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 +3.1–6.42]; ≥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
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 antidiabetic 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 | 33,376 |
| 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 |

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 2.44-fold (95% CI 2.23–2.66) increased incidence of pancreatitis and those patients aged ≥45 years had a 5.26-fold (95% CI 4.31–6.42) increased incidence of pancreatitis.
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 a twofold greater risk of biliary disease than patients without diabetes. The high risk of pancreatitis among younger patients with type 2 diabetes as compared with their nondiabetic counterparts is particularly notable, although the clinical meaning of this finding needs to be elucidated. The 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).
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 non-differential 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 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) |
|----------------|---------------------|------------------------|-------------------------------------------------------------|
|                | 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) | n |
| Overall age    | 333,529            | 4,019                  | 545,088.58                                                  | 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                                                   | 13,354 | 309    | 19,217    | 1,607.90 (1,428.61–1,787.18) | 3.77 (2.92–4.87) |
| 31–44 years    | 78,030             | 599                    | 119,453.07                                                  | 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                                                  | 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                                                  | 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                                                   | 31,476 | 1,243  | 65,356.48  | 1,901.88 (1,796.15–2,007.61) | 1.50 (1.37–1.65) |
| Sex            |                     |                        |                                                            | 147,073 | 2,179  | 237,325.48 | 918.15 (879.60–956.70) | 1.85 (1.76–1.95) |
| Female         | 186,456            | 1,840                  | 307,763.11                                                  | 145,557 | 4,387  | 258,394.28 | 1,697.79 (1,647.55–1,748.03) | 1.99 (1.88–2.10) |
| Male           |                     |                        |                                                            | 185,185 | 3,935  | 331,299.16 | 1,187.75 (1,150.64–1,224.86) | 1.70 (1.59–1.82) |

* 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.
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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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