Gastrointestinal Symptoms in Diabetes: Prevalence, Assessment, Pathogenesis, and Management

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REVIEW

If you haven't measured something, you really don't know much about it.
—Karl Pearson (attributed)

Gastrointestinal (GI) symptoms represent an important and often unappreciated cause of morbidity in diabetes, although the significance of this burden across the spectrum of patients and the underlying pathophysiology, including the relationship of symptoms with glycemic control, remain poorly defined. The relevance of GI symptoms and the necessity for their accurate assessment have increased with the greater focus on the gut as a therapeutic target for glucose lowering. This review addresses the prevalence, assessment, pathogenesis, and management of GI symptoms in diabetes, beginning with broad principles and then focusing on specific segments of the GI tract. We initially performed a literature search of PubMed by using synonyms and combinations of the following search terms: "gastrointestinal symptoms", "diabetes", "prevalence", "pathogenesis", "diagnosis", and "management". We restricted the search results to English only. Review papers and meta-analyses are presented as the highest level of evidence where possible followed by randomized controlled trials, uncontrolled trials, retrospective and observational data, and expert opinion.

PREVALENCE AND SIGNIFICANCE OF GASTROINTESTINAL SYMPTOMS IN DIABETES

Although gastrointestinal (GI) symptoms generally are accepted as more common in people with diabetes than in the general population, the reported prevalence has varied substantially, being much higher (≥70%) in most but not all outpatient samples (1–5) compared with community studies (6–11) (Table 1). These inconsistencies probably reflect differences in the patient populations and the methodology used to evaluate symptoms. Whether symptom prevalence differs substantially between type 1 and type 2 diabetes is uncertain. In an Australian community study, GI symptoms tended to be less common in the former, but the number of patients with type 1 diabetes was small (9). In contrast, patients with type 1 diabetes in a U.S. community study experienced less heartburn but more constipation than those with type 2 diabetes (7).

A high prevalence of GI symptoms exists in the general population, which may be influenced by BMI, sex, psychological comorbidities, *Helicobacter pylori* infection, and age (12). For example, 7–30% of adults in the community have constipation, and 7–10% suffer from bloating (13). GI symptoms, particularly those deemed embarrassing (e.g., fecal incontinence), often are not reported unless patients are specifically questioned (13). In a community-based study of 777 Australian adults, obesity was independently

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Table 1—Reported prevalence of GI symptoms in diabetes

Symptom	Prevalence (%)				Studies showing a significant difference
	Community studies	Tertiary center studies	Community controls	Tertiary center controls	
Esophageal					
Dysphagia	6.1[I] 5.4[IV] 5.9[V]	4.0[A] 12.9[B]	1.2[I] 1.7[IV] 4.1[V]	0[A] 7.8[B]	IV
Reflux/heartburn	~24[I] 11.6[II] (type 1) 19.8[II] (type 2) 13.5[IV] 19[V]	8.1[A] ~32[B] 44[C] ~5[D] 58.8[E]	10–23[I] 23[II] 11[IV] 18[V]	0[A] 22[B] 21[C] 4[D]	I,IV,A,B,C,E
Gastric					
Abdominal pain or discomfort	8.5–12.1[I] 15.1[III] 13.5[IV] 19.3[V]	16.1[A] 12.8–15.2[C] 15.1[D]	12.2–21.4[I] 12.6[III] 10.8[IV] 14.6[V]	4.9[A] 2.2–4.5[C] 10.3[D]	I,IV,V,A,C
Early satiety	26.8I 32.2[III] 5.2[IV]	6.7[A] 55.1[B] 12.5[D]	6.1[I] 20.2[III] 4.3[IV]	1.2[A] 49.6[B] 5.4[D]	I,III,IV,A,D
Postprandial fullness	18.6[I] 8.6[IV]	16.8[A]	8.5[I] 5.2[IV]	1.2[A]	I,IV,A
Bloating/abdominal distension	42.3[I] 21.0[III] 12.3[IV] 29.8[V]	21.5[A] 57.8[B] 19.6[D]	24.4[I] 15.2[III] 11.4[IV] 26.5[V]	13.4[A] 55.0[B] 13.3[D]	I,III,IV,D
Nausea	22.7[I] 16.8[III] 11.6[II] (type 1) 6[II] (type 2) 5.2[IV] 11.9[V]	3.4[A] 45.2[B] 4.3[D]	9.1[I] 5.5–10.6[II] 12.7[III] 3.5[IV] 5.7[V]	1.2[A] 32.1[B] 2.6[D]	I,III,IV,V,B
Vomiting	12.2[I] 5.6[III] 1.7[IV] 3[V]	9.6[B]	3[I] 4.3[III] 1.1[IV] 2.8[V]	3.4[B]	I,IV,B
Small and large intestines					
Diarrhea	18.6[I] 0[II] 15.6[IV] 22[VI] 18.9[V]	34.9[A] 41.0[B] 12.8[C] 17.9[D]	13.4[I] 0[II] 10.0[IV] 11.4[V] 9[VI]	4.9[A] 34.9[B] 2.2[C] 11.7[D]	IV,VI,A,C,D
Constipation	14.3[I] 16.7[II] (type 1) 10.1[II] (type 2) 11.4[IV]	27.5[A] 33.7[B] 16.1[D]	10.3[I] 11.5–13.5[II] 9.2[IV]	7.3[A] 32.1[B] 14.6[D]	IV,A
Fecal incontinence	0.7[II] (type 1) 4.6[II] (type 2) 2.6[IV] 9.9[V]	3.4[A] 8.8[C]	1.2–1.8[II] 0.8[IV] 4.6[V]	0[A] 0[C]	IV,V,C

Only English-language articles with full text available from PubMed; included matched controls and reported crude prevalence rates are shown. [I]Schvarcz et al. (6): community study, questionnaire not validated, 110 patients with long-standing type 1 diabetes, 210 controls. [II]Maleki et al. (7): community study, used validated BDS, 138 patients with type 1 diabetes and 170 controls, 217 patients with type 2 diabetes and 218 controls. [III]Ricci et al. (8): community study, face-to-face interview, 483 patients with diabetes, 422 controls. [IV]Bytzer et al. (9): community study, validated questionnaire that was based on the BDQ, 423 patients with type 1 diabetes (5.2%) and type 2 diabetes (94.8%), 8,185 controls. [V]Icks et al. (10): community study, interview questions derived from Talley et al. (1992) questionnaire (14), 544 patients with type 2 diabetes, 544 controls. [VI]Quan et al. (11): community study, used validated DBSQ, 51 patients with type 1 diabetes, 128 patients with type 2 diabetes, 65 controls. [A]Ko et al. (1): tertiary referral center, interview questions derived from Horowitz et al. (1989) questionnaire (15), 149 patients with type 2 diabetes, 82 controls. [B]Mjörnheim et al. (2): tertiary referral center, questionnaire from Ruth et al. (1991) (16), 364 patients with type 1 diabetes, 242 controls, high crude prevalence rates probably because patients who answered mild, moderate, or severe to any question were considered to have the symptom. [C]Abid et al. (3): tertiary referral center, questionnaire from Talley et al. (32), 250 patients with type 2 diabetes, 264 controls. [D]de Kort et al. (4): tertiary referral center, Gastrointestinal Symptom Rating Scale and PAGI-SYM questionnaires used, 280 patients with type 1 (28.9%) and type 2 (71.1%) diabetes, 355 controls, prevalence rates for clinically relevant GI symptoms (Gastrointestinal Symptom Rating Scale score ≥3, PAGI-SYM score ≥2). [E]Ha et al. (5): tertiary referral center, GERD symptoms evaluated by using Frequency Scale of the Symptoms of GERD questionnaire, 258 patients with type 2 diabetes, 184 controls.

associated with an almost threefold increased risk of heartburn (17). A preponderance of GI symptoms exists in females in control populations (6,9), and the prevalence of functional GI disorders also is higher in women (18). Accordingly, the inclusion of an appropriate control group is essential in studies related to the prevalence of GI symptoms in diabetes.

In both type 1 and type 2 diabetes, GI symptoms occur more frequently in women, who exhibit higher levels of psychosocial distress than men (9); psychological comorbidities, including anxiety and depression (9,19), are strongly associated with GI symptoms. For example, in a community study of >1,000 patients predominantly with type 2 diabetes, symptoms were about twice as frequent in those with anxiety or depression (19). The fundamental issue of whether psychological distress causes symptoms and/or represents the outcome of them remains unclear.

The natural history of GI symptoms in diabetes is poorly defined. In community-based subjects with and without diabetes, there is substantial symptom "turnover" (~15–25% over 2 years [11]); the onset of new symptoms appears to be counterbalanced by the disappearance of others so that the overall prevalence remains relatively constant (11). In community-based patients with type 1 and type 2 diabetes, the onset of depression was associated with about a threefold risk of gaining GI symptoms and its resolution, with a twofold risk of losing them (11). Glycemic control and autonomic neuropathy have not been convincingly associated with symptom turnover (11).

GI symptoms affect quality of life in diabetes negatively and substantially (20). Scores on all Short Form 36 subscales decrease markedly as the number of distinct GI symptom groups increases (20). In patients with symptomatic diabetic gastroparesis, annual income has been reported to be reduced by ~30% (21). In functional GI disorders, improvement in health-related quality of life is concordant with GI symptom improvement (13), but this has not been evaluated in diabetes. GI symptoms also may affect tolerability of diabetes medications. In newly diagnosed patients with type 2 diabetes, the occurrence of GI symptoms with metformin was associated with an ~40% decrease in adherence to therapy (22).

From a population perspective, GI symptoms represent a substantial and probably increasing contribution to health care costs related to diabetes, including outpatient/inpatient services and diagnostic/procedural interventions. In the U.S., diabetic gastroparesis accounted for almost 8,000 inpatient days, costing >$11 million in a single state in 1998 (23).

ASSESSMENT OF GI SYMPTOMS

Methods for determining the presence and severity of GI symptoms have evolved substantially over recent decades, particularly in the area of functional GI disorders (e.g., irritable bowel syndrome [IBS], functional dyspepsia), which after the exclusion of structural disease, are defined exclusively by symptoms and, unlike diabetes, lack objective biomarkers (18). Although validated questionnaires are used widely in diabetes (e.g., to assess neuropathy) (24), most studies, including those related to therapeutics, have not used validated tools to assess GI symptoms, and assessment has been based on self-report, which is known to be unreliable (25). For example, in trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs), a drug class associated with both upper and lower GI adverse effects (26), collection of GI symptom data has mostly been by self-report. Moreover, patients with significant GI symptoms usually have been excluded from such studies by poorly defined criteria. The majority of studies also do not report the information provided to patients at enrollment, which may be important. In functional gut disorders, such as IBS, the placebo response rate is high (~30–40%) (27) and may be up to 50% in studies related to the management of symptomatic diabetic gastroparesis (28). Self-reporting of symptoms also may be influenced by an expectation of adverse GI effects (nocebo effect) or of one drug being less prone to GI effects than another (precebo effect) (27). Furthermore, although validated questionnaires are considered the gold standard for assessment of symptoms, they are limited by recall bias and are less than optimal in monitoring changes in symptoms over time and across contexts. Ecological momentary assessment, which involves repeated sampling of individuals' symptoms in real time and in their natural environment, may minimize the limitations of traditional questionnaires (29).

Individuals' interpretation of terminology such as diarrhea and constipation, varies widely, encompassing altered stool form, changes in the frequency of defecation, and/or symptoms such as fecal urgency or straining (30). Therefore, precise definitions and explicit language must be used. For example, in the Diabetes Bowel Symptom Questionnaire (DBSQ) , diarrhea is defined as loose or watery bowel movements occurring more than one-quarter of the time (30). Language and culture also influence the expectation, perception, and reporting of symptoms. Societal attitudes toward scientifically based medicine may amplify the communication gap beyond that of just a language barrier per se to result in underreporting, or misreporting, of symptoms. Regulatory bodies, including the U.S. Food and Drug Administration (FDA) and European Medicines Agency now, appropriately, require the use of validated questionnaires when assessing treatment outcomes in studies of functional GI disorders (31). An instrument to assess GI symptoms in diabetes must address all relevant symptoms (content validity), relate to other measures of symptom improvement (construct validity), yield comparable results when retested on subjects with stable symptoms (reliability), detect clinically meaningful changes (longitudinal construct validity or responsiveness), and relate to clinically meaningful indicators (31). Ideally, it should be developed with the involvement of patients and include a range that allows detection of meaningful changes without being compromised by floor and ceiling effects (i.e., failure to discriminate among people at the lower and upper ends of the measurement continuum) (31). Some instruments focus solely on the GI dimension, whereas others are multidimensional, encompassing socioeconomic and psychological domains, and are linked to quality-of-life assessments. Examples of the latter include the Bowel Disease Questionnaire (BDQ) (32) and the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) (33). The DBSQ was developed from the BDQ (30). The Gastroparesis Cardinal Symptom Index daily diary (34) can be used to assess symptoms in gastroparesis, and the Diabetic Gastroparesis Symptom Severity Diary, which consists of seven items and a symptom severity composite score, has been validated specifically for use in trials of therapies for diabetic gastroparesis (35).

In summary, patients with diabetes must be specifically questioned about GI symptoms by using validated questionnaires. Future trials of diabetes therapeutics should report the information provided to enrolled patients.

PATHOGENESIS OF GI SYMPTOMS IN DIABETES

In the broadest sense, GI symptoms in diabetes can be regarded as the outcome of a disordered gut-brain axis. Potential pathogenic factors include autonomic (vagal and myenteric) and peripheral neuropathy, structural and functional central nervous system (CNS) changes (diabetic encephalopathy), acute and chronic dysglycemia, psychological dysfunction, and pharmacotherapy. Specific pathogenic factors relevant to each section of the GI tract are discussed subsequently.

The putative association of GI symptoms with disordered GI motor function arising from irreversible autonomic (vagal) neuropathy is long-standing (11). The few tests that specifically evaluate GI autonomic function (e.g., measurement of the pancreatic polypeptide response to sham feeding, postprandial superior mesenteric artery blood flow responses) are not widely available (11), and standardized tests of cardiovascular reflexes typically are used as a surrogate (11). Autonomic neuropathy, as assessed by these tests, is closely associated with symptoms and signs of peripheral neuropathy in diabetes (11). However, the relationships between GI symptoms and the presence of autonomic or peripheral neuropathy are weak (1,2,7).

Structural and functional changes in the CNS may influence the perception and generation of symptoms, with evidence of both gastric hypersensitivity (36) and rectosigmoid hyposensitivity (37). Brock et al. (37) investigated neurophysiological changes in a predominantly type 1 diabetes cohort and reported evidence of rectosigmoid hyposensitivity and bilateral anterior shifting of the insula and cingulate sources of brain activity, which correlated positively with postprandial fullness and nausea.

Acute changes in blood glucose concentration affect both GI motor function and the perception of sensations arising from the gut (38). For example, acute hyperglycemia increases proximal gastric compliance,

slows gastric emptying, and increases perceptions of fullness, nausea, and bloating (38). Modest increases in blood glucose concentration, within the physiological postprandial range (~8 mmol/L or 140 mg/dL), which slow gastric emptying (39), also may affect gut sensations (38). Ketosis and ketoacidosis can cause abdominal pain, perhaps reflecting profound slowing of gastric emptying, or ileus as a result of metabolic acidosis and associated electrolyte abnormalities. Studies are needed to clarify the magnitude of these effects (40). However, a limitation of many studies related to GI symptoms and/or motility in diabetes is that blood glucose concentrations at the time of testing were not measured let alone controlled. Data on the impact of chronic glycemic control, as assessed by glycated hemoglobin, on GI symptoms are limited and inconsistent (6). Whether the incidence of symptoms and disordered motility will diminish with improvement in chronic glycemic control remains to be determined.

ESOPHAGUS

Presentation and Prevalence

Esophageal motility disorders can present with symptoms of gastroesophageal reflux or dysphagia; other specific causes of dysphagia must be excluded. Patients with diabetes are at an increased risk for esophageal candidiasis, which may present with odynophagia. There is a high prevalence of esophageal dysmotility in diabetes, but only a minority of patients have symptoms (41). Gastroesophageal reflux also is frequently asymptomatic, particularly in the presence of established autonomic neuropathy (41). Esophageal dysfunction may result in regurgitation, dysphagia, and pill-induced esophageal erosions and strictures (41). Cough and worsening respiratory function may reflect undetected reflux disease. Whether the risk of Barrett esophagus is increased in diabetes is contentious, but in a large epidemiological study, type 2 diabetes was associated with a 49% increased risk independent of other known risk factors (42).

Pathophysiology

Scintigraphic and manometric studies indicate that esophageal motility and transit are abnormal in 40–60% of patients with long-standing diabetes, but the correlation with symptoms is weak (41). Biomechanical changes in the wall structure, including increased stiffness, reduced compliance, and diminished sensitivity to distension of the esophageal body, have been observed in long-standing diabetes, which correlated with symptoms of postprandial fullness/early satiety and were associated with peripheral neuropathy (43).

Diagnosis

The investigation of esophageal symptoms in patients with diabetes follows a similar approach to patients without diabetes. Reflux disease can be diagnosed on clinical grounds alone in the setting of typical symptoms; response to antisecretory therapy is an unreliable criterion (44). Endoscopy evaluates mucosal complications, whereas esophageal motor function can be assessed with manometry, and contrast video swallow radiology highlights both structural and functional disorders. pH studies may be useful in the assessment of gastroesophageal reflux with or without impedance monitoring, which allows transit of air and fluid to be evaluated (45).

Management

Dysphagia and gastroesophageal reflux disease (GERD) are treated similarly in diabetes as in the general population. Evidence is inconsistent about the efficacy of prokinetic drugs for treating symptoms attributable to dysmotility or acid reflux. Patients with delayed transit should drink a glass of water immediately after taking oral medications to reduce the risk of pill esophagitis.

STOMACH

Presentation and Prevalence

The broad term gastropathy sometimes is used to describe symptoms (including postprandial fullness, early satiety, bloating, nausea, vomiting, and upper abdominal pain [Table 1]) apparently referable to the stomach, irrespective of whether gastric emptying is abnormally slow (46). In contrast, gastroparesis can be defined as the objective finding of delayed gastric emptying without gastric outlet or duodenal obstruction (47); whether symptoms are required for the diagnosis is debated and has an important bearing on prevalence. For example, in a U.S. population-based study, the incidence of symptomatic gastroparesis over a 10-year period was ~5% in type 1 diabetes and 0.2% in controls (48), whereas follow-up of patients with long-standing type 1 diabetes from the Diabetes Control and Complications Trial (DCCT) showed that 47% had delayed gastric emptying, which was associated with GI symptoms, albeit weakly (49). Among patients with type 2 diabetes, obese women with longstanding, poorly controlled diabetes seem particularly predisposed (50). Gastric emptying and symptoms appear to be relatively stable as assessed by follow-up of small cohorts for up to 25 years (51). Other studies compared patients with intractable diabetic and idiopathic gastroparesis (52). Vomiting may be more prominent in the former: ~50% experience weight loss, although weight gain occurs in up to 25% (52); >50% with severe diabetic gastroparesis present with acute symptom onset; and the remainder experience insidious symptoms. About one-third have chronic symptoms with periodic exacerbations, and one-third experience chronic worsening symptoms (52). The clinician may find it helpful to consider clinically significant gastroparesis as delayed gastric emptying associated with symptoms, interfering with nutritional status and/or leading to abnormal changes in postprandial glycemic patterns (e.g., not matching the usual kinetics of rapid-acting insulin preparations and/or erratic peaks and troughs in plasma glucose concentrations).

Pathophysiology

The pathophysiology of symptoms in diabetic gastropathy is complex and includes not only delayed gastric emptying but also impaired gastric accommodation, visceral hypersensitivity, and gastric dysrhythmia (the stomach, like the heart, has a pacemaker) (38,46,53), although the association with any of these abnormalities is weak (46,53,54). Delayed gastric emptying should, therefore, be regarded as a marker of GI dysfunction rather than a direct cause of symptoms, and patients with typical symptoms may have rates of emptying in the normal range or that are even abnormally rapid (55).

The motor abnormalities associated with diabetic gastroparesis include impaired postprandial accommodation, antral hypomotility, excessive pyloric pressure, and disordered antroduodenal coordination (55). Impaired gastric accommodation may play a role in bloating (55), and the perception of gastric distension is increased in patients with type 1 diabetes with (55) and without (38) symptoms. The

availability of full-thickness gastric biopsy samples from patients with severe gastroparesis has demonstrated heterogeneous abnormalities (56), the most consistent of which is a reduction or loss of the interstitial cells of Cajal (the pacemaker cells), which correlates with the magnitude of the delay in gastric emptying (56); other abnormalities include immune infiltrates containing macrophages, decreased intrinsic nerve fibers, loss of neuronal nitric oxide synthase, and a thickened basal lamina around nerves and smooth muscle cells (56) (Fig. 1). Whether these changes represent most patients with delayed gastric emptying secondary to diabetes is uncertain.

Diagnosis

The determination of when to evaluate patients with diabetes and symptoms of gastropathy may be challenging, particularly given the recognition that upper GI symptoms occur frequently but are not strongly predictive of disordered gastric emptying. A history of vomiting food consumed many hours earlier is highly suggestive of gastroparesis but rare. The exclusion of the rumination syndrome, characterized by effortless regurgitation of food (47), is important. Physical examination is usually unremarkable, except in severe cases where gastric distension and/or a succussion splash may be found. Upper GI endoscopy usually is required to exclude gastric outlet or duodenal obstruction as well as mucosal disorders (47).

Measurement of gastric emptying before initiating therapy is appropriate. Many causes of gastroparesis exist apart from diabetes, including the use of medications (e.g., opioids); however, the withdrawal of medications that could slow gastric emptying is not always feasible. The gold standard technique for the measurement of gastric emptying is scintigraphy (47), with stable isotope breath testing being an alternative option (47). Progress has been made toward international standardization of scintigraphy, with a recommended meal of eggs, bread, and jam labeled with ^{99m}Tc-sulfur colloid and scintigraphic imaging at 0, 1, 2, and 4 h postprandially (47). Measurement of gastric emptying ideally should be performed during euglycemia and, at a minimum, with regular blood glucose monitoring (47). A diagnosis of gastroparesis can be made if meal retention is >90% at 1 h, 60% at 2 h, or 10% at 4 h (47). Stable isotope gastric emptying breath tests that use ^{13}C-labeled substrates (typically ^{13}C-octanoic acid or ^{13}C-*Spirulina platensis* [blue-green algae]) can be performed at the point of care, with subsequent centralized analysis of stored breath samples, and do not involve radiation exposure (57). This test relies on the assumption that gastric emptying is the rate-limiting step in the excretion of $^{13}CO_2$ after ingestion of a meal incorporating a ^{13}C substrate (57). The modification of the gastric emptying breath test by using the Wagner-Nelson method has strengthened the correlation with scintigraphy (58). Magnetic resonance imaging is a reliable, noninvasive method for evaluating gastric emptying and motility but remains a research technique (59). Other techniques for assessing gastric motility/emptying in diabetes are summarized elsewhere (57).

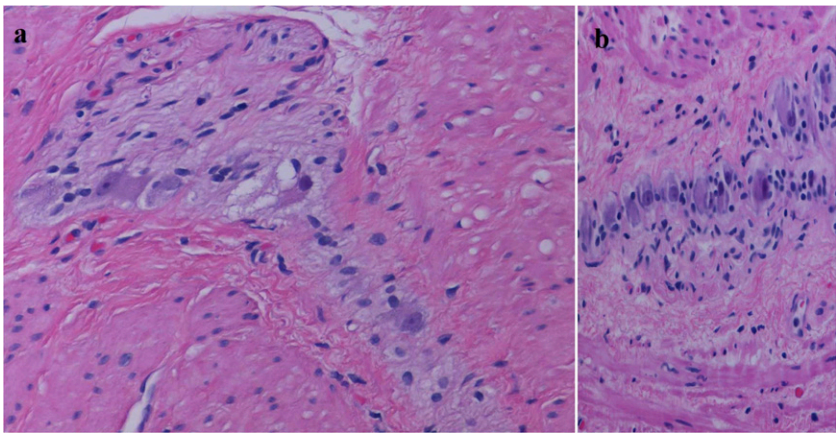

Figure 1—Hematoxylin and eosin staining of the intermyenteric plexus from patients with gastroparesis. *a*: Normal ganglia and nerve fibers (original magnification ×40). *b*: Moderate lymphocytic infiltrate in the intermyenteric plexus (original magnification ×40) in a patient with severe diabetic gastroparesis. Images reprinted with permission from Harberson et al. (56).

Management

Management of symptomatic diabetic gastroparesis should be individualized, influenced by the severity of symptoms (55), and may not necessarily focus on acceleration of gastric emptying (Fig. 2). Anecdotally, treatment is most effective with a multidisciplinary team, but outcomes often are suboptimal, perhaps reflecting the heterogeneous nature of the pathophysiology. Much of the evidence related to treatment of diabetic gastroparesis is also of poor quality, particularly for therapies that have been used for many years where formal reevaluation would now be considered unacceptable. Important goals of treatment in addition to symptom relief include improving nutritional status, addressing weight loss, and optimizing glycemic control.

Symptom improvement may be facilitated by nonpharmacological interventions, including dietary modifications, albeit without a robust evidence base. These include liquid-based or small-particle-size (55) meals (with the rationale that emptying of liquids often is less impaired than that of solids), reducing nondigestible fiber and fat, and having small, frequent meals. A trial of nasojejunal tube feeding should be considered in malnourished patients with refractory symptoms (55), which also allows the evaluation of response to enteral feeding before more permanent solutions, such as a percutaneous jejunal feeding tube, are considered. Ensuring adequate hydration and maintaining electrolyte balance is imperative. Although intuitively it is logical for glycemic control to be optimized (55), the efficacy of this is not established. Uncontrolled data, however, support the use of continuous subcutaneous insulin pump therapy in diabetic gastroparesis to improve glycemic control and reduce hospitalization (55).

Current pharmacological therapies for diabetic gastroparesis have limited efficacy and few head-to-head comparisons have been done. Some therapies aim to accelerate gastric emptying, whereas others strive for symptom control. Given that these two objectives do not usually correlate well, a focus on therapies with evidence of symptomatic benefit is appropriate.

Prokinetics most commonly used to treat gastroparesis include metoclopramide

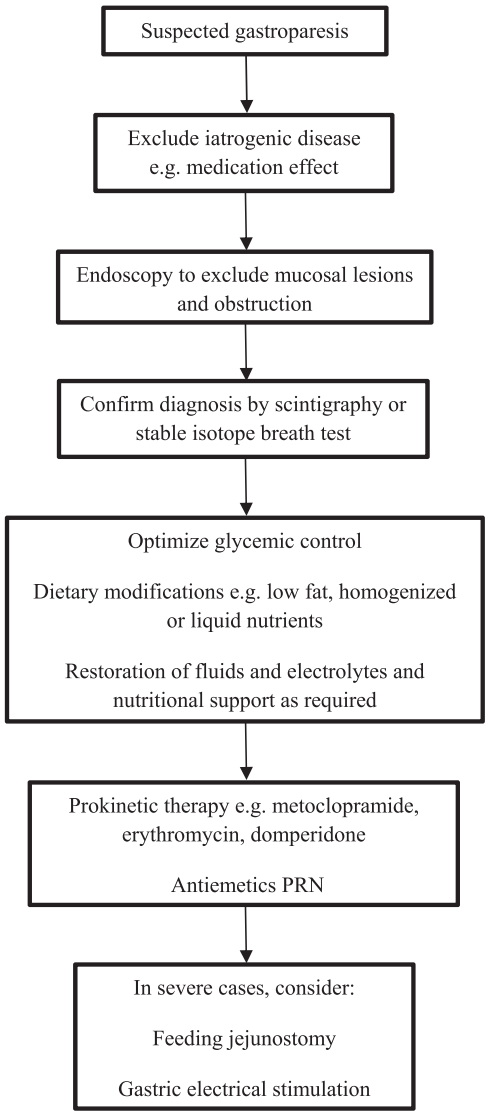

Figure 2—Treatment algorithm for diabetic gastroparesis. PRN, as needed.

(a dopamine D2 antagonist/5-HT4 agonist/5-HT3 antagonist) and erythromycin or azithromycin (both motilin agonists). Along with cisapride and domperidone, both have demonstrated symptomatic benefit in trials, although many of these trials were small, uncontrolled, and not performed exclusively in patients with diabetic gastroparesis. In general, these agents appear to reduce symptoms and accelerate gastric emptying by 25–70% (60). Concerns exist about adverse effects, including tardive dyskinesia with metoclopramide (which has led to an FDA black box warning highlighting this risk, especially in the setting of long-term or high-dose use) and prolongation of corrected QT interval with domperidone (not available in the U.S.) and metoclopramide; cisapride (a 5-HT4 agonist/5-HT3 antagonist) was withdrawn from the market in 2000 because of a risk of fatal arrhythmias. Furthermore, tachyphylaxis limits the use of agents such as metoclopramide and the motilin agonists (attributable to downregulation of the motilin receptor [61]), including erythromycin, for prolonged periods (62). Metoclopramide may be administered subcutaneously, potentially to abort acute attacks of vomiting (55), and as a nasal spray was recently reported to reduce symptoms referable to diabetic gastroparesis in women but not men (63). Anecdotal evidence suggests that antiemetics are useful in the management of nausea and that combining a prokinetic and antiemetic is common practice.

The motilin agonists are an ongoing focus of drug development. Parenteral administration of erythromycin (~3 mg/kg intravenously) may be useful in initial management (64). The outcome of a trial of a small-molecule motilin agonist, camicinal, in diabetic gastroparesis is awaited. Ghrelin, the first identified circulating hormone that controls hunger, also is involved in regulating gastric motility. Relamorelin, a subcutaneously administered pentapeptide ghrelin agonist, was shown to reduce vomiting and accelerate gastric emptying modestly compared with placebo (65), with results of another phase 2B trial pending publication. Newer 5-HT4 agonists have greater selectivity for the GI tract over cardiac muscle and include prucalopride, which has shown efficacy in preliminary studies in gastroparesis (66), and velusetrag, which accelerates gastric emptying in patients with chronic constipation (67) and is undergoing trials in gastroparesis. The tricyclic antidepressant nortriptyline was no better than placebo for symptom improvement in gastroparesis (68).

Pyloric interventions have been applied to the management of gastroparesis on the basis of observations of pylorospasm in some cases and the recognition that pyloric contractions play a major physiological role in regulating gastric emptying (55). Intrapyloric injection of botulinum toxin was not superior to placebo in two randomized controlled trials (69). Transpyloric stents, laparoscopic pyloroplasty, and gastric peroral endoscopic myotomy have been advocated on the basis of uncontrolled studies but require randomized sham-controlled trials to establish their efficacy.

Gastric electrical stimulation (Enterra Therapy; Medtronic, Minneapolis, MN) may improve symptom severity in refractory diabetic gastroparesis (69) and is approved in the U.S. as a compassionate treatment modality. Although one blinded trial failed to establish a difference in symptoms during randomized periods with the stimulator turned on or off (70), a recent multicenter French randomized controlled trial reported symptomatic benefit for vomiting in a cohort of patients with type 1 and type 2 diabetes when assigned to the stimulator being turned on (71). Uncontrolled data suggest that pancreatic transplantation may be associated with improvements in both symptoms and gastric emptying (72). Gastrectomy generally is not recommended (69).

The FDA recently provided clear guidelines for trials related to gastroparesis

(e.g., design, participants, outcome measures) (73), which has already led to substantial improvements in study quality (66). These guidelines include recommendations that patients with diabetic and idiopathic gastroparesis are not included in the same study and that blood glucose concentrations should be stable in diabetic gastroparesis (73).

SMALL AND LARGE INTESTINES

Pathophysiology

Small intestinal transit often is abnormal in patients with diabetes and may be slow or rapid (74); the former may predispose to small intestinal bacterial overgrowth (SIBO), itself a cause of malabsorption and diarrhea. Up to 80% of patients with diabetic gastroparesis have abnormal small intestinal motility (55). Loss of adrenergic innervation of the small intestine has been reported in diabetic rodent models and may contribute (75). Although large intestinal motility has been less well studied in diabetes, colonic transit often is delayed (74). Colonic tissue has revealed myenteric neuronal loss and evidence of increased oxidative stress (76). Anorectal dysfunction in diabetes encompasses impaired external anal sphincter function and diminished rectal sensation to distension (74). As with the upper GI tract, small intestinal and colonic motor function are influenced by acute changes in blood glucose (77).

Diagnosis

Medications always should be considered as the cause of diarrhea (see GI SYMPTOMS AND GLUCOSE-LOWERING DRUGS). The gold standard for the diagnosis of SIBO is jejunal fluid aspiration and culture, but this requires endoscopy and a potential exists for oropharyngeal contamination and false-negative results if patchy overgrowth is missed. Noninvasive methods of diagnosis include hydrogen breath tests, which are reasonably specific (80%) but lack sensitivity (40%) (75) because some bacteria do not produce H_2 from glucose. Celiac disease occurs in 1% of the general population and is approximately five times more prevalent in type 1 diabetes (78), so serological screening is justified in this population, even in the absence of symptoms. Pancreatic exocrine insufficiency also must be considered, particularly because the prevalence of pancreatitis is increased two to four times. Although fecal elastase levels have been reported to be reduced in up to one-third of patients with type 1 and 2 diabetes (75), evidence that supports the use of pancreatic enzymatic replacement is lacking particularly because the majority of patients do not have clinically significant exocrine insufficiency (75). Microscopic colitis may be more prevalent in diabetes (75) and is diagnosed with colonoscopic biopsy. Otherwise, causes of diarrhea that affect the general population, including common causes such as IBS, also can affect patients with diabetes.

The diagnostic approach to constipation and fecal incontinence in diabetes is similar to that for the general population. Red flags for malignancy should dictate careful investigation. Medications that could induce constipation, such as opiates, anticholinergics, and calcium channel blockers, must be recognized as potential causative agents. Investigation with anorectal manometry to identify a defecatory disorder and/or a radiopaque marker test to identify slow transit constipation may be warranted (79).

Management

As with the upper GI tract, the general principles of management involve correction of fluid and electrolyte deficits, improvement of nutritional status, optimization of glycemic control, treatment of specific causes if found, and symptom relief. Antibiotics, such as rifaximin (the most studied antibiotic in the context of bacterial overgrowth), eradicate bacterial overgrowth in up to 84% of patients after 10–14 days of therapy (80) and improve symptoms in 30–90%. Other antibiotics, including amoxicillin-clavulanate, doxycycline, quinolones, and metronidazole, are widely used, largely on an empirical basis. SIBO may recur if attention is not also given to the underlying motility disorder. Pancreatic enzyme supplementation should be tried in patients with clear evidence of exocrine insufficiency; besides the potential for improving steatorrhea/diarrhea, beneficial effects may occur from postprandial glycemic control as a result of restoration of the hormonal feedback (including incretin release) from the small intestine, although Knop et al. (81) found no difference in postprandial glucose despite increases in GLP-1, glucose-dependent insulinotropic polypeptide, and insulin after pancreatic enzyme supplementation.

Symptomatic relief of diarrhea may require opioid medication, although judicious use for limited periods is advisable. Loperamide, which acts on μ-opioid receptors, reduces diarrhea and slightly increases internal sphincter tone and may be helpful in preventing fecal incontinence, especially when outside the home (82). Eluxadoline, which acts on diverse opioid receptors, has recently been approved by the FDA for the management of diarrhea associated with IBS (83). Tricyclic antidepressants may be beneficial because of their anticholinergic properties. Case reports have supported the efficacy of somatostatin analogs in otherwise refractory, apparently secretory, diarrhea in patients with autonomic neuropathy (84). Clonidine, an α-2-adrenergic RA is effective in the treatment of refractory diarrhea (85), but patients must be monitored for hypotension, especially when dehydrated.

Constipation may respond to a high-fiber diet or traditional laxatives such as lactulose. Few pharmacological agents have been specifically evaluated. Lubiprostone, a prostaglandin derivative that activates chloride channels, has been shown to increase spontaneous bowel movements and decrease colonic transit time in patients with diabetes and constipation over an 8-week period (86). Linaclotide, which acts through guanylate cyclase C, is FDA approved for the management of constipation but has not been evaluated specifically in diabetes.

GI SYMPTOMS AND GLUCOSE-LOWERING DRUGS

Several diabetes-specific medications, including metformin, α-glucosidase inhibitors, and, more recently, the amylin analog pramlintide and GLP-1 RAs are strongly associated with GI adverse effects (Fig. 3). As discussed, these studies have almost exclusively assessed symptoms by self-report, compromising data interpretation. Whether preexisting GI symptoms increase the propensity for adverse GI effects from these drugs remains to be determined.

The capacity of metformin to cause GI symptoms is well-recognized. Diarrhea appears to be most common, followed by nausea, flatulence, indigestion, vomiting, and abdominal discomfort (87). Rates of diarrhea resulting from immediate-release metformin were 8–24% in trials involving treatment-naive patients, and 20–60% in real-world observational studies (87). Diarrhea is usually not nocturnal

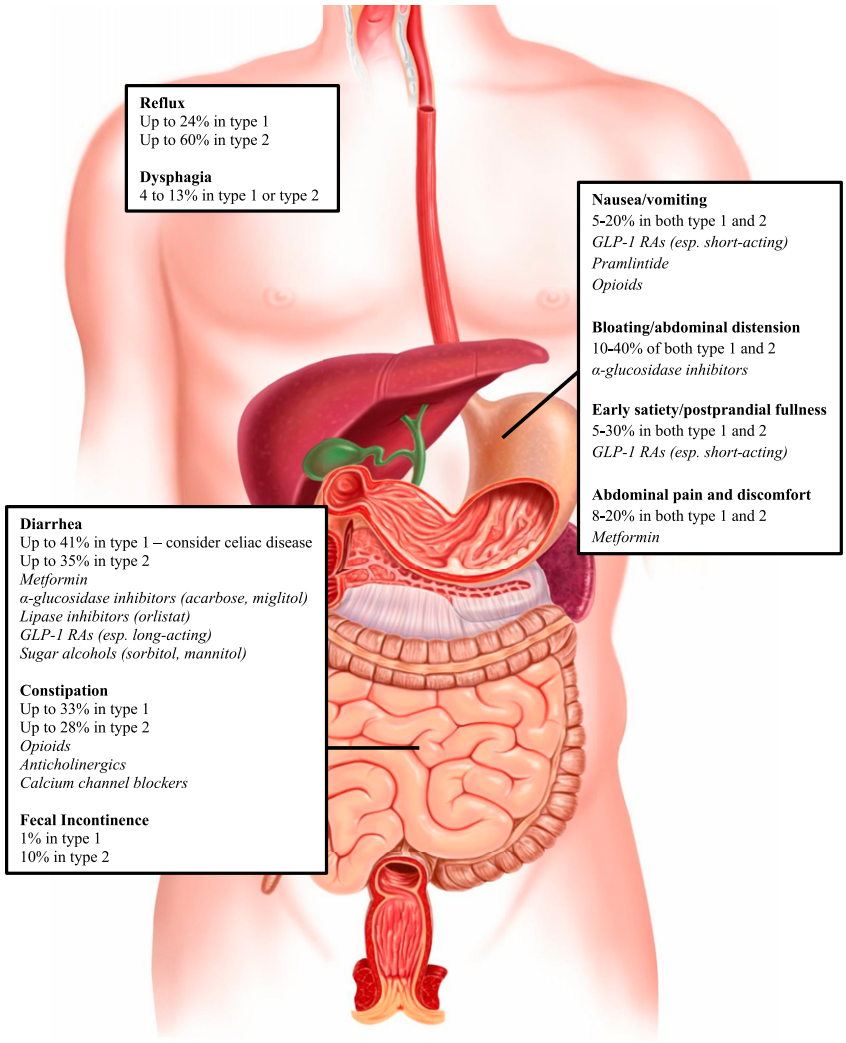

Figure 3—Prevalent GI symptoms in type 1 and 2 diabetes, and medications for diabetes with which they may be associated.

or strongly dose related, ceases when therapy is withheld, and occurs typically at initiation of treatment (87). Increasing evidence shows that metformin's main site of action is the gut rather than the liver (87). Putative mechanisms for GI symptoms include effects on the microbiome, intestinal glucose turnover, bile salt malabsorption, and stimulation of GLP-1 (87). Comorbidities, including asymptomatic chronic gastritis and *H. pylori* infection, and other diabetes medications may increase the potential for GI symptoms with metformin (87). Moderate-quality evidence shows that switching to extended release metformin may alleviate GI intolerance to the immediate release formulation (87). More recently, the once-daily delayed-release metformin, by achieving similar efficacy as metformin extended release but at much lower dose and plasma exposure, holds promise in causing fewer GI symptoms, but this has yet to be convincingly borne out in trials (87).

The α-glucosidase inhibitors (e.g., acarbose, miglitol) frequently induce GI symptoms, including flatulence, loose stools, abdominal distension, and diarrhea (88), reflecting the presence of undigested complex carbohydrates in the large intestine, which undergoes bacterial fermentation with production of short-chain fatty acids and hydrogen (88). In clinical trials, the prevalence of GI symptoms with acarbose has varied widely; symptoms tend to subside with continued treatment and adherence to dietary restrictions (88). Lipase inhibitors such as orlistat and sugar alcohols such as sorbitol and mannitol also may cause diarrhea (75).

Pramlintide, a synthetic analog of amylin (cosecreted with insulin from β-cells) was FDA approved in 2005 for use in both type 1 and 2 diabetes and slows gastric emptying markedly (89). Nausea occurs in 10–60% of cases, particularly with higher doses, but is usually transient (90).

GI symptoms are the most commonly reported adverse effect of GLP-1 RAs, although they are usually transient. GI adverse effects only infrequently (1–6%) necessitate cessation of treatment (26), but this figure may be higher (up to 15%) (89). Nausea is apparently the most common adverse effect, which was reported in up to 50% of subjects in clinical trials (26). Vomiting and diarrhea occur in ~5–20% (26). A recent systematic analysis (91) indicated that nausea and vomiting are dose dependent, occur more frequently with short- rather than long-acting GLP-1 RAs, and occur when metformin is used concurrently. In contrast, diarrhea is apparently not dose dependent and occurs more often with longer-acting compounds (91). Higher rates of nausea and vomiting with short- than with long-acting GLP-1 RAs are unlikely related to differences in their effects on gastric emptying (i.e., more marked and sustained slowing with short-acting drugs [26]), particularly given the weak association between upper GI symptoms and delayed gastric emptying (53); rather, nausea probably is primarily centrally mediated (26). Accordingly, differences among compounds may reflect the greater propensity for smaller molecules (e.g., exenatide, liraglutide, lixisenatide) to cross the blood-brain barrier compared with larger molecules (e.g., albiglutide) (26). GLP-1 RAs also may activate the CNS indirectly through peripheral receptors on the vagus nerve (92). How GLP-1 RAs induce diarrhea is not well understood, although effects on small intestinal motility may be relevant (26).

CONCLUSIONS

GI symptoms occur frequently and have a substantial impact on quality of life in people with diabetes. Symptoms may not be volunteered and should be specifically elicited and quantified by using validated measures. The underlying pathophysiology of symptoms is heterogeneous and poorly understood, which has major implications for effective diagnosis and management. Dietary and pharmacological strategies to achieve glucose lowering in type 2 diabetes are increasingly used. For a number of drugs,

an association with GI symptoms has been established and may, in some cases, lead to cessation of therapy. However, interpretation of the outcomes of the majority of studies is compromised by the suboptimal assessment of symptoms that use self-reported rather than validated measures.

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