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Glycemic Change After Pancreaticoduodenectomy

A Population-Based Study

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Abstract: The purpose of this population-based study was to determine the change of glucose metabolism in patients undergoing pancreaticoduodenectomy (PD).

We conducted a nationwide cohort study using data from Taiwan's National Health Insurance Research Database collected between 2000 and 2010. Our sample included 861 subjects with type 2 diabetes mellitus (DM) and 3914 subjects without DM.

Of 861 subjects with type 2 diabetes, 174 patients (20.2%) experienced resolution of their diabetes after PD, including patients with pancreatic ductal adenocarcinoma (PDAC) (20.5%), and non-PDAC (20.1%). Using a multiple logistic regression model, we found that subjects with comorbid chronic pancreatitis (odds ratio, 0.356; 95% CI, 0.167–0.759; $P = 0.007$) and use of insulin (odds ratio, 0.265; 95% CI, 0.171–0.412; $P < 0.001$) had significantly lower rates of resolution of diabetes. In the 3914 subjects without diabetes, the only statistically significant comorbidity contributing to pancreatogenic diabetes was chronic pancreatitis (odds ratio, 1.446; 95% CI, 1.146–1.823; $P = 0.002$).

Subjects with comorbid chronic pancreatitis and use of insulin had lower rates of resolution of DM after PD. In subjects without diabetes, chronic pancreatitis contributed significantly to the development of pancreatogenic DM.

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Abbreviations: CCI = Charlson comorbidity index, DM = diabetes mellitus, ICD-9 = International Classification of Disease, Ninth Revision, NHIRD = National Health Insurance Research Database, PC = pancreatic cancer, PD = pancreaticoduodenectomy, PDAC = pancreatic ductal adenocarcinoma.

INTRODUCTION

Pancreaticoduodenectomy (PD) is performed for the treatment of periampullary and pancreatic head diseases. PD has previously been associated with high mortality, which limited its use in the treatment of periampullary cancer. With improvements in both surgical skills and perioperative care, PD has become safer and it is now more widely used in the treatment of cancer as well as noncancerous diseases. The favorable survival rates after PD in the treatment of noncancerous diseases make metabolic outcomes after this procedure increasingly important.

Pancreatectomy often results in the deterioration of glucose homeostasis because the pancreas is the main organ responsible for hormonal regulation of glucose metabolism.[1] Pancreatectomy-associated diabetes is defined as pancreatogenic diabetes mellitus (DM; the onset of DM after pancreatectomy), and occurrence rates vary (20–50%) depending on the type of the pancreatic resection procedure as well as the underlying disease. PD includes removal of the pancreatic head; therefore, theoretically, the procedure reduces the number of islet cells and worsens the glycemic status.

However, PD can result in the resolution of diabetes. Several studies have addressed the resolution of diabetes after PD in pancreatic ductal adenocarcinoma (PDAC) patients, particularly in patients diagnosed with new onset diabetes, or pancreatic cancer (PC) development within 2 years of diabetes diagnosis.[2–4] Pannala et al[5] attributed DM resolution after PD to resection of tumor along with tumor-secreted diabetogenic products. However, we found DM resolved after PD in some patients both with and without PDCA and postulated that PD-associated anatomic change may play a role in resolution of DM after PD.[6] PD-associated anatomical changes include resection of pancreatic head, duodenum, and most proximal part of jejunum (10–15 cm). After PD, another 30 to 40-cm-long jejunum will be brought up for pancreatic and biliary anastomosis, which will make the last enteral anastomosis (gastrojejunostomy in standard PD or duodenojejunostomy in pylorus-preserving PD) created on jejunum about 50 to 60 cm distal to Treitz ligament. The change in the food passage route after PD is quite similar to that after Roux-en-Y gastric bypass for morbid obesity. This reconstruction allows food to pass directly into the distal jejunum without passing through the duodenum (foregut and hindgut theories of bariatric surgery). These patients had increased postprandial secretion of gut hormone contributing to improved insulin resistance and glucose metabolism.

According to these findings, PD may have positive and negative effects on glucose metabolism. The aim of this study was to use the reimbursement databases of Taiwan's National Health Insurance (NHI) to investigate the factors contributing to changes in glucose metabolism after PD, and therefore, the resolution of diabetes and pancreatogenic diabetes.

METHODS

Data Source

Data were obtained from Taiwan's NHI Research Database (National Health Insurance Research Database [NHIRD]). This insurance program is a mandatory health care plan initiated in March 1995, by 2008, this program covered more than 99% of the

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population of Taiwan (23 million residents). The NHIRD data used in our study was prepared and provided by the National Health Research Institute. The data include all inpatient and outpatient records of the study subjects. Every record contains the patient's anonymized data, including sex, birth date, as well as the International Classification of Disease, Ninth Revision (ICD-9) code, procedure code, and prescription medication information. The dataset we used for this study contained diagnosis records dated between 2000 and 2011. Patient consent is not required for accessing the NHIRD or the Longitudinal Health Insurance.

Database: This study was approved by the Institutional Review Board of National Taiwan University Hospital (201405043W).

Study Population

We selected patients undergoing PD (ICD-9 procedure code 52.7) between 2000 and 2011 as our study subjects (n = 5885). We excluded subjects who underwent PD in and after 2011 (n = 582) to ensure at least 1 year of follow-up. Patients were further excluded if the duration of follow-up was less than 6 months (n = 500), they were <20 years of age (n = 15) or had type 1 diabetes (ICD-9 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, and 250.93) (n = 13). The diagnostic accuracy of cancer was confirmed by both specific admission ICD-9 codes (ampullary cancer [ICD-9 156.2], PC [ICD-9 157.0–157.9], hepatobiliary cancer [ICD-9 156.1], and duodenal cancer [ICD-9 152.0])[7] and inclusion in the Registry for Catastrophic Illness Patient Database, a subpart of the NHIRD.[8] Thus, we identified 4775 PD subjects between 2000 and 2010. Among them, 861 subjects had type 2 diabetes and 3914 did not have diabetes. We further divided the diagnosis of diabetes into new-onset diabetes (DM diagnosed within 2 years before PD) and long-standing diabetes (DM diagnosed >2 years prior to PD). Finally, we analyzed the resolution of diabetes in subjects with DM and the incidence of pancreatogenic DM after PD in subjects without diabetes.

Definition of Change of Glucose Metabolism

In this study, patients with at least 1 hospital admission or at least 3 outpatient visits for DM (ICD-9 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250. 60, 250.62, 250.70, 250.72, 250.80. 250.82, 250.90, and 250.92) separated by at least 30 days were defined as the DM group, excluding type 1 DM. This definition of diabetes was evaluated and validated in the Taiwan NHIRD with a high level of sensitivity and positive predictive value (93.2% and 92.3%, respectively).[9] The admission date for PD was defined as index date of PD. Any below statement was defined as resolution of diabetes:

(1) Pre-PD DM patients without hypoglycemic medication had no records of DM diagnosis after PD.
(2) Pre-PD DM patients with hypoglycemic medication had no records of hypoglycemic medication on pharmacy claim dataset within 1-year post-PD period.

On the other hand, the definition of pancreatogenic DM was that non-DM subjects had new DM ICD-9 codes on the inpatient or outpatient claim dataset after the date of PD.

Comorbidity

To study comorbidity, we collected data on the diagnoses made prior to PD for each patient: dyslipidemia (ICD-9 272.0, 272.1, and 272.2), chronic pancreatitis (ICD-9 577.1), liver cirrhosis (ICD-9 571.5), hypertension (ICD-9 401–405), and peptic ulcer diseases (ICD-9 531–535).[10]

Baseline Characteristics

Baseline demographic characteristics examined were age (≤49, 50–64, ≥65 years), sex, monthly income (NT$ [New Taiwan dollar] <15,000, NT$ 15,000–$22,798, and >NT$ 22,798), and the Charlson comorbidity index (CCI) score (<2 and ≧2). The CCI score is used to determine overall systemic health.[11]

Statistical Analysis

For statistical analysis, SPSS software (version 22.0, 2012; SPSS Inc., Chicago, IL) was performed. Continuous data are presented as mean ± standard error of the mean unless otherwise

TABLE 1. Demographic Characteristics of Patients with Diabetes Among PDAC and Non-PDAC Patients After PD

	PDAC (n = 264)		Non-PDAC (n = 597)		
	N	%	N	%	*P*-Value
Sex					0.143
Men	164	62.1	339	56.8	
Women	100	37.9	258	43.2	
Age, years					0.098
≤49	22	8.3	75	12.6	
50–64	89	33.7	215	36.0	
≥65	153	58.0	307	51.4	
Charlson comorbidity index scores					0.037
<2	0	0.0	10	1.7	
≧2	264	100.0	587	98.3	
Monthly income, NT$					0.071
<15,000	46	17.4	99	16.6	
15,000–22,798	131	49.6	343	57.5	
>22,798	87	33.0	155	26.0	
Comorbidity					
Peptic ulcer disease					0.684
Yes	160	60.6	353	59.1	
No	104	39.4	244	40.9	
Liver cirrhosis					0.136
Yes	95	36.0	247	41.4	
No	169	64.0	350	58.6	
Dyslipidemia					0.327
Yes	88	33.3	179	30.0	
No	176	66.7	418	70.0	
Chronic pancreatitis					0.027
Yes	27	10.2	95	15.9	
No	237	89.8	502	84.1	
Hypertension					0.444
Yes	183	69.3	398	66.7	
No	81	30.7	199	33.3	
Duration of diabetes					0.534
New-onset	169	64.0	396	66.3	
Long standing	95	36.0	201	33.7	
Use of insulin					0.193
Yes	106	40.2	211	35.3	
No	158	59.8	386	64.7	
DM resolution					0.927
Yes	54	20.5	120	20.1	
No	210	79.5	477	79.9	

NT$ = New Taiwan Dollars. One New Taiwan Dollar equals US$ 0.03, PD = pancreaticoduodenectomy, PDAC = pancreatic ductal adenocarcinoma.

specified. The Student *t*-test was used for comparison between the 2 groups for continuous data. Categorical variables were analyzed using the Fisher exact test and the Pearson Chi-square test if the cell count was less than 5. Multivariate analysis was performed by using the multiple logistic regression model, and the results are shown as odds ratios and 95% confidence intervals (CIs). Factors with $P < 0.10$ on univariate analysis were included in the regression model. All statistical tests were two-sided, and *P*-values of <0.05 were considered statistically significant.

RESULTS

Comparison of PDAC and Non-PDAC Patients With DM

Among the 861 patients with DM, 264 patients had PDAC (169 new-onset diabetes; 64.0%) and 597 did not have PDAC (396 new-onset diabetes; 66.3%). The PDAC group had a higher percentage of higher CCI scores and a less percentage of chronic pancreatitis compared to non-PDAC group (Table 1). There was no statistically significant difference between the PDAC and non-PDAC groups considering the rates of resolution of diabetes (20.5% versus 20.1%; $P = 0.927$).

Factors Influencing Resolution of Diabetes in Patients With DM

Of 861 subjects with diabetes 174 (20.2%) had resolution of diabetes. Results of the univariate comparison between preoperative patients with diabetes with and without resolution of their DM are illustrated in Table 2. Patients diagnosed with chronic pancreatitis ($P < 0.001$) and use of insulin ($P < 0.001$) had lower rates of resolution of diabetes after PD. Patients with periampullary cancer had higher rates of resolution of diabetes

TABLE 2. Influence of Clinicodemographic Characteristics on the Resolution of Diabetes After PD in Preoperative Patients With DM, on Univariate Analysis

	DM Resolution (n = 174)		Persistent DM (n = 687)		
	N	%	N	%	*P*-Value
Sex					0.187
Men	96	55.2	407	59.2	
Women	78	44.8	280	40.8	
Age, years					
≤49	22	12.6	75	10.9	0.177
50–64	51	29.3	253	36.8	
≥65	101	58.1	359	52.3	
Charlson comorbidity index scores					0.033
<2	5	2.9	5	0.7	
≧2	169	97.1	682	99.3	
Monthly income, NT$					0.181
<15,000	34	19.5	111	16.2	
15,000–22,798	85	48.9	389	56.6	
>22,798	55	31.6	187	27.2	
PDAC					0.927
Yes	54	31.0	210	30.6	
No	120	69.0	477	69.4	
Periampullary cancer					0.014
Yes	148	85.1	525	76.4	
No	26	14.9	162	23.6	
Comorbidity					
Peptic ulcer disease					0.931
Yes	103	59.2	410	59.7	
No	71	40.8	277	40.3	
Liver cirrhosis					0.435
Yes	74	42.5	268	39.0	
No	100	57.5	419	61.0	
Dyslipidemia					0.647
Yes	51	29.3	216	31.4	
No	123	70.7	471	68.6	
Chronic pancreatitis					<0.001
Yes	9	5.2	113	16.4	
No	165	94.8	574	83.6	
Hypertension					0.205
Yes	110	63.2	471	68.6	
No	64	36.8	216	31.4	
Type of diabetes					0.532
New-onset	118	67.8	447	65.1	
Long standing	56	32.2	240	34.9	
Use of insulin					<0.001
Yes	27	15.5	290	42.2	
No	147	84.5	397	57.8	
Duration of follow up (mean ± SD; days)	854.6 ± 472.5		977.2 ± 488.5		0.101

Periampullary cancer includes pancreatic ductal adenocarcinoma, distal common bile duct cancer, duodenal cancer, and ampulla of Vater cancer. DM = diabetes mellitus, PD = pancreaticoduodenectomy, PDAC = pancreatic ductal adenocarcinoma.

TABLE 3. Influence of Clinicodemographic Characteristics on the Resolution of Diabetes After PD in Preoperative Patients With DM, on Multivariate Analysis

	P-Value	Odds Ratio	95% Confidence Interval
Use of insulin	<0.001	0.265	0.171–0.412
Periampullary cancer	0.429	1.223	0.742–2.014
Chronic pancreatitis	0.007	0.356	0.167–0.759

Periampullary cancer includes pancreatic ductal adenocarcinoma, distal common bile duct cancer, duodenal cancer, and ampulla of Vater cancer. DM = diabetes mellitus, PD = pancreaticoduodenectomy.

after PD ($P = 0.014$). The multiple logistic regression model was constructed for evaluation of the factors associated with resolution of diabetes (Table 3). On Cox logistic regression model, chronic pancreatitis (odds ratio, 0.356; 95% CI, 0.167–0.759; $P = 0.007$) and use of insulin (odds ratio, 0.265; 95% CI, 0.171–0.412; $P < 0.001$) were significantly associated with less proportion of resolution of diabetes after PD.

Factors of Pancreatogenic Diabetes in Preoperative Patients Without DM

Of the 3914 patients without diabetes, those with pancreatogenic diabetes had liver cirrhosis ($P = 0.059$) and chronic pancreatitis ($P = 0.001$) more often compared to patients with persistent nondiabetes (Table 4). Moreover, subjects with pancreatogenic diabetes had periampullary cancer less often ($P = 0.001$) and had low CCI scores ($P = 0.001$) compared to patients with persistent nondiabetes. A multiple logistic regression model was constructed for evaluation of the factors associated with pancreatogenic diabetes (Table 5). Only chronic pancreatitis (odds ratio, 1.446; 95% CI, 1.146–1.823; $P = 0.002$) was statistically significant in contributing to pancreatogenic diabetes.

DISCUSSION

The pancreas is both an exocrine and endocrine organ. Chronic pancreatitis is a disease characterized by pancreatic inflammation and fibrotic injury, contributing to irreversible parenchymal damage.[12] Therefore, chronic pancreatitis may cause not only progressive nutrient maldigestion and malabsorption, but also glucose intolerance. In addition, nutrient

TABLE 4. Influence of Clinicodemographic Characteristics on the Occurrence of Pancreatogenic Diabetes After PD in Preoperative Patients Without DM, on Univariate Analysis

	Pancreatogenic DM (n = 632)		No DM (n = 3282)		
	n	%	N	%	*P*-Value
Sex					0.200
Men	390	61.7	1935	59.0	
Women	242	38.3	1347	41.0	
Age, years					
≤49	115	18.2	634	19.3	0.126
50–64	250	39.6	1159	35.3	
≥65	267	42.2	1489	45.4	
Charlson comorbidity index scores					
<2	53	8.4	162	4.9	0.001
≧2	579	91.6	3120	95.1	
Monthly income, NT$					
<15,000	100	15.8	517	15.8	0.297
15,000–22,798	337	53.3	1848	56.3	
>22,798	195	30.9	917	27.9	
Periampullary cancer	462	73.1	2625	80.0	0.001
PDAC	194	30.7	1017	31.0	0.925
Biliary duct cancer	56	8.9	302	9.2	0.822
Ampulla of Vater cancer	190	30.1	1143	34.8	0.022
Duodenal cancer	22	3.4	163	4.9	0.262
Comorbidity					
Peptic ulcer disease	352	55.7	1862	56.7	0.630
Liver cirrhosis	211	33.4	971	29.6	0.059
Dyslipidemia	69	10.9	316	9.6	0.308
Chronic pancreatitis	99	15.7	255	7.8	0.001
Hypertension	270	42.7	1299	39.6	0.144
DM medication					
OHA	386	61.7			
Insulin use	240	38.3			
Duration of follow-up (mean ± SD; days)	1547.2 ± 1049.4		1439.8 ± 929.0		0.230

NT$ = New Taiwan Dollars. One New Taiwan Dollar equals US$ 0.03, OHA = oral hypoglycemia agent, PDAC = pancreatic ductal adenocarcinoma.

TABLE 5. Influence of Clinicodemographic Characteristics on the Occurrence of Pancreatogenic Diabetes After PD in Preoperative Patients Without DM, on Multivariate Analysis

	P-Value	Odds Ratio	95% Confidence Interval
Liver cirrhosis	0.318	1.090	0.921–1.289
Chronic pancreatitis	0.002	1.446	1.146–1.823
Charlson comorbidity index score ≧2	0.321	1.182	0.850–1.643
Periampullary cancer	0.229	1.140	0.921–1.412

DM = diabetes mellitus, PD = pancreaticoduodenectomy.

maldigestion results in impaired secretion of incretin and decreased insulin release from β-cells.[13] In our study, patients with chronic pancreatitis showed higher rates of pancreatogenic diabetes among patients previously without diabetes and lower rates of diabetes resolution among DM cases after PD.

DM secondary to pancreatic disease is classified as pancreatogenic diabetes or type 3c DM.[14] In contrast to type 1 and type 2 diabetes, clinical data on type 3c diabetes are lacking. The prevalence of type 3c DM among all patients with DM has been estimated to be approximately 5% to 10%.[15] Owing to the diverse pathophysiology of type 3c DM, its clinical features differ from those of both type 1 and type 2 DM. Among the causes of type 3c DM, chronic pancreatitis is the main etiology and may be accompanied by syndromes of exocrine pancreatic insufficiency such as steatorrhea or gastrointestinal complaints. Patients with type 3c DM should receive hyperglycemia-lowering medications according to the same guidelines used for type 2 diabetes. However, patients with type 3c DM with exocrine pancreatic insufficiency should take adequate supplements of pancreatic enzymes, which may not only prevent a lack of fat-soluble vitamins but also reverse the decreased release of incretin.[12]

In this study, 20.5% of patients with diabetes and PDAC had resolution of diabetes after PD. Previous studies[5,16,17] emphasized that PDAC patients had resolution of diabetes, and that the resolution of diabetes was attributed to removal of products secreted by PDAC during the PD procedure.[18,19] PDAC patients often have diabetes, which frequently manifests as early as 2 to 3 years before a diagnosis of PDAC. Additionally, patients with new-onset diabetes have a 5- to 8-fold increased risk of being diagnosed with PDAC within 1 to 3 years of developing diabetes.[4,17] New-onset diabetes can be a clue in the early diagnosis of PDAC, especially for patients whose glucose control worsens in the face of profound weight loss.[3] Furthermore, long-standing diabetes is predictive of poor outcomes for PDAC, whereas postoperatively resolved new-onset diabetes is associated with better oncological results.[20] In our study, 20.1% of non-PDAC subjects with diabetes also had resolution of diabetes after PD. As there was no removal of PDAC-secreted hyperglycemic products, it can be suggested that the mechanism of diabetes resolution may result from the complex gastrointestinal reconstructions during PD, such as removal of the duodenum and gastroenteral bypass.

The association between diabetes and PDAC has been studied for more than a century and is complicated by the existence of a bidirectional relationship between the 2 entities.[21,22] Although, more current evidences support PC-induced paraneoplastic diabetes, epidemiological data illustrate a causal relationship between long-standing diabetes and PC. The use of insulin, insulin analogs, and insulin secretagogues appear to increase the risk of PC because of the enhanced activation of insulin-associated pathways.[23] Most important, the successful control of diabetes and/or body weight is associated with a decreased risk of PC.[21] In this study, we did not investigate the relationship between PDAC and diabetes. In contrast, we focused on researching the mechanisms for the resolution of diabetes. The resolution of diabetes may be associated to PD-associated anatomic changes alike bariatric surgery.

One of the strengths of this study was the use of a population-based database, which is highly representative of the general population. Our study also has several limitations. First, the NHIRD does not include laboratory data, family history, or information on major risk factors in the development of diabetes such as body weight, alcohol abuse, or diet. Second, the quality of medical evidence derived from an observational cohort study is inferior to that from randomized trials because of other unknown confounders and selection bias. Third, coding error is inevitable in a database. To decrease coding error in this study, the diagnostic accuracy of coding of DM was confirmed by both specific admission ICD-9 codes and hyperglycemia-lowering medication in pharmacy databases. Moreover, the diagnosis of comorbidities was confirmed if patients had 1 relevant inpatient code from the ICD-9 or 3 outpatient ICD-9 codes separated by at least 30 days. Lastly, there were no statistically significant differences in the resolution of diabetes between the PDAC and non-PDAC groups; however, the mean duration of follow-up with the PDAC group was shorter than the non-PDAC group (2.4 ± 1.6 versus 3.8 ± 2.6 years; $P < 0.01$). We adjusted the bias of the length of follow-up by incidence rate ratio (IRR). The IRR in the PDAC and non-PDAC groups was measured for the resolution of diabetes by using a Poisson regression analysis. These adjustments indicated that there were no significant differences regarding the resolution rate of diabetes between PDAC and non-PDAC groups (1.91 versus 1.87 per 100 person-year; IRR = 1.021; range: 0.743–1.412; $P = 0.876$). Moreover, the median interval between PD and resolution of diabetes was 5.3 months (3.1–11.7 months). Therefore, the bias of the duration of follow-up may be minimal in this study.

In summary, this population-based cohort retrospective study showed subjects with comorbid chronic pancreatitis, and the use of insulin had lower rates of resolution of DM after PD. In subjects without diabetes, chronic pancreatitis significantly contributed to the development of pancreatogenic DM. Clinicians-treating patients with PD should be alert for PD patients with chronic pancreatitis to closely assess the parameters of glucose metabolism.

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