Obesity and Treatment of Diabetes With Glyburide May Both Be Risk Factors for Acute Pancreatitis

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OBJECTIVE — To evaluate risk factors, notably drugs, for acute pancreatitis.

RESEARCH DESIGN AND METHODS — A population-based case-control study was conducted of 1.4 million inhabitants, aged 20–85 years, of four regions in Sweden between 1 January 1995 and 31 May 1998. A total of 462 case subjects were hospitalized in surgery departments for their first episode of acute pancreatitis without previous gallbladder disease. A total of 1,781 control subjects were randomly selected from a population register. Information was obtained from case records and through telephone interviews.

RESULTS — A total of 27 case subjects (6%) and 55 control subjects (3%) had prevalent diabetes. A total of 53 case subjects (11%) and 130 control subjects (7%) had a BMI >30 kg/m^2. Use of glyburide had a crude odds ratio (OR) of 3.2 (95% CI 1.5–5.9), and in a multivariate logistic regression adjusted for covariates, the OR for use of glyburide was 2.5 (1.1–5.9). BMI had a continuous OR of 1.2 (1.1–1.4) per 5 units of BMI. The relative risk for hospitalization longer than 14 days or treatment in an intensive care unit was 2.4 (1.1–5.4) among patients with a BMI >30 kg/m^2 when compared with patients with a BMI between 20 and 25 kg/m^2.

CONCLUSIONS — Use of glyburide and obesity may both be risk factors for acute pancreatitis. Obesity is associated with an extended hospitalization time in subjects with acute pancreatitis.

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Acute pancreatitis may be caused by intrapancreatic activation of digestive enzymes leading to autodigestion. Activation of trypsin is regarded as central for initiating the process. The major causes are reported to be excessive intake of alcohol and cholelithiasis, which account for ~80–90% of cases (1,2). Pancreatic trauma, gastrointestinal perforations and infections, tumors, hyperlipidemia, hypercalcemia, inflammatory bowel disease, and exposure to pancreatoxic drugs have been suggested as additional risk factors. Diabetes is a known complication of severe acute pancreatitis (3,4), but there are no studies describing diabetes or its treatment as risk factors for acute pancreatitis. High BMI has been associated with increased risk of complications in the clinical course of acute pancreatitis (5–10).

In a nationwide case-control study, we investigated risk factors for acute pancreatitis. In this first report, we analyzed whether use of glyburide, diabetes, and obesity are risk factors for acute pancreatitis and whether obesity is related to the severity of the disease.

RESEARCH DESIGN AND METHODS

— The Medical Product Agency is responsible for pharmacovigilance in Sweden. The operation is decentralized; one surveillance center is located in each of the six health care regions. The centers are staffed by nurses who trained in clinical pharmacology, pharmacovigilance, and epidemiology in the Departments of Clinical Pharmacology at the regional university hospitals, and clinical pharmacologists serve as consultants. The centers run both the reporting system for suspected adverse drug reactions and a case-control study network, which was used in the present study. The central and regional research ethics committees approved the study.

Study population

Four regions, Umeå, Uppsala, Stockholm, and Malmö, comprise 2.2 million inhabitants. The population from which the case subjects and control subjects were drawn was restricted to individuals aged 20–85 years who resided in the study area for at least 6 months, had a telephone with a publicly listed number, and spoke Swedish. This population was estimated to be 1.4 million people. Collection of data took place between 1 January 1995 and 31 May 1998; the study base comprised 4.7 million person years.

Case subjects

Case subjects were patients hospitalized in surgery departments in eight participating hospitals for their first episode of acute pancreatitis without previously known gallstone disease. Potential case subjects were identified through daily scanning of laboratory printouts of serum amylase levels in the participating hospitals. A potential case of acute pancreatitis was considered any patient admitted to the department of surgery with a serum amylase level of at least twice the upper limit of the normal reference value within

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Abbreviations: ICU, intensive care unit; OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Reasons for nonparticipation among eligible case and control subjects*

	Case subjects	Control subjects
Total eligible	779	2,129
Transferred to another clinic	21 (2.7)	
Too ill because of concomitant disease	15 (1.9)	21 (0.90)
Unreliable interview	3 (0.4)	1 (0.04)
No permission of physician	2 (0.3)	
Dementia	64 (8.2)	7 (0.30)
Refusal	55 (7.1)	187 (8.80)
Missed medical records	22 (2.8)	
Failure to establish contact	74 (9.4)	129 (6.00)
No monitor available	17 (2.2)	1 (0.04)
Erroneous exclusions	33 (4.2)	
Deceased; no interview	11 (1.4)	2 (0.09)
Case and control subjects providing information	462 (59)	1,781 (84)

Data are *n* (%).

72 h after admission to the hospital and with abdominal pain. All such patients were screened by the nurse monitors concerning inclusion and exclusion criteria. These patients were followed and a copy of the medical case summary, including relevant clinical investigations, was collected. Quality assurance was performed by the study coordinator (K.B.) before subsequent evaluation by two surgeons (S.G, S.S) who were specialists in gastrointestinal diseases and who were unaware of the patients' medication histories. For each case subject, an index day was defined as the date on which abdominal pain leading to admission was first experienced.

Case definition

A "possible" case of acute pancreatitis was diagnosed if the patient had clinical symptoms compatible with acute pancreatitis and if the serum amylase level, within 72 h of admission to hospital, was increased to at least twice the upper limit of the normal reference value.

A "probable" case was diagnosed if, in addition, findings on ultrasonography were typical.

A "certain" case was diagnosed if, in addition, findings on computed tomography were typical or if an operation or postmortem diagnosis of acute pancreatitis was made irrespective of laboratory values.

A case subject was at least a possible case; all others were excluded from the study.

Exclusions

A total of 2,453 patients were screened as potential cases of acute pancreatitis. Patients who did not have telephone service and those who could not speak Swedish were excluded as a restriction in the study base. Exclusion criteria included malignancy in the gastrointestinal tract (including the pancreas) (180 subjects, 7.3%), previously known gallstone disease (390 subjects, 16%), episodes of pancreatitis (509 subjects, 20.8%), and endoscopic retrograde cholangiopancreatography–induced pancreatitis (168 subjects, 6.8%). Among the potential cases, there were many intercurrent reasons (194 subjects, 7.9%) for increased serum amylase levels, e.g., perforation and bleeding within the gastrointestinal tract, ileus, abdominal trauma, or aneurysm of the abdominal aorta. Patients hospitalized for >72 h before the first increased serum amylase level were regarded as having pancreatitis that developed in the hospital and were excluded (33 subjects, 1.3%). Patients hospitalized for >30 days after admission (42, 1.7%) were also excluded because the interview was to be conducted within 30 days. We have no information about this category, apart from the inclusion data from the screening forms. These patients had a similar distribution of age and sex as those included in the study. Of the total 2,453 individuals screened, 779 eligible case subjects were identified (Table 1).

Data collection

The nurse monitors obtained clinical and laboratory information by reviewing clinical records. They recorded the admitting diagnosis, including relevant investigations, initial values of serum amylase, and liver screening. Patients without obvious exclusion criteria were interviewed by telephone within 30 days of admission to the hospital. The interviews were performed according to a standardized format. Information was collected about demographic details, all previous hospitalizations, all previous and present diseases, and all drugs taken during the last 6 months. The questions about diseases were used as prompts for treatments and drug intake. A total of 12 disease groups were included. For each group including one or more specific diseases, the standard question was "Do you have/have you had ____?" (inserting the specific disease, e.g., hypertension, diabetes, etc., in the blank). If the response was affirmative, the follow-up question was "Have you taken any drugs to treat this condition during the last 6 months?" If the response to this question was affirmative, the interviewee was asked, "Which drug/drugs have you used?" When a drug was mentioned, the time of last use was determined, as well as day-by-day intake for the last 4 weeks and week-by-week intake for the balance of the 6-month period. Information about drug strength, dosage, and total treatment time was also obtained. An interview typically lasted 20–50 min.

A disease mentioned and diagnosed by a physician classified the interviewee as "exposed" to the condition. All conditions were coded according to the International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM). Self-reported body height and weight were also recorded to calculate the BMI. Extensive mapping of alcohol and tobacco use during the past 6 months was performed.

Exposure definition

To be classified as exposed to a medicine, the case subjects and control subjects must have taken the drug ≥5 days during each of the 2 weeks before the index day. Subjects were classified as nonexposed if the medication was stopped more than 1 week before the index day.

Table 2—*Diabetes and its current treatment among case and control subjects*

	Case subjects (462)	Control subjects (1,781)	OR	95% CI
Diabetes	27 (5.8)	55 (3.1)	1.9	1.2–3.1
Diet treatment only	6 (1.3)	11 (0.6)	2.1	0.8–5.1
Glyburide only	10 (2.2)	13 (0.7)	3.0	1.3–6.9
Glyburide and metformin	3 (0.6)	2 (0.1)	5.8	1.0–34.9
Glyburide and insulin	0 (0.0)	1 (0.06)	NA	
Glimeperide only	1 (0.2)	4 (0.2)	1.0	0.1–8.6
Glipizide only	0 (0.0)	5 (0.3)	NA	
Glipizide and metformin	1 (0.2)	2 (0.1)	1.9	0.2–21.3
Glipizide and insulin	0 (0.0)	1 (0.06)	NA	
Metformin only	0 (0.0)	1 (0.1)	NA	
Insulin only	5 (1.1)	14 (0.8)	1.4	0.5–3.9
Insulin and metformin	1 (0.2)	1 (0.1)	3.9	0.2–61.9
Glyburide and any other antidiabetic	13 (2.8)	16 (0.9)	3.2	1.5–6.7
Glipizide and any other antidiabetic	1 (0.2)	8 (0.4)	0.5	0.1–3.9
Metformin and any other antidiabetic	5 (1.1)	6 (0.3)	3.2	1.0–10.7
Insulin and any other antidiabetic	6 (1.3)	17 (1.0)	1.4	0.5–3.5
Glyburide, not metformin	10 (2.2)	14 (0.8)	2.8	1.2–6.3
Metformin, not glyburide	2 (0.4)	4 (0.2)	1.9	0.4–10.6

Data are frequency (%) unless otherwise indicated. NA, not analyzed.

Control subjects

Control subjects were selected as a random sample from a population register of individuals residing within the geographic areas specified in the study base. Control subjects were selected and interviewed continuously, and no matching to the case subjects was performed. A total of 2,245 control subjects were screened. The reasons for exclusions were the same as for the case subjects. Initially, we tried to contact control subjects with unlisted telephone numbers, but due to a minimal response rate, we decided to exclude such persons. Of 5,065,000 telephone subscriptions in Sweden, 8–10% of the numbers are unlisted. Of the total 2,245 individuals screened, 2,129 eligible control subjects were identified (Table 1).

Analyses

Relative risks were depicted by crude odds ratios (ORs). ORs were also calculated by unconditional logistic regression models, allowing for adjustment by covariates. A priori, we identified gallstone disease, inflammatory bowel disease, and use of alcohol, diuretics, ACE inhibitors, nonsteroidal anti-inflammatory drugs, didanosine, azathioprine, and valproate as potential risk factors and age, sex, obesity, and use of tobacco, alcohol, and the above-mentioned drugs as potentially confounding factors. By means of a screening procedure of all medications and diseases, we identified a number of other potentially confounding factors, all of which that showed a significant crude OR were included in the final multivariate logistic regression model. Variables included in this model were age; sex; hypertension; angina pectoris; cardiac failure; history of myocardial infarction; hyperlipidemia; gastrointestinal, renal, prostatic, and psychiatric disorders; and use of alcohol, tobacco, statines, fibrates, diuretics, ACE inhibitors, nitrates, calcium channel blockers, β-blockers, low-dose aspirin, and proton pump inhibitors.

95% CIs were calculated and presented (11). Goodness of fit was investigated by Hosmer-Lemeshaw's test (12). The *P* value was 0.6 for the final model. Prevalence ratio of disease severity measured the influence of obesity. ORs adjusted according to the Mantel-Haenzel's method (11) were used in the stratified analysis of the diabetic population.

RESULTS — Nonparticipation due to dementia was more common among case subjects than control subjects. The case group had some unique reasons for nonparticipation (death, transfer to another clinic, erroneous exclusions, and refusal by physician). Of the 11 deceased case subjects, 2 patients had a BMI of 33.7 and 30.2 kg/m^2, respectively, and 4 patients weighed 93–117 kg; otherwise, the patterns were similar in the two groups. Information by telephone interview was obtained from 462 (59%) of the eligible case subjects and 1,781 (84%) of the control subjects (Table 1). Mean ± SD and median (range) age was 56.3 ± 16.4 and 56 (20–85) years, respectively, among case subjects and 51.9 ± 16.9 and 53 (20–85) years, respectively, among control subjects. The percentage of current smokers was 32.9% (95% CI 28.6–37.2) in case subjects compared with 22.6% (20.6–24.5) in control subjects. The proportion of alcohol users was similar in the two groups (85.0 and 87.3%), but the average weekly consumption of pure alcohol was higher in case subjects 15.0 (12.8–17.2) than in control subjects 10.6 (10.0–11.1) cl.

A total of 27 (6%) case subjects and 55 (3%) control subjects had prevalent diabetes (crude OR 1.9 [1.2–3.1]). Diabetes treatment with diet or insulin was not significantly associated with an increased risk of acute pancreatitis. Oral treatment with glyburide had a crude OR of 3.2 (1.5–6.7). Patients treated with metformin, including combinations, had a crude OR of 3.2 (1.0–10.7) (Table 2). However, among individuals treated with metformin, three (60%) of the case subjects and two (33%) of the control subjects were also treated with glyburide. The age distribution among the case subjects and control subjects treated with glyburide did not differ.

We stratified for factors that showed a significant crude OR and could be potential confounders: age, male sex, current smoking, use of alcohol ≥26 cl week, BMI ≥25 kg/m^2, hypertension, angina pectoris, history of myocardial infarction, cardiac failure, and use of β-blockers, diuretics, calcium channel blockers, and ACE inhibitors. The relative risk of glyburide was significantly increased in diabetic case subjects <70 years of age (OR 7.8 [2.4–25]) but not in those >70 years of age (1.3 [0.5–3.3]). The relative risk of acute pancreatitis with glyburide was much higher among diabetic subjects using β-blockers (16.0 [2.5–∞]) than those who did not (1.9 [0.8–4.6]), but this dif-

Table 3—*Risk of acute pancreatitis by BMI class (left 3 columns) and severity* of pancreatitis by BMI class (right 8 columns)*

Crude OR of BMI				Length of hospitalization among cases (days)							
				≤7		>7≤14		>14 or ICC		RR >14 days/or ICU versus ≤14	
BMI	OR (95% CI)	Control subjects (*n*)	Case subjects (*n*)	N	%	N	%	N	%	RR	95% CI
<20	2 (0.7–2.2)	124	30	26	86.6	2	6.6	2	6.6	0.97	0.23–4.06
≥20<25	Reference	919	204	143	70.0	47	23.0	14	7.0	Reference	
≥25<30	1.3 (1.0–1.6)	581	171	110	64.3	45	26.3	16	9.4	1.36	0.69–2.71
≥30	1.8 (1.3–2.6)	130	53	36	68.0	8	15.0	9	17.0	2.47	1.13–5.40
Unknown		27	4	3		1		0		NA	
Total		1,781	462	318		103		41			

RR, relative risk; NA, not analyzed. *Length of hospital stay or treatment in ICU were used as proxy variables for severity.

ference in OR did not reach statistical significance ($P = 0.06$). Otherwise, we could not find any influence on the risk with glyburide by the potential confounders.

In this material, we found that 53 (11%) case subjects and 130 (7.3%) control subjects had a BMI >30 kg/m^2, giving an OR of 1.8 (1.3–2.6) for developing acute pancreatitis when compared with individuals with a BMI of 20–25 kg/m^2 (Table 3).

In the same table, the cohort of case subjects was grouped according to duration of hospital stay or treatment in an intensive care unit (ICU). The relative risk of a hospital stay >14 days or treatment in ICU was 2.3 (1.0–5.0) among case subjects with a BMI >30 kg/m^2 when compared with case subjects with a BMI of 20–25 kg/m^2 (Table 3). This indicates that a high BMI is a risk factor for developing acute pancreatitis and a predictor of extended hospitalization or treatment in an ICU. There is a link between high BMI and type 2 diabetes. Alcohol use, smoking, and other exposures may be confounding factors for the association between glyburide and acute pancreatitis. In a multivariate logistic regression analysis, the adjusted OR for diabetes (irrespective of treatment) was 1.4 (0.8–4.2). For glyburide, the OR was 2.7 (1.2–5.9) when adjusting for the a priori identified potential confounders and 2.5 (1.1–5.9) when using the full model (Table 4). There was no increased risk of acute pancreatitis with the other diabetes variables. For each 5 units of BMI, the risk increased 24% (OR 1.2 [1.1–1.4]).

CONCLUSIONS — We found that intake of glyburide increased the risk of acute pancreatitis, particularly among young subjects. Obesity also seems to be a risk factor for acute pancreatitis in addition to being related to the severity of the disease.

Glyburide has previously not been identified as a risk factor for acute pancreatitis. However, there were 38 reports of glyburide-associated acute pancreatitis in the World Health Organization database during the period from 1975–1999 (personal communication, C. Biriell, World Health Organization Drug Monitoring Center). The number of diabetic subjects in our control population was 3%, which is consistent with other studies performed in Sweden concerning prevalence of diabetes (13–15). The prevalence of glyburide use in our control material (1%) matches sales data (0.8–1.2%) during the study period (13). Obesity has not been reported to be a risk factor for acute pancreatitis per se. In our study, the crude OR for developing acute pancreatitis was 1.8 (1.3–2.6). In a multivariate analysis, the risk of acute pancreatitis increased with 24% for each 5 units of BMI.

A high BMI has been discussed as a predictor of a serious course, including complications of acute pancreatitis (5–10). In this material, we have not classified the degree of severity according to the Ranson (16) or APACHE II (17) criteria. Our proxy variable was the length of hospitalization and ICU treatment, which has less precision as a measure of severity. For the patient group with a BMI >30 kg/m^2, the risk ratio was 2.5 (1.1–5.4) for treatment >14 days or treatment in the ICU (Table 3). Moreover, at least 6 of the 11 deceased case subjects were overweight. These observations support the finding of obesity as a risk factor for a severe course of acute pancreatitis. Results from previous studies differ regarding the character of complications appearing in obese patients with acute pancreatitis. In one recent study, obese patients had a higher risk of

Table 4—*Logistic regression ORs for pancreatitis related to BMI, diabetes, and treatment*

Variable	Adjusted OR	95% CI
BMI	1.2*	1.1–1.4
Diabetes		
Diet	1.7	0.6–5.2
Glyburide	2.5	1.1–5.9
Glipizide or glimiperide	0.2	0.04–1.4
Insulin	1.1	0.4–3.0
Metformin	1.8	0.4–8.6

*Effect of BMI measured in units of 5. Variables included in the model were age (OR 1.2, 95% CI 1.1–1.2 per 10 years of age); sex; alcohol use (OR 1.3, 1.1–1.4 for each 10 centiliters of alcohol per week); tobacco use (OR 1.4, 1.2–1.6 for each 10 cigarettes per day); hypertension; angina pectoris; heart failure; history of myocardial infarction; hyperlipidemia; psychiatric, renal, prostatic, and gastrointestinal disorders (inflammatory bowel diseases OR 3.7, 1.2–12.0); and use of statines, fibrates, β-blockers, calcium channel blockers, diurectics, ACE inhibitors, nitrates, low-dose aspirin, and proton pump inhibitors.

local but not systemic complications or fatal outcome (8). However, in four other studies, obesity inferred an increased risk of extrapancreatic complications such as shock, renal failure, respiratory insufficiency, and fatal outcome (5–7,9). The validity of the present study must be scrutinized. Measuring errors of outcome were minimized by the case-validation process by the experts.

The quality assurance process identified 33 erroneous exclusions. There are, however, no indications that this misclassification was selective. We tried to minimize misclassification of exposure by applying a very detailed and standardized interview using diseases and symptoms as prompts for drug exposures. We studied patients aged 20–85 years from defined geographic areas with a first episode of acute pancreatitis and who did not have a previously diagnosed gallstone disease. This procedure decreases the problem of finding relevant controls for patients with previous pancreatitis or gallstone disease because it is possible that these diseases could influence drug exposures. We decided not to match control subjects to case subjects by age or sex, thereby allowing evaluation of these variables as risk factors. Selection may have been a problem if drug exposures differed in patients transferred to other clinics, those hospitalized for >30 days, or those who had a fatal outcome. We could not totally exclude this, but at least the age and sex distribution of these patients was similar to that of the included cases. It can be suspected that the group of "failure to establish contact" would contain a higher proportion of severe alcoholics. This would lead to an underestimate of the risk of very high consumption of alcohol but would not distort the estimate of the risk with glyburide. We cannot explain the increased risk for pancreatitis during treatment with glyburide by confounding by age, sex, BMI, smoking, alcohol use, and cardiovascular, gastrointestinal, psychiatric, or prostatic diseases or their treatments. There may be effect modification by concomitant use of β-blockers and glyburide, but our material was too small to analyze this possibility in detail. We are not able to suggest mechanisms involved in glyburide-induced pancreatitis, but this is rarely the case when new adverse drug reactions are detected. Given that we studied multiple potential risk factors for acute pancreatitis, further studies are needed to corroborate or refute our observations.

It may still be prudent to carefully consider the choice of antidiabetes treatment in patients with risk factors for acute pancreatitis. It may be of clinical value to determine the BMI in addition to previous parameters (e.g., Ranson criteria) for prediction of the clinical course when patients with acute pancreatitis are hospitalized.

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