Chapter 21

Digestive Diseases and Diabetes

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SUMMARY

This chapter focuses on the relationships of common digestive disorders with diabetes. National data on self-reported diabetes and digestive diseases indicate that diabetic subjects are more likely than the general U.S. population to report a number of digestive conditions, including ulcers, diverticulitis, symptoms of irritable bowel syndrome (IBS), abdominal pain, constipation, diarrhea, and gallstones. Data from a national survey using oral glucose challenge criteria for diabetes confirm an association with gallstones. Although subject to a number of biases, national hospitalization data suggest that diabetic patients may also be more prone than the general population to gastrointestinal infections, cancers of the liver and pancreas, gastritis and other stomach disorders, intestinal impaction, liver disease, pancreatitis, and hematemesis.

Review of published clinical and epidemiologic studies reveal that it is difficult to demonstrate that people with diabetes are at much higher risk of digestive conditions than the general population, even for well characterized syndromes such as diabetic gastropathy and diabetic diarrhea. Reaching conclusions regarding relationships between diabetes and most digestive conditions is limited by inconsistent case definitions and the cross-sectional nature of most studies. Given such limitations, the data suggest that diabetic subjects are more likely than the general population to have constipation, but evidence is inconsistent regarding other gastrointestinal symptoms. People with diabetes may have increased risk of liver disease and gallstones, although these relationships are entangled with those of obesity and hyperinsulinemia. Patients with insulin-dependent diabetes mellitus (IDDM) have an increased risk of celiac disease, and those with non-insulin-dependent diabetes mellitus (NIDDM) have an increased risk of pancreatic cancer. The risk of developing diabetes is markedly increased by diseases of the exocrine pancreas, particularly pancreatic cancer and chronic pancreatitis, and may also be increased by chronic liver disease.

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INTRODUCTION

The digestive tract plays a unique role relative to diabetes: Not only is every digestive organ potentially affected by diabetes, but the liver and exocrine pancreas may also have a modulating if not causal role in the development of diabetes. Physiological abnormalities associated with diabetes have been described in every part of the digestive tract where measurements can be made[1-9]. This chapter focuses on the relationships between diabetes and common or otherwise significant digestive disorders. The first sections examine associations of diabetes with digestive disorders in three national surveys that provide U.S. population-based data. The remaining sections evaluate and summarize the clinical and epidemiologic literature that pertains to diabetes and selected digestive diseases. For each digestive disease the discussion is organized to address two issues: whether diabetic subjects are at greater risk than nondiabetic subjects, and what characterizes the minority of diabetic people who develop the digestive disease. A similar approach has been taken for the few digestive diseases that may increase the risk of developing diabetes, such as liver cirrhosis and chronic pancreatitis.

NATIONAL SURVEYS

NATIONAL HEALTH INTERVIEW SURVEY

The National Health Interview Survey (NHIS) is an ongoing household survey conducted by the National Center for Health Statistics to provide information on

health and health care for representative samples of the U.S. population. Supplements, termed Current Health Topics, are incorporated into the survey yearly. The 1989 NHIS contained Current Health Topics on diabetes and on digestive diseases[10], which provided a unique opportunity to study their associations in a large national sample. Every adult with diabetes identified in the survey was selected for interview. One randomly selected adult from each household was also selected for the digestive disease component. Of the 2,405 diabetic subjects who were interviewed, 1,412 also received the digestive diseases component. There were 40,980 persons without diagnosed diabetes who answered the digestive disease questions.

The purpose of the digestive diseases Current Health Topic was to gain better information about the prevalence of common conditions such as ulcers and to obtain information regarding common symptoms of gastrointestinal disturbance, particularly those characteristic of IBS. Table 21.1 summarizes the results of the analyses according to diabetes status. Age standardization to the U.S. population distribution tended to reduce the prevalence of conditions whose association with diabetes is confounded by older age. For example, the prevalence of a history of physician-di-

Table 21.1

Prevalence and Age-Standardized Prevalence and Prevalence Ratios for Digestive Conditions, by Sex and Diabetes Status, U.S., 1989

Condition	Prevalence (%)		Age-standardized prevalence (%)		Age-standardized prevalence ratio and 95% CI
	Diabetic	Nondiabetic	Diabetic	Nondiabetic	
Both sexes					
Ever had physician-diagnosed gallstones or gallbladder trouble	20.2	7.2	12.7	7.3	1.7 (1.4-2.1)
Physician-diagnosed gallstones or gallbladder trouble in past 12 months	2.8	1.4	2.0	1.4	1.4 (0.75- 2.6)
Ever had physician-diagnosed ulcer	17.0	10.1	13.7	10.1	1.4 (1.1-1.7)
Physician-diagnosed ulcer in past 12 months	5.9	3.3	5.4	3.2	1.7 (1.1-2.5)
Ever had physician-diagnosed diverticulitis	7.8	2.6	3.7	2.8	1.4 (1.0-1.7)
Physician-diagnosed diverticulitis in past 12 months	4.6	1.4	2.1	1.4	1.5 (1.1-2.0)
Ever hospitalized overnight for diverticulitis	3.2	0.8	1.6	0.8	1.9 (1.2-3.1)
Ever had physician-diagnosed IBS	7.9	5.4	6.8	5.4	1.3 (0.90-1.7)
Physician-diagnosed IBS in past 12 months	4.8	3.4	4.9	3.4	1.5 (0.96-2.2)
IBS by symptom criteria*	6.7	3.5	5.6	3.5	1.6 (1.1-2.2)
Physician-diagnosed hemorrhoids in past 12 months	11.2	8.4	8.4	8.5	1.0 (0.76-1.3)
Ever had hemorrhoid surgery	30.1	20.9	15.5	18.5	0.84 (0.62-1.1)
Abdominal pain ≥3 times in past 12 months	16.4	9.7	17.2	9.7	1.8 (1.5-2.2)
Physician visit for abdominal pain ≥3 times in past 12 months	11.8	6.8	12.6	6.8	1.9 (1.4-2.4)
Pain caused restricted activity in past 30 days†	28.0	22.0	18.1	21.6	0.84 (0.62-1.1)
<3 bowel movements per week	6.5	6.2	7.7	6.1	1.3 (0.87-1.8)
≥3 bowel movements per day	6.4	3.9	7.2	3.9	1.9 (1.2-2.9)
Hard stools at least some of the time	40.3	38.5	44.1	38.3	1.2 (1.0-1.3)
Straining at least some of the time	27.0	15.5	25.5	15.6	1.6 (1.4-1.9)
Incomplete evacuation at least some of the time	19.9	13.6	18.9	13.6	1.4 (1.2-1.7)
Constipated at least some of the time	27.1	17.0	24.4	17.1	1.4 (1.2-1.7)
Diarrhea at least some of the time	17.2	13.8	18.9	13.8	1.4 (1.1-1.7)
Laxative use in past 30 days	22.7	9.9	14.8	10.1	1.5 (1.2-1.9)
Daily laxative use	6.1	2.0	3.0	2.1	1.4 (1.1-1.9)
Men					
Ever had physician-diagnosed gallstones or gallbladder trouble	9.9	3.7	5.2	4.1	1.3 (0.86-1.9)
Physician-diagnosed gallstones or gallbladder trouble in past 12 months	1.9	0.8	0.6	0.9	0.73 (0.35-1.5)
Ever had physician-diagnosed ulcer	15.6	10.7	10.7	10.9	0.98 (0.69-1.4)
Physician-diagnosed ulcer in past 12 months	4.7	3.0	4.2	3.0	1.4 (0.69-2.9)
Ever had physician-diagnosed diverticulitis	4.4	1.8	2.2	2.0	1.1 (0.62-1.9)

Table 21.1—Continued next page

Table 21.1 Continued

Condition	Prevalence (%)		Age-standardized prevalence (%)		Age-standardized prevalence ratio and 95% CI
	Diabetic	Nondiabetic	Diabetic	Nondiabetic	
Men					
Physician-diagnosed diverticulitis in past 12 months	2.1	0.9	0.9	1.0	0.89 (0.49-1.6)
Ever hospitalized overnight for diverticulitis	2.0	0.6	1.2	0.7	1.9 (0.77-4.7)
Ever had physician-diagnosed IBS	4.4	3.1	2.7	3.2	0.83 (0.48-1.4)
Physician-diagnosed IBS in past 12 months	2.6	1.8	1.8	1.8	1.0 (0.50-2.0)
IBS by symptom criteria*	3.5	2.8	2.8	2.8	1.0 (0.48-2.2)
Physician-diagnosed hemorrhoids in past 12 months	11.0	6.6	7.6	6.8	1.1 (0.80-1.6)
Ever had hemorrhoid surgery	29.5	28.8	13.0	23.7	0.55 (0.38-0.79)
Abdominal pain ≥3 times in past 12 months	11.0	7.5	10.2	7.5	1.4 (0.94-2.0)
Physician visit for abdominal pain ≥3 times in past 12 months	7.9	4.9	7.5	5.0	1.5 (0.92-2.4)
Pain caused restricted activity in past 30 days†	24.8	20.3	16.1	20.2	0.80 (0.49-1.3)
<3 bowel movements per week	3.8	3.3	3.9	3.3	1.2 (0.59-2.4)
≥3 bowel movements per day	5.4	4.7	6.8	4.7	1.5 (0.63-3.4)
Hard stools at least some of the time	37.6	38.0	43.3	37.7	1.2 (0.92-1.4)
Straining at least some of the time	21.0	10.8	16.6	11.0	1.0 (1.1-2.1)
Incomplete evacuation at least some of the time	12.1	10.5	10.5	10.5	1.0 (0.67-1.5)
Constipated at least some of the time	20.1	10.6	14.1	10.8	1.3 (0.98-1.7)
Diarrhea at least some of the time	11.8	12.0	11.4	11.9	0.96 (0.61-1.5)
Laxative use in past 30 days	15.5	6.0	8.2	6.5	1.3 (0.97-1.7)
Daily laxative use	4.8	1.4	2.2	1.5	1.5 (0.88-2.5)
Women					
Ever had physician-diagnosed gallstones or gallbladder trouble	28.0	10.2	19.2	10.2	1.9 (1.5-2.4)
Physician-diagnosed gallstones or gallbladder trouble in past 12 months	3.7	1.9	3.2	1.9	1.7 (0.80-3.5)
Ever had physician-diagnosed ulcer	18.0	9.5	16.5	9.5	1.8 (1.3-2.3)
Physician-diagnosed ulcer in past 12 months	6.9	3.5	6.5	3.5	1.8 (1.2-2.9)
Ever had physician-diagnosed diverticulitis	10.4	3.4	5.0	3.3	1.5 (1.1-2.0)
Physician-diagnosed diverticulitis in past 12 months	6.5	1.7	3.0	1.7	1.8 (1.2-2.5)
Ever hospitalized overnight for diverticulitis	4.1	1.0	1.9	1.0	2.0 (1.2-3.3)
Ever had physician-diagnosed IBS	10.5	7.4	10.7	7.5	1.4 (0.97-2.1)
Physician-diagnosed IBS in past 12 months	6.5	4.8	7.9	4.8	1.6 (0.99-2.7)
IBS by symptom criteria*	9.1	4.2	8.0	4.2	1.9 (1.3-2.8)
Physician-diagnosed hemorrhoids in past 12 months	11.4	10.0	9.1	10.1	0.90 (0.65-1.3)
Ever had hemorrhoid surgery	30.5	16.3	17.9	13.8	1.3 (0.83-2.0)
Abdominal pain ≥3 times in past 12 months	20.5	11.7	23.8	11.8	2.0 (1.6-2.6)
Physician visit for abdominal pain ≥3 times in past 12 months	14.9	8.4	17.5	8.4	2.1 (1.4-2.4)
Pain caused restricted activity in past 30 days†	29.3	23.0	20.1	22.8	0.88 (0.62-1.1)
Fewer than 3 bowel movements per week	8.6	8.8	11.3	8.8	1.3 (0.87-1.8)
≥3 bowel movements per day	7.1	3.1	7.2	3.9	1.9 (1.5-4.0)
Hard stools at least some of the time	42.3	38.9	44.8	38.9	1.2 (0.99-1.3)
Straining at least some of the time	31.5	19.8	33.7	19.8	1.7 (1.4-2.1)
Incomplete evacuation at least some of the time	25.8	16.4	26.7	16.4	1.6 (1.3-2.1)
Constipated at least some of the time	32.4	22.9	34.1	22.8	1.5 (1.2-1.8)
Diarrhea at least some of the time	21.2	15.5	25.9	15.5	1.7 (1.3-2.1)
Laxative use in past 30 days	28.1	13.5	20.7	13.4	1.6 (1.2-2.0)
Daily laxative use	7.2	2.7	3.6	2.6	1.4 (0.93-2.0)

CI, confidence interval; IBS, irritable bowl syndrom. Data are standardized to the 1989 U.S. population distribution, age ≥18 years, using the following weights: men, age 18-34, 0.1863; 35-44, 0.0980; 45-54, 0.0667; 55-64, 0.0563; 65-74, 0.0442; ≥75, 0.0234; women, age 18-34, 0.1936; 35-44, 0.1024; 45-54, 0.0708; 55-64, 0.0631; 65-74, 0.0551; ≥75, 0.0400. *Pain ≥3 times in past year that was relieved by defecation or was accompanied by more frequent or looser bowel movements and at least one of the following: hard stools, straining, incomplete evacuation, or mucus in the stool at least some of the time, or ≥3 bowel movements per day or ≤3 bowel movements per week. †Among persons with pain ≥3 times in previous year.

Source: 1989 National Health Interview Survey

agnosed gallstones or gallbladder trouble in diabetic subjects was reduced from 20.2% to 12.7% with age standardization.

Most digestive conditions were positively associated with diabetes. However, the ratio of age-adjusted prevalence of digestive conditions in subjects with diabetes versus those without was generally <2. The ratio tended to be greater for women than men. A reporting bias could be partly responsible for the positive associations, because diabetic patients receive greater medical attention than the general population. The higher prevalence of gastrointestinal symptoms reported by diabetic subjects would not have been affected by this bias, but it could be affected by labeling, in which people once labeled as having a disease think of themselves as sick and may report problems that "healthy" people would ignore. Keeping in mind this potential limitation, the conditions of abdominal pain, infrequent bowel movements, frequent bowel movements, hard stools, straining, incomplete evacuation, constipation, diarrhea, and laxative use were all reported more often by diabetic than by nondiabetic subjects (Table 21.1).

Interestingly, a collection of symptoms compatible with IBS (i.e., abdominal pain with altered bowel habits) had approximately the same elevation in prevalence as a doctor visit for IBS. The associations of diabetes with ulcer and diverticulitis in Table 21.1 have not been adequately evaluated in other epidemiologic studies and would be worthy of further investigation. Most of the other associations in Table 21.1 are discussed in the sections on individual diseases that follow.

SECOND NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

Until the results of the 1988-94 Third National Health and Nutrition Examination Survey (NHANES III) are analyzed, the 1976-80 NHANES II will remain unique among national surveys in that oral glucose tolerance tests (OGTTs) were administered to determine the prevalence of undiagnosed diabetes in the adult U.S. population[11]. By including the ~50% of diabetic people not previously known to have diabetes, less biased estimates of the association of diabetes and other conditions can be made. Information on digestive conditions and digestive tract procedures was self-reported. Of these conditions and procedures, only five were common enough to compute prevalence ratios and 95% confidence intervals (CI): a history of hiatus hernia, ulcers, gallstones, gallbladder operation (cholecystectomy), and hernia repair other than for hiatus hernia (Table 21.2). Only a history of gallstones was reported significantly more commonly by diabetic than by nondiabetic subjects. With the exception of gallbladder operation, the diabetic to nondiabetic age-adjusted prevalence ratios were higher for women than for men. The age-standardized prevalence of hernia repairs was actually lower for diabetic than nondiabetic men due to an absence of hernia surgery reported by diabetic men age 20-44 years.

NATIONAL HOSPITAL DISCHARGE SURVEY

Diabetes and digestive diseases are both common reasons for hospitalization. Based on the National Hospital Discharge Survey (NHDS) over the 5-year period 1987-91, there was an annual average of 2.48 million short-stay nonfederal hospitalizations with a diagnosis of diabetes in persons age ≥45 years. Of these hospitalizations, 32.0% also had at least one digestive disease diagnosis (32.5% when age- and sex-adjusted to the 1990 U.S. population). A digestive disease diagnosis was found on 40.8% (40.0% age- and sex-adjusted) of the 14.4 million hospital discharge records per year without mention of diabetes as a diagnosis. As a result, a digestive disease diagnosis was only 81% as likely to be found on discharge records with a diabetes diagnosis as on discharge records without a diabetes diagnosis (Table 21.3). Because diabetic patients are unlikely to be at lower risk of most digestive diseases compared with people without diabetes, other reasons should be considered for the generally negative associations of diabetes and digestive diseases in hospital discharge records. First and most important, the percentages are of hospitalizations, not of a defined population. For hospital discharges, an association of diabetes and another disease will be unbiased only if at least one of two conditions is met: 1) the rate of admission for diabetic patients is equal to the rate of admission for the general population, and 2) the other disease does not affect hospitalization, that is, no person is hospitalized simply because of the presence of the disease[12]. Failure to meet these two conditions is called selection or Berksonian bias. Berkson's original description of selection bias was illustrated by an apparently protective effect of diabetes for cholecystitis in hospitalized patients[13]. Similarly, this bias occurs in the NHDS because persons with diabetes are more likely to be hospitalized than nondiabetic subjects and because having a digestive disease also increases hospitalization risk. The result is a spuriously low percentage of digestive diseases among discharges with diabetes relative to the percentage of digestive diseases among discharges without diabetes.

Table 21.2

Prevalence of Self-Reported Physician-Diagnosed Hiatus Hernia, Ulcers, and Gallstones and of Gallbladder and Non-Hiatal Hernia Operations, by Sex, Age, and Diabetes Status, U.S., 1976-80

Sex	Age (years)	Diabetes	Physician-diagnosed Hiatus hernia	Ulcers	Gallstones	Gallbladder operation	Hernia repair
Both sexes	20-44	yes	2.1	10.0	7.4	3.2	0.0
		no	1.4	6.3	2.8	2.4	4.3
	45-54	yes	9.3	13.8	11.0	11.7	12.6
		no	6.1	11.8	6.4	6.3	11.1
	55-64	yes	8.0	16.2	11.2	12.1	13.0
		no	6.3	14.9	8.7	7.4	11.3
	65-74	yes	10.3	11.0	16.5	13.3	12.5
		no	10.5	16.7	12.6	11.4	12.8
	20-74	yes	8.0	13.0	12.1	10.9	10.6
		no	3.8	9.4	5.2	4.6	7.2
Age-adjusted prevalence ratio*			1.27	1.21	1.60	1.20	0.74
95% CI			0.86-1.87	0.81-1.80	1.01-2.53	0.84-1.72	0.47-1.18
Men	20-44	yes	0.0	8.6	1.1	0.0	0.0
		no	1.4	8.9	0.7	0.8	5.8
	45-54	yes	10.1	13.7	6.0	8.9	7.4
		no	5.7	14.0	4.9	2.8	18.3
	55-64	yes	12.1	22.0	4.4	2.7	18.7
		no	6.9	18.9	5.4	4.3	17.1
	65-74	yes	8.2	14.5	15.2	10.2	20.8
		no	7.9	20.9	8.4	5.9	20.9
	20-74	yes	8.4	15.4	8.1	6.5	14.0
		no	3.4	12.2	2.7	2.0	10.8
Age-adjusted prevalence ratio*			1.22	0.97	1.34	1.39	0.56
95% CI			0.59-2.53	0.63-1.49	0.81-2.22	0.82-2.36	0.33-0.97
Women	20-44	yes	3.3	10.8	10.8	5.0	0.0
		no	1.5	3.9	4.7	4.0	2.8
	45-54	yes	8.6	13.8	15.1	13.9	16.5
		no	6.5	9.7	7.8	9.5	4.2
	55-64	yes	5.9	13.1	14.8	17.1	9.9
		no	5.8	11.2	11.8	10.3	6.0
	65-74	yes	12.2	7.8	17.6	16.0	4.8
		no	12.4	13.5	15.9	15.6	6.5
	20-74	yes	7.7	11.4	14.9	13.9	8.2
		no	4.1	6.9	7.4	7.0	3.9
Age-adjusted prevalence ratio*			1.32	1.60	1.71	1.33	1.24
95% CI			0.73-2.39	0.90-2.85	0.98-2.99	0.88-2.02	0.60-2.55

*Prevalence ratio is adjusted to the 1976-80 U.S. population distribution, age 20-74 years, using the following weights: men, age 20-44, 0.2739; 45-54, 0.0832; 55-64, 0.0719; 65-74, 0.0471; women, age 20-44, 0.2929, 45-54, 0.0892; 55-64, 0.0804; 65-74, 0.0614. CI, confidence interval.

Source: 1976-80 Second National Health and Nutrition Examination Survey

The second major reason for the low ratios in Table 21.3 is due to misclassification: Diabetes diagnoses are underreported on hospital discharge records. Thus, an unknown portion of the hospitalizations failed to mention diabetes as a discharge diagnosis, either because diabetes was undetected or simply not reported. This bias would particularly affect discharges for surgical conditions such as gallbladder disease and hernia, in which few other conditions are likely to be noted, and potentially terminal conditions such as stomach cancer, in which only directly related complications and conditions affecting outcome are likely to be noted. Quantifying the effects of selection and misclassification bias is not possible without other external sources of information. In the 1971-75 NHANES I Epidemiologic Followup Survey, diabetes was recorded as a discharge diagnosis for only 61.5% of hospitalizations of persons known to have diabetes[14]. This percentage would likely be lower if restricted to discharges with a digestive disease diagnosis. For a condition such as gallstones, which would be strongly affected by these biases, the true ratio

Table 21.3

Age- and Sex-Adjusted Percent of Hospital Discharges with Selected Digestive Disease Diagnoses, According to Diabetes Diagnosis, Age ≥45 Years, U.S., 1987-91

Digestive disease diagnosis (ICD9-CM code)	Diabetes diagnosis present: percent with digestive disease diagnosis	Diabetes diagnosis absent: percent with digestive disease diagnosis	Ratio
All digestive diseases	32.5	40.0	0.81
Intestinal infections NEC (008)	0.44	0.35	1.26*
Other bacterial (008.49)	0.15	0.15	1.03*
Other viral (008.8)	0.27	0.17	1.56*
Malignant neoplasm stomach (151)	0.12	0.23	0.51
Malignant neoplasm colon (153)	0.56	0.89	0.63
Sigmoid colon (153.3)	0.13	0.22	0.60
Colon NOS (153.9)	0.16	0.28	0.57
Malignant neoplasm rectum/anus (154)	0.27	0.39	0.67
Rectosigmoid junction (154.0)	0.13	0.14	0.91
Rectum (154.1)	0.11	0.22	0.52
Malignant neoplasm liver (155)	0.11	0.09	1.23*
Malignant neoplasm pancreas (157)	0.39	0.27	1.43*
NOS (157.9)	0.19	0.14	1.40*
Other benign gastrointestinal neoplasm (211)	0.50	0.66	0.75
Colon (211.3)	0.34	0.51	0.67
Hemorrhoids (455)	0.37	1.07	0.35
Bleeding esophageal varices in diseases classified elsewhere (456.2)	0.11	0.10	1.13*
Diseases of esophagus (530)	1.76	2.45	0.71
Esophagitis (530.1)	1.24	1.64	0.76
Ulcer of esophagus (530.2)	0.12	0.17	0.72
Esophageal stricture (530.3)	0.13	0.22	0.58
Dyskinesia of esophagus (530.5)	0.11	0.18	0.60
Gastric ulcer (531)	0.81	0.91	0.90
Chronic gastric ulcer with hemorrhage (531.4)	0.30	0.30	0.99
Gastric ulcer NOS (531.9)	0.27	0.31	0.87
Duodenal ulcer (532)	0.56	0.75	0.75
Chronic duodenal ulcer with hemorrhage (532.4)	0.22	0.24	0.92
Duodenal ulcer (NOS) (532.9)	0.16	0.22	0.71
Peptic ulcer, site NOS (533)	0.83	0.82	1.01*
Peptic ulcer NOS (533.9)	0.60	0.59	1.02*
Gastritis and duodenitis (535)	2.02	2.31	0.88
Acute gastritis (535.0)	0.44	0.46	0.95
Atrophic gastritis (535.1)	0.12	0.15	0.76
Other specified gastritis (535.4)	0.33	0.39	0.84
Gastritis or duodenitis NOS (535.5)	0.82	0.81	1.01*
Duodenitis (535.6)	0.28	0.37	0.75
Disorders of stomach function (536)	0.91	0.43	2.13*
Persistent vomiting (536.2)	0.12	0.08	1.46*
Functional stomach disorder NEC (536.8)	0.67	0.23	2.85*
Other gastroduodenal disorders (537)	0.18	0.26	0.72
Acute appendicitis (540)	0.18	0.35	0.52
Acute appendicitis with peritonitis (540.0)	0.10	0.13	0.73
Inguinal hernia (550)	0.34	1.22	0.28
Unilateral inguinal hernia (550.90)	0.18	0.75	0.24
Other abdominal hernia with obstruction (552)	0.20	0.27	0.76
Other abdominal hernia without obstruction (553)	1.93	2.48	0.78
Umbilical hernia (553.1)	0.17	0.21	0.82
Ventral hernia NOS (553.20)	0.17	0.18	0.98
Incisional hernia (553.21)	0.18	0.26	0.67
Diaphragmatic hernia (553.3)	1.36	1.74	0.78
Idiopathic proctocolitis (556)	0.11	0.12	0.91
Vascular insufficiency of intestine (557)	0.25	0.26	0.97
Acute (557.0)	0.10	0.13	0.80

Table 21.3—Continued next page

Table 21.3—Continued

Digestive disease diagnosis (ICD9-CM code)	Diabetes diagnosis present: percent with digestive disease diagnosis	Diabetes diagnosis absent: percent with digestive disease diagnosis	Ratio
Other noninfectious gastroenteritis and colitis (558)	1.49	1.45	1.03*
Other and unspecified (558.9)	1.46	1.38	1.06*
Intestinal obstruction (560)	1.34	2.12	0.63
Other impaction (560.39)	0.26	0.22	1.14*
Intestinal adhesions with obstruction (560.81)	0.14	0.38	0.37
Unspecified (560.9)	0.39	0.68	0.57
Diverticula of intestine (562)	1.51	2.26	0.67
Diverticulosis of colon (562.10)	0.94	1.25	0.75
Diverticulitis of colon (564.11)	0.53	0.94	0.56
Functional digestive disorders NEC (564)	0.69	0.90	0.77
Constipation (564.0)	0.35	0.37	0.94
Irritable colon (564.1)	0.24	0.37	0.65
Anal tissue or fistula (565)	0.10	0.19	0.54
Anal or rectal abscess (566)	0.18	0.13	1.40*
Peritonitis (567)	0.31	0.31	1.00
Other suppurative peritonitis (567.2)	0.21	0.19	1.11*
Other peritoneal disorders (568)	0.33	0.57	0.58
Peritoneal adhesions (568.0)	0.31	0.54	0.58
Other intestinal disorders (569)	0.52	0.92	0.57
Hemorrhage of rectum and anus (569.3)	0.11	0.19	0.58
Chronic liver disease and cirrhosis (571)	1.78	1.40	1.27*
Alcoholic cirrhosis (571.2)	0.49	0.45	1.07*
Other chronic hepatitis (571.49)	0.11	0.06	1.66*
Cirrhosis without mention of alcohol (571.5)	0.76	0.39	1.93*
Other chronic liver disease (571.8)	0.14	0.06	2.26*
Sequelae of chronic liver disease (572)	0.62	0.49	1.27*
Hepatic coma (572.2)	0.31	0.21	1.48*
Portal hypertension (572.3)	0.18	0.12	1.43*
Other liver disorders (573)	0.35	0.33	1.05*
Hepatitis, unspecified (573.3)	0.14	0.10	1.31*
Cholelithiasis (574)	2.82	3.64	0.78
With acute cholecystitis (574.0)	0.56	0.72	0.78
With other cholecystitis (574.1)	1.05	1.72	0.61
Without mention of cholecystitis (574.2)	0.89	0.84	1.05*
Choledocholithiasis with other cholecystitis (574.4)	0.12	0.14	0.85
Other gallbladder disorders (575)	0.57	0.69	0.83
Acute cholecystitis (575.0)	0.20	0.17	1.19*
Other cholecystitis (575.1)	0.16	0.21	0.76
Other disorders of biliary tract (576)	0.28	0.38	0.74
Cholangitis (576.1)	0.11	0.12	0.90
Diseases of pancreas (577)	1.31	1.00	1.31*
Acute pancreatitis (577.0)	0.80	0.74	1.09*
Chronic pancreatitis (577.1)	0.29	0.17	1.76*
Other specified diseases (577.8)	0.16	0.03	5.19*
Gastrointestinal hemorrhage (578)	2.05	2.24	0.92
Hematemesis (578.0)	0.22	0.19	1.19*
Melena (578.1)	0.54	0.59	0.91
Unspecified (578.9)	1.29	1.46	0.88
Other abdominal/pelvic symptoms (784)	1.54	1.75	0.88
Gastrointestinal symptoms (787)	0.86	1.21	0.71
Nausea and vomiting (787.0)	0.62	0.89	0.70
Dysphagia (787.2)	0.19	0.23	0.83
Abdominal pain (789.0)	0.92	1.12	0.82
Ascites (789.5)	0.44	0.41	1.06*

Diabetes diagnoses identified by ICD9-CM code 250; only conditions listed on at least 0.1% of discharges with diabetes are included in the table; NEC, not elsewhere classified; NOS, not otherwise specified. *Digestive condition diagnosis found on a higher percentage of discharge records that included diabetes as a discharge diagnosis than on records that did not include diabetes.

Source: 1987-91 National Hospital Discharge Surveys

might actually be ~50%-100% higher than the 0.78 that was found (Table 21.3). Thus, ratios of <1.0 should not be considered evidence of a negative association; ratios of at least 1.0 may deserve further investigation.

The digestive diseases in Table 21.3 include only those that were found on at least 0.1% of discharges that recorded diabetes during the 5-year period 1987-91 (at least ~82 sample records, representing ~12,000 discharges). Some groups of diagnoses stand out. The higher ratios for *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD9-CM) code 008.8, other viral intestinal infections not elsewhere classified (ratio of 1.56) and ICD9-CM 558.9, other noninfectious gastroenteritis and colitis (1.06) (which, despite the name, is often a self-limited gastrointestinal infection[15]) suggest that an increased frequency of hospitalizations for gastrointestinal infections in diabetes is possible. The associations of liver disease and its consequences (ICD9-CM 155, 571-572, 789.5) and pancreatic diseases (ICD9-CM 157 and 577) with diabetes, which also have ratios >1.0, are considered later in this chapter. Peptic ulcer is not generally considered to be common in diabetic patients, and only the least specific ulcer diagnosis (ICD9-CM 533) had a ratio greater than unity (1.01). On the other hand, diabetic gastropathy is a well known complication of diabetes and would characteristically be coded as a disorder of stomach function not elsewhere classified (ICD9-CM 536.8), which had a ratio of 2.85. Higher ratios for anal or rectal abscess (ICD9-CM 566) (1.40) and other suppurative peritonitis (ICD9-CM 567.2) (1.11) also indicate a possible greater risk of infection with diabetes. In a study of the 12-year hospital experience of a defined cohort of 77 Navajo Indians with diabetes and their 77 matched controls, 22 of 26 hospitalizations for gastroenteritis occurred in those with diabetes[16]. Because few studies have dealt with diabetes and the occurrence of gastrointestinal infections, the issue will not be considered further in this chapter.

Hematemesis (ICD9-CM 578.0) is a consequence of a number of upper gastrointestinal disorders. One prospective cohort study of >8,000 elderly men and women found that diabetes was a risk factor for gastrointestinal hemorrhage (relative risk=1.8), although not specifically for hematemesis[17]. An association of gastrointestinal bleeding with diabetes would suggest that diabetes is related to one or more of the major diseases that result in gastrointestinal bleeding or that diabetic patients with these conditions are particularly prone to bleeding.

Physiological abnormalities of the esophagus, stomach, and intestines are common in patients with diabetes and may result in gastrointestinal syndromes such as diabetic gastropathy and diabetic diarrhea. It remains to be shown that gastrointestinal abnormalities are appreciably more common in diabetic subjects than in the general population. In addition, there are few indicators as to why a small number of diabetic patients develop severe gastrointestinal symptoms and the majority do not.

Five mechanisms have been proposed to account for gastrointestinal abnormalities in diabetes[18,19]. Autonomic neuropathy resulting in motor weakness and hypotonia is considered the most important mechanism. The others are diabetic microangiopathy, electrolyte imbalances that accompany uncontrolled diabetes, altered hormonal production of glucagon and insulin resulting in depression of gastrointestinal motility and secretion, and an increased susceptibility to gastrointestinal infections. These mechanisms are all biologically plausible, and experimental evidence exists to support their existence. However, evidence is largely lacking for their effect on symptomatic gastrointestinal complications in diabetic patients.

GASTROPATHY

Diabetic gastropathy, a term that has supplanted the more melodious gastroparesis diabeticorum, was originally described in six patients with difficult-to-manage diabetes and no upper gastrointestinal symptoms[20]. More typically, the symptoms are similar to those of gastric outlet obstruction: nausea and vomiting, early satiety, bloating, and abdominal pain[21]. Diagnosis is confirmed through radiologic tests with an upper gastrointestinal series or ingestion of a radiolabeled meal that shows delayed gastric emptying in the absence of obstruction[21]. Most patients with diabetic gastropathy have autonomic neuropathy and other chronic complications of diabetes.

The prevalence of diabetic gastropathy is unknown. Of 43,900 diabetic patients hospitalized at the New England Deaconess Hospital in Boston, MA in 1954-67, only 35 had a confirmed diagnosis of diabetic gastropathy[22]. In a group of 136 diabetic outpatients, nausea and vomiting were reported by 29%, but almost no information was supplied regarding the patients or how the history of symptoms was obtained[21]. In a study of 114 diabetic outpatients, about half with IDDM, a history of either nausea or vomiting in the

previous year was found in 28%[23]. This prevalence was the same for patients with and without peripheral neuropathy.

Upper gastrointestinal symptoms have not been found more commonly in patients with diabetes than in the general population. In a population-based study in Finland, 538 middle-aged persons with well-characterized NIDDM or IDDM did not report more frequent nausea or vomiting than age-matched nondiabetic controls (Table 21.4)[24]. Nausea was reported by 56% of those with diabetes and 55% of controls, and vom-

Table 21.4
Prevalence, Odds Ratios for Diabetes Relative to Nondiabetic Controls, and 95% Confidence Intervals for Various Gastrointestinal Symptoms, According to Type of Diabetes

		Nondiabetic control	IDDM			NIDDM	
Symptom	Weekly frequency	prevalence (%)	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI
Nausea	≥1	15	6	0.47	0.14-1.26	18	1.39	0.95-2.02
	0-<1	40	52	1.39	0.85-2.29	37	0.97	0.74-1.28
	Never	45	42	1		45	1	
Vomiting	≥1	5	2	0.45	0.05-1.86	6	1.05	0.58-1.88
	0-<1	25	31	1.30	0.76-2.18	25	1.01	0.75-1.35
	Never	70	69	1		69	1	
Dysphagia	≥1	6	7	1.19	0.39-3.00	9	1.82*	1.10-3.03
	0-<1	13	8	0.60	0.22-1.36	18	1.60*	1.12-2.28
	Never	81	85	1		73	1	
Odynophagia	≥1	4	5	1.01	0.25-3.03	6	1.34	0.74-2.44
	0-<1	18	15	0.83	0.40-1.58	15	0.85	0.60-1.21
	Never	78	80	1		79	1	
Globus	≥1	9	9	0.87	0.34-1.94	10	1.13	0.72-1.77
	0-<1	26	14	0.46*	0.22-0.90	26	1.04	0.77-1.41
	Never	65	77	1		64	1	
Heartburn	≥1	24	9	0.26*	0.10-0.60	26	1.16	0.82-1.64
	0-<1	45	45	0.69	0.41-1.11	44	1.06	0.78-1.42
	Never	31	46	1		30	1	
Regurgitation	≥1	11	5	0.32*	0.08-0.91	12	0.96	0.63-1.45
	0-<1	44	38	0.68	0.41-1.11	37	0.74*	0.56-0.97
	Never	45	57	1		51	1	
Belching	≥1	39	34	0.56	0.31-1.01	38	0.76	0.54-1.06
	0-<1	40	32	0.51	0.28-0.93	35	0.68*	0.49-0.95
	Never	21	34	1		27	1	
Abdominal pain	≥1	29	18	0.89	0.41-1.90	27	0.92	0.66-1.29
	0-<1	41	60	1.97*	1.10-3.67	42	0.99	0.73-1.34
	Never	30	22	1		31	1	
Flatulence	≥1	62	62	1.45	0.54-4.94	68	1.90	0.57-1.44
	0-<1	30	32	1.40	0.49-4.90	23	0.61	0.37-1.03
	Never	8	6	1		9	1	
Abdominal distension	≥1	29	26	0.80	0.42-1.52	29	0.93	0.67-1.30
	0-<1	40	40	0.95	0.54-1.68	39	0.89	0.66-1.21
	Never	31	34	1		32	1	
Urgency	≥1	20	17	0.77	0.39-1.45	30	1.79*	1.31-2.44
	0-<1	23	17	0.67	0.34-1.24	20	1.04	0.75-1.43
	Never	57	66	1		50	1	
Diarrhea	≥1	7	1	0.13*	0.01-0.78	10	1.39	0.85-2.20
	0-<1	43	38	0.69	0.42-1.13	45	1.14	0.87-1.49
	Never	50	63	1		45	1	
Constipation	Usual/aways	14	21	1.65	0.81-3.31	20	1.51*	1.04-2.20
	Seldom	39	36	0.97	0.56-1.65	37	1.01	0.76-1.34
	Never	47	43	1		43	1	
Laxative use	≥1/month	8	16	2.13*	1.05-4.38	17	2.35*	1.57-3.53
	<1/month or never	92	84	1		83	1	

OR, odds ratio; CI, confidence interval. *Significantly different ($p<0.05$), diabetic versus control subjects. Odds ratios were computed for at least weekly or less than weekly relative to never; laxative use comparison was computed for at least monthly relative to less than monthly or never.

Source: Adapted from Reference 24; prevalence, sex-adjusted odds ratios, and exact confidence intervals were calculated from data in the published reference

iting was reported by 31% and 30%, respectively. As a result, the odds for these conditions did not differ between diabetic subjects and controls.

Diabetic gastropathy is usually ascribed to the effects of autonomic neuropathy on the parasympathetic vagus nerve[25,26], and a prevalence of neuropathy of ≥50% has been found in groups of patients with this condition[22,27]. However, autonomic neuropathy is common in diabetes and is not a good predictor of gastroparesis[28-31]. One study found that affective disorders and anxiety states were predictive of upper gastrointestinal symptoms, whereas neuropathy was not[23]. There are more reports of diabetic gastropathy in patients with IDDM than NIDDM, but a direct comparison of prevalence of gastropathy in the two types of diabetes has not been made. It is not known whether duration of diabetes has an effect on the risk of gastropathy. Acute hyperglycemia delays gastric emptying[32], but whether prolonged hyperglycemia directly affects emptying is unknown. This is a difficult issue to study: because gastropathy itself may worsen blood glucose control, an association of the two does not necessarily suggest a causal direction.

Symptomatic diabetic gastropathy is unlikely to improve spontaneously[22]. Prokinetic drugs are standard treatment, but their effectiveness beyond a year is not known. Gastric bezoars are persistent concretions of food associated commonly with motility disorders and are therefore an important complication of diabetic gastropathy. Although bezoars were found in only 14 of 3,247 patients (0.4%) undergoing gastroduodenoscopies at one hospital, four of these 14 patients had diabetes with autonomic neuropathy[33].

DIARRHEA AND FECAL INCONTINENCE

Chronic diarrhea may be clinically defined as stool output of ≥200 g per day for ≥3 weeks[34]. More practically, diarrhea may be considered an abnormal increase in stool weight, stool liquidity, or stool frequency[34,35]. Patients are more likely to focus on disturbing symptoms of stool looseness and frequency than on increased mass. The diarrhea associated with diabetes characteristically occurs at night following meals and is watery. Clinical evaluation should distinguish diarrhea from fecal incontinence, the recurrent uncontrolled passage of fecal matter[36], because a patient with fecal incontinence may complain of diarrhea even though stool volume and consistency are unaltered[34].

The diarrhea of diabetes may have a number of mechanisms. In a series of 33 diabetic patients with chronic diarrhea seen in a tertiary referral practice[37], autonomic neuropathy was thought to underlie the more direct cause in 22 patients. These direct causes were bacterial overgrowth in the small bowel in eight patients, anorectal dysfunction in seven patients, and intestinal motility or secretory disorder in seven patients. Two conditions associated with diabetes, celiac sprue and bile acid malabsorption, caused five cases. Incidental causes not related to diabetes were found in three patients, and no cause could be found in three patients. Of note, in only seven patients was a definite diagnosis based on the demonstration of a mechanism and response to treatment of that specific disturbance.

Diarrhea is considered a common gastrointestinal complication of diabetes and was found in ~20% of two groups of patients[21,23]. However, there is conflicting evidence whether diarrhea is much more common in people with diabetes than in the general population. In the 1989 NHIS, 17.2% of those with diabetes reported diarrhea at least some of the time, which when age-adjusted was 1.4 times the prevalence of diarrhea in nondiabetic subjects (Table 21.1). Diabetic subjects were also more likely than nondiabetic subjects to report ≥3 bowel movements per day. In contrast, in a Finnish case-control study, diarrhea defined as abnormally liquid stools or stool frequency ≥3 times per day was reported to occur at least once per week by only 1% of patients with IDDM, 10% of patients with NIDDM, and 7% of population controls (Table 21.4)[24]. The odds of diarrhea were actually substantially lower for IDDM patients than for controls. Self-reported diarrhea was slightly more common in 200 British diabetic patients than in their age- and sex-matched nondiabetic controls (Table 21.5)[38]. The higher prevalence approached statistical significance ($p=0.09$) for patients without autonomic neuropathy.

Diarrhea may be produced by the ingestion of large amounts of sorbitol, a popular sugar substitute used as a sweetener in dietetic foods. A group of 100 consecutive patients referred to a diabetic clinic and 100 age- and sex-matched controls without diabetes were interviewed regarding sorbitol ingestion and history of diarrhea, defined as ≥3 loose bowel movements per day for ≥10 days per month[39]. Thirty-six percent of the diabetic patients and 10% of the controls reported sorbitol intake. Of those ingesting sorbitol, 56% of diabetic patients and no controls reported diarrhea. Of those not ingesting sorbitol, 9.4% of diabetic patients and 2.2% of controls reported diarrhea ($p<0.001$ for differences between diabetic and control rates). Thus, diabetic patients reported considerably increased diarrhea, the majority of which was associated with sorbitol intake.

Table 21.5
Functional Bowel Symptoms in Diabetic and Age- and Sex-Matched Controls

Symptom	Autonomic neuropathy	Prevalence (%) Diabetic	Control	Prevalence ratio	95% CI
Irritable bowel syndrome	+	8.5	3.4	2.50	0.50-12.38
	-	16.3	12.1	1.35	0.76-2.42
Abdominal pain	+	18.6	15.3	1.22	0.55-2.73
	-	21.3	22.0	0.97	0.62-1.51
Distension	+	23.7	16.9	1.40	0.68-2.90
	-	38.3	28.4	1.35	0.97-1.89
Abnormal bowel habit	+	33.9	11.7	2.86	1.31-6.24
	-	26.2	23.4	1.12	0.75-1.68
Constipation	+	22.0	6.8	3.25	1.12-9.39
	-	9.2	14.2	0.65	0.34-1.26
Diarrhea	+	5.1	3.4	1.50	0.26-8.65
	-	11.3	5.7	2.00	0.88-4.52
Alternating constipation and diarrhea	+	6.8	1.7	4.00	0.46-34.73
	-	5.7	3.5	1.60	0.54-4.77

CI, confidence interval; +, autonomic neuropathy present, -, absent; sample sizes were 200 diabetic subjects (59 with autonomic neuropathy and 141 without) and 200 control subjects.

Source: Adapted from Reference 38; prevalence ratios and 95% CIs were calculated from data in the published reference

Diarrhea, defined as ≥2 unformed stools per day, was reported by 8% of 85 diabetic patients in a large British referral clinic and 8% of 150 nondiabetic patients attending other, nongastrointestinal clinics[40]. However, diarrhea was found in 20% of diabetic patients treated with the oral hypoglycemic agent metformin. Several of these patients had symptoms more suggestive of fecal incontinence than of diarrhea. This report and the sorbitol report demonstrate that gastrointestinal disturbances may be associated with diabetic treatment and are not necessarily directly caused by diabetes.

Lactose malabsorption, a common cause of diarrhea in adults due to lactase deficiency, is more difficult to diagnose in diabetic patients because the conventional lactose tolerance test consists of serial blood glucose determinations after an oral lactose load. Nevertheless, more specific tests have demonstrated that lactose malabsorption is not more common in diabetic than nondiabetic subjects[41].

As noted above, patients may report fecal incontinence as diarrhea. Although diarrhea may accentuate the problem, the pathophysiology of fecal incontinence is largely different. The problem is not so much with motility as with impaired sensation of anorectal contents and diminished resting anal sphincter pressure[37,42-45]. Fecal incontinence was reported by 20% of a group of 136 diabetic outpatients, but no definition was given[21]. This high prevalence has not been substantiated in other studies of diabetic patients. For example, in a British study, fecal incontinence was reported by only two of 59 diabetic subjects with autonomic neuropathy and none of 141 diabetic subjects without autonomic neuropathy[38]. A German study comparing 12 incontinent and 15 continent diabetic patients found no correlation of peripheral or autonomic neuropathy with the presence or degree of incontinence[46].

CONSTIPATION AND OTHER BOWEL DISTURBANCES

Constipation is one of the most common and least well defined symptoms of gastrointestinal disturbance. Although constipation should be defined by persistent symptoms of difficult, infrequent, or seemingly incomplete defecation, individuals have a variety of perceptions as to what constitutes constipation[35]. Hyperglycemia may directly inhibit intestinal transit[32], but autonomic neuropathy is most often considered the major cause[3,21,26,47]. Despite differences in definition, the majority of studies have found an association of diabetes and constipation. In the 1989 NHIS, diabetic subjects were more likely than subjects without diabetes to report constipation, hard stools, straining, incomplete evacuation, and laxative use (Table 21.1). In the 1987-91 NHDS, intestinal impaction, which can be a consequence of severe constipation, was found in a higher percentage of discharges with diabetes than without diabetes (Table 21.3). Constipation that was usual or always was reported more often by both NIDDM and IDDM patients than controls in a Finnish population-based study (Table 21.4)[24]. These diabetic patients were also more than twice as likely as nondiabetic subjects to report at

least monthly laxative use. Constipation and laxative use were reported more commonly by women than men, as found in other studies[48]. Laxative use was 4.3 times as frequent in diabetic than in nondiabetic subjects in an audit of outpatient pharmaceutical usage at U.S. Public Health Service clinics[49]. This figure was not age-adjusted, but in every age group diabetic persons had 50%-100% greater use of laxatives.

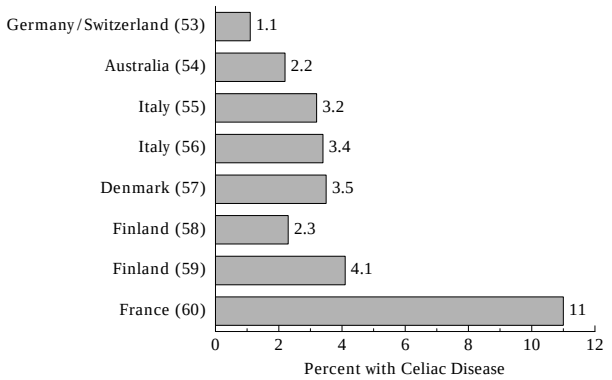
It has been hypothesized that diabetic patients with autonomic neuropathy might have fewer functional bowel symptoms than controls if an intact autonomic nervous system were needed to manifest these common symptoms[38]. To investigate this, functional bowel symptoms were elicited from 200 diabetic patients screened for autonomic neuropathy and 200 age- and sex-matched nondiabetic controls[38]. In contrast to the hypothesis, the 59 diabetic patients with autonomic neuropathy tended to report such symptoms more commonly than controls. Abnormal bowel habit and its principle component, constipation, were reported significantly more commonly by the diabetic patients with autonomic neuropathy than controls (Table 21.5, $p<0.05$). In a study of 114 diabetic outpatients, neither peripheral neuropathy nor psychiatric symptoms were predictive of constipation[23]. Too few patients had neurologic testing to evaluate an association of autonomic neuropathy with constipation.

CELIAC DISEASE

Gluten-sensitive enteropathy, or celiac disease, results from the sensitization of T-lymphocytes of the small bowel mucosa to gliadin and related proteins found in wheat, rye, barley, and oats[50]. The disorder is manifested by malabsorption that results in varying degrees of diarrhea, flatulence, weight loss, and, among diabetic persons, poor glycemic control. Extraintestinal symptoms involving several organs may result from defective absorption of nutrients from the gut. A firm diagnosis requires characteristic jejunal biopsy findings and their improvement while on a gluten-free diet[51]. The presence of circulating antibodies to endomysium, gliadin, or reticulin is supportive of the diagnosis and may be useful as screening tests in high-risk groups.

Celiac disease is rare except in northern Europe, where >0.1% of the population may be affected[52]. Among patients with diabetes, it is most commonly found in children subsequent to the diagnosis of IDDM and is not associated with NIDDM. Figure 21.1 summarizes the prevalence of celiac disease in patients with IDDM in Europe and Australia[53-60]. Prevalence ranged from 1.1% to 11%, which was many times higher than the prevalence in the background populations and was approximately the prevalence found in first-degree relatives of patients with celiac disease[61]. IDDM has also been reported in a high proportion of patients with celiac disease: 5.4% of 335 cases versus 1.5% of age- and sex-matched controls in one study[62]. The common link between the two disorders is the high prevalence of the HLA-DR3 and HLA-DQ2 histocompatibility phenotypes[63,64]. These phenotypes are common in northern Europeans with IDDM, but are more common in patients who have both IDDM and celiac disease[57,65]. People with diabetes who develop celiac disease tend to be younger when diabetes occurs[53,55], but duration of diabetes does not appear to be strongly associated with celiac disease. It is possible that other risk factors or the metabolic abnormalities of IDDM may lead more frequently to celiac disease, particularly since only a minority of persons with the known genetic predispositions develop either condition. The degree of association of IDDM and celiac disease in the United States is unknown but could be evaluated at centers that see large numbers of patients with IDDM. Certainly IDDM patients with unexplained chronic diarrhea and highly varying glycemia should be evaluated for celiac disease[66].

Figure 21.1
Prevalence of Celiac Disease Following Antibody Screening in Patients with IDDM in Europe and Australia



Sample sizes are: Reference 53, 1,024; Reference 54, 180; Reference 55, 498; Reference 56, 146; Reference 57, 201; Reference 58, 215; Reference 59, 195; Reference 60, 54. The percents shown for References 53, 56, and 57 are minimum percents and assume that no patients who refused jejunal biopsy had celiac disease.

Source: References are listed in parentheses within the figure

SPECTRUM OF LIVER DISEASE

Liver diseases found in either obese subjects or diabetic patients are similar to alcoholic liver diseases[67,68]. Histologic findings of steatosis (fat accumulation in hepatocytes), steatohepatitis (steatosis with necrosis and inflammation and the presence of Mallory's hyaline in hepatocytes), and fibrosis and cirrhosis have all been described[69,70]. These conditions cannot be differentiated by histologic appearance from alcoholic liver disease[71-73]. Elevation of liver-associated enzymes is a frequent finding in liver disease, but this is not accurate in predicting either the type or extent of liver tissue abnormalities[74-77]. Liver biopsy is necessary to make a specific diagnosis. Liver ultrasonography may be a useful noninvasive test to identify steatosis or fibrosis as a "bright" liver echo pattern, but it is unable to differentiate between the two conditions[78-80].

Many clinical case series and a few epidemiologic studies suggest that diabetes and liver disease occur together more often than would be expected by chance. For example, in the 1987-91 NHDS, the diagnosis of chronic liver disease and cirrhosis (ICD9-CM 571) was found on a higher percentage of discharge records of diabetic patients (1.78%) than nondiabetic patients (1.40%) (Table 21.3). As was discussed in the section on the NHDS, this finding indicates that liver disease is commonly associated with diabetes but does not provide quantitative certainty. Sequelae of chronic liver disease and other liver disorders (ICD9-CM 572 and 573) were also found more commonly with diabetic discharges than with discharges that did not mention diabetes (Table 21.3).

Beyond this apparent association, it cannot be categorically stated that either diabetes causes liver diseases or liver disease causes diabetes, although it is quite possible that they cause or at least potentiate each other. Likewise, the clinical significance of the association is unknown. For example: What is the risk of developing liver disease with diabetes or diabetes with liver disease? Should people with diabetes be advised not to drink alcohol? Should people with chronic liver disease be tested for diabetes? For patients with NIDDM, would effective glycemic control or weight loss prevent liver disease? Does the occurrence of liver disease in diabetic patients increase the likelihood of other diabetic complications or death?

DOES DIABETES CAUSE LIVER DISEASE?

A causal role for diabetes in liver disease would be indicated if a high incidence and rate of progression of liver disease occurred in people with diabetes who did not have other causes of liver disease (particularly high alcohol consumption), or if prevention or improvement in liver disease occurred in patients during effective therapy for diabetes. Such studies have not been conducted, but less compelling evidence does exist for a causal relationship.

It is understandable that only a few studies have determined the prevalence of liver disease in persons with diabetes. Such studies require examination of liver tissue from persons who do not necessarily have an indication for liver biopsy. A special circumstance in which hepatic tissue can be easily obtained is during gastrointestinal surgery for morbid obesity. In a study of liver biopsies performed in 100 consecutive patients undergoing gastric bypass, 46 patients had normal glucose tolerance, 23 had impaired glucose tolerance (IGT), and 31 had diabetes according to National Diabetes Data Group criteria[75]. Although steatosis was common in all groups, every diabetic patient had some steatosis, and 42% had severe steatosis. Steatosis was more severe in the diabetic subjects than the other two groups ($p=0.04$). Compared with persons with normal glucose tolerance, fibrosis (found in 81% of diabetic patients) but not cirrhosis (found in 10% of diabetic patients) was significantly associated with diabetes ($p=0.001$). A similar study of 118 morbidly obese men and women undergoing jejunoileal bypass found odds ratios for extensive (>25%) steatosis of 11.2 (95% CI 1.6-25.6) and for fibrosis of 17.3 (95% CI 5.5-54.9) for diabetic women relative to women with normal glucose tolerance[81]. No association of liver abnormalities and diabetes was reported for men. Among 100 middle-aged diabetic patients with stable weight, a cytological diagnosis of steatosis was found in only three of 32 normal-weight subjects but in 75% of subjects who were >20% overweight, indicating that steatosis is common in diabetes only in the presence of obesity[82].

Raised serum activities of liver enzymes, particularly alanine amino transferase and γ-glutamyl transpeptidase, occur in diabetic subjects more frequently than in the general population. In stable diabetes, these elevations are typically mild, not more than two times the upper limit of the normal range[77,78]. Elevations of these enzymes have been found more commonly in patients with NIDDM than in patients with IDDM and are associated with overweight. In a Finnish study of diabetic outpatients, serum activities of both alanine amino transferase and γ-glutamyl transpeptidase were

raised in ~23% of the 118 patients with NIDDM, which was a significantly higher percentage than for the 57 patients with IDDM[77]. Similarly, a study in Scotland of 166 diabetic outpatients found elevations in alanine amino transferase activity in 21% and γ-glutamyl transpeptidase activity in 31% of patients with NIDDM, but in no more than 5% of either controls or patients with IDDM[83]. For the diabetic patient with persistent enzyme activity elevation and after exclusion of other causes of liver diseases, it must be decided if liver biopsy and other expensive and invasive tests are necessary. As indicated above, most of these patients can be expected to have steatosis and some will also have fibrosis[77].

Whether nonalcoholic fatty liver or steatohepatitis proceed to cirrhosis is controversial. Several cross-sectional studies found a small number of patients with severe fibrosis or cirrhosis among patients with steatosis[72,75,84-86]. More persuasive are long-term studies that found progression to severe liver disease among obese patients with steatosis. Because these studies each followed ≤6 patients, it can only be concluded that progression to cirrhosis may occur, but the risk is unknown[87-91]. It is also not clear from these studies whether progression of liver disease occurs more quickly or is more likely in the presence of diabetes. A disturbing finding was progression of fatty liver to fibrosis in five of 41 patients treated with intensive, short-term weight loss[92]. In contrast, results from a controlled clinical trial of nondiabetic, overweight, hypertensive men treated with either diet or antihypertensive drugs for a year indicated that weight loss improves hepatic enzyme abnormalities[93]. In the diet-treated group, 10 of 31 patients had elevated serum alanine aminotransferase activities at entry, decreasing to four patients after weight loss ($p=0.04$). No changes in enzyme activities were observed in the drug-treated group. A similar clinical trial conducted in diabetic patients would be informative regarding cause as well as treatment of liver disease in diabetes.

Cirrhosis and diabetes are associated in autopsy studies, with cirrhosis being found at least twice as commonly in diabetic than in nondiabetic patients[94,95]. It is impossible to infer causation from these studies. For example, alcohol abuse could cause cirrhosis, and cirrhosis could then affect glucose tolerance. Presumably, cirrhosis due to obesity or diabetes would have similar consequences as that caused by alcohol or other exposures. Liver cancer, a sequela of cirrhosis, and diabetes were associated on hospital discharge records (Table 21.3) and in a longitudinal population-based study in Sweden[96]. A large Italian case-control study of primary liver cancer found a significant association of diabetes with liver cancer (odds ratio 2.5, 95% CI 1.7-3.8) which persisted after controlling for cirrhosis[97]. In a long-term followup of >1,200 Japanese diabetic subjects, the observed number of deaths from cirrhosis was 2.7 times and from liver cancer was 3.6 times the expected number based on rates in the general population[98]. Mortality followup of a Paris, France prospective cohort study revealed that 10 of 80 deaths of diabetic subjects were due to cirrhosis[99]. Relative to persons with normal glucose tolerance, persons with diabetes had 13 times and persons with IGT seven times the cirrhosis mortality rates.

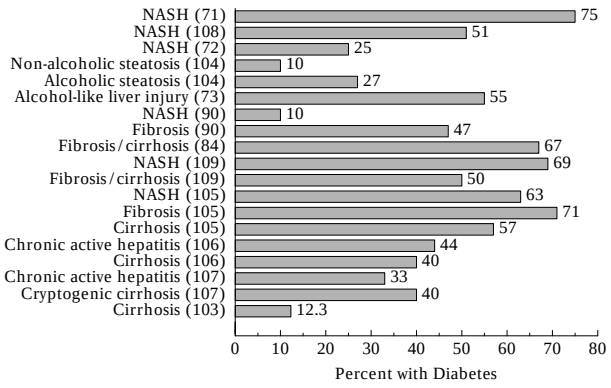
Not all studies have shown a relationship of diabetes to liver disease mortality. For Pima Indians, deaths from chronic liver disease were not more common in diabetic than nondiabetic subjects[100]. Despite the high prevalence of alcoholism in this community, a higher rate of liver disease mortality in diabetic than in nondiabetic people might have been expected if diabetes were a contributor to cirrhosis.

DOES LIVER DISEASE CAUSE DIABETES?

Direct evidence for liver disease causing diabetes would come from prospective studies that demonstrate a higher incidence of diabetes in persons with liver disease than in persons without. This increased risk would be independent of or additive to the effects of obesity and other common risk factors for diabetes. Such a study has not been performed, although there is less direct evidence for liver disease causing diabetes. In a population-based study of urban Swedish men age 54 years, the risk of diabetes 13.5 years after a baseline examination was higher with increasing serum glutamic pyruvic transaminase activity and serum bilirubin, both of which are markers of liver disease[101]. Although there was no testing for diabetes at baseline, the analysis did control for body mass index (BMI) and a family history of diabetes. A study of 100 patients with liver cirrhosis in Naples, Italy who had normal glucose tolerance at a baseline examination found a 20% cumulative incidence of diabetes diagnosed by OGTT within 4 years[102]. There was no comparison group, no reporting of BMI or other risk factors, and, oddly, no one who developed IGT. Nevertheless, a 20% risk of NIDDM over 4 years in persons with initially normal glucose tolerance would be considered high in almost any population.

Figure 21.2 shows the prevalence of diabetes in clinical studies of persons with liver disease[71-73,84,90,103-109]. The liver disease ranged from steatosis to cirrhosis. The prevalence of diabetes ranged from 10% to 75% but did not appear related to the severity of liver

Figure 21.2
Prevalence of Diabetes According to Liver Pathology



NASH, non-alcoholic steatohepatitis. Sample sizes are: Reference 71, 16; Reference 108, 49; Reference 72, 20; Reference 104, non-alcoholic steatosis, 64; Reference 104, alcoholic steatosis, 206; Reference 73, 39; Reference 90, NASH, 42; Reference 90, fibrosis, 15; Reference 84, 6; Reference 109, NASH, 13; Reference 109, fibrosis/cirrhosis, 8; Reference 105, NASH, 8; Reference 105, fibrosis, 7; Reference 105, cirrhosis, 7; Reference 106, hepatitis, 48; Reference 106, cirrhosis, 50; Reference 107, hepatitis, 6; Reference 107, cirrhosis, 10; Reference 103, 851.

Source: References are listed in parentheses within the figure

disease. Being cross-sectional, these results demonstrate that liver disease and diabetes are associated, but not a causal direction. A similar conclusion can be made about the association of OGTT results and abnormal serum γ-glutamyl transpeptidase activity (GGT), which is a sensitive marker of alcohol consumption and liver injury[110,111]. One such study performed an OGTT on >4,000 middle-aged men without fasting hyperglycemia in a multiphasic screening program in Malmö, Sweden[110]. Based on a dose of 30 g glucose/m^2 body surface area and 2-hour blood glucose of ≥7.0 mmole/l, the prevalence of abnormal glucose tolerance was determined for three groups: 2,196 men with a serum GGT activity lower than the median (9% with abnormal glucose tolerance), 35 men with elevated GGT but with a negative history of alcohol consumption (17% with abnormal glucose tolerance), and 136 men with elevated GGT and history of moderate to heavy alcohol consumption (26% with abnormal glucose tolerance). Although the authors argued that it was alcohol consumption and not underlying liver disease that caused the abnormal glucose tolerance, similar results could have occurred if diabetes promoted liver injury. Other studies have found at least a modest association of alcohol and diabetes[112-114], but this has not been a universal finding[115,116]. Because chronic alcohol consumption has effects throughout the body, an association of alcohol consumption with diabetes does not necessarily mean that liver injury is the cause of the diabetes.

Considerable inquiry has been made into the metabolic basis for diabetes as a consequence of cirrhosis. The more informative studies have found abnormalities of glucose metabolism in cirrhotic patients without diabetes[117-126]. These studies indicate that the primary metabolic defect is peripheral insulin resistance and that inadequate insulin secretion and hepatic insulin resistance appear to be later phenomena, just as occurs in NIDDM unrelated to liver disease. Although its underlying cause remains to be determined, it has been suggested that peripheral insulin resistance may develop as compensation for hyperinsulinemia due to diminished hepatic insulin metabolism[118]. This hyperinsulinemia is more likely due to liver cell damage than to porto-systemic shunting, because surgical shunts have not been found to affect insulin resistance in cirrhosis[122]. Not all studies support the hypothesis that cirrhosis leads to insulin resistance. For example, 30 nondiabetic alcoholic subjects had similarly elevated fasting and post-OGTT plasma insulin concentrations regardless of whether they had histological liver disease[127].

Persons with diabetes, particularly in developing countries, have a history of hepatitis B more commonly than do persons without diabetes[128]. Contaminated needles used for injecting insulin do not seem to be the only cause, since the seroprevalence of hepatitis B was similar for patients using and not using insulin[128]. Such unexpected associations suggest that it may be instructive to compare glucose tolerance and insulin levels in persons with differing causes and stages of liver disease. Two common conditions suggest themselves: heavy drinkers and persons with chronic viral hepatitis with or without cirrhosis or other chronic liver disease.

GALLSTONES

Gallstones are classified according to their predominant constituents into three types: cholesterol, black pigment, and brown pigment gallstones. Possibly 80% of gallstones in the United States are cholesterol gallstones, although the exact percentage is not known. Increasing age, female sex, and overweight are strongly associated with risk of developing gallstones[129]. Cholecystectomy is the main treatment for symptomatic gallstones; gallstone disease refers to having the condition of gallstones or a history of cholecystectomy. Currently, three metabolic factors are considered important in the development of cholesterol gallstones: 1) a high proportion of cholesterol in the bile relative to solubilizing bile acids and phospholipids, 2) an imbalance of pro-nucleating factors

relative to anti-nucleating factors in the bile, and 3) diminished gallbladder motility, which prolongs the opportunity for cholesterol nucleation in the gallbladder[130-132]. Potentially, diabetes could increase the likelihood of gallstones through each of these processes. Biliary cholesterol supersaturation is associated with diabetes, particularly among the overweight and insulin-treated[133-136]. However, it has not been shown that this association is independent of the strong association of cholesterol supersaturation with overweight[137,138]. Long-standing diabetes is associated with impaired gallbladder motility, particularly if autonomic neuropathy is present[139-143], whereas obesity has not been associated with impaired motility[144-147]. Whether diabetes accelerates cholesterol nucleation has not been adequately investigated.

Gallstones may be detected by oral cholecystography, but abdominal ultrasonography has become the favored diagnostic test because of its safety and accuracy[148,149]. The results of four cross-sectional studies that combined one of these diagnostic tests with OGTTs were inconclusive regarding an increased prevalence of gallstone disease in diabetic patients

Table 21.6
Prevalence and Relative Risk of Gallstone Disease (Gallstones or Cholecystectomy), According to Diabetes Status

Ref.	Diagnosis of GSD	Diabetes status	No.	GSD (%)	Adjusted RR	95% CI
Studies with glucose tolerance testing						
150	Oral cholecystogram	Diabetes	128	63.2	1.06	0.59-1.90
		No diabetes	206	64.1	1	
151	Ultrasonography	Women				
		Diabetes			1.9	0.9-3.9
		IGT			1.4	0.9-2.2
		Normal OGTT			1	
		Men				
		Diabetes			0.9	0.3-2.9
		IGT			1.3	0.5-3.3
		Normal OGTT			1	
152	Ultrasonography	Men				
		Diabetes	165	3.0	0.8	0.3-2.1
		IGT	302	6.0	1.6	0.9-2.7
		Normal OGTT	2,272	3.3	1	
153	Ultrasonography	Diabetes	67	11.9	2.59	1.12-5.96
		Nondiabetic OGTT	791	3.9	1	
154	Self-report	Women				
		Diabetes			1.83	1.07-3.14
		Nondiabetic OGTT			1	
		Men				
		Diabetes			1.71	0.63-4.65
		Nondiabetic OGTT			1	
155	Self-report	Women				
		Diabetes	171	35.7	1.60	1.00-2.37
		Nondiabetic OGTT	1,485	12.5	1	
		Men				
		Diabetes	97	7.2	1.19	0.46-2.09
		Nondiabetic OGTT	1,153	3.0	1	
156	Prospective development of clinical GSD	serum glucose (mmole/L)				
		≥10.50	1,824	7.0	1.4*	1.0-1.8
		8.30-10.49	1,835	7.1	1.3*	1.0-1.7
		8.77-8.29	1,827	6.1	1.1*	1.1-1.8
		<6.77	1,849	5.3	1.0	
		per mole/L serum glucose			1.2	0.9-1.6
					1	
NHANES II†	Self-report	Diabetes	948	12.1	1.60*	1.01-2.53
		Nondiabetic OGTT	3,521	5.2	1	

Table 21.6—Continued next page

Table 21.6 Continued

Ref.	Diagnosis of GSD	Diabetes status	No.	GSD (%)	Adjusted RR	95% CI
Studies without glucose tolerance testing						
157	Self-report	Diabetes	105	6.7	1.25	0.5-2.3
		No diabetes	4,900		1	
158	Cholecystectomy	Diabetes	60		0.66	0.35-1.19
		No diabetes	2,023		1	
159	Ultrasonography	Diabetes	54	11.1	1.31	0.45-3.11
		No diabetes	2,266	8.7	1	
160	Ultrasonography	Diabetes	41	17.1	1.12	0.57-2.21
		No diabetes	1,738	10.8	1	
161	Ultrasonography	Diabetes	67	13.4	1.80*	0.77-3.73
		No diabetes	3,350	9.1	1	
162	Self-report	Diabetes	76	32.9	2.13*	1.18-3.92
		No diabetes	462	16.2	1	
163	Self-report	Diabetes	262	21.8	1.07	0.81-1.40
		No diabetes	1,026	11.8	1	
24	Self-report	IDDM	87	2.3	0.18	0.02-0.74
		NIDDM	451	18.8	1.98	1.35-2.88
		No diabetes	588	11.0	1	

GSD, gallstone disease; RR, relative risk; CI, confidence interval; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test. *Not adjusted for overweight; †1976-80 Second National Health and Nutrition Examination Survey, see Table 21.2; adjusted relative risk values of 1 are the reference group.

Source: Reference are listed within the table

(Table 21.6)[150-153]. Two of these studies were conducted in the United States. In Pima Indians, in whom gallstone disease was diagnosed by oral cholecystography or history of cholecystectomy, no association was found between diabetes and gallstone disease[150]. A recalculation of the age- and sex-adjusted odds ratio of diabetes as a risk factor for gallbladder disease confirms the lack of association: the odds ratio and 95% CI were 1.06 (0.59-1.90). In women in the 1982-84 Hispanic Health and Nutrition Examination Survey (HHANES), the odds ratio of gallstone disease for diabetic glucose tolerance relative to normal glucose tolerance was 1.9 (95% CI 0.9-3.9) and for IGT relative to normal glucose tolerance was 1.4 (95% CI 0.9-2.2)[151]. The odds ratios were adjusted for age, BMI, ethnicity, and other factors. Persons who reported previously diagnosed diabetes were not included in the analysis. Such people generally have had diabetes for a longer time and are more likely to have complications than newly diagnosed diabetic patients. For men in HHANES, no association was found between diabetes or IGT and gallstone disease, although the number of men with gallstone disease (n=53) was only about one-fifth the number of women with gallstone disease (n=253) and may have been too few to detect an association.

Glucose tolerance tests using standard World Health Organization (WHO) criteria and gallbladder ultrasonography were conducted in >2,700 Japanese men age 48-56 years[152]. IGT was associated with gallstone disease after adjustment for BMI and other risk factors (odds ratio 1.6, 95% CI 0.9-2.7) whereas diabetes was not associated (odds ratio 0.8, 95% CI 0.3-2.1). This study stands out because of its large size and the elimination of any confounding effect of age.

The study with the strongest association of gallstones with diabetes employed a standard glucose tolerance test and ultrasonography in a population-based survey of three villages in Taiwan[153]. The relative risk of diabetes for gallstone disease declined from 3.22 to 2.59 with control for other risk factors, including age and percent body weight, but remained strongly significant.

Other studies of the association of gallstone disease and diabetes have been subject to selection or measurement bias because either one or both conditions were ascertained by self-report or medical history[24,154-163]. For several of the studies, the risk of gallstone disease for diabetic relative to nondiabetic subjects was not provided in the paper but could be calculated from frequency counts and prevalence, although adequate adjustment for age and overweight could not be made.

The results in Table 21.6 indicate that diabetes may be a risk factor for gallstone disease in some populations, such as eastern Asians, but not in other populations.

Such inconsistent results may relate to the cross-sectional nature of most of the studies but could also indicate that confounding factors may be influencing the observed associations with diabetes. Also, the clinical characteristics of diabetes have not had a consistent relationship with gallstone disease. For example, a followup of patients with NIDDM in one study that had found a positive association with gallstones reported the following: self-reported gallstone disease was associated with duration of diabetes, was inversely associated with fasting glucose concentration, and was unrelated to the type of diabetic therapy[164].

It may be that hyperinsulinemia has a greater role in gallstone development than diabetes itself. Hyperinsulinemia is more common in people with clinically identified gallstone disease than in controls[155,165-167]. Thus, an increased risk of gallstone disease in persons with NIDDM may depend on the insulin resistance and hyperinsulinemia that characterizes the development of NIDDM.

Gallstones appear to be a more dangerous condition for persons with diabetes than for the general population. People with diabetes have higher morbidity and mortality for both elective and emergency cholecystectomy[168,169]. Diabetic subjects with gallstones are also more likely to be older than other persons with gallstones and have other medical problems that may contribute to higher rates of complications[168,170]. For example, one study found that diabetic patients had more frequent postoperative complications (24.6% versus 12.5%) and higher mortality (7.9% versus 3.0%) than nondiabetic patients, but the increased morbidity was due to older age and greater comorbidity in those with diabetes[168]. A decision analysis that compared no immediate surgery with prophylactic cholecystectomy in diabetic patients with asymptomatic gallstones recommended against cholecystectomy[171], but it was based on the assumption of high mortality rates for elective surgery (at least 1%) and without consideration of the impact of laparoscopic alternatives to open cholecystectomy.

PANCREAS

CONCURRENT DIABETES AND PANCREATIC CANCER

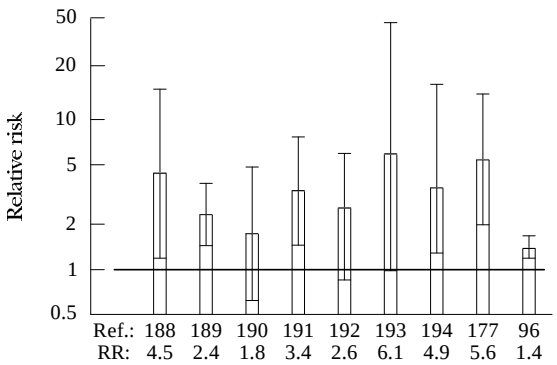
Diabetes or IGT has been found in the majority of patients with pancreatic cancer[172,173]. In one study, a standard OGTT was conducted in 44 patients with pancreatic adenocarcinoma evaluated at a referral center in Sweden[172]. Two patients had known diabetes for at least 7 years, seven had had a diagnosis of diabetes within the previous 14 months, 19 had previously undiagnosed diabetes, and five had IGT. Thus, 33 of the 44 patients had abnormal glucose tolerance. Although these results are not necessarily representative of all patients with pancreatic cancer, they are consistent with other reports of the co-occurrence of clinically recognized diabetes and pancreatic cancer. Among 305 patients with pancreatic cancer and diabetes in five reports, 34.8% had diabetes diagnosed within a year of the diagnosis of pancreatic cancer[174-178]. In addition, pancreatic cancer was overrepresented in the discharge diagnoses of diabetic patients in the 1987-91 NHDS, with a co-occurrence that was 43% higher than discharges without diabetes mentioned (Table 21.3).

Patients with diabetes and cancer of the pancreas do not usually have a limited ability to secrete insulin due to pancreatic tumor infiltration. In fact, serum insulin in these patients is typically higher than in controls, and the metabolic profile is similar to that of patients with NIDDM: peripheral insulin resistance with diminished insulin and C-peptide response to a glucose challenge[179,180]. One study observed that, following subtotal pancreatectomy for pancreatic cancer, patients had either resolution of diabetes or lower insulin requirements, marked by improved insulin sensitivity and diminished insulin secretion[181]. However, all of these patients had lost weight prior to post-operative testing, and nearly all were jaundiced prior to surgery, which may in itself be a cause of glucose intolerance[182]. Islet amyloid polypeptide, a hormone secreted by beta cells that reduces insulin sensitivity, is elevated in patients with pancreatic cancer and declines with improved glucose tolerance following resection of the tumor[183]. Further investigation into the mechanisms of the hyperglycemia of pancreatic cancer may provide insight into NIDDM pathogenesis. Accordingly, the high risk of diabetes in patients with pancreatic cancer may be of more interest to diabetes researchers than to oncologists.

DIABETES AS A RISK FACTOR FOR PANCREATIC CANCER

Because pancreatic cancer may present with diabetes, reviewers have refrained from concluding that diabetes is a risk factor for the occurrence of pancreatic cancer[3,7,184-186]. To address this issue, a meta-analysis was conducted with the consideration that diabetes may also be a consequence of pancreatic cancer[187]. Twenty of 30 case-control and cohort studies met the two inclusion criteria: diabetes duration of ≥1 year prior to either diagnosis of or death from pancreatic

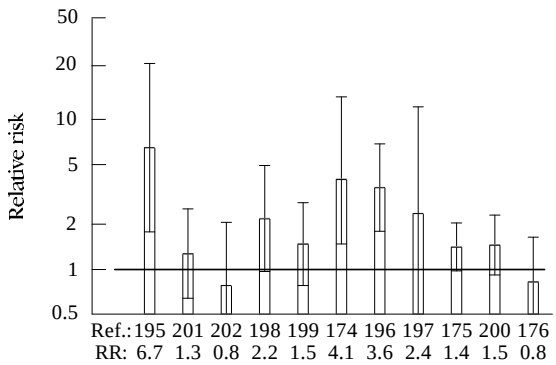
Figure 21.3
Relative Risk and 95% Confidence Interval of Pancreatic Cancer for Patients in Cohort Studies



RR, relative risk.

Source: References are listed within the figure

Figure 21.4
Relative Risk and 95% Confidence Interval of Pancreatic Cancer for Patients in Case-Control Studies



RR, relative risk.

Source: References are listed within the figure

cancer, and the provision of age-adjusted relative risks and estimates of their precision. Of the nine cohort studies[96,177,188-194] and the 11 case-control studies[174-176,195-202], 18 demonstrated a positive association between preexisting diabetes and the occurrence of pancreatic cancer (Figures 21.3 and 21.4). The pooled relative risk of pancreatic cancer for diabetic relative to nondiabetic subjects was 2.1 (95% CI 1.6-2.8). The exclusion of persons with diabetes of <5 years duration also resulted in an elevated relative risk of 2.0 (95% CI 1.2-3.2).

A weakness common to most studies of diabetes and pancreatic cancer is the poor characterization of diabetes. Only two of the studies included in the meta-analysis diagnosed diabetes by glucose tolerance testing[177,194]; all other studies based the diagnosis on medical history. A clear distinction was made between IDDM and NIDDM in only two studies[175,194]. This distinction might be important because pancreatic duct cells, from which most pancreatic tumors arise, are exposed to low levels of exogenously administered insulin in IDDM, but generally to high levels of insulin for years both before and after the development of NIDDM. The majority of cases of pancreatic cancer occur after age 70 years, when NIDDM is the predominant form of diabetes. Studies that presumably had a higher proportion of patients with IDDM, including cohorts from the Joslin Clinic in Boston, MA[178] and insulin-treated diabetic patients in Denmark[203], had lower relative risks than most of the studies in the meta-analysis. A potential role of hyperinsulinemia in the pathogenesis of pancreatic cancer would be through increases in local blood flow and cell division within the pancreas[204].

EXOCRINE PANCREAS

Worldwide, there is a strong association of tropical or nutritional pancreatitis and diabetes. Because this form of pancreatitis is largely found in tropical countries, it has a negligible effect on diabetes prevalence in developed countries. With no data available from the United States on this condition, it will not be considered further.

The major function of the exocrine pancreas is secretion of digestive enzymes and bicarbonate into the duodenum. Secretory abnormalities of the exocrine pancreas are common in diabetes. For example, a study of 55 diabetic patients without pancreatitis found that 73% had diminished bicarbonate output in response to secretin administration[205]. But while this and other studies[206-210] have shown that abnormal exocrine pancreatic function occurs in a high proportion of diabetic patients, correlation with malabsorption or other clinically significant abnormality has been difficult to demonstrate[205,210,211], perhaps because of the high secretory capacity of the pancreas. For example, none of a group of 33 patients with chronic diarrhea and diabetes had the cause attributed to pancreatic insufficiency[37]. Nevertheless, the association of exocrine and endocrine pancreatic disorders is interesting; diminished exocrine activity found with diabetes has been considered evidence that pancreatic islets and acini do not function independently[212]. In particular, exocrine pancreatic atrophy in IDDM may be caused by insulin deficiency[212,213]. Sized by ultrasonography, the pancreas in patients with IDDM has been found, on average, to be smaller than in patients with NIDDM and in controls[214].

Table 21.7
Diabetes in 335 Patients with Chronic Pancreatitis Followed for a Median of 10 Years

	Diabetes absent No. (%)	Diabetes, not insulin-treated No. (%)	Diabetes, insulin-treated No. (%)	OR (95% CI), any diabetes vs. no diabetes	OR (95% CI), insulin-treated diabetes vs. no diabetes
At pancreatitis onset	307 (92)	13 (4)	15 (5)		
At followup	75 (22)	127 (38)	133 (40)		
Nonalcoholic pancreatitis	35 (33)	36 (34)	34 (33)	1	1
Alcoholic pancreatitis	40 (17)	91 (40)	99 (43)	2.4 (1.4-4.2)	2.6 (1.3-4.8)
Alcohol abstainers	22 (33)	19 (29)	25 (38)	1	1
Nonabstainers	18 (12)	66 (42)	72 (46)	3.8 (1.8-8.3)	3.5 (1.5-8.2)
Severe exocrine insufficiency	5 (5)	51 (50)	46 (45)	7.6 (2.4-27.8)	24.5 (5.7-113.8)
Moderate exocrine insufficiency	14 (21)	35 (53)	17 (26)	1.5 (0.6-3.6)	3.2 (0.9-12.7)
Slight exocrine insufficiency	16 (28)	35 (61)	6 (11)	1	1

OR, odds ratio; CI, confidence interval.

Source: Adapted from Reference 218

The diagnoses of acute and, in particular, chronic pancreatitis were found on a higher percentage of hospital discharges with diabetes than on hospital discharges without diabetes (Table 21.3). Hyperglycemia complicating acute pancreatitis is considered a prognostic sign for early mortality[215]. Diabetes diagnosed prior to pancreatitis may also be an important prognostic factor. Among 405 deaths due to acute pancreatitis, diabetes was present in 23.2%, about twice as often as in a control group[216]. Little has been published on long-term followup of glucose tolerance following acute pancreatitis. In a study of Italian patients with the severe necrohemorrhagic form of acute pancreatitis, three of 27 patients reported diabetes prior to pancreatitis, whereas four had a diabetic glucose tolerance test and 12 had IGT 1-2 years following resolution of the acute pancreatitis[217].

The risk of developing diabetes with chronic pancreatitis is quite high. A prospective study in Germany of 335 patients with chronic pancreatitis followed for a median of 10 years found that diabetes was present in 8% at diagnosis of pancreatitis and in 78% by the conclusion of followup (Table 21.7)[218]. Half of the diabetic patients were treated with insulin. Alcoholism was a significant predictor of diabetes development: the odds of diabetes were elevated for patients with alcoholic pancreatitis relative to patients with other causes, and patients with alcoholic pancreatitis who continued to consume alcohol had higher odds of diabetes than abstainers. Diabetes was also correlated with the degree of pancreatic exocrine insufficiency: at the end of the study, patients with severe exocrine insufficiency had an odds of insulin-treated diabetes that was 24.5 times that of patients with slight insufficiency. Studies in France, Switzerland, Japan, and Finland have also found a high risk of diabetes in patients with chronic pancreatitis[219-222]. A similar longitudinal study of a cohort of patients with chronic pancreatitis has not been reported for patients in the United States, but there is no reason to believe the risk of diabetes would be low.

The cause of the diabetes in chronic pancreatitis is most likely fibrosis and vascular insufficiency that affects the entire pancreas[223]. It is also possible that significant nonlocal effects may occur, particularly in alcoholic persons, many of whom also have chronic liver disease. It has been suggested that peripheral insulin resistance is a cause of diabetes in chronic pancreatitis[224], but patients have not been sequentially studied with standard tests for insulin-mediated glucose disposal to verify this hypothesis.

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