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Original Article

Sitagliptin use and risk of acute pancreatitis in type 2 diabetes mellitus: A population-based case-control study in Taiwan

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ABSTRACT

Background: There is still lack of definite evidence to establish the association between sitagliptin use and acute pancreatitis. The study aimed to test this issue in Taiwan.
Methods: This case-control study was designed to analyze the database of the Taiwan National Health Insurance Program. There were 349 subjects with type 2 diabetes mellitus aged 20–84 with a first-attack of acute pancreatitis from 2009 to 2011 as the case group and 1116 randomly selected subjects with type 2 diabetes mellitus without acute pancreatitis as the control group. Both groups were matched with sex, age, comorbidities, and index year of diagnosing acute pancreatitis. Current use of sitagliptin was defined as subjects who had their last tablet of sitagliptin ≤7 days before the date of diagnosing acute pancreatitis. Late use of sitagliptin was defined as subjects who had their last tablet of sitagliptin between 8 and 30 days before the date of diagnosing acute pancreatitis. Never use of sitagliptin was defined as subjects who never had a sitagliptin prescription. The risk of acute pancreatitis associated with sitagliptin use was estimated by the odds ratio (OR) and 95% confidence interval (CI) using the multivariable logistic regression model.
Results: After statistical correction for potential confounders, the adjusted OR of acute pancreatitis was 2.47 for subjects with current use of sitagliptin (95% CI 0.84, 7.28), when compared with those never using sitagliptin, but without statistical significance. The adjusted OR decreased to 1.14 for subjects with late use of sitagliptin (95% CI 0.66, 1.98), but without statistical significance.
Conclusions: No significant association is detected between sitagliptin use and acute pancreatitis in type 2 diabetes mellitus.

1. Introduction

Sitagliptin is one of dipeptidyl peptidase-4 inhibitors, also called DPP-4 inhibitors, which are classified as novel oral anti-hyperglycemic agents and are commonly used to treat type 2 diabetes mellitus. Overall, sitagliptin is generally well tolerated and relatively effective and safe in patients with type 2 diabetes mellitus. However, the commonly seen adverse events of sitagliptin mainly include infections, gastrointestinal disorders, musculoskeletal and connective tissue disorders, angioedema and skin disorders [1,2]. In addition, DPP-4 inhibitors-related acute pancreatitis has raised public health concern. Case report and adverse drug event are usually used to establish a plausible hypothesis linking the offending drug and the specific adverse effect. Till now, only few cases of acute pancreatitis were reported to be possibly related to sitagliptin use [3,4]. The U.S. Food and Drug Administration (FDA) has reported that 21 people (2.44%) had acute pancreatitis among 860 people reporting to have side effects when taking sitagliptin since 2009 to 2012 [5].

To date, no definite conclusion is established to confirm the association between sitagliptin use and acute pancreatitis. Given acute pancreatitis having considerable morbidity and mortality, and based on the aforementioned case reports and the U.S. FDA report, we make a plausible hypothesis that sitagliptin use may increase the risk of acute pancreatitis. If the association between sitagliptin use and acute pancreatitis can be established, physicians should take this risk into account. Therefore, we conducted a population-based case-control study using the database of the Taiwan National Health Insurance Program to examine this issue.

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2. Methods

2.1. Design and data source

This population-based case-control study was designed to analyze the database of the Taiwan National Health Insurance Program. Briefly speaking, this program began in March 1, 1995, which covered almost 99% of the whole 23 million residents living in Taiwan [6]. The details of the program were adequately described in previous high-quality papers [7–9]. This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

2.2. Selection of cases and controls

On the basis of the International Classification of Diseases (ICD) 9th Revision, we identified subjects with type 2 diabetes mellitus aged 20–84 years with a first-attack of acute pancreatitis during the period of 2009–2011 as the case group (ICD-9 code 577.0). Subjects with type 2 diabetes mellitus without acute pancreatitis were randomly selected from the same database as the control group. Both case and control groups were matched with sex, age (5-year interval), comorbidities, and the index year of diagnosing acute pancreatitis. The index date for each case was defined as the date of diagnosing acute pancreatitis. The index date for each control subject was a randomly assigned date within the index year of the matched case subject. To decrease biased results, subjects with chronic pancreatitis (ICD-9 code 577.1) or pancreatic cancer (ICD-9 code 157) before the index date were excluded from this study. To focus on the association between sitagliptin use only and acute pancreatitis, subjects who at least received one prescription for other DPP-4 inhibitors, including vildagliptin, saxagliptin and linagliptin, were also excluded from this study.

2.3. Definition of sitagliptin exposure

Based on the prescription date of each subject, the last tablet of sitagliptin can be calculated. To decrease biased results, subjects who had their last tablet of sitagliptin >1 month before the date of diagnosing acute pancreatitis were excluded from this study. Therefore, only those who had their last tablet of sitagliptin within 1 month before the date of diagnosing acute pancreatitis were included in this study. The elimination half-life of sitagliptin ranges from 8 to 14 h in subjects with normal renal function [10]. The elimination half-life increases with decreasing renal function and ranges from 16.1 to 28.4 h in subjects with impaired renal function, depending on the renal function preserved [11]. Therefore, we used the period of 7 days as a cut-off point. Current use of sitagliptin was defined as subjects who had their last tablet of sitagliptin ≤7 days before the date of diagnosing acute pancreatitis or those who still had sitagliptin tablets remaining at the date of diagnosing acute pancreatitis. Late use of sitagliptin was defined as subjects who had their last tablet of sitagliptin between 8 and 30 days before the date of diagnosing acute pancreatitis. Never use of sitagliptin was defined as subjects who never had a sitagliptin prescription.

2.4. Potential confounders

In order to control for confounding effects, comorbidities before the index date potentially related to acute pancreatitis were included as follows based on ICD-9 codes: alcohol-related disease (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0–571.3, 790.3 and V11.3), biliary stone (ICD-9 code 574), cardiovascular disease including coronary artery disease, heart failure, cerebrovascular disease and peripheral atherosclerosis (ICD-9 codes 410–414, 428, 430–438 and 440–448), chronic kidney disease (ICD-9 codes 585–586 and 588.8–588.9), chronic obstructive pulmonary disease (ICD-9 codes 491, 492, 493 and 496), hepatitis B (ICD-9 codes V02.61, 070.20, 070.22, 070.30 and 070.32), hepatitis C (ICD-9 codes V02.62, 070.41, 070.44, 070.51 and 070.54), hyperparathyroidism (ICD-9 code 252.0), and hypertriglyceridemia (ICD-9 codes 272.1, 272.2 and 272.4). In order to avoid subjects who were mistakenly diagnosed or mistakenly coded by accident, only those who had at least two consensus same diagnoses in the ambulatory care or at least one hospitalization diagnosis were included to make sure the diagnosis validity of acute pancreatitis and other comorbidities.

2.5. Statistical analysis

We compared the differences in demographic status, sitagliptin use, and comorbidities between the acute pancreatitis cases and the controls using the chi-square test and Fisher-exact test for categorized variables, and *t*-test for continuous variables. Initially, all variables were included in the univariable unconditional logistic regression model. Only those found to be significant in the univariable unconditional logistic regression model were further analyzed in the multivariable unconditional logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) for risk of acute pancreatitis associated with sitagliptin use and comorbidities. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA). Two-tailed $p < 0.05$ was considered statistically significant.

3. Results

3.1. Informative profiles of the study population

Table 1 discloses the informative profiles between the acute pancreatitis cases and the controls. In total, the study consisted of 349 subjects with acute pancreatitis as the cases and 1116 subjects without acute pancreatitis as the controls, with similar distributions in sex, age and duration of type 2 diabetes mellitus. The mean ages (standard deviation) were 61.9 (14.1) years in cases and 62.7 (13.4) years in controls (*t*-test, $P = 0.38$). The mean duration of type 2 diabetes (standard deviation) were 6.30 (4.00) years in cases and 6.74 (3.80) years in controls (*t*-test, $P = 0.06$). The cases were more likely to have higher proportions

Table 1
Informative profiles of acute pancreatitis cases and controls.

Variable	Controls N = 1116		Cases N = 349		*P* value*
	n	(%)	n	(%)	
Sex					0.78
Female	521	(46.7)	160	(45.9)	
Male	595	(53.3)	189	(54.1)	
Age group (year)					0.82
20–39	79	(7.1)	28	(8.0)	
40–64	538	(48.2)	169	(48.4)	
65–84	499	(44.7)	152	(43.6)	
Age (year), mean (standard deviation)†	62.7	(13.4)	61.9	(14.1)	0.38
Duration of type 2 diabetes (year), mean (standard deviation)†	6.74	(3.80)	6.30	(4.00)	0.06
Sitagliptin					0.22
Never use	1054	(94.44)	324	(92.84)	
Current use	8	(0.72)	6	(1.72)	
Late use	54	(4.84)	19	(5.44)	
Comorbidities before index date					
Alcohol-related disease	168	(15.1)	68	(19.5)	0.047
Biliary stone	199	(17.8)	86	(24.6)	0.005
Cardiovascular disease	633	(56.7)	197	(56.5)	0.93
Chronic kidney disease	118	(10.6)	53	(15.2)	0.02
Chronic obstructive pulmonary disease	300	(26.9)	96	(27.5)	0.82
Hepatitis B	51	(4.57)	32	(9.17)	0.001
Hepatitis C	36	(3.23)	27	(7.74)	<0.001
Hyperparathyroidism &	2	(0.18)	3	(0.86)	0.06
Hypertriglyceridemia	650	(58.2)	198	(56.7)	0.62

Data are presented as the number of subjects in each group, with percentages given in parentheses or mean with standard deviation given in parentheses.
*Chi-square test, &Fisher-exact test and †*t*-test comparing subjects with and without acute pancreatitis.