Increased Risk of Acute Pancreatitis and Biliary Disease Observed in Patients With Type 2 Diabetes

A retrospective cohort study

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OBJECTIVE — The objective of this study was to assess the risk of acute pancreatitis in patients with type 2 diabetes compared with that in patients without diabetes. We also examined the risk of biliary disease (defined as occurrence of cholelithiasis, acute cholecystitis, or cholecystectomy), which is a major cause of pancreatitis.

RESEARCH DESIGN AND METHODS — We conducted a retrospective cohort study using a large, geographically diverse U.S. health care claims database. Eligible patients (≥18 years) were enrolled for at least 12 continuous months (1999–2005), with no incident events of pancreatitis or biliary disease during that 1 year baseline period. ICD-9 codes and prescription data were used to identify patients with type 2 diabetes; ICD-9 codes were also used to identify cases of pancreatitis and biliary disease. Overall, 337,067 patients with type 2 diabetes were matched on age and sex with 337,067 patients without diabetes. Incidence rates of disease and 95% CI were calculated per 100,000 person-years of exposure.

RESULTS — The type 2 diabetic cohort had a 2.83-fold (95% CI 2.61–3.06) greater risk of pancreatitis and 1.91-fold (1.84–1.99) greater risk of biliary disease compared with the nondiabetic cohort. Relative to patients of corresponding age without diabetes, younger type 2 diabetic patients had the highest risk of pancreatitis (<45 years: incidence rate ratio [IRR] 5.26 [95% CI 4.31–6.42]; ≥45 years: 2.44 [2.23–2.66]).

CONCLUSIONS — These data suggest that patients with type 2 diabetes may have an increased risk of acute pancreatitis and biliary disease.

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Acute pancreatitis is an inflammatory condition of the pancreas. Worldwide annual incidence of acute pancreatitis varies 10-fold, with western countries reporting an increased incidence over the past 40 years (1). Gallstones and alcohol abuse are the most common causes of acute pancreatitis, accounting for 60–80% of cases (2). The etiology of acute pancreatitis remains unknown in ~20% of patients (3). Acute pancreatitis is a risk factor for subsequent development of recurrent pancreatitis in 4–14% of patients (4).

The reason for the increased incidence of acute pancreatitis is unknown. However, it is notable that a concurrent trend has been the rapid, worldwide increase in type 2 diabetes and obesity. Several clinical factors associated with type 2 diabetes (5,6) and obesity (7–11) are known or putative risk factors for acute pancreatitis; therefore, it seems likely that the risk of acute pancreatitis in patients with type 2 diabetes would be higher than that of the general population. However, the published literature appears to be largely silent regarding whether type 2 diabetes is a risk factor for pancreatitis (7).

Exenatide was approved in April 2005 by the U.S. Food and Drug Administration as adjunctive therapy to improve glycemic control in patients with type 2 diabetes. After market introduction, there were spontaneous reports of pancreatitis that prompted this investigation. Specifically, the objective of this study was to assess the risk of acute pancreatitis and biliary disease in patients with type 2 diabetes compared with that in patients without diabetes.

RESEARCH DESIGN AND METHODS

— A retrospective claims database analysis was performed using a proprietary research database containing eligibility information and pharmacy and medical claims data from a large commercial U.S. health plan providing coverage for physician, hospital, and prescription-drug services. The plan subscribers represent a geographically diverse sampling from all regions of the U.S., with the greatest proportions of members in the Midwest and South. The database includes medical and prescription drug benefit claims data for ~14 million patients during 2007. Data derived from this source have been used for a variety of utilization, safety, and economic analyses (12–14).

Eligible patients were ≥18 years and enrolled for at least 12 continuous months from 1999 to 2005, with at least 30 days of follow-up from the end of the 1-year enrollment (n = 9,249,211). The index date was defined as the date when the patient accrued 1 year of prior continuous enrollment (the baseline period).

Table 1 presents the patient selection process. Patients were assigned to the nondiabetic cohort if during the study period, they had no medical claims for diabetes (ICD-9 code 250.xx), no claim for an antidiabetic medication, and at least one medical claim processed (n = 6,947,299). Patients were assigned to the type 2 diabetic cohort if during the study

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Table 1—*Patient selection criteria for a retrospective claims database study of the risk of pancreatitis or biliary disease associated with type 2 diabetes*

	Patients remaining	Patients removed
Enrolled in health plan at any time from 1 January 1999 through 31 December 2005	29,332,477	—
Total population aged ≥18 years as of 1 January 2000, continuous enrollment for ≥1 year from 1 January 1999 through 31 December 2005	12,210,809	17,121,668
At least 30 days of continuous enrollment from the end of 1-year enrollment	9,249,211	2,961,598
Control cohort: patients without diabetes		
No medical claims for diabetes (250.xx) during the study period	8,579,024	670,187
No claims for antidiabetes medication during study period	8,521,490	57,534
Sex is unknown	8,519,558	1,932
Any medical claims during the study period	6,947,299	1,572,259
Study cohort: type 2 diabetes		
Claim for type 2 diabetes or antidiabetic medication at any time from 1 January 1999 through 31 December 2005	1,337,081	—
Claim for type 2 diabetes or antidiabetes medication during the continuous enrollment period	640,504	696,577
Medical claim for type 2 diabetes (250.x0 or 250.x2) during the continuous enrollment period	563,827	76,677
Claim for antidiabetes medication during the continuous enrollment period	463,046	100,781
Medical claim for type 2 diabetes (250.x0 or 250.x2) AND a claim for an antidiabetes medication during 1 January 1999 through 31 December 2005	386,369	76,677
Drop patients on insulin-only therapy AND claim for type 1 diabetes (250.x1 or 250.x3)	352,633	33,736
Sex is known	352,569	64
Matching		
Pairs matched 1:1 by sex and age category	352,569	—
Pairs with available claims data	337,067	15,502

period, they had a claim for type 2 diabetes (250.x0 or 250.x2) and a filled prescription for an antidiabetes medication (n = 386,369). Antidiabetes medications were defined as biguanides, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, meglitinides, D-phenylalanine derivatives, pramlintide, exenatide, or insulins. Patients receiving insulin-only therapy with a claim for type 1 diabetes (250.x1 or 250.x3) were excluded from the study (n = 352,633 patients remaining).

Only patients of known sex were included in either cohort. Cohorts were pair-matched 1:1 on sex and age (n = 352,569). The pairs with available claims data after matching were used for this analysis (n = 337,067).

Patients with acute pancreatitis (ICD-9 code 577.0), cholelithiasis (574.2x, 574.5x, 574.9x, 576.1x, and 576.2x), acute cholecystitis (574.0x, 574.3x, 574.6x, 574.8x, 575.0, and 575.12), and cholecystectomy (51.2x) were identified based on the presence of the relevant diagnosis code on any medical claim. To ensure that this was a study of disease incidence, patients were excluded if they experienced outcome events during the 1-year baseline period. Specifically, for the pancreatitis analysis, patients were excluded if they had any claim for acute or chronic pancreatitis during the 1-year pre-enrollment period. For the biliary analysis, patients were excluded if they had any claim for cholelithiasis, acute cholecystitis, or cholecystectomy during the 1 year pre-enrollment. Laboratory, radiology, and pathology claims were not used to identify outcome events.

The total time at risk began on the index date and ended on the date of the first outcome event, disenrollment date, or the end of study date—whichever occurred first. For each cohort, exposure-adjusted incidence rates (per 100,000 patient-years of exposure) and 95% CI were calculated using Wald's method (15) for the overall cohort, stratified by age category and sex. Exposure-adjusted incidence rate ratios (IRRs) and accompanying 95% CIs between the two groups and within each stratum were also calculated (16). Patients with a diagnostic code for acute pancreatitis, cholelithiasis, acute cholecystitis, or cholecystectomy served as the numerators for the incidence calculations. All patient-years within each cohort served as the denominators.

RESULTS — The incidence rate for pancreatitis in the type 2 diabetic cohort was 422 cases per 100,000 patient-years compared with 149 cases per 100,000 patient-years in the nondiabetic cohort. In the diabetic cohort, the incidence rate was relatively constant across age-groups in contrast to the nondiabetic cohort, in which age was positively correlated with the incidence of pancreatitis (Table 2).

Overall, the type 2 diabetic cohort was at 2.83-fold (95% CI 2.61–3.06) greater risk of pancreatitis compared with the nondiabetic cohort. Relative to patients of corresponding age without diabetes, the youngest type 2 diabetes age-group (18–30 years) had the highest IRR of acute pancreatitis (7.75 [95% CI 3.89–15.43]), whereas patients aged ≥65 years with type 2 diabetes had the lowest IRR (1.64 [1.36–1.98]). Because type 2 diabetes typically occurs in patients aged ≥45 years, the IRRs of pancreatitis were calculated among individuals aged older and younger than 45 years. The results indicated that type 2 diabetic patients between the ages of 18 and 44 years experienced a 5.26-fold (95% CI 4.31–6.42) increased incidence of pancreatitis and those patients aged ≥45 years had a 2.44-fold (2.23–2.66) increased inci-

Table 2—*Incidence of acute pancreatitis associated with type 2 diabetes stratified by age and sex from a retrospective claims database study, 2000–2005*

	Nondiabetic cohort				Type 2 diabetic cohort				IRR: type 2 diabetic cohort vs. nondiabetic cohort (95% CI)
	*n**	Incident cases	Person-years of follow-up	Incidence rate per 100,000 person-years (95% CI)	*n*	Incident cases	Person-years of follow-up	Incidence rate per 100,000 person-years (95% CI)	
Overall age	336,410	827	553,959.28	149.29 (139.11–159.46)	334,930	2,551	604,684.35	421.87 (405.50–438.24)	2.83 (2.61–3.06)
18–30 years	13,628	9	17,029.62	52.85 (18.32–87.38)	13,553	81	19,780.12	409.50 (320.32–498.68)	7.75 (3.89–15.43)
31–44 years	78,518	105	120,783.10	86.93 (70.30–103.56)	78,051	584	132,996.11	439.11 (403.50–474.72)	5.05 (4.10–6.22)
45–54 years	120,354	272	200,359.38	135.76 (119.62–151.89)	119,823	862	217,352.86	396.59 (370.11–423.07)	2.92 (2.55–3.35)
55–64 years	91,859	273	154,084.70	177.18 (156.16–198.19)	91,526	723	167,069.73	432.75 (401.21–464.30)	2.44 (2.13–2.81)
≥65 years	32,051	168	61,702.48	272.27 (231.10–313.45)	31,977	301	67,485.52	446.02 (395.63–496.41)	1.64 (1.36–1.98)
Sex									
Female	148,868	370	242,728.54	152.43 (136.90–167.97)	148,288	1058	267,658.93	395.28 (371.46–419.10)	2.59 (2.30–2.92)
Male	187,542	457	311,230.74	146.84 (133.37–160.30)	186,642	1493	337,025.42	442.99 (420.52–465.46)	3.02 (2.72–3.35)

*Patients with events of acute pancreatitis (n = 594 from the nondiabetic cohort and n = 1,883 from the type 2 diabetic cohort) or chronic pancreatitis (n = 162 from the nondiabetic cohort and n = 656 from the type 2 diabetic cohort) during the 1-year baseline period were excluded from the numerator and the denominator. In addition, patients with chronic pancreatitis during follow-up were excluded (n = 26 from the nondiabetic cohort and n = 161 from the type 2 diabetic cohort). Note that some patients may have had more than one exclusionary event.

dence of pancreatitis compared with their nondiabetic counterparts of the corresponding age-group. For acute pancreatitis, the IRRs were similar between males and females in the two cohorts.

The incidence rate for biliary disease in the type 2 diabetic cohort was 1,411 cases per 100,000 patient-years compared with 737 cases per 100,000 patient-years in the nondiabetic cohort. In the diabetic cohort, the incidence rate was highest in the youngest (18–30 years) and oldest (≥65 years) age-groups, in contrast to the nondiabetic cohort in which age was positively correlated with the incidence of pancreatitis (Table 3). In both cohorts, the incidence of biliary disease was notably higher in women than in men, although the IRRs were similar between the sexes for the two cohorts.

Overall, the type 2 diabetic cohort had a 1.91-fold (95% CI 1.84–1.99) greater risk of biliary disease than the nondiabetic cohort. Relative to patients of corresponding age without diabetes, the youngest type 2 diabetes age-group (18–30 years) had the highest IRR of biliary disease (3.77 [95% CI 2.92–4.87]), whereas patients aged ≥65 years with type 2 diabetes had the lowest IRR (1.50 [1.37–1.65]).

Examination of the biliary disease subgroups revealed that cholelithiasis contributed ~50% of the total incident cases of cholecystitis, cholecystectomy, and cholelithiasis among both cohorts, and the incidence of cholelithiasis in type 2 diabetic patients was considerably higher (1,229 cases per 100,000 patient-years) than that in patients without diabetes (647 cases per 100,000 patient-years) (data not shown).

CONCLUSIONS — This study suggests that patients with type 2 diabetes have an almost threefold greater risk of pancreatitis and twofold greater risk of biliary disease than patients without diabetes. The high risk of pancreatitis among younger patients with type 2 diabetes relative to their nondiabetic peers is particularly notable, although the clinical meaning of this finding needs to be elucidated.

This study was limited by the data available in a managed care claims database, given that claims data are collected for payment and not for research. Patient compliance with prescription medications and use of physician samples were not captured. In addition, data regarding other possible risk factors for pancreatitis

Table 3—*Incidence of biliary disease associated with type 2 diabetes stratified by age and sex from a retrospective claims database study, 2000–2005*

	Nondiabetic cohort				Type 2 diabetic cohort				IRR: type 2 diabetic cohort vs. nondiabetic cohort (95% CI)
	*n**	Incident cases	Person-years of follow-up	Incidence rate per 100,000 person-years (95% CI)	*n*	Incident cases	Person-years of follow-up	Incidence rate per 100,000 person-years (95% CI)	
Overall age	333,529	4,019	545,088.58	737.31 (714.52–760.11)	330,742	8,322	589,693.44	1,411.24 (1,380.92–1,441.56)	1.91 (1.84–1.99)
18–30 years	13,557	72	16,884.62	426.42 (327.92–524.92)	13,354	309	19,217.66	1,607.90 (1,428.61–1,787.18)	3.77 (2.92–4.87)
31–44 years	78,030	599	119,453.07	501.45 (461.29–541.61)	77,222	1,574	130,181.10	1,209.08 (1,149.35–1,268.82)	2.41 (2.19–2.65)
45–54 years	119,356	1,300	197,277.31	658.97 (623.15–694.79)	118,355	2,839	212,090.87	1,338.58 (1,289.34–1,387.82)	2.03 (1.90–2.17)
55–64 years	90,942	1,286	151,221.24	850.41 (803.93–896.89)	90,335	2,357	162,847.33	1,447.37 (1,388.94–1,505.80)	1.70 (1.59–1.82)
≥65 years	31,644	762	60,252.34	1,264.68 (1,174.88–1,354.48)	31,476	1,243	65,356.48	1,901.88 (1,796.15–2,007.61)	1.50 (1.37–1.65)
Sex									
Female	147,073	2,179	237,325.48	918.15 (879.60–956.70)	145,557	4,387	258,394.28	1,697.79 (1,647.55–1,748.03)	1.85 (1.76–1.95)
Male	186,456	1,840	307,763.11	597.86 (570.54–625.18)	185,185	3,935	331,299.16	1,187.75 (1,150.64–1,224.86)	1.99 (1.88–2.10)

*Biliary disease was defined as occurrence of cholelithiasis, acute cholecystitis, or cholecystectomy. Patients with biliary disease ($n = 2,911$ from the nondiabetic cohort and $n = 5,173$ from the type 2 diabetic cohort) or chronic cholecystitis ($n = 452$ from the nondiabetic cohort and $n = 890$ from the type 2 diabetic cohort) during the 1-year baseline period were excluded from the numerator and the denominator. Note that some patients may have had more than one exclusionary event.

(such as alcohol use, obesity, weight loss, and concomitant medications) were not available. Another potential limitation is error in disease ascertainment, given that diagnostic codes may be incorrectly coded or included as rule-out criteria rather than actual disease. For example, although we used a conservative algorithm for identifying patients with type 2 diabetes (ICD-9 code AND use of an antidiabetic agent), some patients with type 1 diabetes were probably included in the cohorts, particularly in the younger age-groups. It is also noteworthy that the incidence rate of pancreatitis for the nondiabetic cohort reported in this epidemiologic study is approximately threefold greater than published estimates for the general population (1,4). The higher incidence of pancreatitis found in this study may be representative of an increase in pancreatitis, claims miscoding for pancreatitis, population differences, or the reporting method. A study of the accuracy of ICD-9 codes for pancreatitis conducted in a large VA population reported excellent sensitivity (93%) but lower specificity (79%) for acute pancreatitis (17); hence, it is likely that false-positive reports of pancreatitis were included in this study. Although the reason for the higher incidence of pancreatitis observed in this study is unknown, it is likely to be nondifferential across the two cohorts such that the increased risk of pancreatitis observed among the patients with type 2 diabetes is valid.

Strengths of this study include the large sample size, which is necessary given that pancreatitis is a rare event. These data also allow for the examination of health outcomes in a "real world" setting including a nationwide sample of patients with diverse medical histories. Nonetheless, the data used for this study come from a managed care population, and results are applicable primarily to the prevalence of outcomes in managed care settings. Age and sex bias were controlled for by pair matching. Finally, these results are probably conservative, given that subjects with undiagnosed diabetes may have been included in the nondiabetic cohort, a problem that is not unique to claims data.

In summary, the nearly threefold increased risk of pancreatitis for patients with type 2 diabetes reported here, combined with the increasing prevalence of diabetes and the associated risk factors, may be contributing to a meaningful increase in the incidence of acute pancreati-

tis in the U.S. Further studies are required to confirm these findings and to identify causal factors that may account for the observed increased risk of pancreatitis associated with diabetes.

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