CHAPTER 27

# GASTROINTESTINAL MANIFESTATIONS OF DIABETES

*Adil E. Bharucha, MD, G. Richard Locke, MD, and Joseph A. Murray, MD*

*Dr. Adil E. Bharucha is Professor of Medicine and Dr. G. Richard Locke is Professor of Medicine, and both are consultants in the Division of Gastroenterology and Hepatology and the Clinical Enteric Neuroscience Translational and Epidemiological Research Program, and Dr. Joseph A. Murray is Professor of Medicine and a consultant in the Division of Gastroenterology and Hepatology, Gastroenterology Research Unit and Department of Immunology, Mayo Clinic, Rochester, MN.*

## SUMMARY

Although most attention has traditionally focused on the stomach, diabetes can affect the entire gastrointestinal (GI) tract, as implied by the term diabetic *enteropathy*. This chapter details the epidemiology and summarizes the salient features of the pathophysiology, clinical features, and management of diabetic enteropathy.

Diabetic enteropathy may be asymptomatic or manifest with upper (i.e., heartburn, dysphagia, dyspepsia, gastroparesis) or lower GI symptoms (i.e., diarrhea, constipation, and fecal incontinence). GI symptoms are not uncommon (abdominal pain experienced in 7.6%, vomiting in 1.7%) in patients with diabetes presenting for care. However, in community studies, the prevalence of GI symptoms is, for the most part, either not different or only slightly higher in type 1 and type 2 diabetes than in people without diabetes. For example, 17% of persons with type 1 diabetes and 14% of those without diabetes had constipation in one study.

Limited data are available on the epidemiology, particularly risk factors, and natural history of these specific GI manifestations among patients with diabetes in the community. For example, the risk of developing gastroparesis over 10 years was 5% in type 1 diabetes and 1% in type 2 diabetes versus <1% in persons without diabetes. GI dysmotility in diabetes is multifactorial: extrinsic and intrinsic (i.e., enteric) neural dysfunction, hyperglycemia, and hormonal disturbances have been implicated. Delayed gastric emptying in diabetes is often asymptomatic and is associated with impaired glycemic control.

Approaches to manage diabetic enteropathy primarily focus on correcting the motor disturbance, symptom relief, managing complications, and improving glycemic control. However, there is no evidence that improving glycemic control is beneficial in diabetic enteropathy. From a public health perspective, further studies to better understand the risk factors for diabetic enteropathy and the relationship between diabetic enteropathy and impaired glycemic control and to develop novel approaches to managing diabetic enteropathy are critical.

Type 1 diabetes is associated with gluten-sensitive enteropathy (also known as celiac disease [CD]). CD is very common (approximately 5%) in patients with type 1 diabetes, is often overlooked clinically, and may be asymptomatic while patients accrue health consequences, including growth retardation, bone demineralization, and eventually, symptoms. CD is readily detectable, and at the very least, those looking after patients with type 1 diabetes should have a very low threshold for testing. Screening at initial diabetes diagnosis and yearly for at least 5 years later should be considered in children and at least once in adults. Conversely, there is also a twofold increase in type 1 diabetes in patients with a prior diagnosis of CD (hazard ratio 2.4, 95% confidence interval 1.9–3.0).

Gastric autoantibodies are common in type 1 diabetes and can lead to progressive loss of parietal cell mass and hypochlorhydria (low stomach acid) in a significant percentage of patients. It behooves the physician to be aware of this association and vigilant of its consequences as the patient ages.

In summary, studies suggest the prevalence of selected GI symptoms (e.g., constipation) are greater in individuals with diabetes than in controls. For other symptoms, the prevalence is generally not different in persons with diabetes compared to those without. Further studies are necessary to accurately estimate the prevalence of GI symptoms in people with diabetes and to identify the risk factors for these symptoms.

*Received in final form August 20, 2015.*

## INTRODUCTION

Although most attention has traditionally focused on the stomach, diabetes can affect the entire gastrointestinal (GI) tract, as implied by the term diabetic *enteropathy*. This chapter details the epidemiology and summarizes the salient features of the pathophysiology, clinical features, and management of diabetic enteropathy.

This chapter does not address the relationship between diabetes and certain chronic liver diseases and gallstone disease, which can be found in Chapter 26 *Liver and Gallbladder Disease in Diabetes*. In addition, this chapter does not discuss pancreatitis leading to diabetes, which is covered in Chapter 6 *Other Specific Types of Diabetes*, or pancreatitis in those with diabetes, which is very infrequent, but for which diabetes may be a risk factor (1,2). Information on diabetes and cancers, including those of the GI tract, is presented in Chapter 29 *Cancer and Diabetes*.

## DATA RESOURCES AND THEIR LIMITATIONS

There are no national studies on the epidemiology of GI symptoms and sensory motor disturbances in diabetes. The understanding of these issues is primarily derived from the Rochester Epidemiology Project and other community-based studies that are described in the individual sections.

The Rochester Epidemiology Project resides in Olmsted County, Minnesota. The Olmsted County population comprises approximately 100,000 persons, of whom 96% are white; sociodemographically, the community is similar to the U.S. white population (3). In Olmsted County, 80% of the population resides within 5 miles of Rochester, and residents receive their medical care almost exclusively from two group practices, Mayo Medical Center and Olmsted Medical Center. Annually, more than 80% of the entire population is attended by one or both of these practices, and nearly everyone is seen at least once during any given 3-year period (3). A unique medical record linkage system, the Rochester Epidemiology Project, enables this population to be enumerated, allowing samples to be drawn.

Studies from Australia were primarily conducted in randomly selected adults age ≥18 years who were on the electoral rolls for Penrith and the Blue Mountains areas west of Sydney, Australia (4,5) and in another cohort of randomly selected subjects from the mailing list of Diabetes Australia, a nonprofit organization that provides informational support to some 100,000 individuals with diabetes (6). While the Olmsted County studies included people with type 1 and 2 diabetes, the studies from Australia were predominantly conducted in people with type 2 diabetes.

## FUNCTIONAL GASTROINTESTINAL DISTURBANCES AND SYNDROMES

### GASTROINTESTINAL SYMPTOMS: PREVALENCE AND RISK FACTORS

Studies conducted in selected patient groups, often at tertiary referral centers, suggest that GI symptoms are common in persons with diabetes. However, these studies are prone to selection and other biases. In community studies, which avoid these biases, the prevalence of GI symptoms is, for the most part, either not different or only slightly higher than in people without diabetes (Tables 27.1–27.3).

Thus, in the Rochester Diabetic Neuropathy Study, only 1% of diabetes patients had symptoms of gastroparesis, and only 0.6% had nocturnal diarrhea (Table 27.1) (7). In another study from Olmsted County, Minnesota, the prevalence of upper or lower (i.e., irritable bowel syndrome, constipation, and fecal incontinence) GI symptoms was not significantly different between individuals with either type 1 or type 2 diabetes and age-matched controls (Table 27.1) (8). However, laxative use, and hence the combination of constipation and/or laxative use, was more common in persons with type 1 diabetes (27.0%) than controls (19.0%) but similar in those with type 2 diabetes (17.0%) and controls (15.0%) (Table 27.2) (8). Calcium channel blockers, female sex, and higher psychosomatic symptom scores were associated with constipation and/or laxative use (8). While the prevalence of constipation and/or laxative use was more common in type 1 diabetic individuals than controls, the higher prevalence was influenced by sex and psychosomatic symptom checklist score. The latter is a measure of physical symptoms (e.g., low back pain, high blood pressure) that might be related to stress. In males, but not females, with type 1 diabetes, constipation and/or laxative use were more prevalent than in sex-matched controls even after adjusting for psychosomatic symptom checklist score and regardless of the use of constipating drugs.

Two studies (i.e., from Olmsted County and a Finnish population) reported that people with type 1 diabetes had a lower prevalence of heartburn (8,9). In contrast, a study from Australia found that the prevalence of several upper and lower GI symptoms was higher in 423 patients with predominantly (95%) type 2 diabetes than in controls (Table 27.1 and Table 27.3) (4).

Taken together, these data suggest that GI manifestations are common among patients with diabetes presenting for care. However, in the general population, the prevalence of GI manifestations is not substantially higher among people with diabetes compared to matched controls, perhaps partly because the prevalence of GI symptoms, mostly attributable to functional GI disorders (e.g., irritable

**TABLE 27.1.** Community-Based Epidemiologic Studies of Gastrointestinal Symptoms in Diabetes

| YEARS (REF.) | RESPONDENTS | RESPONSE RATE (NUMBER OF RESPONDENTS) | KEY FINDINGS | |
|---|---|---|---|---|
| | | | Upper GI | Lower GI |
| 1986 (7) | Residents of Rochester, Minnesota, with diabetes | 44% (102 type 1 diabetes, 278 type 2 diabetes) | Gastroparesis:<br>0% type 1 diabetes<br>1% type 2 diabetes | Diarrhea: 0.6% overall<br>1% type 1 diabetes<br>0.4% type 2 diabetes |
| 1982–1984 (9) | All residents in a hospital district in Finland with diabetes and a randomly selected control group | 92%–100% (89 type 1 diabetes, 481 type 2 diabetes, 635 controls) | Symptoms of nausea and vomiting were not different between cases with diabetes and controls. | Diarrhea was not different from controls. |
| 1995 (8) | Samples of Olmsted County, Minnesota, residents with type 1 and type 2 diabetes and corresponding age- and sex-stratified controls | 59% (138 type 1 diabetes, 217 type 2 diabetes, 388 controls) | No difference in proportions with stomach symptoms was found between diabetes and controls; less heartburn was reported by type 1 diabetes patients. | Constipation:<br>17% type 1 diabetes vs. 14% controls<br>10% type 2 diabetes vs. 12% controls<br>Diarrhea:<br>0% for all groups<br>Fecal incontinence:<br>0.7% type 1 diabetes vs. 1.2% controls<br>4.6% type 2 diabetes vs. 1.8% controls |
| 1999 (4,5) | Sex-stratified sample of 15,000 people in Sydney, Australia | 60% for entire sample (423 of 8,555 respondents had diabetes, 95% had type 2 diabetes) | Small differences were detected with the highest adjusted odds ratio for vomiting, 1.7% vs. 1.1% (OR 2.51). When upper gut dysmotility symptoms were evaluated, the results were 18.2% vs. 15.3% (OR 1.75). | Diarrhea or constipation:<br>15.6% diabetes vs. 10% controls<br>Fecal incontinence:<br>2.6% diabetes vs. 0.8% controls |
| NR (6) | Two surveys of subjects with type 2 diabetes on the mailing list of Diabetes Australia at a 3-year interval | 64% returned second survey (892 type 2 diabetes in first survey) | Not applicable | Similar symptom prevalence for first (second) surveys<br>Abdominal pain:<br>7.6% (8.3%)<br>Constipation:<br>25.7% (23.7%)<br>Diarrhea:<br>2.6% (2.2%)<br>Fecal incontinence:<br>7.2% (diabetes) vs. 7.2% |
| 1995–2006 (31) | Follow-up of 1,413 subjects (269 with type 1 diabetes, 409 type 2 diabetes) and 735 controls matched for age and sex in Olmsted County, Minnesota | 87% (1,226 subjects) authorized review of medical records; questionnaires at interviews were not performed. | Over 10 years, gastroparesis developed in 5.2% (type 1 diabetes), 1% (type 2 diabetes), and 0.2% (controls). Higher risk (HR 4.4, 95% CI 1.1–17) was found in those with type 1 versus type 2 diabetes. | |

All surveys used a mailed questionnaire. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NR, not reported; OR, odds ratio.

SOURCE: References are listed within the table.

bowel syndrome), among people without diabetes in the community is relatively high and approaches 10% (10).

## FUNCTIONAL GASTROINTESTINAL DISORDERS

Gastrointestinal dysmotility in diabetes is multifactorial: a role for extrinsic (i.e., sympathetic and parasympathetic) neural dysfunction, hyperglycemia, hormonal disturbances, and even intrinsic (i.e., enteric) neural dysfunction, which results from loss of excitatory and inhibitory neurons and interstitial cells of Cajal, have been implicated (11). Studies in animal models demonstrate that neural dysfunctions are attributed to several mechanisms (e.g., hyperglycemia, oxidative stress) (12). The specific GI disturbances contributing to gastroparesis, diarrhea, dysphagia and heartburn, constipation, abdominal pain, and fecal incontinence are covered in subsequent sections.

In addition to these factors, it is also important to consider the role of psychological factors in the perception of GI symptoms. Indeed, anxiety and depression are significantly associated with the reporting of GI tract symptoms in the community and in case series (8,13,14,15). Likewise, anxiety and depression are not related to the severity of gastric retention and independently predict symptom severity in diabetic gastroparesis (14,15). This may also partly explain the similar prevalence of symptoms between people with diabetes and controls in population-based studies (8,9).

**TABLE 27.2.** Prevalence of Gastrointestinal Tract and Neurological Symptoms Among Residents of Olmsted County, Minnesota, With Diabetes Compared With Their Respective Community Controls

| SYMPTOMS | PREVALENCE (%) | | | |
|---|---|---|---|---|
| | Type 1 Diabetes | | Type 2 Diabetes | |
| | Patients (n=138) | Controls (n=170) | Patients (n=217) | Controls (n=218) |
| Irritable bowel syndrome | | | | |
| Rome criteria (Ref. 131) | 10.9 | 7.6 | 5.1 | 8.3 |
| Manning *et al.* criteria (Ref. 132) | 8.0 | 8.8 | 5.5 | 7.8 |
| Constipation | | | | |
| Symptoms only | 16.7 | 13.5 | 10.1 | 11.5 |
| Symptoms and/or laxatives | 27.0 | 19.0 | 17.0 | 15.0 |
| Dyschezia | 2.9 | 3.5 | 2.3 | 2.3 |
| Diarrhea | 0 | 0 | 0 | 0 |
| Fecal incontinence | 0.7 | 1.2 | 4.6 | 1.8 |
| Nausea and/or vomiting | 11.6 | 10.6 | 6.0 | 5.5 |
| Dyspepsia | 18.8 | 20.6 | 13.4 | 17.4 |
| Heartburn | | | | |
| Symptoms only | 11.6 | 22.9 | 19.8 | 24.3 |
| Symptoms and/or antacids | 18.8 | 36.5 | 24.0 | 36.2 |
| Peripheral neuropathy symptoms (overall) | 50.0 | 47.1 | 65.9* | 50.5 |
| Numbness | 34.8 | 28.2 | 41.5* | 21.6 |
| Muscular weakness | 33.3 | 31.2 | 54.4* | 43.6 |
| Autonomic neuropathy symptoms (overall) | 9.4 | 5.9 | 7.8 | 7.3 |
| Insufficient sweating | 6.5 | 1.8 | 5.5 | 5.5 |
| Gustatory sweating | 3.6 | 4.1 | 2.3 | 2.8 |

* $p<0.05$ (univariate association, subgroup with diabetes versus corresponding controls)

SOURCE: Reference 8, copyright © 2000 American Medical Association, reproduced with permission. All rights reserved; and references listed within the table

**FIGURE 27.1.** Pathophysiology of Diabetes Enteropathy in Humans

| GI manifestations of diabetes | Associated disease | Clinical presentation |
|---|---|---|
| ↓ Gallbladder motility | | Gallstones |
| Antral hypomotility pylorspasm | | Gastric stasis, bezoars |
| ↓ Gastric accommodation | | Dyspepsia |
| ↓ α2-adrenergic tone in enterocytes | Exocrine pancreatic insufficiency | Diarrhea, steatorrhea, intestinal pseudoobstruction |
| Small bowel (SB) dysmotility | Celiac sprue | Gastric or SB stasis or rapid SB transit |
| | SB bacterial overgrowth<br>Bile acid malabsorption | Diarrhea, malabsorption |
| Colonic dysmotility | | Constipation or diarrhea |
| Anorectal dysfunction<br>Sensory neuropathy<br>*IAS-sympathetic dysfunction*<br>*EAS-pudendal neuropathy* | | Disordered defecation or fecal incontinence |

EAS, external anal sphincter; GI, gastrointestinal; IAS, internal anal sphincter; SB, small bowel.

SOURCE: Adapted from Reference 16, copyright © 1996 Elsevier, reproduced with permission

### *Dyspepsia and Gastroparesis*

**Definition.** Gastroparesis is a syndrome characterized by delayed gastric emptying (GE), absence of mechanical obstruction, and upper GI symptoms (i.e., early satiety, postprandial vomiting, bloating, and upper abdominal pain). Consistent with the concept of a paralyzed stomach, the term gastroparesis should preferably be restricted to patients with markedly delayed GE. When the delay in GE is not severe, the term diabetic dyspepsia is perhaps more appropriate. Dyspepsia is characterized by one or more, generally postprandial, upper GI symptoms (i.e., bloating, postprandial fullness, and upper abdominal pain).

**Pathophysiology.** Patients with diabetes may have accelerated or delayed GE, increased and reduced gastric sensation, and impaired gastric accommodation (Figure 27.1) (16). Antral hypomotility and/or pylorospasm, which can result from a vagal neuropathy, can delay GE (17). The mechanisms of rapid GE in diabetes are less well understood. While impaired gastric accommodation resulting from a vagal neuropathy (18) may increase gastric pressure and thereby accelerate GE of liquids, the relationship between impaired gastric accommodation and rapid GE has not been substantiated. Small intestinal dysmotility, more frequently characterized by reduced than by increased motility (19), may also contribute to gastric stasis in diabetes.

Acute hyperglycemia can suppress antral motility and migrating motor activity (i.e., the intestinal "housekeeper") (20,21,22) and delay GE in healthy subjects and in persons with type 1 diabetes (23,24,25,26). However, the effects of acute hyperglycemia on GE are modest. Indeed, even in type 1 diabetes, severe acute hyperglycemia (i.e., 16–20 mmol/L [288–360 mg/dL] vs. 4–8 mmol/L [72–144 mg/dL]) prolonged the GE $t_{1/2}$ by only 17 minutes (i.e., from 124 to 141 minutes) (24). While strict glycemic control improves neural, renal, and retinal functions in diabetes, the impact on GE is unclear (27). In addition to hyperglycemia, medications (e.g., opiates) and electrolyte

**TABLE 27.3.** Prevalence of Gastrointestinal Symptoms, by Diabetes Status, Sydney, Australia, 1999

| | PREVALENCE (%) | | | |
|---|---|---|---|---|
| | Diabetes* (N=423) | No Diabetes (N=8,185) | UNADJUSTED ODDS RATIO (95% CI) | ADJUSTED† ODDS RATIO (95% CI) |
| **Symptom** | | | | |
| Abdominal pain or discomfort | 13.5 | 10.8 | 1.30 (0.97–1.73) | 1.63 (1.21–2.20) |
| Early satiety | 5.2 | 4.3 | 1.22 (0.79–1.91) | 1.62 (1.02–2.56) |
| Postprandial fullness | 8.6 | 5.2 | 1.72 (1.21–2.45) | 2.07 (1.43–3.01) |
| Bloating | 12.3 | 11.4 | 1.09 (0.81–1.46) | 1.51 (1.11–2.07) |
| Heartburn | 13.5 | 10.8 | 1.30 (0.97–1.73) | 1.38 (1.03–1.86) |
| Nausea | 5.2 | 3.5 | 1.51 (0.97–2.35) | 2.31 (1.45–3.68) |
| Vomiting | 1.7 | 1.1 | 1.58 (0.73–3.44) | 2.51 (1.12–5.66) |
| Dysphagia | 5.4 | 1.7 | 3.33 (2.12–5.23) | 2.71 (1.69–4.36) |
| Diarrhea or constipation | 15.6 | 10.0 | 1.69 (1.29–2.21) | 2.04 (1.54–2.71) |
| Anal blockage | 7.7 | 5.0 | 1.60 (1.10–2.32) | 1.80 (1.22–2.66) |
| >3 bowel movements per day | 8.4 | 5.3 | 1.64 (1.14–2.34) | 1.84 (1.27–2.66) |
| <3 bowel movements per week | 4.3 | 3.6 | 1.19 (0.73–1.93) | 1.80 (1.08–3.00) |
| Lumpy or hard stools | 7.4 | 5.5 | 1.36 (0.93–1.98) | 1.66 (1.22–2.46) |
| Loose or watery stools | 10.0 | 5.4 | 1.95 (1.40–2.72) | 2.34 (1.65–3.31) |
| Urgency | 9.3 | 5.2 | 1.88 (1.33–2.65) | 2.22 (1.55–3.17) |
| Fecal incontinence | 2.6 | 0.8 | 3.39 (1.77–6.47) | 2.74 (1.40–5.37) |
| **Symptom complex** | | | | |
| Esophageal symptoms‡ | 15.4 | 11.5 | 1.40 (1.06–1.83) | 1.44 (1.09–1.91) |
| Upper dysmotility symptoms§ | 18.2 | 15.3 | 1.24 (0.96–1.59) | 1.75 (1.34–2.29) |
| Any bowel symptom‖ | 26.0 | 18.9 | 1.51 (1.21–1.89) | 1.84 (1.45–2.33) |
| Diarrhea symptoms¶ | 15.6 | 10.0 | 1.67 (1.27–2.19) | 2.06 (1.56–2.74) |
| Constipation symptoms# | 11.4 | 9.2 | 1.26 (0.92–1.72) | 1.54 (1.12–2.13) |

All symptoms and symptom complexes were rated often or very often. CI, confidence interval.
* Patients had self-reported diabetes based on a physician diagnosis.
† Adjusted for age and sex.
‡ Heartburn, dysphagia, or both
§ Early satiety, postprandial fullness, bloating, nausea, or vomiting
‖ Self-reported diarrhea or constipation, loose or watery stools, >3 bowel movements per day, urgency, fecal incontinence, <3 bowel movements per week, lumpy or hard stools, or anal blockage
¶ >3 bowel movements per day, urgency, or loose or watery stools
# <3 bowel movements per week, lumpy or hard stools, or anal blockage



imbalances due to diabetic ketoacidosis (e.g., hypokalemia) and uremia may also aggravate impaired motor function in diabetic patients. Iatrogenic gastroparesis may result from treatment with amylin or glucagon-like peptide-1 (GLP-1) analogs (28,29,30).

**Epidemiology.** Only one population-based study, which was conducted in 227 residents with type 1 diabetes, a random sample of 360 residents with type 2 diabetes, and an age- and sex-stratified random sample of 639 nondiabetic residents from Olmsted County, has evaluated the risk of developing gastroparesis in diabetes (Table 27.1) (31). Over a 10-year time period, the risk of developing gastroparesis was 5.2% in persons with type 1 diabetes (hazard ratio [HR] 33, 95% confidence interval [CI] 4.0–274, adjusted for age and sex versus controls), 1% in those with type 2 diabetes (HR 7.5, 95% CI 0.8–68, adjusted for age and sex versus controls), and 0.2% in controls. The risk of gastroparesis in type 1 diabetes was significantly greater than in type 2 diabetes (HR 4.4, 95% CI 1.1–17). Gastroparesis was documented by physician diagnosis, by evaluating GE with scintigraphy, or by symptoms and retained food at endoscopy. However, because gastroparesis was identified only in people who presented for care, people who had an asymptomatic delay in GE may not have been identified in this study. Table 27.4 provides the risk factors for diabetic gastroparesis identified in this study (31). Among persons with type 1 diabetes, only heartburn predicted the incidence of gastroparesis.

Longitudinal studies from Australia suggest that similar to functional GI disorders, GI symptom turnover also occurs in diabetes. Turnover refers to appearance and disappearance of symptoms over time. In one study, considerable turnover in GI symptoms was observed 3 years after the initial assessment in patients with type 2 diabetes (6). However, appearance and resolution was balanced; hence, overall prevalence was comparable at follow-up. Several factors, but not glycemic control, predicted symptom change; these factors varied among symptoms. In another cohort of 139 diabetic subjects, of whom approximately 50% had type 1 diabetes and 5% had severe autonomic dysfunction, symptom turnover varied between 15% and 25% in the diabetic group and was not significantly different from controls (32). Symptom turnover was not associated with glycemic control or autonomic neuropathy but, rather, with depression (i.e., appearance and disappearance of depression were associated with gain and loss of GI symptoms, respectively).

**Natural History.** Minimal data are available on the natural history of diabetic gastroparesis. From clinic-based literature, the natural history of diabetic gastroparesis may result in nutritional compromise, impaired glucose control, and a poor quality of life, independent of other factors, such as age, tobacco use, alcohol use, or type of diabetes (33). From a group of 86 patients assessed at a tertiary referral center, 20 patients, of whom 16 had type 1 diabetes, were reevaluated 12 years later, and 13 patients (12 had type 1 diabetes) were reevaluated approximately 25 years after the first study (34,35). While GE was not significantly different 25 years after the baseline assessment,

**TABLE 27.4.** Cumulative Incidence and Predictors of Developing Gastroparesis Over 10 Years in Patients With Type 1 Diabetes, Olmsted County, Minnesota, 1995–2006

| CHARACTERISTICS | NUMBER OF PATIENTS STUDIED | CUMULATIVE INCIDENCE (%) (95% CI) | HAZARD RATIO (95% CI)* |
|---|---|---|---|
| Age (years) | | | |
| <40 | 71 | 8.5 (1.1–15) | 1.2 (0.7–2.2)† |
| ≥40 | 62 | 7.2 (0.1–14) | 1.0 (ref) |
| Sex | | | |
| Men | 59 | 2.1 (0–6.2) | 0.2 (0.02–1.2) |
| Women | 74 | 12.2 (3.9–20) | 1.0 (ref) |
| Diabetes duration (years) | | | |
| ≤20 | 56 | 11.1 (1.4–20) | 0.9 (0.6–1.3)‡ |
| >20 | 77 | 6.0 (0.1–12) | 1.0 (ref) |
| Per year | | | 0.98 (0.92–1.05) |
| Heartburn | 15 | 26.7 (0.5–46) | 6.6 (1.7–25) |
| No heartburn | 118 | 5.2 (0.6–9.6) | 1.0 (ref) |
| Acid regurgitation | 38 | 14.4 (0–27) | 2.5 (0.6–9.6) |
| No acid regurgitation | 90 | 6.2 (0.8–11) | 1.0 (ref) |
| Nausea | 15 | 14.4 (0–31) | 1.9 (0.4–9.5) |
| No nausea | 118 | 7.0 (1.8–12) | 1.0 (ref) |
| Vomiting | 5 | 0 | NE |
| No vomiting | 124 | 8.5 (3.0–14) | |
| Dyspepsia | 25 | 9.1 (0–20) | 10 (0.2–5.0) |
| No dyspepsia | 108 | 7.6 (2.0–13) | 1.0 (ref) |
| Straining | 6 | 0 | NE |
| No straining | 127 | 8.3 (2.9–13) | |
| Hard or lumpy stools | 21 | 4.8 (0–13) | 0.8 (0.1–6.5) |
| No hard or lumpy stools | 112 | 8.5 (2.7–14) | 1.0 (ref) |
| Loose stools | 8 | 16.7 (0–42) | 1.5 (0.2–12) |
| No loose stools | 125 | 7.4 (2.3–12) | 1.0 (ref) |
| Abdominal pain | 25 | 9.1 (0–20) | 1.0 (0.2–5.0) |
| No abdominal pain | 108 | 7.6 (2.0–13) | 1.0 (ref) |
| Peripheral neuropathy | 66 | 11.9 (3.7–20) | 3.1 (0.6–15) |
| No peripheral neuropathy | 62 | 3.9 (0–9.0) | 1.0 (ref) |
| Numbness | 46 | 14.0 (2.9–24) | 2.6 (0.6–11) |
| No numbness | 82 | 4.5 (0–9.3) | 1.0 (ref) |
| Muscular weakness | 44 | 15.9 (3.2–27) | 4.1 (0.99–17) |
| No muscular weakness | 84 | 4.1 (0–8.6) | 1.0 (ref) |
| Autonomic neuropathy | 13 | 16.7 (0–35) | 2.6 (0.5–14) |
| No autonomic neuropathy | 115 | 7.3 (1.9–12) | 1.0 (ref) |
| Insufficient sweating | 9 | 22.2 (0–45) | 3.3 (0.6–19) |
| No insufficient sweating | 119 | 7.1 (1.9–12) | 1.0 (ref) |
| Facial sweating | 5 | 0 | NE |
| No facial sweating | 123 | 8.6 (3.0–14) | |

CI, confidence interval; NE, not estimable due to zero category counts; ref, reference group.
* Adjusted for age, sex, and disease duration.
† Hazard ratio per 10 years of age
‡ Hazard ratio per 5 years of disease duration

SOURCE: Reference 31, copyright © 2012 Nature Publishing Group, reproduced with permission

correlation between initial and subsequent assessments was limited, as evidenced by a correlation coefficient of 0.56 (34).

Two studies have evaluated the association between diabetic gastroparesis and mortality or morbidity. In a study of 86 patients with diabetes, of whom 56% had delayed emptying of solids and 28% had delayed emptying of liquids, approximately 25% had died by follow-up at least 9 years later. Gastroparesis was not associated with mortality after adjustment for other disorders (36). However, this study did not ascertain the relationship between diabetic gastroparesis and other medical conditions. A second study compared three parallel cohorts of patients with diabetes (i.e., 94 with symptoms and delayed GE, 94 with classic symptoms of delayed GE but normal scintigraphy, and 94 with no symptoms of gastroparesis) (37). In this study, diabetic gastroparesis was associated with cardiovascular disease, hypertension, retinopathy, and increased hospitalization. Compared to patients with GI symptoms alone, patients with diabetic gastroparesis also had more hospital days (25.5 vs. 5.1 per 1,000 patient-days). Mortality was statistically nonsignificantly higher in the group with diagnosed gastroparesis. In the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium, the incident death rate (IDR) was 0.015 deaths per person-year. The IDRs were significantly higher in diabetic patients compared with idiopathic cases (0.0266 vs. 0.0094) and in those with delayed compared to normal gastric emptying (0.0189 vs. 0.0031) (38).

Thus, among patients with GI symptoms, the GE assessment can identify patients with a worse prognosis. Whether this increased morbidity is driven by gastroparesis is unknown. Data on long-term natural history in the community are lacking.

**Diagnostic Tests.** Diagnostic testing is guided by symptom pattern and severity. Since delayed GE may predispose to hypoglycemia in type 1 diabetes (39), consideration should be given to evaluating emptying even in patients with unexplained hypoglycemia without GI symptoms.

In patients with upper GI symptoms, an upper GI endoscopy is necessary to exclude peptic ulcer disease, celiac disease (CD), and neoplasms, any of which can cause gastric outlet obstruction. Upper endoscopy may reveal gastric food, which suggests antral hypomotility. Delayed GE can be documented by scintigraphy or by finding a large amount of retained food in the stomach. 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.

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 99mTc 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 $^{13}CO_2$ 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., antropyloroduodenojejunal 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

(53). Octreotide may reduce small bowel bacterial overgrowth in chronic intestinal pseudoobstruction (54); however, this study assessed for bacterial overgrowth by breath testing. Indeed, by delaying small intestinal transit, octreotide may predispose to bacterial overgrowth.

### *Constipation*

**Definition.** Constipation is defined by bowel symptoms: infrequent bowel movements, 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 (55). Although diarrhea may alternate with constipation, these bowel disturbances usually occur in isolation.

**Pathophysiology.** In general, primary constipation results from colonic motor dysfunction or a defecatory disorder (i.e., disordered rectal evacuation). Similar to idiopathic chronic constipation, patients with diabetes and constipation may have colonic dysmotility and/or anorectal dysfunctions (i.e., impaired relaxation of the anal sphincter or pelvic floor during defecation) (56). Patients with colonic dysmotility have an impaired colonic contractile response to a meal and delayed colonic transit (57). Patients with reduced rectal sensation may not perceive the desire to defecate. Compared to euglycemia, acute hyperglycemia inhibited the colonic contractile response to gastric distention and proximal colonic contraction elicited by colonic distention in healthy subjects (58). However, acute hyperglycemia did not significantly affect fasting or postprandial colonic tone, motility, compliance, and sensation, or rectal compliance and sensation in healthy people (59). Secondary causes of constipation include medications; calcium channel blockers were associated with an increased risk of constipation in a community-based study (8).

**Epidemiology.** The epidemiology of constipation is presented in the section *Gastrointestinal Symptoms: Prevalence and Risk Factors*.

**Diagnostic Tests.** Anorectal manometry and rectal balloon expulsion are initial tests and generally suffice to diagnose or exclude defecatory disorders (60). After excluding or managing defecatory disorders, consideration should be given to evaluating colonic transit by radiopaque markers or by scintigraphy. In one community-based study of 10 patients with diabetes and constipation, three had prolonged 24-hour colonic transit, and three had abnormal evacuation. Overall colonic transit was slower in diabetic patients with constipation than controls (56). Intraluminal assessments of colonic phasic motility (by manometry) and tone (by barostat) are only available in highly specialized centers and provide a refined assessment of colonic motor dysfunction in patients with slow transit constipation.

**Management.** With one exception (i.e., the use of pyridostigmine) (61), these recommendations for managing constipation in diabetes are adapted from recommendations for managing idiopathic constipation; no specific trials have been conducted in diabetic patients with constipation. The pelvic floor disorders are preferably managed with pelvic floor retraining by biofeedback therapy rather than laxatives; magnetic resonance imaging or barium proctography are only required in selected patients (60). Pelvic floor retraining by biofeedback therapy is the cornerstone for managing defecatory disorders; laxatives are used as an adjunct to pelvic floor retraining. In the absence of pelvic floor dysfunction, fiber supplementation and pharmacological agents (i.e., osmotic and stimulant laxatives) are the mainstays for chronic constipation (60,62). The cholinesterase inhibitor pyridostigmine has been shown to accelerate colonic transit and improve symptoms (61).

## OTHER CLINICAL MANIFESTATIONS

### *Dysphagia and Heartburn*

Esophageal dysmotility, typically characterized by impaired peristalsis with simultaneous contractions, may cause dysphagia and may be related to cardiovascular autonomic neuropathy in diabetes (63). Two studies (i.e., from Olmsted County and a Finnish population) reported that people with type 1 diabetes had a lower prevalence of heartburn (8,9). Case series suggest that gastroesophageal reflux and dysfunctional esophageal peristalsis are correlated to the duration of type 2 diabetes (64). In another study, erosive esophagitis was more prevalent in type 2 diabetic patients with than without peripheral neuropathy (65). Diabetes was also an independent risk factor for Barrett's esophagus in the population. Indeed, type 2 diabetes was associated with a 49% increase in the risk of Barrett's esophagus, independent of other known risk factors, including obesity (odds ratio 1.49, 95% CI 1.16–1.91). This association was stronger in women than men (66). Diabetes may predispose to gastroesophageal reflux either directly or through obesity. Obesity predisposes to gastroesophageal reflux, by disrupting the gastroesophageal junction reflux barrier (67,68,69) and independently via injurious effects of increased abdominal visceral fat (70). Also, delayed GE may conceivably predispose to GE reflux in diabetes.

### *Fecal Incontinence*

Fecal incontinence refers to uncontrolled leakage of liquid or solid stool in the absence of a temporary diarrheal illness (e.g., acute gastroenteritis). The incidence, prevalence, and risk factors of fecal incontinence in diabetes are unknown. Loose stools and anorectal dysfunctions contribute to fecal incontinence in diabetic diarrhea. Compared to patients with diabetes without fecal incontinence and healthy controls, patients with diabetes and fecal incontinence have a higher threshold for rectal perception of balloon distention (i.e., reduced sensation) (71,72). A sympathetic neuropathy may impair internal anal sphincter functional and anal resting pressures, while a pudendal neuropathy may result in reduced anal squeeze pressure (73,74,75). Reduced rectal sensation has also been reported. Regulating stool consistency is the initial approach for managing 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 (72). 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.

### *Abdominal Pain*

Diabetic patients are susceptible to the usual causes of abdominal pain. Diabetes is associated with an increased prevalence of gallstones and of mesenteric ischemia caused by generalized atherosclerosis (76). Thoracolumbar radiculopathy may result in pain in a dermatome distribution that does not cross the midline. Tests and management are guided by the specific features of pain and associated symptoms.

## ASSOCIATION OF TYPE 1 DIABETES WITH IMMUNE-RELATED GASTROINTESTINAL DISORDERS

### CELIAC DISEASE IN TYPE 1 DIABETES

This section reviews the association between CD and type 1 diabetes. Much of the CD in persons with type 1 diabetes is minimally or not at all symptomatic. The prevalence of type 1 diabetes in patients with CD is summarized. In addition, data on the impact of the detection and treatment of CD on the management of type 1 diabetes are reviewed. It is important for clinicians, epidemiologists, and others involved in the care and management of patients with type 1 diabetes to recognize the common association with CD.

There are few data on the prevalence of CD or even celiac autoimmunity in patients with latent autoimmune diabetes of adults (LADA) and type 2 diabetes. One very small study identified no increased risk of CD markers in patients with LADA and type 2 diabetes (77). A second smaller study suggested an increase in antigliadin antibodies in patients with LADA compared to type 2 diabetes; however, no significant differences were made with any of the celiac-specific serology of tissue transglutaminase (TTG) immunoglobulin A (IgA) antibodies or endomysial antibodies (78).

#### *Definition, Genetics, and Immune Response*

CD is primarily an enteropathy that occurs in individuals with a genetic predisposition who are on a gluten-containing diet. The disease usually responds to gluten withdrawal; though, complete resolution is not universal, especially when subjects are detected as adults.

The known genetic predisposition primarily includes the human leukocyte antigen (HLA) type DQ2 or DQ8, encoded by DQA1'05XX:DQB1'02XX or DQA1'03XX:DQB1'0302. The HLA genes are considered essential for the disease, but not sufficient. Additionally, other non-HLA genes have been associated with risk for CD, and some of these genes also overlap those associated with type 1 diabetes (Table 27.5). (Please see Chapter 12 *Genetics of Type 1 Diabetes* for more information on genes associated with type 1 diabetes risk.) Each of these gene loci accounts for a very small contribution to the actual risk, and all collected contribute no more than 10% of familial risk of CD. Insufficient data have been collected to identify the precise polymorphisms and their functional consequences associated with these non-HLA markers for CD susceptibility, though incorporation of the non-HLA gene polymorphisms can improve prediction of disease risk (79).

In CD, the immune response to gluten and especially to incompletely digested immunogenetic peptides that are transformed via targeted deamidation of specific glutamines to glutamic acid enable a potent cellular and humoral immune response. The primary drivers of the cellular immune response to gluten that occurs in CD are gluten-responsive CD4 T cells resident in the lamina propria of the intestine. These CD4 cells recognize gliadin peptides and most especially deamidated gliadin peptides when presented by antigen-presenting cells expressing DQ2 or, more rarely, DQ8. This cellular response results in the release of cytokines that drives an inflammatory cascade that produces the lesion characteristic of CD (80). This results in substantial damage to the small intestinal architecture and reduction in absorptive capacity, increased net secretion, and other consequences of inflammation. The humoral response is characterized by IgA and immunoglobulin G (IgG) antibodies directed against native and deamidated gliadin, as well as IgA antibody to the widely expressed autoantigen TTG. Selective IgA deficiency is substantially more common in CD, and CD is more common in selective IgA deficiency (81). In IgA deficiency, the TTG antibodies are of the IgG isotype. In addition to the adaptive immune response, a potent innate immune response occurs to other protein components of wheat (82). This involves a stress response of the enterocyte, activating CD8 intraepithelial lymphocytes that become cytotoxic in concert with interleukin (IL)-15 (83). In addition, other changes in the mucosa occur, including increased expression of surface transferrin receptor, which also functions as a soluble IgA receptor and may permit transcellular transport of gliadin molecules.

CD has been associated with type 1 diabetes, but not with type 2 diabetes. While some first thought that hidden CD might trigger diabetes, it has since become clear that the association is due to shared genetic and perhaps overlapping environmental triggers (Table 27.5) (84). CD appears to be seen primarily in the DQ2+ subjects and much less so in the DQ8+ patients with type 1 diabetes (85).

Combined, the inflammatory responses in CD result in dramatic alteration of the architecture of the small intestine characterized by mixed cellular infiltration of the lamina propria with lymphocytes, macrophages, eosinophils, plasma cells, leading to crypt hyperplasia and cytotoxic CD8 T cells in the epithelium, producing shortening and eventually flattening of the villi (86). These changes predominately affect a variable length of the proximal

**TABLE 27.5.** Genetic Risk Loci Shared Between Celiac Disease and Type 1 Diabetes

| CHROMOSOME | CHROMOSOME POSITION | SNP | GENE(S) | P-VALUE | CELIAC DISEASE ODDS RATIO | RISK ASSOCIATED WITH TYPE 1 DIABETES |
|---|---|---|---|---|---|---|
| **Similar risk for type 1 diabetes and celiac disease** | | | | | | |
| 2 | 204510823 | rs4675374 | *CTLA4* | $5.79x10^{-9}$ | 1.14 | ↑ |
| 18 | 12799340 | rs1893217 | *PTPN2* | $2.52x10^{-10}$ | 1.17 | ↑ |
| 3 | 46210205 | rs130989 / rs644196 | *CCR1,2,3,5,9 CCRL2* | $3.26x10^{-17}$ | 1.30 | ↑ |
| 6 | 90983333 | rs10806425 | *BACH2* | $3.89x10^{-10}$ | 1.13 | ↑ |
| 4 | 123334952 | rs1315196 | *IL-2* | $2.18x10^{-27}$ | 0.74 | ↓ |
| 6 | 32713862 | rs2187668 | *HLA* | $<1x10^{-50}$ | Required | ↑↑↑ |
| 12 | 111884608 | rs3184504 | *SH2B3* | $1.33x10^{-7}$ | 1.21 | ↑ |
| **Opposite risk effects** | | | | | | |
| 2 | 102437000 | rs917997 | *IL18RAP IL18R1 IL1RL1 IL1RL2* | $1.11x10^{-15}$ | 1.19 | ↓ |
| 12 | 110892139 | rs653178 | *SH2B3* | $7.15x10^{-21}$ | 1.20 | ↓ |
| 1 | 190803436 | rs2816316 | *RGS1* | $2.2x10^{-17}$ | 0.80 | ↑ |
| 6 | 159465977 | rs1738074 | *TAGAP* | $6.7x10^{-9}$ | 1.21 | ↓ |
| 6 | 138014761 | rs2327832 | *TNFAIP2* | $4.46x10^{-19}$ | 1.23 | ↓ |

Data were collected from studies in Europe, United States, and United Kingdom. SNP, single nucleotide polymorphism.

SOURCE: References 79, 133, 134, and 135

small intestine (87). This injury increases permeability and impacts absorption, as well as secretion. In addition, the inflammation can result in discomfort, pain, obstruction, ulceration, and even perforation. Beyond the small intestine, manifestations of malabsorption can include metabolic bone disease, iron deficiency, anemia, coagulopathy from vitamin K deficiency, and peripheral neuropathy from vitamin B12, vitamin B6, vitamin E, or copper deficiency. Other systemic manifestations include dermatitis herpetiformis, peripheral neuropathy, male and female infertility, recurrent miscarriages, cerebellar ataxia, and severe cognitive impairment, hyposplenism, predisposition to infection, or predisposition to malignancies. The malignancies include enteropathy-associated lymphoma, small bowel adenocarcinoma, and those outside of the small intestine, including esophageal cancer, melanoma, non-Hodgkin lymphoma, and nasopharyngeal carcinoma (88).

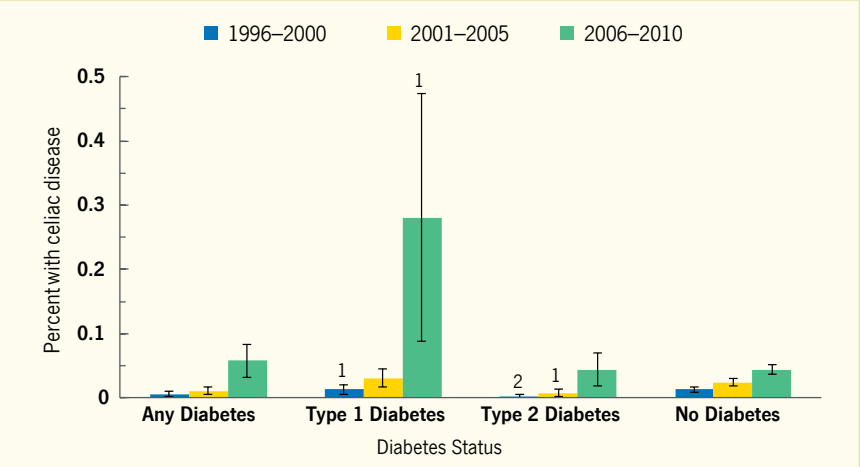
## *Epidemiology*

CD affects 0.71% of the U.S. population age ≥6 years (89) and similar or greater numbers in most global locations studied (90). Studies undertaken in the general population, as well as in groups at risk for CD, have demonstrated that CD affects approximately 1% of non-Hispanic whites. Most patients with CD in the United States, as many as 83%–93%, remain undetected (89). The proportion of CD among hospital discharge diagnoses is less than 0.1%, though it is higher—0.28%—in patients who also have a diagnosis of type 1 diabetes (Figure 27.2). This proportion has risen significantly from previous years according to a new analysis of data from the National Hospital Discharge Surveys 1996–2010 performed for *Diabetes in America, 3rd edition* (Figure 27.2). Of note, CD was defined based on International Classification of Diseases, Ninth Revision (ICD-9), code 579.0, and the standard errors are relatively underestimated because of the complex sampling design of the National Hospital Discharge Survey.

CD is also quite common in patients with family history of CD, affecting 3%–20% of the first-degree relatives (91,92). The risk for family members varies according to the precise relationship to the index case and increases with the number of affected relatives (93). The prevalence of CD is significantly higher in various segments of the population, including patients with type 1 diabetes, but not those with type 2 diabetes. The association between type 1 diabetes and CD has been known for over 50 years, with excellent evidence that CD affects 4%–10% of people with type 1 diabetes. Numerous studies have confirmed this increased prevalence compared with the general population in non-Hispanic white populations (Table 27.6). While much of the data on the prevalence of CD in type 1 diabetes have been collected in non-American populations, several studies support this level of association in the North American population; few of these studies are population-based, with most being derived from referral populations attending academic centers (Table 27.6) (94,95). There are some

exceptions to this high level of association. One small study of type 1 diabetes patients that included African Americans did not find a high frequency of CD (Table 27.6) (96). Many studies have been cross-sectional, based on a single screening test either at the time of diagnosis of diabetes or at some unspecified time point later. A few studies have followed children over time. One such study from Denver had one of the highest cumulative frequencies of TTG (>11%) in a large cohort of nondiabetic high-risk children (97). While a substantial proportion of the CD is detected at the time of diabetes diagnosis, as many as 40% of total cases occur in the years following diagnosis (98). The mean age of diagnosis of CD in children is approximately 10 years, while diagnosis of type 1 diabetes occurs significantly earlier. The likelihood of developing CD may be related to an early age of diagnosis of diabetes (99).

**FIGURE 27.2.** Percent of Hospital Discharges Listing Celiac Disease, by Diabetes Status, U.S., 1996–2010




Celiac disease is defined as International Classification of Diseases, Ninth Revision, code 579.0. Error bars represent 95% confidence intervals. Confidence intervals were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design.

[1] Relative standard error 30%–40%

[2] Relative standard error 40%–50%

SOURCE: National Hospital Discharge Surveys 1996–2010

**TABLE 27.6.** Epidemiologic Studies of Celiac Disease in Type 1 Diabetes

| LOCATION, YEARS (REF.) | STUDY POPULATION | NUMBER IN STUDY | NUMBER AFFECTED |
|---|---|---|---|
| **United States** | | | |
| 1980–1990 (136) | Cohort children | 211 | 10 EMA positive, 3/4 biopsy confirmed |
| NR (137) | Referral population with type 1 diabetes (adults) | 185 | 9 EMA positive, 4/5 biopsy confirmed |
| 1996–1998 (138) | Consecutive cohort children referral | 218 | 17 EMA positive (7.7%), biopsy confirmed 4.6% |
| 1996–1997 (139) | Consecutive cohort of asymptomatic diabetic children | 612 | 5.4% EMA positive<br>8.2% TTG-IgA positive |
| 1994–2004 (94) | Population-based cohort adults and children | 158 | 11 biopsy confirmed CD (7%) |
| NR (96) | Cohort African American children, New York | 34 | 1 TTG-IgA positive, biopsy negative |
| NR (112) | Asymptomatic diabetic children | 58 | 48 TTG/EMA positive |
| **Canada and Mexico** | | | |
| Canada, 1995–1997 (140) | Cohort | 236 | 19 EMA positive, 12/17 biopsy proven |
| Canada, 1998–1999 (141) | Cohort children | 233 | 19 elevated TTG and EMA, 18 biopsy proven (1 clinically diagnosed) |
| Mexico, NR (142) | Cohort adults with diabetes in Mexico City | 84 | 9 positive for TTG-IgA (10.7%), 5.9% biopsy confirmed |
| **Europe and rest of world** | | | |
| Switzerland, Germany, 1983–1986 (143) | Children | 1,032 | 17 AGA positive, 2 diagnosed by biopsy |
| Sweden, 1976–1998 (144) | Community cohort, children | 115 | 6 EMA positive, 2 diagnosed prior |
| Italy, 1993–1999 (98) | Children | 274 | 15 EMA positive at initial test and 10 more during ongoing follow-up |
| United Kingdom, 1998–2006 (145) | Cohort children | 556 | 22 TTG/EMA positive |
| United Kingdom, NR (113) | Referral population, age >16 years with diabetes | 1,000 | 33 TTG/EMA positive |
| India, 2002–2008 (146) | Consecutive cohort | 189 | 21 TTG-IgA positive and biopsy confirmed 11.1%, 2 diagnosed prior |
| Libya, 2008 (85) | Consecutive cohort, children | 218 | 24/218 had biopsy-confirmed CD |

AGA, antigliadin antibody; CD, celiac disease; EMA, endomysial antibody; IgA, immunoglobulin A; NR, not reported; TTG, tissue transglutaminase.

SOURCE: References are listed within the table.

CD is more common in family members of people who have type 1 diabetes than in the general population (Table 27.7).

**Risk of Type 1 Diabetes in Patients With a Diagnosis of Celiac Disease.** As alluded to above, epidemiologic studies suggest that patients who already have a diagnosis of CD may be at increased risk of subsequently developing type 1 diabetes. One particularly large study from Sweden, which followed more than 9,000 children with a diagnosis of CD, found that risk of subsequent type 1 diabetes before these children attained the age of 20 years was more than doubled compared to those without diagnosed CD. The same patients were also at increased risk of ketoacidosis or diabetic coma. This suggests that families of patients diagnosed with CD earlier in childhood need to be aware of a potential risk of type 1 diabetes or at least be aware of how it can present. However, the absolute risk of developing type 1 diabetes is not high (Table 27.8) (100).

**TABLE 27.7.** Frequency of Celiac Disease Among Family Members of Those With Type 1 Diabetes

| LOCATION, YEARS (REF.) | STUDY POPULATION | SCREEN POSITIVE PARTICIPANTS (%) | KEY FINDINGS |
|---|---|---|---|
| Germany, NR (147) | Children of patients with type 1 diabetes | 32/913 (3.5%) | Prevalence increased with age |
| Germany, NR (148) | First-degree relatives (485 parents; 382 siblings; 15 children) of type 1 diabetes patients | 28/882 (3.2%) | Not increased compared with controls |
| United States, 1996–1997 (139) | Asymptomatic relatives of diabetic children (n=577) | 15/577 | 2.6% EMA positive |
| United States, 1996–1997 (139) | Asymptomatic relatives of diabetic children (668 children and 312 adults) | 33/980 | 3.4% TTG-IgA positive |
| Germany, NR (149) | Children of patients with type 1 diabetes | 63/1,511 children (4.3%) | Based on seropositivity by age 8 years; associated with DR3, low birth weight infants |

DR3 is defined by the carriage of the HLA DRB1*03 genotype. EMA, endomysial antibody; NR, not reported; TTG-IgA, tissue transglutaminase immunoglobulin A.

SOURCE: References are listed within the table.

### *Prevention*

There are no specific data on the prevention of CD in patients with type 1 diabetes. Rather, a broader focus on prevention of CD has recently demonstrated that delaying the timing of first gluten in the diet from 6 months to 12 months in an infant diet does not impact the likelihood of development of CD (101). It may delay its onset, but by 5 years, both groups have attained a similar prevalence of CD. A second study, also in infants, examined whether introducing gluten in small quantities overlapping with breastfeeding would reduce the likelihood of childhood CD (102). Not only was this not successful, but there may even have been a slight increase in infant CD in girls.

Both studies did not identify any protective effect of breastfeeding on the occurrence of CD in those genetically at risk for the disease; however, these studies do not address whether CD can be prevented in diabetes.

### *Diagnosis*

CD primarily damages the small intestine, and while classically this results in symptoms or signs of malabsorption (e.g., diarrhea, steatorrhea, weight loss, failure to thrive, multiple vitamin/mineral deficiencies), it often produces much more subtle GI symptoms due to the altered handling of secretions, producing diarrhea, inflammation that produces pain, rarely obstruction/perforation, and pancreatitis. First presentation

**TABLE 27.8.** Risk of Subsequent Type 1 Diabetes Before Age 20 Years in Relation to Celiac Disease

| | | TYPE 1 DIABETES | | | KETOACIDOSIS OR DIABETIC COMA | | |
|---|---|---|---|---|---|---|---|
| CHARACTERISTICS | NUMBER OF PATIENTS STUDIED | Events | Hazard Ratio (95% CI) | P-Value | Events | Hazard Ratio (95% CI) | P-Value |
| No celiac disease | 45,680 | 199 | 1.0 | | 45 | 1.0 | |
| Any celiac disease | 9,243 | 96 | 2.4 (1.9–3.0) | <0.001 | 22 | 2.3 (1.4–3.9) | 0.001 |
| Age at first recorded celiac disease diagnosis (years) | | | | | | | |
| 0–2 | 7,090 | 77 | 2.2 (1.7–2.9) | <0.001 | 19 | 2.3 (1.3–3.9) | 0.004 |
| 3–20 | 2,153 | 19 | 3.4 (1.9–6.1) | <0.001 | 3 | 2.9 (0.7–12.2) | 0.143 |
| Sex | | | | | | | |
| Male | 3,889 | 37 | 1.9 (1.3–2.9) | 0.001 | 8 | 1.5 (0.7–3.4) | 0.301 |
| Female | 5,354 | 59 | 2.7 (2.0–3.8) | <0.001 | 14 | 3.3 (1.7–6.6) | 0.001 |

Events refers to the number of positive events before end of follow-up (diagnosis of type 1 diabetes or ketoacidosis/diabetic coma). Estimates derived from Cox regression internally stratified for sex, age, year of study entry, and county of residence (e.g., children with celiac disease diagnosed before age 3 years were at 2.2-fold increased risk of developing subsequently type 1 diabetes before age 20 years). CI, confidence interval.

may be with consequences seemingly far removed from the GI tract, such as neuropathy, ataxia, cognitive impairment, bone disease, arthralgias, skin lesions—classically, dermatitis herpetiformis—and mouth ulcers (Table 27.9) (81).

CD is usually detected by testing for IgA antibodies directed against TTG. Many serum testing strategies for CD include a measurement of total IgA. If IgA is found to be deficient, then IgG antibodies are sought. IgA deficiency occurs in 5% of patients with CD (81). The diagnosis is confirmed by obtaining biopsies from the proximal small intestine, usually accomplished by upper endoscopy. Typically, four biopsies are obtained from the second part of the duodenum and two biopsies from the duodenal bulb (103). The diagnosis is made on a combination of serologic testing, biopsy, and response to a gluten-free diet (GFD). There is much controversy regarding avoidance of biopsy for the diagnosis of CD. The European Society of Pediatric Gastroenterology and Nutrition has advocated that in cases of a high positive serology (i.e., TTG IgA more than 10 times the upper limit of normal), CD could be confirmed if a separate blood sample provides a positive endomysial antibody and carriage of the appropriate at-risk HLA susceptibility genotype, as well as a response of symptoms to a GFD. Intestinal biopsies, while still recommended for the confirmation of CD, are subject to sampling and interpretation error. Documenting a response to a GFD by histologic improvement is not often performed and is considered unnecessary to confirm the initial diagnosis. However, some practitioners will routinely rebiopsy an adult with CD to ensure that healing is occurring.

In type 1 diabetes, as in other circumstances, a positive TTG antibody test alone is not sufficient to confirm CD. Indeed, those with low-level positives may revert to negative despite remaining on a gluten-containing diet (104). There is insufficient evidence to support starting a GFD in patients with even sequentially positive TTG antibodies, though persistently high titer TTG is a strong predictor of CD (105). The positive predictive value varies substantially. HLA type is unlikely to be helpful in that a large proportion of patients with type 1 diabetes will carry the same HLA susceptibility for CD; though, it should be noted that 50% of type 1 diabetes patients do not carry DQ2, and their risk of CD is 10 times lower than those with at least one copy of the high-risk haplotype. The need for biopsy confirmation of the diagnosis of CD is especially important in those without symptoms of CD (106).

### *Management*

The treatment of CD requires a GFD—the avoidance of wheat, barley, and rye. Occasionally, patients are also sensitive to oats, though they are the exception.

Once CD is detected, treatment is justified in all patients given the increased risk of long-term complications (107). Symptomatic patients will respond to a GFD (Table 27.10). Even patients who do not report any symptoms at the time of diagnosis can subsequently report benefit with the GFD (108). In those with type 1 diabetes, CD is often discovered as part of a screening program and may have few symptoms. The treatment with a GFD presents special challenges to add to the disease management burden of type 1 diabetes. The reported compliance with GFD varies but is less than perfect (Table 27.11) (109). While virtually none of these studies are from the United States, differences in community support and the recent popularity of the GFD may make treatment easier to achieve.

**TABLE 27.9.** Manifestations of Celiac Disease

| | |
|---|---|
| 1. | Classic malabsorption: diarrhea, steatorrhea, weight loss, fat soluble vitamin deficiencies (D, E, A, and K), deficiencies of iron, B12, zinc, and copper |
| 2. | Monosymptomatic gastrointestinal presentations: anemia, diarrhea, constipation, lactose intolerance, and vomiting |
| 3. | Rare gastrointestinal manifestations: intestinal lymphoma, adenocarcinoma of the small intestine, intussusception, perforation, obstruction |
| 4. | Extraintestinal manifestations: peripheral neuropathy, ataxia, cognitive impairment, oral ulcers, dermatitis herpetiformis, osteomalacia, premature osteoporosis, short stature, brittle type 1 diabetes, delayed menarche |

SOURCE: Reference 81, copyright © 2013 Nature Publishing Group, reproduced with permission

**TABLE 27.10.** Symptoms of Celiac Disease in Children With Type 1 Diabetes

| LOCATION, YEARS (REF.) | NUMBER OF PATIENTS STUDIED | SYMPTOMS AT DIAGNOSIS (%) | EFFECT OF GFD ON SYMPTOMS |
|---|---|---|---|
| Finland, NR (150) | 18 | 95 | Improved |
| Germany, 1994–1999 (151) | 9 | 33 | Improved |
| Denmark, 1997–2003 (152) | 28 | 85 | Improved |
| United Kingdom, 1998–2006 (145) | 22 | 76 | Improved |
| Israel, 1983–2008 (153) | 68 | 26 | Not provided |

Symptoms of celiac disease include diarrhea, bloating, abdominal pain, and weight loss. GFD, gluten-free diet; NR, not reported.

SOURCE: References are listed within the table.

**TABLE 27.11.** Adherence to the Gluten-Free Diet in Pediatric Patients With Type 1 Diabetes

| LOCATION, YEARS (REF.) | NUMBER OF PATIENTS STUDIED | ADHERENCE (%) |
|---|---|---|
| United Kingdom, 1994–1996 (154) | 7 | 100 |
| Australia, NR (155) | 20 | 30 |
| Italy, 2005 (156) | 21 | 80 |
| Australia, 1989–1999 (157) | 52 | 60 |

NR, not reported.

SOURCE: Reference 109 and references listed within the table

### *Effect of Gluten-Free Diet on Growth and Nutritional Status*

In general, studies showed some improvement in body mass index or weight in patients treated with GFD, but there is quite variable response of symptoms and effect on quality of life in patients adopting the GFD (Table 27.12). No substantial benefit on quality of life was noted as a result of the double diagnosis, though it was a source of additional concern for parents of doubly affected children (110). Some data on so-called asymptomatic patients were reported by Paavola *et al*., but this study was not specific for type 1 diabetes patients (111). While it is well accepted that CD is associated with diminished bone health in both adults and children, there are relatively few data in those with type 1 diabetes. A single study has suggested that the diminished bone density found at the time of detection of CD improves with a GFD (112).

### *Effect of Gluten-Free Diet on Diabetes Control and Complications*

It has been suggested that a GFD may have subtle consequences on glycosylated hemoglobin (A1c) and increased total insulin dose needed. This may be due to improved carbohydrate digestion and absorption. The impact on A1c has either been no effect or a beneficial effect (Table 27.13). Studies have usually compared patients before and after institution of a GFD.

The risk of vascular complications may be greater in patients with CD, though it is not yet known whether the detection and treatment of CD in these doubly affected patients impact the likelihood of development of vascular disease (84,113,114). One small study of 21 patients by Malalasekera *et al*. (115) demonstrated that institution of a GFD led to reduction in urinary microalbuminuria. A very small study of 19 subjects by Skovbjerg *et al*. (116) suggested that CD was more common in patients with nephropathy compared to those diabetic individuals without nephropathy. One paper suggested lower values of cholesterol and triglycerides in the patients with CD and type 1 diabetes compared to those with type 1 diabetes alone (117). Further studies on the role of CD with type 1 diabetes in vascular risk factors are needed.

### *Role of Gluten in Triggering Diabetes*

Two-thirds of prospective cohort studies have suggested that early cereal introduction at age 3 months or earlier is associated with increased risk of islet cell autoimmunity in newborns (118,119). However, the BABYDIET trial showed that delaying gluten introduction until age 12 months in those at risk of type 1 diabetes does not appear to protect from the development of diabetes-related autoimmunity or diabetes itself (118).

## INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases (IBD) are immune-based disorders affecting the small and large intestine. IBD incorporates both Crohn's disease and ulcerative colitis.

**TABLE 27.12.** Impact of Gluten-Free Diet for Celiac Disease Detected in Patients With Type 1 Diabetes

| LOCATION, YEARS (REF.) | STUDY POPULATION | NUMBER FOLLOWED | KEY FINDINGS | COMPLIANCE |
|---|---|---|---|---|
| **North America** | | | | |
| United States, started in 1998 (158) and 1999 (105) | Cohort children | 71 | Low BMI, lower BMD, ferritin, and vitamin D over time. No effect of delay in GFD. | |
| United States, NR (112) | Asymptomatic diabetic children | 11 | Improvement in A1c after GFD; also bone mineral density | |
| Canada, 2009–2010 (110) | Cohort children | 28 | No effect on quality of life, increased worry in parents | |
| **Europe and rest of world** | | | | |
| Austria, 1996; Czech Republic, 1996; Hungary, 1996; Portugal, 1998; Netherlands, 1997; Slovakia, 1995; Slovenia, 1996 (159) | Cohort children | 98 | No difference at baseline, less weight gain in CD boys | |
| United Kingdom, 1998–2006 (145) | Cohort children | 22 | 13/17 had gastrointestinal symptoms at time of detection, much more than CD-negative diabetes; improved BMI and weight in GFD compliant. | 57.1% compliant |
| United Kingdom, NR (113) | Referral population; age >16 years with diabetes | 33 | Positive patients had more vascular complications than negative patients; also, compliant patients reduced A1c and nephropathy. | |
| United Kingdom, 1994–1998 (160) | Cohort of screen-found CD in children | 11 | Lower BMI, SDS, and A1c in CD-positive; improved A1c and BMD | |
| Germany, 1994–1999 (151) | Cohort children | 9 | Increase in height and improvement in A1c | |

All surveys used mailed questionnaires. A1c, glycosylated hemoglobin; BMD, bone mineral density; BMI, body mass index (kg/m$^2$); CD, celiac disease; GFD, gluten-free diet; NR, not reported; SDS, standard deviation scores.

SOURCE: References are listed within the table.

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

## ACKNOWLEDGMENTS/ FUNDING

Dr. Bharucha was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (DK068055). Dr. Murray was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (DK057892).

## 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.

## REFERENCES


1. Everhart JE: Digestive diseases and diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 95-1468, 1995, p. 457–483
2. Noel RA, Braun DK, Patterson RE, Bloomgren GL: Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 32:834–838, 2009
3. Melton LJ 3rd: History of the Rochester Epidemiology Project. *Mayo Clin Proc* 71:266–274, 1996
4. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M: Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med* 161:1989–1996, 2001
5. Hammer J, Howell S, Bytzer P, Horowitz M, Talley NJ: Symptom clustering in subjects with and without diabetes mellitus: a population-based study of 15,000 Australian adults. *Am J Gastroenterol* 98:391–398, 2003
6. Talley NJ, Howell S, Jones MP, Horowitz M: Predictors of turnover of lower gastrointestinal symptoms in diabetes mellitus. *Am J Gastroenterol* 97:3087–3094, 2002
7. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, Wilson DM, O'Brien PC, Melton LJ 3rd, Service FJ: The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 43:817–824, 1993
8. Maleki D, Locke GR 3rd, Camilleri M, Zinsmeister AR, Yawn BP, Leibson C, Melton LJ 3rd: Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med* 160:2808–2816, 2000
9. Janatuinen E, Pikkarainen P, Laakso M, Pyorala K: Gastrointestinal symptoms in middle-aged diabetic patients. *Scand J Gastroenterol* 28:427–432, 1993
10. Lovell RM, Ford AC: Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 10:712–721.e4, 2012
11. Ordog T: Interstitial cells of Cajal in diabetic gastroenteropathy. *Neurogastroenterol Motil* 20:8–18, 2008
12. Chandrasekharan B, Srinivasan S: Diabetes and the enteric nervous system. *Neurogastroenterol Motil* 19:951–960, 2007
13. de Kort S, Kruimel JW, Sels JP, Arts IC, Schaper NC, Masclee AA: Gastrointestinal symptoms in diabetes mellitus, and their relation to anxiety and depression. *Diabetes Res Clin Pract* 96:248–255, 2012
14. Hasler WL, Parkman HP, Wilson LA, Pasricha PJ, Koch KL, Abell TL, Snape WJ, Farrugia G, Lee L, Tonascia J, Unalp-Arida A, Hamilton F; NIDDK Gastroparesis Clinical Research Consortium: Psychological dysfunction is associated with symptom severity but not disease etiology or degree of gastric retention in patients with gastroparesis. *Am J Gastroenterol* 105:2357–2367, 2010
15. Hasler WL, Wilson LA, Parkman HP, Koch KL, Abell TL, Nguyen L, Pasricha PJ, Snape WJ, McCallum RW, Sarosiek I, Farrugia G, Calles J, Lee L, Tonascia J, Unalp-Arida A, Hamilton F: Factors related to abdominal pain in gastroparesis: contrast to patients with predominant nausea and vomiting. *Neurogastroenterol Motil* 25:427–438, e300–e301, 2013
16. Camilleri M: Gastrointestinal problems in diabetes. *Endocrinol Metab Clin North Am* 25:361–378, 1996
17. Feldman M, Corbett DB, Ramsey EJ, Walsh JH, Richardson CT: Abnormal gastric function in longstanding, insulin-dependent diabetic patients. *Gastroenterology* 77:12–17, 1979
18. Samsom M, Salet GA, Roelofs JM, Akkermans LM, Vanberge-Henegouwen GP, Smout AJ: Compliance of the proximal stomach and dyspeptic symptoms in patients with type I diabetes mellitus. *Dig Dis Sci* 40:2037–2042, 1995
19. Camilleri M, Malagelada JR: Abnormal intestinal motility in diabetics with the gastroparesis syndrome. *Eur J Clin Invest* 14:420–427, 1984
20. Barnett JL, Owyang C: Serum glucose concentration as a modulator of interdigestive gastric motility. *Gastroenterology* 94:739–744, 1988
21. Hasler WL, Soudah HC, Dulai G, Owyang C: Mediation of hyperglycemia-evoked gastric slow-wave dysrhythmias by endogenous prostaglandins. *Gastroenterology* 108:727–736, 1995
22. Samsom M, Akkermans LM, Jebbink RJ, van Isselt H, vanBerge-Henegouwen GP, Smout AJ: Gastrointestinal motor mechanisms in hyperglycaemia induced delayed gastric emptying in type I diabetes mellitus. *Gut* 40:641–646, 1997
23. MacGregor IL, Gueller R, Watts HD, Meyer JH: The effect of acute hyperglycemia on gastric emptying in man. *Gastroenterology* 70:190–196, 1976
24. Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Dent J: Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 33:675–680, 1990
25. Oster-Jorgensen E, Pedersen SA, Larsen ML: The influence of induced hyperglycaemia on gastric emptying rate in healthy humans. *Scand J Clin Lab Invest* 50:831–836, 1990
26. Schvarcz E, Palmer M, Aman J, Horowitz M, Stridsberg M, Berne C: Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology* 113:60–66, 1997
27. Colwell JA: Intensive insulin therapy in type II diabetes: rationale and collaborative clinical trial results. *Diabetes* 45(Suppl 3):S87–S90, 1996
28. Vella A, Lee JS, Camilleri M, Szarka LA, Burton DD, Zinsmeister AR, Rizza RA, Klein PD: Effects of pramlintide, an amylin analogue, on gastric emptying in type 1 and 2 diabetes mellitus. *Neurogastroenterol Motil* 14:123–131, 2002
29. Schirra J, Leicht P, Hildebrand P, Beglinger C, Arnold R, Goke B, Katschinski M: Mechanisms of the antidiabetic action of subcutaneous glucagon-like peptide-1(7-36)amide in non-insulin dependent diabetes mellitus. *J Endocrinol* 156:177–186, 1998
30. Zander M, Madsbad S, Madsen JL, Holst JJ: Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 359:824–830, 2002
31. Choung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Melton LJ 3rd, Talley NJ: Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. *Am J Gastroenterol* 107:82–88, 2012

32. Quan C, Talley NJ, Jones MP, Spies J, Horowitz M: Gain and loss of gastrointestinal symptoms in diabetes mellitus: associations with psychiatric disease, glycemic control, and autonomic neuropathy over 2 years of follow-up. *Am J Gastroenterol* 103:2023–2030, 2008
33. Talley NJ, Young L, Bytzer P, Hammer J, Leemon M, Jones M, Horowitz M: Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. *Am J Gastroenterol* 96:71–76, 2001
34. Jones KL, Russo A, Berry MK, Stevens JE, Wishart JM, Horowitz M: A longitudinal study of gastric emptying and upper gastrointestinal symptoms in patients with diabetes mellitus. *Am J Med* 113:449–455, 2002
35. Chang J, Russo A, Bound M, Rayner CK, Jones KL, Horowitz M: A 25-year longitudinal evaluation of gastric emptying in diabetes. *Diabetes Care* 35:2594–2596, 2012
36. Kong MF, Horowitz M, Jones KL, Wishart JM, Harding PE: Natural history of diabetic gastroparesis. *Diabetes Care* 22:503–507, 1999
37. Hyett B, Martinez FJ, Gill BM, Mehra S, Lembo A, Kelly CP, Leffler DA: Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis. *Gastroenterology* 137:445–452, 2009
38. Pasricha PJ, Yates KP, Clarke JO, Unalp A, Tonascia J, Koch KL, Hasler WL, Miriel LA, Abell TL, Snape WJ, Calles J, McCallum RW, Sarosiek I, Hamilton FA, Farrugia G, Nguyen L, Parkman HP; GpCRC Consortium: Mortality and predictors of improvement in patients with gastroparesis: 4-year outcomes from the Gastroparesis Clinical Research Consortium. *Gastroenterology* 146(Suppl 1):S-136, 2014
39. Chang J, Rayner CK, Jones KL, Horowitz M: Diabetic gastroparesis and its impact on glycemia. *Endocrinol Metab Clin North Am* 39:745–762, 2010
40. Camilleri M, Zinsmeister AR, Greydanus MP, Brown ML, Proano M: Towards a less costly but accurate test of gastric emptying and small bowel transit. *Dig Dis Sci* 36:609–615, 1991
41. Abell TL, Camilleri M, Donohoe K, Hasler WL, Lin HC, Maurer AH, McCallum RW, Nowak T, Nusynowitz ML, Parkman HP, Shreve P, Szarka LA, Snape WJ, Jr., Ziessman HA; American Neurogastroenterology and Motility Society; Society of Nuclear Medicine: Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol* 103:753–763, 2008
42. Szarka LA, Camilleri M, Vella A, Burton D, Baxter K, Simonson J, Zinsmeister AR: A stable isotope breath test with a standard meal for abnormal gastric emptying solids in the clinic and in research. *Clin Gastroenterol Hepatol* 6:635–643, 2008
43. Bharucha AE, Camilleri M, Veil E, Burton D, Zinsmeister AR: Comprehensive assessment of gastric emptying with a stable isotope breath test. *Neurogastroenterol Motil* 25:e60–e69, 2013
44. Ziegler D, Schadewaldt P, Pour Mirza A, Piolot R, Schommartz B, Reinhardt M, Vosberg H, Brosicke H, Gries FA: [13C]octanoic acid breath test for non-invasive assessment of gastric emptying in diabetic patients: validation and relationship to gastric symptoms and cardiovascular autonomic function. *Diabetologia* 39:823–830, 1996
45. Kuo B, McCallum RW, Koch KL, Sitrin MD, Wo JM, Chey WD, Hasler WL, Lackner JM, Katz LA, Semler JR, Wilding GE, Parkman HP: Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. *Aliment Pharmacol Ther* 27:186–196, 2008
46. Bharucha AE, Camilleri M, Low PA, Zinsmeister AR: Autonomic dysfunction in gastrointestinal motility disorders. *Gut* 34:397–401, 1993
47. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology: Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 108:18–37, 2013
48. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, Marinopoulos SS, Puhan MA, Ranasinghe P, Block L, Nicholson WK, Hutfless S, Bass EB, Bolen S: Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med* 154:602–613, 2011
49. Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, Murray JA: Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc* 87:732–738, 2012
50. Posserud I, Stotzer PO, Bjornsson ES, Abrahamsson H, Simren M: Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. *Gut* 56:802–808, 2007
51. Fedorak RN, Field M, Chang EB: Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 102:197–199, 1985
52. von der Ohe MR, Camilleri M, Thomforde GM, Klee GG: Differential regional effects of octreotide on human gastrointestinal motor function. *Gut* 36:743–748, 1995
53. Mourad FH, Gorard D, Thillainayagam AV, Colin-Jones D, Farthing MJ: Effective treatment of diabetic diarrhoea with somatostatin analogue, octreotide. *Gut* 33:1578–1580, 1992
54. Soudah HC, Hasler WL, Owyang C: Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. *N Engl J Med* 325:1461–1467, 1991
55. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC: Functional bowel disorders. *Gastroenterology* 130:1480–1491, 2006
56. Maleki D, Camilleri M, Burton DD, Rath-Harvey DM, Oenning L, Pemberton JH, Low PA: Pilot study of pathophysiology of constipation among community diabetics. *Dig Dis Sci* 43:2373–2378, 1998
57. Battle WM, Snape WJ, Jr., Alavi A, Cohen S, Braunstein S: Colonic dysfunction in diabetes mellitus. *Gastroenterology* 79:1217–1221, 1980
58. Sims MA, Hasler WL, Chey WD, Kim MS, Owyang C: Hyperglycemia inhibits mechanoreceptor-mediated gastrocolonic responses and colonic peristaltic reflexes in healthy humans. *Gastroenterology* 108:350–359, 1995
59. Maleki D, Camilleri M, Zinsmeister AR, Rizza RA: Effect of acute hyperglycemia on colorectal motor and sensory function in humans. *Am J Physiol* 273:G859–G864, 1997
60. Bharucha AE, Pemberton JH, Locke GR 3rd: American Gastroenterological Association technical review on constipation. *Gastroenterology* 144:218–238, 2013
61. Bharucha AE, Low P, Camilleri M, Veil E, Burton D, Kudva Y, Shah P, Gehrking T, Zinsmeister AR: A randomised controlled study of the effect of cholinesterase inhibition on colon function in patients with diabetes mellitus and constipation. *Gut* 62:708–715, 2013

62. Bharucha AE, Dorn SD, Lembo A, Pressman A: American Gastroenterological Association medical position statement on constipation. *Gastroenterology* 144:211–217, 2013
63. Ascaso JF, Herreros B, Sanchiz V, Lluch I, Real JT, Minguez M, Mora F, Benages A: Oesophageal motility disorders in type 1 diabetes mellitus and their relation to cardiovascular autonomic neuropathy. *Neurogastroenterol Motil* 18:813–822, 2006
64. Kinekawa F, Kubo F, Matsuda K, Kobayashi M, Furuta Y, Fujita Y, Okada H, Muraoka T, Yamanouchi H, Inoue H, Uchida Y, Masaki T: Esophageal function worsens with long duration of diabetes. *J Gastroenterol* 43:338–344, 2008
65. Lee SD, Keum B, Chun HJ, Bak YT: Gastroesophageal reflux disease in type II diabetes mellitus with or without peripheral neuropathy. *J Neurogastroenterol Motil* 17:274–278, 2011
66. Iyer PG, Borah BJ, Heien HC, Das A, Cooper GS, Chak A: Association of Barrett's esophagus with type II diabetes mellitus: results from a large population-based case-control study. *Clin Gastroenterol Hepatol* 11:1108–1114.e5, 2013
67. Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ: Obesity: a challenge to esophagogastric junction integrity. *Gastroenterology* 130:639–649, 2006
68. Wu JC, Mui LM, Cheung CM, Chan Y, Sung JJ: Obesity is associated with increased transient lower esophageal sphincter relaxation. *Gastroenterology* 132:883–889, 2007
69. El-Serag HB, Ergun GA, Pandolfino J, Fitzgerald S, Tran T, Kramer JR: Obesity increases oesophageal acid exposure. *Gut* 56:749–755, 2007
70. Lagergren J, Mattsson F, Nyren O: Gastroesophageal reflux does not alter effects of body mass index on risk of esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 12:45–51, 2014
71. Schiller LR, Santa Ana CA, Schmulen AC, Hendler RS, Harford WV, Fordtran JS: Pathogenesis of fecal incontinence in diabetes mellitus: evidence for internal-anal-sphincter dysfunction. *N Engl J Med* 307:1666–1671, 1982
72. Wald A, Tunuguntla AK: Anorectal sensorimotor dysfunction in fecal incontinence and diabetes mellitus. Modification with biofeedback therapy. *N Engl J Med* 310:1282–1287, 1984
73. Rogers J, Levy DM, Henry MM, Misiewicz JJ: Pelvic floor neuropathy: a comparative study of diabetes mellitus and idiopathic faecal incontinence. *Gut* 29:756–761, 1988
74. Caruana BJ, Wald A, Hinds JP, Eidelman BH: Anorectal sensory and motor function in neurogenic fecal incontinence. Comparison between multiple sclerosis and diabetes mellitus. *Gastroenterology* 100:465–470, 1991
75. Russo A, Botten R, Kong MF, Chapman IM, Fraser RJ, Horowitz M, Sun WM: Effects of acute hyperglycaemia on anorectal motor and sensory function in diabetes mellitus. *Diabet Med* 21:176–182, 2004
76. Pazzi P, Scagliarini R, Gamberini S, Pezzoli A: Review article: gall-bladder motor function in diabetes mellitus. *Aliment Pharmacol Ther* 14(Suppl 2):62–65, 2000
77. Sanchez JC, Cabrera-Rode E, Sorell L, Galvan JA, Hernandez A, Molina G, Perich PA, Licea ME, Dominguez E, Diaz-Horta O: Celiac disease associated antibodies in persons with latent autoimmune diabetes of adult and type 2 diabetes. *Autoimmunity* 40:103–107, 2007
78. Kucera P, Novakova D, Behanova M, Novak J, Tlaskalova-Hogenova H, Andel M: Gliadin, endomysial and thyroid antibodies in patients with latent autoimmune diabetes of adults (LADA). *Clin Exp Immunol* 133:139–143, 2003
79. Romanos J, Rosen A, Kumar V, Trynka G, Franke L, Szperl A, Gutierrez-Achury J, van Diemen CC, Kanninga R, Jankipersadsing SA, Steck A, Eisenbarth G, van Heel DA, Cukrowska B, Bruno V, Mazzilli MC, Nunez C, Bilbao JR, Mearin ML, Barisani D, Rewers M, Norris JM, Ivarsson A, Boezen HM, Liu E, Wijmenga C; PreventCD Group: Improving coeliac disease risk prediction by testing non-HLA variants additional to HLA variants. *Gut* 63:415–422, 2014
80. du Pre MF, Sollid LM: T-cell and B-cell immunity in celiac disease. *Best Pract Res Clin Gastroenterol* 29:413–423, 2015
81. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology: ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 108:656–676, 2013
82. Junker Y, Zeissig S, Kim SJ, Barisani D, Wieser H, Leffler DA, Zevallos V, Libermann TA, Dillon S, Freitag TL, Kelly CP, Schuppan D: Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *J Exp Med* 209:2395–2408, 2012
83. Abadie V, Sollid LM, Barreiro LB, Jabri B: Integration of genetic and immunological insights into a model of celiac disease pathogenesis. *Annu Rev Immunol* 29:493–525, 2011
84. Rewers M, Eisenbarth GS: Autoimmunity: celiac disease in T1DM—the need to look long term. *Nat Rev Endocrinol* 8:7–8, 2011
85. Ghawil M, Miotti V, Tonutti E, Tenore A, Hadeed I, Sindici C, Visentini D, Morgham A, Abusrewil S: HLA-DQ types of celiac disease in Libyan children with type 1 diabetes mellitus. *Eur J Gastroenterol Hepatol* 24:59–63, 2012
86. Walker MM, Murray JA: An update in the diagnosis of coeliac disease. *Histopathology* 59:166–179, 2011
87. Rubio-Tapia A, Murray JA: Celiac disease beyond the gut. *Clin Gastroenterol Hepatol* 6:722–723, 2008
88. Potter DD, Murray JA, Donohue JH, Burgart LJ, Nagorney DM, van Heerden JA, Plevak MF, Zinsmeister AR, Thibodeau SN: The role of defective mismatch repair in small bowel adenocarcinoma in celiac disease. *Cancer Res* 64:7073–7077, 2004
89. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE: The prevalence of celiac disease in the United States. *Am J Gastroenterol* 107:1538–1544, 2012
90. Rubio-Tapia A, Murray JA: Celiac disease. In *GI Epidemiology*. Talley NJ, Locke GR 3rd, Saito YA, Eds. Malden, Blackwell Publishing, 2007, p. 157–163
91. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Guandalini S, Hill ID, Pietzak M, Ventura A, Thorpe M, Kryszak D, Fornaroli F, Wasserman SS, Murray JA, Horvath K: Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 163:286–292, 2003
92. Rubio-Tapia A, Van Dyke CT, Lahr BD, Zinsmeister AR, El-Youssef M, Moore SB, Bowman M, Burgart LJ, Melton LJ 3rd, Murray JA: Predictors of family risk for celiac disease: a population-based study. *Clin Gastroenterol Hepatol* 6:983–987, 2008
93. Book L, Zone JJ, Neuhausen SL: Prevalence of celiac disease among relatives of sib pairs with celiac disease in U.S. families. *Am J Gastroenterol* 98:377–381, 2003

94. Mahmud FH, Murray JA, Kudva YC, Zinsmeister AR, Dierkhising RA, Lahr BD, Dyck PJ, Kyle RA, El-Youssef M, Burgart LJ, Van Dyke CT, Brogan DL, Melton LJ: Celiac disease in type 1 diabetes mellitus in a North American community: prevalence, serologic screening, and clinical features. *Mayo Clin Proc* 80:1429–1434, 2005
95. Dube C, Rostom A, Sy R, Cranney A, Saloojee N, Garritty C, Sampson M, Zhang L, Yazdi F, Mamaladze V, Pan I, Macneil J, Mack D, Patel D, Moher D: The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. *Gastroenterology* 128:S57–S67, 2005
96. Kaistha A, Castells S: Celiac disease in African American children with type 1 diabetes mellitus in inner city Brooklyn. *Pediatr Endocrinol Rev* 5(Suppl 4):994–998, 2008
97. Norris JM, Barriga K, Hoffenberg EJ, Taki I, Miao D, Haas JE, Emery LM, Sokol RJ, Erlich HA, Eisenbarth GS, Rewers M: Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *JAMA* 293:2343–2351, 2005
98. Barera G, Bonfanti R, Viscardi M, Bazzigaluppi E, Calori G, Meschi F, Bianchi C, Chiumello G: Occurrence of celiac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study. *Pediatrics* 109:833–838, 2002
99. Cerutti F, Bruno G, Chiarelli F, Lorini R, Meschi F, Sacchetti C; Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetology: Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. *Diabetes Care* 27:1294–1298, 2004
100. Ludvigsson JF, Ludvigsson J, Ekbom A, Montgomery SM: Celiac disease and risk of subsequent type 1 diabetes: a general population cohort study of children and adolescents. *Diabetes Care* 29:2483–2488, 2006
101. Lionetti E, Castellaneta S, Francavilla R, Pulvirenti A, Tonutti E, Amarri S, Barbato M, Barbera C, Barera G, Bellantoni A, Castellano E, Guariso G, Limongelli MG, Pellegrino S, Polloni C, Ughi C, Zuin G, Fasano A, Catassi C; SIGENP (Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition) Working Group on Weaning and CD Risk: Introduction of gluten, HLA status, and the risk of celiac disease in children. *N Engl J Med* 371:1295–1303, 2014
102. Vriezinga SL, Auricchio R, Bravi E, Castillejo G, Chmielewska A, Crespo Escobar P, Kolacek S, Koletzko S, Korponay-Szabo IR, Mummert E, Polanco I, Putter H, Ribes-Koninckx C, Shamir R, Szajewska H, Werkstetter K, Greco L, Gyimesi J, Hartman C, Hogen Esch C, Hopman E, Ivarsson A, Koltai T, Koning F, Martinez-Ojinaga E, te Marvelde C, Pavic A, Romanos J, Stoopman E, Villanacci V, Wijmenga C, Troncone R, Mearin ML: Randomized feeding intervention in infants at high risk for celiac disease. *N Engl J Med* 371:1304–1315, 2014
103. Evans KE, Aziz I, Cross SS, Sahota GR, Hopper AD, Hadjivassiliou M, Sanders DS: A prospective study of duodenal bulb biopsy in newly diagnosed and established adult celiac disease. *Am J Gastroenterol* 106:1837–1842, 2011
104. Waisbourd-Zinman O, Hojsak I, Rosenbach Y, Mozer-Glassberg Y, Shalitin S, Phillip M, Shamir R: Spontaneous normalization of anti-tissue transglutaminase antibody levels is common in children with type 1 diabetes mellitus. *Dig Dis Sci* 57:1314–1320, 2012
105. Simmons JH, Klingensmith GJ, McFann K, Rewers M, Ide LM, Taki I, Liu E, Hoffenberg EJ: Celiac autoimmunity in children with type 1 diabetes: a two-year follow-up. *J Pediatr* 158:276–281.e1, 2011
106. Husby S, Koletzko S, Korponay-Szabo IR, Mearin ML, Phillips A, Shamir R, Troncone R, Giersiepen K, Branski D, Catassi C, Lelgeman M, Maki M, Ribes-Koninckx C, Ventura A, Zimmer KP; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 54:136–160, 2012
107. Rubio-Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, Brantner TL, Kim WR, Phelps TK, Lahr BD, Zinsmeister AR, Melton LJ 3rd, Murray JA: Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology* 137:88–93, 2009
108. Kurppa K, Collin P, Maki M, Kaukinen K: Celiac disease and health-related quality of life. *Expert Rev Gastroenterol Hepatol* 5:83–90, 2011
109. Camarca ME, Mozzillo E, Nugnes R, Zito E, Falco M, Fattorusso V, Mobilia S, Buono P, Valerio G, Troncone R, Franzese A: Celiac disease in type 1 diabetes mellitus. *Ital J Pediatr* 38:10, 2012
110. Sud S, Marcon M, Assor E, Daneman D, Mahmud FH: Quality of life in children with diabetes and celiac disease: minimal impact of the 'double diagnosis'. *Pediatr Diabetes* 13:163–169, 2012
111. Paavola A, Kurppa K, Ukkola A, Collin P, Lahdeaho ML, Huhtala H, Maki M, Kaukinen K: Gastrointestinal symptoms and quality of life in screen-detected celiac disease. *Dig Liver Dis* 44:814–818, 2012
112. Artz E, Warren-Ulanch J, Becker D, Greenspan S, Freemark M: Seropositivity to celiac antigens in asymptomatic children with type 1 diabetes mellitus: association with weight, height, and bone mineralization. *Pediatr Diabetes* 9:277–284, 2008
113. Leeds JS, Hopper AD, Hadjivassiliou M, Tesfaye S, Sanders DS: High prevalence of microvascular complications in adults with type 1 diabetes and newly diagnosed celiac disease. *Diabetes Care* 34:2158–2163, 2011
114. Mollazadegan K, Kugelberg M, Montgomery SM, Sanders DS, Ludvigsson J, Ludvigsson JF: A population-based study of the risk of diabetic retinopathy in patients with type 1 diabetes and celiac disease. *Diabetes Care* 36:316–321, 2013
115. Malalasekera V, Cameron F, Grixti E, Thomas MC: Potential reno-protective effects of a gluten-free diet in type 1 diabetes. *Diabetologia* 52:798–800, 2009
116. Skovbjerg H, Tarnow L, Locht H, Parving HH: The prevalence of coeliac disease in adult Danish patients with type 1 diabetes with and without nephropathy. *Diabetologia* 48:1416–1417, 2005
117. Picarelli A, Sabbatella L, Di Tola M, Vetrano S, Casale C, Anania MC, Porowska B, Vergari M, Schiaffini R, Gargiulo P: Anti-endomysial antibody of IgG1 isotype detection strongly increases the prevalence of coeliac disease in patients affected by type I diabetes mellitus. *Clin Exp Immunol* 142:111–115, 2005
118. Hummel S, Pfluger M, Hummel M, Bonifacio E, Ziegler AG: Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study. *Diabetes Care* 34:1301–1305, 2011
119. Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich HA, Rewers M: Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA* 290:1713–1720, 2003

120. Wang K, Baldassano R, Zhang H, Qu HQ, Imielinski M, Kugathasan S, Annese V, Dubinsky M, Rotter JI, Russell RK, Bradfield JP, Sleiman PM, Glessner JT, Walters T, Hou C, Kim C, Frackelton EC, Garris M, Doran J, Romano C, Catassi C, Van Limbergen J, Guthery SL, Denson L, Piccoli D, Silverberg MS, Stanley CA, Monos D, Wilson DC, Griffiths A, Grant SF, Satsangi J, Polychronakos C, Hakonarson H: Comparative genetic analysis of inflammatory bowel disease and type 1 diabetes implicates multiple loci with opposite effects. *Hum Mol Genet* 19:2059–2067, 2010
121. Kappelman MD, Galanko JA, Porter CQ, Sandler RS: Association of paediatric inflammatory bowel disease with other immune-mediated diseases. *Arch Dis Child* 96:1042–1046, 2011
122. Cohen R, Robinson D, Jr., Paramore C, Fraeman K, Renahan K, Bala M: Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001–2002. *Inflamm Bowel Dis* 14:738–743, 2008
123. Hemminki K, Li X, Sundquist J, Sundquist K: Familial association between type 1 diabetes and other autoimmune and related diseases. *Diabetologia* 52:1820–1828, 2009
124. Akerkar GA, Peppercorn MA, Hamel MB, Parker RA: Corticosteroid-associated complications in elderly Crohn's disease patients. *Am J Gastroenterol* 92:461–464, 1997
125. Ungar B, Stocks AE, Martin FI, Whittingham S, Mackay IR: Intrinsic-factor antibody, parietal-cell antibody, and latent pernicious anaemia in diabetes mellitus. *Lancet* 2:415–417, 1968
126. De Block CE, De Leeuw IH, Bogers JJ, Pelckmans PA, Ieven MM, Van Marck EA, Van Hoof V, Maday E, Van Acker KL, Van Gaal LF: Helicobacter pylori, parietal cell antibodies and autoimmune gastropathy in type 1 diabetes mellitus. *Aliment Pharmacol Ther* 16:281–289, 2002
127. Alonso N, Granada ML, Soldevila B, Salinas I, Joaquin C, Reverter JL, Junca J, Martinez Caceres EM, Sanmarti A: Serum autoimmune gastritis markers, pepsinogen I and parietal cell antibodies, in patients with type 1 diabetes mellitus: a 5-year prospective study. *J Endocrinol Invest* 34:340–344, 2011
128. Borch K, Renvall H, Liedberg G: Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anemia. *Gastroenterology* 88:638–648, 1985
129. Wenzlau JM, Gardner TJ, Frisch LM, Davidson HW, Hutton JC: Development of a novel autoantibody assay for autoimmune gastritis in type 1 diabetic individuals. *Diabetes Metab Res Rev* 27:887–890, 2011
130. Maclaren NK, Riley WJ: Thyroid, gastric, and adrenal autoimmunities associated with insulin-dependent diabetes mellitus. *Diabetes Care* 8(Suppl 1):34–38, 1985
131. Drossman DA: The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 130:1377–1390, 2006
132. Manning AP, Thompson WG, Heaton KW, Morris AF: Towards positive diagnosis of the irritable bowel. *Br Med J* 2:653–654, 1978
133. Dubois PC, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, Zhernakova A, Heap GA, Adany R, Aromaa A, Bardella MT, van den Berg LH, Bockett NA, de la Concha EG, Dema B, Fehrmann RS, Fernandez-Arquero M, Fiatal S, Grandone E, Green PM, Groen HJ, Gwilliam R, Houwen RH, Hunt SE, Kaukinen K, Kelleher D, Korponay-Szabo I, Kurppa K, MacMathuna P, Maki M, Mazzilli MC, McCann OT, Mearin ML, Mein CA, Mirza MM, Mistry V, Mora B, Morley KI, Mulder CJ, Murray JA, Nunez C, Oosterom E, Ophoff RA, Polanco I, Peltonen L, Platteel M, Rybak A, Salomaa V, Schweizer JJ, Sperandeo MP, Tack GJ, Turner G, Veldink JH, Verbeek WH, Weersma RK, Wolters VM, Urcelay E, Cukrowska B, Greco L, Neuhausen SL, McManus R, Barisani D, Deloukas P, Barrett JC, Saavalainen P, Wijmenga C, van Heel DA: Multiple common variants for celiac disease influencing immune gene expression. *Nat Genet* 42:295–302, 2010
134. Smyth DJ, Plagnol V, Walker NM, Cooper JD, Downes K, Yang JH, Howson JM, Stevens H, McManus R, Wijmenga C, Heap GA, Dubois PC, Clayton DG, Hunt KA, van Heel DA, Todd JA: Shared and distinct genetic variants in type 1 diabetes and celiac disease. *N Engl J Med* 359:2767–2777, 2008
135. Eyre S, Hinks A, Bowes J, Flynn E, Martin P, Wilson AG, Morgan AW, Emery P, Steer S, Hocking LJ, Reid DM, Harrison P, Wordsworth P, Thomson W, Worthington J, Barton A; Yorkshire Early Arthritis Consortium; Biologics in RA Control Consortium: Overlapping genetic susceptibility variants between three autoimmune disorders: rheumatoid arthritis, type 1 diabetes and coeliac disease. *Arthritis Res Ther* 12:R175, 2010
136. Rossi TM, Albini CH, Kumar V: Incidence of celiac disease identified by the presence of serum endomysial antibodies in children with chronic diarrhea, short stature, or insulin-dependent diabetes mellitus. *J Pediatr* 123:262–264, 1993
137. Talal AH, Murray JA, Goeken JA, Sivitz WI: Celiac disease in an adult population with insulin-dependent diabetes mellitus: use of endomysial antibody testing. *Am J Gastroenterol* 92:1280–1284, 1997
138. Aktay AN, Lee PC, Kumar V, Parton E, Wyatt DT, Werlin SL: The prevalence and clinical characteristics of celiac disease in juvenile diabetes in Wisconsin. *J Pediatr Gastroenterol Nutr* 33:462–465, 2001
139. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ: Celiac disease associated with type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 33:197–214, 2004
140. Fraser-Reynolds KA, Butzner JD, Stephure DK, Trussell RA, Scott RB: Use of immunoglobulin A-antiendomysial antibody to screen for celiac disease in North American children with type 1 diabetes. *Diabetes Care* 21:1985–1989, 1998
141. Gillett PM, Gillett HR, Israel DM, Metzger DL, Stewart L, Chanoine JP, Freeman HJ: High prevalence of celiac disease in patients with type 1 diabetes detected by antibodies to endomysium and tissue transglutaminase. *Can J Gastroenterol* 15:297–301, 2001
142. Remes-Troche JM, Rios-Vaca A, Ramirez-Iglesias MT, Rubio-Tapia A, Andrade-Zarate V, Rodriguez-Vallejo F, Lopez-Maldonado F, Gomez-Perez FJ, Uscanga LF: High prevalence of celiac disease in Mexican Mestizo adults with type 1 diabetes mellitus. *J Clin Gastroenterol* 42:460–465, 2008
143. Koletzko S, Burgin-Wolff A, Koletzko B, Knapp M, Burger W, Gruneklee D, Herz G, Ruch W, Thon A, Wendel U, Zuppinger K: Prevalence of coeliac disease in diabetic children and adolescents. A multicentre study. *Eur J Pediatr* 148:113–117, 1988
144. Carlsson AK, Axelsson IE, Borulf SK, Bredberg AC, Lindberg BA, Sjoberg KG, Ivarsson SA: Prevalence of IgA-antiendomysium and IgA-antigliadin autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children and adolescents. *Pediatrics* 103:1248–1252, 1999
145. Narula P, Porter L, Langton J, Rao V, Davies P, Cummins C, Kirk J, Barrett T, Protheroe S: Gastrointestinal symptoms in children with type 1 diabetes screened for celiac disease. *Pediatrics* 124:E489–E495, 2009

146. Bhadada SK, Kochhar R, Bhansali A, Dutta U, Kumar PR, Poornachandra KS, Vaiphei K, Nain CK, Singh K: Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north India. *J Gastroenterol Hepatol* 26:378–381, 2011
147. Hummel M, Bonifacio E, Stern M, Dittler J, Schimmel A, Ziegler AG: Development of celiac disease-associated antibodies in offspring of parents with type I diabetes. *Diabetologia* 43:1005–1011, 2000
148. Jaeger C, Hatziagelaki E, Petzoldt R, Bretzel RG: Comparative analysis of organ-specific autoantibodies and celiac disease-associated antibodies in type 1 diabetic patients, their first-degree relatives, and healthy control subjects. *Diabetes Care* 24:27–32, 2001
149. Hummel S, Hummel M, Banholzer J, Hanak D, Mollenhauer U, Bonifacio E, Ziegler AG: Development of autoimmunity to transglutaminase C in children of patients with type 1 diabetes: relationship to islet autoantibodies and infant feeding. *Diabetologia* 50:390–394, 2007
150. Saukkonen T, Vaisanen S, Akerblom HK, Savilahti E; Childhood Diabetes in Finland Study Group: Coeliac disease in children and adolescents with type 1 diabetes: a study of growth, glycaemic control, and experiences of families. *Acta Paediatr* 91:297–302, 2002
151. Sanchez-Albisua I, Wolf J, Neu A, Geiger H, Wascher I, Stern M: Coeliac disease in children with type 1 diabetes mellitus: the effect of the gluten-free diet. *Diabet Med* 22:1079–1082, 2005
152. Hansen D, Brock-Jacobsen B, Lund E, Bjorn C, Hansen LP, Nielsen C, Fenger C, Lillevang ST, Husby S: Clinical benefit of a gluten-free diet in type 1 diabetic children with screening-detected celiac disease: a population-based screening study with 2 years' follow-up. *Diabetes Care* 29:2452–2456, 2006
153. Taler I, Phillip M, Lebenthal Y, de Vries L, Shamir R, Shalitin S: Growth and metabolic control in patients with type 1 diabetes and celiac disease: a longitudinal observational case-control study. *Pediatr Diabetes* 13:597–606, 2012
154. Acerini CL, Ahmed ML, Ross KM, Sullivan PB, Bird G, Dunger DB: Coeliac disease in children and adolescents with IDDM: clinical characteristics and response to gluten-free diet. *Diabet Med* 15:38–44, 1998
155. Westman E, Ambler GR, Royle M, Peat J, Chan A: Children with coeliac disease and insulin dependent diabetes mellitus—growth, diabetes control and dietary intake. *J Pediatr Endocrinol Metab* 12:433–442, 1999
156. Valerio G, Spadaro R, Iafusco D, Lombardi F, Del Puente A, Esposito A, De Terlizzi F, Prisco F, Troncone R, Franzese A: The influence of gluten free diet on quantitative ultrasound of proximal phalanxes in children and adolescents with type 1 diabetes mellitus and celiac disease. *Bone* 43:322–326, 2008
157. Saadah OI, Zacharin M, O'Callaghan A, Oliver MR, Catto-Smith AG: Effect of gluten-free diet and adherence on growth and diabetic control in diabetics with coeliac disease. *Arch Dis Child* 89:871–876, 2004
158. Simmons JH, Klingensmith GJ, McFann K, Rewers M, Taylor J, Emery LM, Taki I, Vanyi S, Liu E, Hoffenberg EJ: Impact of celiac autoimmunity on children with type 1 diabetes. *J Pediatr* 150:461–466, 2007
159. Rami B, Sumnik Z, Schober E, Waldhor T, Battelino T, Bratanic N, Kurti K, Lebl J, Limbert C, Madacsy L, Odink RJ, Paskova M, Soltesz G: Screening detected celiac disease in children with type 1 diabetes mellitus: effect on the clinical course (a case control study). *J Pediatr Gastroenterol Nutr* 41:317–321, 2005
160. Amin R, Murphy N, Edge J, Ahmed ML, Acerini CL, Dunger DB: A longitudinal study of the effects of a gluten-free diet on glycemic control and weight gain in subjects with type 1 diabetes and celiac disease. *Diabetes Care* 25:1117–1122, 2002
161. Kaspers S, Kordonouri O, Schober E, Grabert M, Hauffa BP, Holl RW; German Working Group for Pediatric Diabetology: Anthropometry, metabolic control, and thyroid autoimmunity in type 1 diabetes with celiac disease: a multicenter survey. *J Pediatr* 145:790–795, 2004
162. Frohlich-Reiterer EE, Kaspers S, Hofer S, Schober E, Kordonouri O, Pozza SB, Holl RW; Diabetes Patienten Verlaufsdokumentationssystem-Wiss Study Group: Anthropometry, metabolic control, and follow-up in children and adolescents with type 1 diabetes mellitus and biopsy-proven celiac disease. *J Pediatr* 158:589–593.e2, 2011
163. Pham-Short A, Donaghue KC, Ambler G, Chan AK, Hing S, Cusumano J, Craig ME: Early elevation of albumin excretion rate is associated with poor gluten-free diet adherence in young people with coeliac disease and diabetes. *Diabet Med* 31:208–212, 2014
164. Riley WJ, Toskes PP, Maclaren NK, Silverstein JH: Predictive value of gastric parietal cell autoantibodies as a marker for gastric and hematologic abnormalities associated with insulin-dependent diabetes. *Diabetes* 31:1051–1055, 1982
165. Goldstein DE, Drash A, Gibbs J, Blizzard RM: Diabetes mellitus: the incidence of circulating antibodies against thyroid, gastric, and adrenal tissue. *J Pediatr* 77:304–306, 1970
166. Kokkonen J: Parietal cell antibodies and gastric secretion in children with diabetes mellitus. *Acta Paediatr Scand* 69:485–489, 1980
167. Irvine WJ, Clarke BF, Scarth L, Cullen DR, Duncan LJ: Thyroid and gastric autoimmunity in patients with diabetes mellitus. *Lancet* 2:163–168, 1970