucose breath test 62% and 83%, respectively [73].

Management

The principles of management are to address fluid and nutritional requirements, improve glycemic control and treat symptoms.

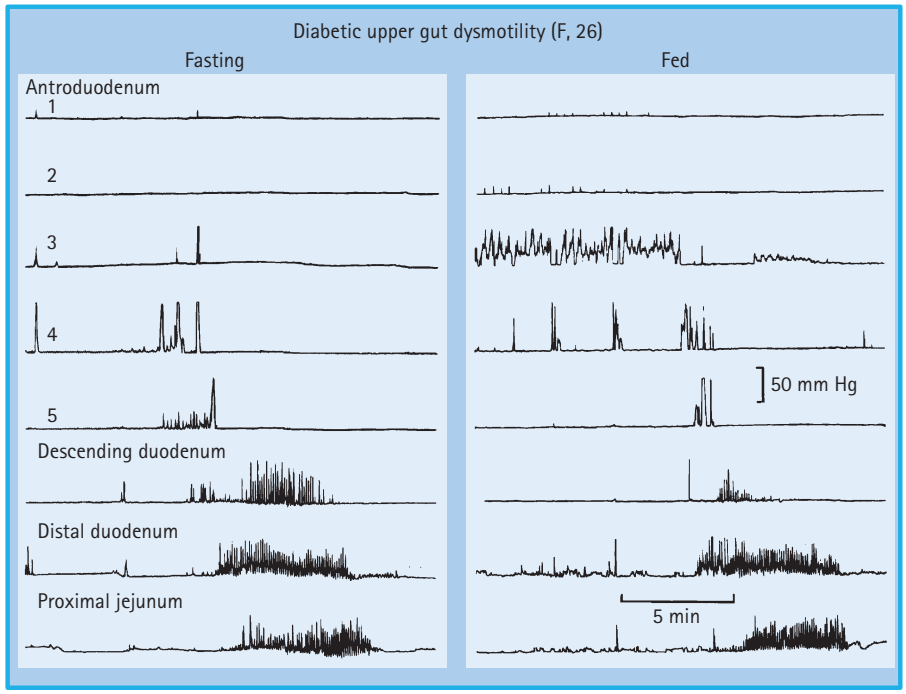


Figure 46.7 Manometric profile in 26-year-old woman with diabetes and autonomic neuropathy, showing abnormal propagation of phase III of interdigestive motor complex and lack of a well-developed antral component in fasting tracing. Post-prandially, note antral hypomotility, pylorospasm, and failure of meal to induce a fed pattern. Reproduced from Colemont LJ, Camilleri M. Chronic intestinal pseudo-obstruction: diagnosis and treatment. *Mayo Clin Proc* 1989; **64**:60–70, with permission.

Gastroparesis and dyspepsia

While nutritional requirements and symptoms can be addressed to a variable extent in patients with mild and compensated gastroparesis, patients with severe gastroparesis often require hospitalization for one or more of the following measures: intravenous hydration and correction of metabolic derangements (ketoacidosis, uremia, hypo-/hyperglycemia), nasoenteric decompression, and/or enteral nutrition to manage vomiting and nutritional requirements [54]. Parenteral nutrition may become necessary in cases of malnutrition. Bezoars may be mechanically disrupted during endoscopy, followed by gastric decompression to drain residual non-digestible particles. Erythromycin at a dose of 3 mg/kg body weight intravenously every 8 hours can accelerate gastric emptying [75,76]. When oral intake is resumed, treatment with oral 250 mg erythromycin t.i.d. for 1–2 weeks is worthwhile. Thereafter, the prokinetic effects of erythromycin are limited by tachyphylaxis. Anecdotal findings suggest that erythromycin may be effective if courses are separated by a drug-free period (e.g. lasting 2 weeks). Hyperglycemia interferes with the prokinetic effect of intravenous erythromycin on gastric emptying in healthy subjects and patients with diabetes [34]. Because both liquids and homogenized solids are more readily emptied from the stomach than solids, liquid or blenderized food will be better tolerated. Frequent monitoring of blood glucose levels is essential during this phase.

For patients with severe gastroparesis who do not respond to the measures outlined above, it may be necessary to bypass the stomach with a jejunal feeding tube. This procedure should be preceded by a trial of nasojejunal feeding for a few days of with infusion rates of at least 60 mL iso-osmolar nutrient per hour. It is preferable to place jejunal feeding tubes directly into the jejunum either by endoscopy, or if necessary by laparoscopy or mini laparotomy, rather than via percutaneous endoscopic gastrostomy tubes. Such tubes allow restoration of normal nutritional status but they are not without adverse effects. There is no evidence to suggest that gastrectomy relieves symptoms or enhances quality of life. Patients with gastroparesis often have concomitant small intestinal denervation which is likely to cause persistent symptoms after gastrectomy [27,77].

If the patient remains symptomatic, other prokinetic agents may be considered as adjuncts. In the USA, the only available medication is metoclopramide, a peripheral cholinergic and antidopaminergic agent. During acute administration, it initially enhances gastric emptying of liquids in patients with diabetic gastroparesis, but its symptomatic efficacy is probably related to its central antiemetic effects. Its long-term use is restricted by a decline in efficacy and by a troubling incidence of central nervous system side effects. Therefore, the authors prefer to prescribe a dose of 10 mg t.i.d., administered 30 minutes before meals, for a short duration; the higher dose is 20 mg t.i.d. A systematic review of trials concluded there was limited evidence to support the use of domperidone, which is another dopaminergic antagonist not approved for use in the USA [78]. Endoscopic injection of botulinum toxin into the pylorus was not effective in controlled studies primarily of patients with idiopathic gastroparesis [79,80].

Although the Food and Drug Administration (FDA) recognizes gastric electrical stimulation as a humanitarian use device for refractory gastroparesis, its use for this indication is controversial. While published data suggest that the device reduces

vomiting frequency only when the device is on, data submitted to the FDA concluded that electrical stimulation reduced vomiting frequency to a similar extent with the device turned off or on, suggesting a placebo response [81,82]. Moreover, the device is expensive and does not accelerate gastric emptying. Between 10 and 20% of patients have device-related complications.

Diabetic diarrhea

Diabetic diarrhea is treated symptomatically with loperamide, preferably administered 30 minutes before meals, in the dose range of 2–16 mg/day. Consumption of artificial sweeteners that contain the osmotically active sugar substitute sorbitol should be reduced. Second-line approaches are clonidine, 0.1 mg orally or by patch, in patients who do not experience significant postural hypotension [83]. Amitriptyline, which has anticholinergic effects, may reduce intestinal cramping and transit. Octreotide (25–50 µg subcutaneously 5–10 minutes before meals) delays small intestinal transit [84] and may also reduce secretory diarrhea associated with rapid intestinal transit [85]. While it has been suggested that octreotide reduces small bowel bacterial overgrowth in chronic intestinal pseudo-obstruction [86], this study assessed for bacterial overgrowth by breath testing. Indeed, by delaying small intestinal transit, octreotide may predispose to bacterial overgrowth. Regulating stool consistency may also improve fecal continence. In addition, pelvic floor retraining with biofeedback therapy can improve rectal sensation, and enhance coordination between perception of rectal distention and contraction of the external anal sphincter [44]; however, biofeedback therapy is less effective in patients with markedly reduced rectal sensation. A descending colostomy may be required and may improve the quality of life in patients with severe diarrhea associated with fecal incontinence.

Constipation

For patients without pelvic floor dysfunction, chronic constipation can be generally managed with pharmacologic agents such as osmotic and stimulant laxatives [87]. Pelvic floor retraining by biofeedback therapy is the cornerstone for managing defecatory disorders; laxatives are used as an adjunct to pelvic floor retraining [88]. Fiber supplementation, either with dietary supplementation or with fiber products (e.g. psyllium 15–18 g/day), should be considered in patients with inadequate fiber intake. Of the osmotic laxatives, polyethylene glycol (up to 17 g in 8 ounces of water once or twice per day) is a widely used and safe over-the-counter agent. While lactulose is a poorly absorbed disaccharide, lactulose syrup contains small amounts of absorbable sugars and may increase hyperglycemia. Magnesium compounds are safe but patients with impaired renal function may develop magnesium retention. Bisacodyl or glycerin suppositories are useful rescue agents in patients who do not have a bowel movement for 2 days. If possible, suppositories should be administered 30 minutes after a meal to synergize pharmacologic therapy with the physiologic response to a meal. By activating chloride channels and inducing colonic secretion, lubiprostone accelerates colonic transit in healthy subjects and improves symptoms in functional constipation [89–91]. While there are no studies in patients with diabetes and constipation, lubiprostone should be considered in patients who have not responded to osmotic agents.

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