

During GE scintigraphy, postprandial scans at 1 hour can identify accelerated GE, while scans at 2 and 4 hours distinguish normal function from delayed GE with a sensitivity of 90% and a specificity of 70% (40). For solid-phase testing, most centers use a ^{99m}Tc sulfur colloid-labeled egg sandwich as the test meal, with imaging at 0, 1, 2, and 4 hours. The Society of Nuclear Medicine and the American Neurogastroenterology and Motility Society recommend a 4-hour test using a radiolabeled EggBeaters® meal with jam, toast, and water (41). Sometimes there is a discrepancy between test results, i.e., patients have retained food at endoscopy but normal GE by scintigraphy. This discrepancy may be explained by day-to-day variations in GE, the use of medications (e.g., opioids) that can delay GE before either study, ingestion of food before an endoscopy, or differences between the gastric motor mechanisms responsible for antral motility and emptying of smaller particles during scintigraphy (i.e., type 2 antral motor activity) and indigestible larger particles (i.e., ≥ 3 mm size) ingested with meals, which are emptied by the antral component of the migrating motor complex during fasting or sleeping.

Gastric emptying breath tests (GEBT) offer an alternative approach for measuring solid phase GE. The meal includes *Spirulina platensis* or the medium chain triglyceride octanoate enriched with ^{13}C , which is a stable isotope. After GE and duodenal digestion, ^{13}C is released from the substrate, exhaled, and measured by isotope ratio mass spectrometry, allowing GE $t_{1/2}$ to be calculated (42,43,44). In contrast to scintigraphy, GEBT does not require elaborate detection equipment or entail radiation exposure and can be performed at the point of care, as in the office or bedside, because the collected breath samples are collected simply with a straw and sealable container, and the excreted $^{13}\text{CO}_2$ is stable. A ^{13}C -spirulina GEBT has been approved for use in the United States by the Food and Drug Administration.

GE can also be measured by a nondigestible capsule, SmartPill® wireless motility capsule, which records luminal pH, temperature, and pressure during GI transit, providing a measure of GE time. In the pivotal study, GE measured by a capsule and by scintigraphy at 4 hours were significantly correlated with a coefficient of 0.73 (45). Compared to scintigraphic emptying at 4 hours, the capsule had 86% sensitivity and 92% specificity for diagnosing gastroparesis. After initial testing to identify disturbances of transit, more detailed testing with intraluminal techniques (i.e., antro-pyloroduodeno-jejunal manometry) may be useful for characterizing motor dysfunctions and guiding therapy (16). Autonomic function tests are useful for identifying autonomic dysfunctions (e.g., vagal neuropathy) that are associated with gastroparesis. Reduced variability of the cardiac RR interval provides a simple screening assessment of vagal dysfunction (46).

Management. The principles of gastroparesis management are to address fluid and nutritional requirements, improve glycemic control, and treat symptoms. These measures have been summarized in guidelines (47).

Diarrhea

Definition. Diabetic diarrhea is defined by loose and frequent stools, generally more than three bowel movements daily in patients with diabetes.

Epidemiology. Some, but not all, population-based studies, which have been exclusively based on type 2 diabetes (4,5) or combined both patients with type 1 diabetes and type 2 diabetes (8), reported a higher prevalence of diarrhea in patients with diabetes than in nondiabetic controls (Table 27.1). For example, in a sample of 423 patients with predominantly (95%) type 2 diabetes, 15.6% reported diarrhea or constipation versus 10% of nondiabetic controls (4). A systematic review of all English-language observational studies and trials from inception through April 2010 highlighted the known link between metformin and diarrhea (48). For example, among 5,021 participants in

five randomized controlled trials, the incidence of diarrhea was higher for subjects treated with metformin (15%–24%) than for those treated with thiazolidinediones (3%–8%) (48). Likewise, the incidence was higher for metformin (2.5%–50%) than for sulfonylureas (0%–13%) treatment (48). No systematic assessments have been conducted of the clinical features, risk factors, or natural history of diabetic diarrhea.

Diagnostic Tests. If diarrhea cannot be attributed to metformin or ingestion of incompletely absorbed carbohydrates, further assessment should be considered, particularly in type 1 diabetes. Drugs used in diabetes may also result in diarrhea (49). The association between type 1 diabetes and CD is considered separately in this chapter. A 24-hour stool collection to quantify stool weight and fat content should be performed to identify fat malabsorption. While CD and bacterial overgrowth can cause malabsorption, testing for these conditions should be considered even when stool examination does not reveal malabsorption. A duodenal aspirate to assess for bacterial overgrowth and duodenal biopsies to exclude CD can be obtained at upper GI endoscopy. While lactulose or glucose hydrogen breath tests are widely used to identify bacterial overgrowth, their use is limited, since rapid delivery of the substrate to the colon can also give rise to an early breath hydrogen peak (50).

Management. Diabetic diarrhea is treated symptomatically with loperamide, preferably administered 30 minutes before meals, in the dose range of 2–16 mg per 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 (51) or by patch in patients who do not experience significant postural hypotension. 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 (52) and may also reduce secretory diarrhea associated with rapid intestinal transit

TABLE 27.13. Growth and Glycemic Control in Patients With Type 1 Diabetes With Treatment of Celiac Disease

LOCATION, YEARS (REF.)	NUMBER OF PATIENTS STUDIED	GROWTH AT DIAGNOSIS OF CD		EFFECT OF GFD ON GROWTH		GLYCEMIC CONTROL (A1C)	
		Weight	Height	Weight	Height	At Diagnosis	On a GFD
Finland, 1994–1999 (150)	18	↓	→	↑	→	→	→
Germany, Austria, 1985–2002 (161)	127	↓	↓	→	→	↓	→
Australia, 1989–1999 (156)	21	↓	↓	↑	→	-----	→
Denmark, 1997, 2002–2003 (152)	28	↓	↓	↑	↑	→	→
United States, NR (112)	30	↓	→	↑	↑	-----	-----
United Kingdom, 1998–2006 (145)	22	→	-----	↑	→	-----	-----
Austria, Germany, 1995–2009 (162)	183	↓	↓	→	→	→	→
Israel, 1983–2008 (153)	68	→	→	→	→	→	→
Germany, 1994–1999 (151)	9	→	→	→	↑	→	→
Australia, 1990–2010 (163)	129	-----	-----	-----	-----	↓	↓*

↓, decreased; →, no change; ↑, increased; -----, no data; A1c, glycosylated hemoglobin; CD, celiac disease; GFD, gluten-free diet; NR, not reported.

* Compared to those nonadherent to a GFD.

SOURCE: References are listed within the table.

These conditions are associated with inflammatory injury of usually the distal small intestine and/or colon. Ulcerative colitis only affects the large intestine. IBD and type 1 diabetes share some genetic predispositions (120). Despite that, there is only a weak positive association between ulcerative colitis and type 1 diabetes, and in particular, this is seen for pediatric IBD. The odds ratio for diabetes in pediatric-onset IBD is 2.7 (95% CI 1.1–6.6) (121). In two larger datasets, the IMS Health Integrated Queens Database and the Market Scan Commercial Claims and Encounters Database, no association was seen between IBD and type 1 diabetes (122). A secondary association was reported from the Multigeneration Registry Study in Sweden showing that the risk of type 1 diabetes was increased modestly in offspring of parents with ulcerative colitis with a standardized incidence ratio of 1.23, though this was less than that of CD at 2.73 (123).

The treatment, especially for ulcerative colitis, often is based on the use of corticosteroids. Studies that report the development of diabetes in patients with ulcerative colitis generally have little data measuring the actual risk. While it is well recognized that the chronic use of corticosteroids substantially increases the risk of diabetes, there are relatively few case-control studies and very few data for patients with IBD. In one case-control

series of 55 adult patients with active Crohn's disease, treatment with systemic corticosteroids substantially increased the risk of hyperglycemia (124), though the confidence intervals overlapped 1.0. There are very few data regarding the risk of diabetes in patients with IBD treated with corticosteroids.

AUTOIMMUNE GASTRITIS

Autoimmune gastritis can also be associated with type 1 diabetes because of a common genetic background or tendency to autoimmunity (125,126). Autoimmune gastritis is a T cell-mediated disease marked by the presence of autoantibodies directed against the H+/K+ ATPase in the parietal cells of the stomach. This tissue-specific autoimmunity can result in reduction of acid production in the stomach, hypochlorhydria, and iron deficiency. The gastric mucosa can become atrophic. Consequent to the loss of ability of the parietal cells to produce acid, the neuroendocrine cells of the stomach reduce the negative regulation that is exerted by the acid pH via somatostatin, thereby leading to unrestrained gastrin secretion. Hypergastrinemia may be seen in 7% of patients with type 1 diabetes (127). Vitamin B12 deficiency is uncommon, though it can occur in patients with markers for pernicious anemia (127).

This hypersecretion of gastrin leads to hypertrophy of enterochromaffin cells in the stomach, which in turn can lead to carcinoid development (128). The loss of parietal cell mass leads to reduced digestive acid that is needed for effective cleavage of vitamin B12 from food sources and also reduces intrinsic factor production. Both lead to vitamin B12 deficiency (i.e., pernicious anemia) (125). The acid-producing cells of the stomach also produce pepsinogen, which is activated by low pH to aid in digestion.

Diagnosis

Atrophic gastritis can be detected by the identification of parietal cell antibodies (PCAs) or, more recently, the ATP4A autoantibody (129) in the serum, low serum pepsinogen I, the demonstration of atrophy of the gastric body mucosa on endoscopic biopsies, and often by very high levels of gastrin in the fasting state. Autoantibodies may exist long before the results of loss of parietal cell mass and function become apparent in the form of iron and vitamin B12 deficiency. While noninvasive tests may suggest atrophic gastritis, biopsies are needed for confirmation and to distinguish from other forms of gastritis. Other consequences, such as small intestinal bacteria overgrowth and calcium malabsorption, may also occur.

Autoimmune Gastritis in Type 1 Diabetes

Several cross-sectional studies have documented a three to five times increased prevalence of autoimmune gastritis in patients with type 1 diabetes compared with healthy controls from the general population (Table 27.14). Much less data are available on the natural history of autoimmune gastritis in type 1 diabetes (127), however, suggesting that many patients with PCA may not progress to parietal cell organ failure. Pernicious anemia, the classic endpoint of autoimmune gastritis, may take years or decades to become evident.

Duration of diabetes, independent of age, does not appear to be associated with likelihood of atrophic gastritis. Females have somewhat greater risk than males, though studies do not always agree. African Americans seem to be equally likely to have PCA as whites (130).

TABLE 27.14. Epidemiologic Studies of Autoimmune Gastritis in Type 1 Diabetes

LOCATION, YEARS (REF.)	STUDY POPULATION	NUMBER IN STUDY	PARIETAL CELL ANTIBODY	KEY FINDINGS
United States				
NR (164)	Referral population with type 1 diabetes (age 2–30 years)	771	9% PCA positive, F>M	6/11 PCA positive had achlorhydria
NR (165)	Cohort children	211	10 PCA positive, 3/4 biopsied	
NR (130)	Consecutive cohort children and adults	1,696	186 PCA positive (11%)	Equal in blacks; slight female predominance
Europe and rest of world				
Finland, NR (166)	Referral population, diabetic children	147	8 PCA positive	Hypochlorhydria
Belgium, 1998–2000 (126)	Community cohort, adults	229	69 PCA positive	Associated with <i>H. pylori</i> , HLA, hypergastrinemia, iron deficient anemia
United Kingdom, NR (167)	Children and adults	366	48 PCA positive	Mixed group
Spain, 2001–2006 (127)	Cohort adults	168	44 PCA positive	11 also had low PI, 96% DQ2

DQ2 is defined by the carriage of the gene pair DQA1:05.DQB1:02. HLA, human leukocyte antigen; NR, not reported; PCA, parietal cell antibody; PI, pepsinogen I.

SOURCE: References are listed within the table.

LIST OF ABBREVIATIONS

A1c glycosylated hemoglobin	HR hazard ratio
CD celiac disease	IBD inflammatory bowel disease
CI confidence interval	IDR incident death rate
GE gastric emptying	IgA immunoglobulin A
GEBT gastric emptying breath tests	IgG immunoglobulin G
GFD gluten-free diet	LADA latent autoimmune diabetes of adults
GI gastrointestinal	PCA parietal cell antibody
HLA human leukocyte antigen	TTG tissue transglutaminase

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CONVERSIONS

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

DUALITY OF INTEREST

Drs. Bharucha, Locke, and Murray reported no conflicts of interest.

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