Risk and Preventive Medication of Acute Pancreatitis in Patients with Type 2 Diabetes Mellitus in Taiwan: A Population-based Cohort Study

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Study Highlights

Type 2 DM increases the risk of acute pancreatitis. Anti-diabetic drugs can reduce the risk.

Abstract

Objectives. To assess the risk and preventive medication of acute pancreatitis for patients with Type 2 diabetes mellitus (DM).

Methods. From the claims data of one million randomly sampled from 23 million enrollees of the Taiwan National Health Insurance, we identified 19,518 adult patients with newly diagnosed Type 2 DM in 2000–2005. We also identified 78,072 patients without the disease, frequency matched with sex and age during the same period as controls. Both groups were followed up until the end of 2008 to measure the incidences of acute pancreatitis and the effectiveness of anti-diabetes medication in reducing the risk.

Results. Both cohorts were similar in sex and age distributions. Patients with Type 2 DM had an incidence rate of acute pancreatitis 1.95-fold greater than non-diabetics (27.7 vs. 14.2 per 10,000 person-years). Results of the multivariable Cox model analysis showed a slightly decreased hazard ratio (HR) of 1.89 (95% confidence interval (CI) = 1.65–2.18). Alcoholism (HR = 6.92, 95% CI = 3.28–14.6), gallstones (HR = 2.52, 95% CI = 1.35–4.72), and hepatitis C infection (HR = 3.35, 95% CI = 1.72–6.52) were also significant factors predicting acute pancreatitis. Patients taking biguanides, sulfonylureas, thiazolidinediones, or alpha-glucosidase inhibitors were benefited with 37% to 56% of risk reduction of the disease.

Conclusions. There is a higher risk of acute pancreatitis in patients with Type 2 DM

in Taiwan. Alcoholism, gallstones, and hepatitis C infection are the other risk factors for the disease. Anti-diabetic drugs can reduce the risk.

Key words: acute pancreatitis; alcoholism; gallstones; Type 2 diabetes mellitus

Introduction

Acute pancreatitis is a condition of pancreatic inflammation with varied incidence among populations. In a systematic review, Yadav et al. [1] found that the annual incidence of acute pancreatitis ranged 4.2–45.3 per 100,000 in Europeans from 1966–2005. The annual incidence in California increased from 33.2 per 100,000 in 1994 to 43.8 per 100,000 in 2001 [2]. Fagenholz et al. [3] found that the hospitalization rate for acute pancreatitis in the US increased from 40 per 100,000 in 1988 to 70 per 100,000 in 2003. Clinically, acute pancreatitis is often associated with significant co-morbidity and substantial mortality rates. The overall fatality of the disease ranges approximately from 2%–5% [3–5].

The etiology of acute pancreatitis is undoubtedly multifactorial. Extant epidemiological studies have shown that gallstones, hypertriglyceridemia, obesity, viral hepatitis, and lifestyle are significant factors associated with acute pancreatitis [6–9]. Two large cohort studies have demonstrated that patients with Type 2 diabetes mellitus (DM) are at a higher risk for acute pancreatitis [9,10]. The retrospective cohort analysis of the US claims data found a 2.83-fold greater risk of acute pancreatitis for Type 2 DM patients than non-DM persons [10]. The analysis of the UK General Practice Research Database also showed a 1.49-fold increased risk for Type 2 DM patients [9]; however, both cohort studies were limited to Western populations and had no data on preventive measures.

The prevalence of DM in Taiwan was approximately 8.2%–11.4% in 1986–2002 [11–13]. Since 2009, the disease has become the fifth leading cause of death [14]. No cohort study has explored the association between acute pancreatitis and Type 2 DM in Asian populations. Assessment of this association requires a large population size. We took the advantage of a large dataset available from the National Health Insurance (NHI) program in Taiwan to conduct a follow-up assessment of this association. We estimated the incidence of acute pancreatitis among patients with Type 2 DM relative to a population without diabetes. We also characterized other risk factors associated with acute pancreatitis, and investigated whether anti-diabetic drugs are beneficial in reducing risk.

Materials and Methods

Data sources

The NHI program was reformed from 13 insurance-related systems of Taiwan in March 1995. By the end of 2008, this insurance program covered more than 99% of the entire population of Taiwan (23 million) [15]. We obtained a dataset of reimbursement claims from the National Health Research Institutes (NHRI), which manages the NHI databank. The dataset represented the registry of a randomly sampled cohort of one million people enrolled in the NHI system with claims from 1996–2008. This dataset included information on ambulatory cares, in-patient care, dental services, prescription drugs, medical institutions, physicians, and registration entries, with individual personal identification coded for public access. Limited data on personal socio-demographic status, such as sex, birth date, affiliation to insured occupational group, income level for insurance fee estimate, and residential area, were also available.

Criteria and definition

The criteria of diseases were defined according to the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM). We used a retrospective cohort design to identify patients aged 20 and older newly diagnosed with Type 2 DM (ICD-9 codes 250 x 0 or 250 x 2) and currently using anti-diabetic drugs in

2000–2005. The anti-diabetes drugs included biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, D-phenylalanine derivatives, dipeptidyl peptidase 4 inhibitors, incretin mimetic agents, and insulin. For each DM case, we randomly selected four persons without medical claims for diabetes frequency matching with age (every five-year span) and sex in the same time period. Patients with known history of pancreatic cancer, chronic pancreatitis, Type 1 DM, and gestational diabetes were excluded from this study. To measure the incidence of acute pancreatitis (ICD-9 codes 577.0), both Type 2 diabetic and non-diabetic cohorts were followed up until the end of 2008, or were censored because of death or withdrawal from the insurance program. The entry study index date for a study subject was defined by the date the individual was identified from the claims data.

Statistical analysis

We estimated the incidence rate as the number of acute pancreatitis identified and divided by the total follow-up person-years for each cohort by sex, specific age, and follow-up years. Cox proportional hazard analysis was used to estimate the hazard ratio (HR) of acute pancreatitis and 95% confidence intervals (CI) for patients with Type 2 DM compared with non-DM people. Univariate and multivariate models were used to assess the risk levels associated with demographic factors and co-morbidities identified in the baseline. The potential co-morbidities included obesity,

hypertriglyceridemia, alcoholism, gallstones, hepatitis B infection, and hepatitis C infection. Data analyses also compared the risk of acute pancreatitis associated with anti-diabetes medication. The statistical significance level was set at two-sided probability value of < 0.05. All analyses used the SAS software version 9.1 (SAS Institute Inc., Cary, North Carolina).

Ethical considerations

All individual personal data in the insurance reimbursement claims data were scrambled to secure patient privacy for public access. This study was exempted from a full review by the Institution Review Board.

Results

Baseline characteristics of the study population

Eligible study subjects consisted of 19,518 patients in Type 2 diabetic cohort and 78,072 persons in non-diabetic cohort, with similar sex and age distributions and mean ages of 56.7 years (Table 1). The Type 2 diabetic cohort had higher prevalence of obesity, hypertriglyceridemia, alcoholism, gallstones, hepatitis B, and hepatitis C infections at the baseline ($P < 0.0001$).

During the follow-up period, the incidence of acute pancreatitis was 1.95-fold greater in Type 2 diabetic cohort than in non-diabetic cohort (27.7 vs. 14.2 per 10,000 person-years), with the adjusted HR decreased slightly to 1.89 (Table 2). The sex-specific hazard ratio (HR) shows that men were at higher risk than women. The age-specific HR was higher in Type 2 diabetic subjects aged 20–39 years (HR = 5.48, 95% CI = 3.64–8.25), followed by aged 40–64 (HR = 2.02, 95% CI = 1.66–2.45), and aged 65 years and older (HR = 1.34, 95% CI = 1.05–1.71), compared with non-diabetic age-matched group. The risk of acute pancreatitis was higher in patients with a diabetic duration of more than five years (HR = 2.40, 95% CI = 1.78–3.25). The cumulative incidence of acute pancreatitis was twofold higher in diabetic patients than the non-diabetic group during the entire follow-up period, and the difference increased with follow-up time (Figure 1).

Co-morbidity and acute pancreatitis by univariate and multivariate Cox proportional hazard analysis

Adjusted hazard ratios and 95% confidence intervals of acute pancreatitis associated with Type 2 DM and co-morbidities are shown in Table 3. The age- and sex-adjusted HR of acute pancreatitis for patients with Type 2 DM was reduced slightly to 1.89 (95% CI = 1.65–2.18). Hyperlipidemia, alcoholism, gallstones and hepatitis C infection were identified as co-morbidities independently associated with acute pancreatitis. The risk increased further for the diabetic patients with alcoholism (HR = 6.92, 95% CI = 3.28–14.6) and hepatitis C infection (HR = 3.35, 95% CI = 1.72–6.52), but not hyperlipidemia and gallstones.

Influence of anti-diabetic drugs on the risk of acute pancreatitis

Table 4 shows the effectiveness of taking anti-diabetic drugs in reducing the risk of acute pancreatitis. Controlling for sex, age, and co-morbidities, the results show that HR of developing acute pancreatitis were 0.46 (95% CI = 0.35–0.61) for those taking biguanides, 0.63 (95% CI = 0.47–0.83) for sulfonylureas, 0.63 (95% CI = 0.46–0.87) for thiazolidinediones, and 0.44 (95% CI = 0.31–0.62) for alpha-glucosidase inhibitors. The beneficial effect of using insulin was not statistically significant (HR = 0.81, 95% CI = 0.64–1.02).

Discussion

Though not utterly novel, to the best of our knowledge, this is the first population-based cohort study that simultaneously determines the risk of developing acute pancreatitis and the effectiveness of anti-diabetic medication in reducing the risk for diabetic patients in Taiwan. In the present study, the incidence of acute pancreatitis in Type 2 diabetic cohort was approximately two-fold greater than that in non-diabetic cohort, a moderate risk consistent with previous studies [9-10]. The incidence of acute pancreatitis measured by sex and age was consistently higher in patients with Type 2 DM. The age-specific incidence also showed that Type 2 diabetic patients 20–39 years of age had the highest incidence rate ratio compared to non-diabetics, which was consistent with the finding of Noel et al. [10]. This indicates that the risk of acute pancreatitis is relatively great for young patients of DM.

The risk of developing acute pancreatitis in patients with Type 2 DM varied moderately among studies. The multivariate Cox model analysis in this study measured an adjusted HR slightly higher than the finding of 1.49-fold in the UK General Practice Research Database (GPRD) study [9]; however, it was lower than the HR of 2.83 in the study using a US insurance claims database [10]. Although the biological mechanism between Type 2 DM and acute pancreatitis could not be proven from this observational study, these cohort studies suggest that patients with Type 2 DM are at an increased risk for acute pancreatitis.

We also found that patients with both DM and hepatitis C infection were at higher risk to develop acute pancreatitis. A previous study has reported that patients with acute hepatitis A, B, and E infections are at higher risk of acute pancreatitis [8], without mentioning the risk for hepatitis C. Some case reports have shown that interferon therapy in patients with chronic hepatitis C infection can induce acute pancreatitis [16, 17]. In this study, 50 patients with chronic hepatitis C infection received interferon therapy; however, no patient developed acute pancreatitis during the follow-up period (data not shown). Because there was no data of hepatitis C RNA in this dataset, we cannot posit a plausible biological explanation for why patients with hepatitis C infection are at an elevated risk of acute pancreatitis. However, our data show that patients having both hepatitis C and Type 2 diabetes at a higher risk of acute pancreatitis.

Epidemiological studies have consistently reported the association between acute pancreatitis with other co-morbidities, particularly gallstones and alcohol consumption [6, 7]. Our study also demonstrates the evidence of a slight additional effect from diabetes to those with co-morbidity of alcoholism, with an HR increase from 6.05 to 6.92. This indicates that alcoholism has a greater influence than Type 2 diabetes in the risk of developing acute pancreatitis. No such additional effects were evident in patients with both gallstones and diabetes.

In further analysis, we found that patients using biguanides, sulfonylureas, thiazolidinediones, or alpha-glucosidase inhibitors had 37%–56% reduction of acute pancreatitis risk. Using insulin decreased risk of developing acute pancreatitis; however, the association was not statistically significant. Gonzalez-Perez et al. found that diabetic patients had decreased risks of developing acute pancreatitis using insulin [odds ratio (OR) = 0.34, 95% CI = 0.13–0.91] or long-term (more than 3 years) use of metformin (OR = 0.5, 95% CI = 0.28–0.91) [18]. In contrast, Gonzalez-Perez et al. also found patients taking sulfonylureas for more than 3 years were at higher risk (OR) = 1.66, 95% CI = 1.01–2.74) [18]. Because of lack of prospective studies, we cannot posit any further explanation regarding the relation of anti-diabetic drugs to the risk of acute pancreatitis. Further studies are required to explore the implication of anti-diabetic drugs on acute pancreatitis.

Our study has several strengths. This study was based on a Taiwan population-based study with a large sample size and with an increased statistical power testing significant. The representative large sample size increased the validity of identifying rare diseases such as acute pancreatitis for this study.

The limitations in the present study should be noted. A number of suspected risk factors of acute pancreatitis, such as cigarette smoke, were not available. This was due to the inherent limitation of insurance dataset. However, women in Taiwan rarely

smoke, and account for less than 5% of the smokers [19]. Smoking is not likely an important risk factor associated with acute pancreatitis because the risk difference between men and women in this study is small.

Conclusion

Patients with Type 2 diabetes mellitus are at an elevated risk of acute pancreatitis, and the risk is relatively greater for young patients. Patients infected with hepatitis C and who suffer from alcoholism may be at additional risk. In contrast, we have also found that anti-diabetic drugs demonstrate an effective mechanism of reducing the risk of acute pancreatitis, particularly for those taking biguanides, sulfonylureas, thiazolidinediones, or alpha-glucosidase inhibitors.

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Conflict of Interest Statement

The authors disclose no conflicts of interest.

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Table 1. Baseline characteristics between Type 2 diabetic cohort and non-diabetic cohort identified in 2000–2005

	Type 2 diabetes				
	No N=78,072		Yes N=19,518		
	N	%	n	%	*P* value*
Sex					1.00
Women	35,092	(45.0)	8,773	(45.0)	
Men	42,980	(55.0)	10,745	(55.0)	
Age group (years)					1.00
20–39	7,772	(10.0)	1,943	(10.0)	
40–64	48,012	(61.4)	12,003	(61.4)	
≥65	22,288	(28.6)	5,572	(28.6)	
Mean (SD) (years)	56.7	(13.7)	56.8	(13.3)	0.80
Baseline co-morbidity					
Obesity	402	(0.5)	505	(2.6)	<0.0001
Hypertriglyceridemia	441	(0.6)	421	(2.2)	<0.0001
Alcoholism	404	(0.5)	158	(0.8)	<0.0001
Gallstones	1,525	(2.0)	511	(2.6)	<0.0001
Hepatitis B	1,509	(1.9)	508	(2.6)	<0.0001
Hepatitis C	859	(1.1)	328	(1.7)	<0.0001

*Chi-square test comparing patients with and without Type 2 diabetes.

Table 2. Incidence density of acute pancreatitis estimated by sex, age, and follow-up years for Type 2 diabetic and non-diabetic cohorts identified in 2000–2005

	Non-diabetes				Type 2 diabetes					
	N	Cases	Person-years	Incidence†	N	Cases	Person-years	Incidence †	HR	(95% CI)
All	78,072	621	436,653	14.2	19,518	295	106,512	27.7	1.95	(1.70–2.24)
Sex										
Women	35,092	258	198,319	13.0	8,773	121	48,534	24.9	1.92	(1.54–2.38)
Men	42,980	363	238,334	15.2	10,745	174	57,978	30.0	1.97	(1.65–2.36)
Age, years										
20–39	7,772	40	44,678	8.95	1,943	54	10,996	49.1	5.48	(3.64–8.25)
40–64	48,012	314	276,147	11.4	12,003	155	67,605	22.9	2.02	(1.66–2.45)
≥ 65	22,288	267	115,827	23.1	5,572	86	27,911	30.8	1.34	(1.05–1.71)
Follow-up										
<1 years	78,072	104	77,332	13.5	19,518	46	19,205	24.0	1.78	(1.26–2.52)
1	76,607	113	75,890	14.9	18,931	54	18,685	28.9	1.94	(1.40–2.68)
2	75,202	98	74,490	13.2	18,464	47	18,261	25.7	1.96	(1.38–2.77)
3	73,744	100	66,893	15.0	18,031	43	16,295	26.4	1.77	(1.24–2.52)
4	60,304	89	53,131	16.8	14,645	38	12,884	29.5	1.76	(1.20–2.57)
≥ 5	46,381	117	88,916	13.2	11,212	67	21,182	31.6	2.40	(1.78–3.25)

† Incidence rate: per 10,000 person-years.

HR (hazard ratio): Type 2 diabetes vs. non-diabetes (95% CI)

Cases of outpatient services for acute pancreatitis.

Table 3. Interaction effect on acute pancreatitis between diabetes and co-morbidities

	Non-diabetes				Type 2 diabetes			
	Cases	Incidence†	HR	(95% CI)	Cases	Incidence†	Adjusted HR	(95% CI)
All	621	14.2	1.00	(reference)	295	27.7	1.89	(1.65–2.18)
Hypertriglyceridemia								
No	612	14.1	1.00	(reference)	290	27.8	1.93	(1.68–2.22)
Yes	9	39.0	2.39	(1.24–4.62)	5	22.1	1.45	(0.60–3.49)
Alcoholism								
No	606	13.9	1.00	(reference)	288	27.2	1.92	(1.67–2.21)
Yes	15	80.5	6.05	(3.62–10.1)	7	96.0	6.92	(3.28–14.6)
Gallstones								
No	577	13.4	1.00	(reference)	285	27.4	2.01	(1.74–2.32)
Yes	44	58.2	3.78	(2.77–5.15)	10	40.2	2.52	(1.35–4.72)
Hepatitis C								
No	607	14.0	1.00	(reference)	286	27.2	1.90	(1.65–2.19)
Yes	14	34.7	2.03	(1.18–3.47)	9	59.3	3.35	(1.72–6.52)

† Incidence: per 10,000 person-years.

HR: adjusted for age, sex and co-morbidities.

Table 4. Cox model measured hazard ratios and 95% confidence intervals of acute pancreatitis associated with anti-diabetic drugs identified in 2000–2005

	N	Case	Person-year	Incidence[†]	Crude HR (95% CI)	Adjusted HR (95% CI)
Insulin						
Non-use	7,892	124	39,770	31.2	1.00 (reference)	1.00 (reference)
Use	11,626	171	66,741	25.6	0.81 (0.64–1.02)	0.81 (0.64–1.02)
Biguanide						
Non-use	3,161	73	14,488	50.4	1.00 (reference)	1.00 (reference)
Use	16,357	222	92,023	24.1	0.47 (0.36–0.62)	0.46 (0.35–0.61)
Sulfonylurea						
Non-use	3,348	62	15,403	33.8	1.00 (reference)	1.00 (reference)
Use	16,170	233	91,109	25.6	0.62 (0.47–0.83)	0.63 (0.47–0.83)
Thiazolidinedione						
Non-use	15,721	250	83,143	30.1	1.00 (reference)	1.00 (reference)
Use	3,797	45	23,368	19.3	0.63 (0.46–0.87)	0.63 (0.46–0.87)
Alpha-glucosidase inhibitor						
Non-use	15,098	257	80,072	32.1	1.00 (reference)	1.00 (reference)
Use	4,420	38	26,440	14.4	0.44 (0.32–0.62)	0.44 (0.31–0.62)

Adjusted HR: adjusted for age, sex, and co-morbidities.

[†] Incidence: per 10,000 person-years.

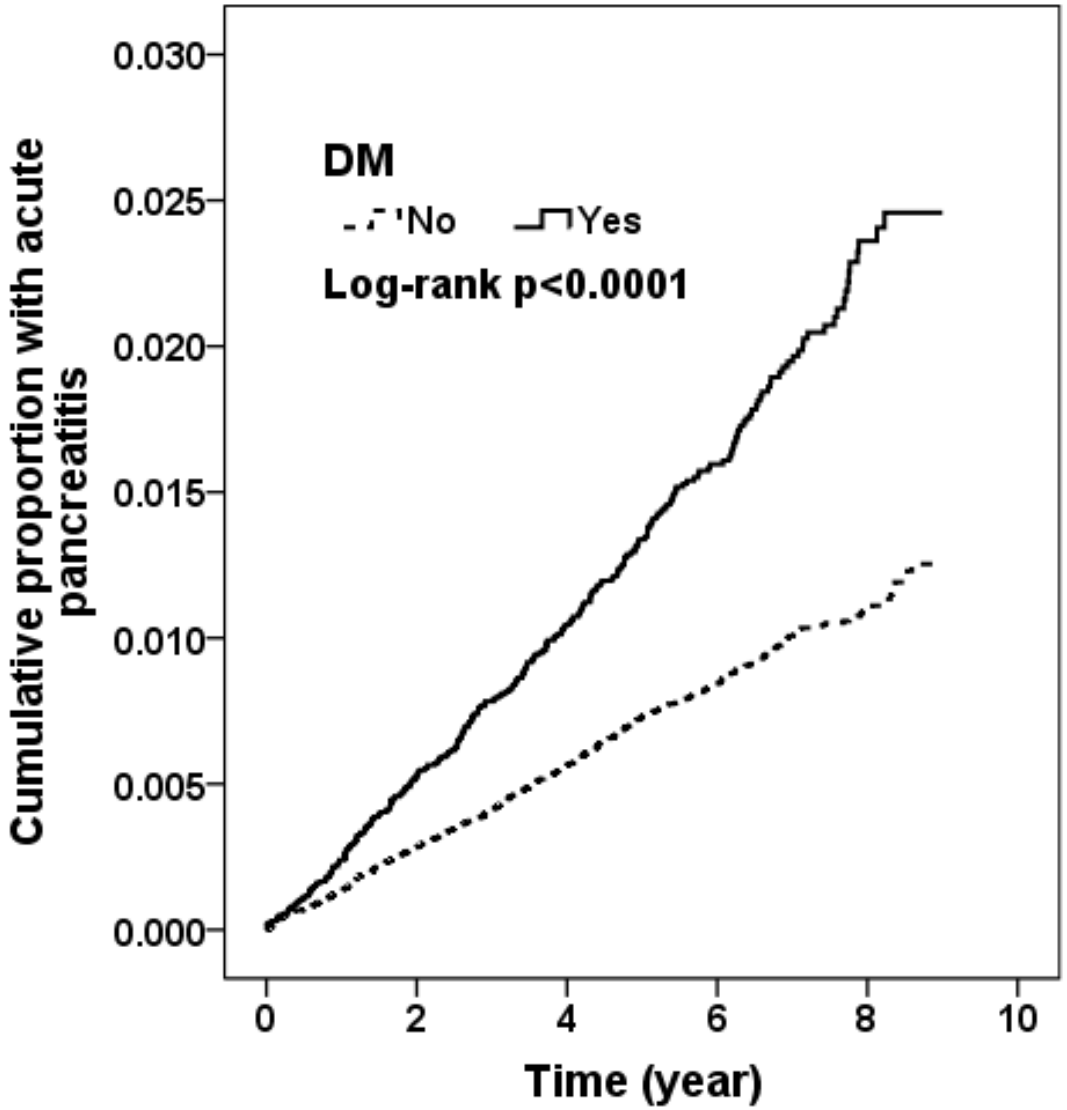

Figure 1. Cumulative incidence of acute pancreatitis for patients with Type 2 diabetes mellitus and compared subjects