Characteristics and Clinical Course of Diabetes of the Exocrine Pancreas: A Nationwide Population-Based Cohort Study

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OBJECTIVE

The natural course of diabetes of the exocrine pancreas (DEP) is not well established. We aimed to compare the risk of insulin initiation, diabetic complications, and mortality between DEP and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Using the Korean National Health Insurance Service–Health Screening Cohort between 2012 and 2017, we divided patients with diabetes into those with diabetes without prior pancreatic disease (indicated type 2 diabetes, *n* = 153,894) and diabetes with a prior diagnosis of pancreatic disease (indicated DEP, *n* = 3,629). ICD-10 codes and pharmacy prescription information were used to define type 2 diabetes, DEP, and acute and chronic diabetes complications. Kaplan-Meier curves were produced to compare insulin use over time between groups. We created logistic regression models for odds of progression to diabetic complications and mortality.

RESULTS

DEP was associated with a higher risk of insulin use than type 2 diabetes (adjusted hazard ratio 1.38 at 5 years [95% CI 1.30–1.47], $P < 0.0001$). Individuals with DEP showed higher risks of hypoglycemia (odds ratio 1.85 [1.54–2.21], $P < 0.0001$), diabetic neuropathy (1.38 [1.28–1.49], $P < 0.0001$), nephropathy (1.38 [1.27–1.50], $P < 0.0001$), retinopathy (1.10 [1.01–1.20], $P = 0.0347$), coronary heart disease (1.59 [1.48–1.70], $P < 0.0001$), cerebrovascular disease (1.38 [1.28–1.49], $P < 0.0001$), and peripheral arterial disease (1.34 [1.25–1.44], $P < 0.0001$). All-cause mortality was higher in those with DEP (1.74 [1.57–1.93], $P < 0.0001$) than in those with type 2 diabetes.

CONCLUSIONS

DEP is more likely to require insulin therapy than type 2 diabetes. Hypoglycemia, micro- and macrovascular complications, and all-cause mortality events are higher in DEP compared with type 2 diabetes.

Diabetes of the exocrine pancreas (DEP) results from the structural or functional loss of insulin secretion in the context of exocrine pancreatic dysfunction (1). It has been described by alternate terminology, including pancreatic, pancreatogenic, and type 3c diabetes. The causes of DEP include pancreatitis, cystic fibrosis, or pancreatic

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malignancy (2). DEP tends to be less frequently considered in practice because of its etiologic heterogeneity and unique pathophysiology and is commonly misdiagnosed as type 2 diabetes (3,4). Re search from primary care records in the U.K. showed that 87.8% of cases of DEP were classified as type 2 diabetes, with only 2.7% correctly diagnosed as DEP (4). The prevalence of DEP also varies from 0.8 to 9.2% among patients with diabetes and mainly arises from chronic pancreatitis (3–7). A recent study demonstrated the prevalence of DEP has nearly tripled over the past decades in New Zealand (5). DEP is likely to become a more important condition with the increase in chronic pancreatitis, pancreatic surgery, and longer survival of patients with cystic fibrosis (8).

Impaired insulin secretion arises from the isolated autoimmune destruction of β-cells in type 1 diabetes and insulin resistance in type 2 diabetes (9,10), whereas DEP affects the hormone release capacity of all cell subtypes within islets of Langerhans, such as β, α, and pancreatic polypeptide (PP) cells. While insulin deficiency due to loss of β-cell mass is the main cause, the combination with other hormonal deficiencies of DEP contribute to its unique features, which differ from those of type 1 and type 2 diabetes. Glucagon deficiency due to the destruction of α-cells in DEP increases the risk of severe hypoglycemia by impairing hepatic gluconeogenesis but, conversely, reduces the risk of ketoacidosis (11,12). On the other hand, the lack of PP by diminished PP cell mass increases hepatic insulin resistance and contributes to hyperglycemia (13). The secretion of incretin hormones, such as glucagon-like peptide 1, is also impaired, resulting in decreased glucose-dependent insulin secretion (14). In addition to endocrine cell damages, pancreatic exocrine dysfunction affects DEP through malnutrition, cross talk with gut microbiota, and dysregulation of incretin secretion (15). Because of the different distributions of β, α, and PP cells in the pancreas and the diverse etiology of DEP, the clinical features of DEP vary, depending on the lesion and the severity of pancreatic damage.

Unlike type 2 diabetes, there are few studies on the clinical course of DEP. There is only one comparative study on insulin therapy between DEP and type 2 diabetes, which showed that patients with DEP initiated insulin at a higher rate than those with type 2 diabetes (4). There are few large-scale, population-based epidemiological studies of acute diabetic complications in DEP, such as hypoglycemia, diabetic ketoacidosis (DKA), and hyperosmolar hyperglycemic state (HHS) (7). Only a few studies have been conducted on risk in DEP of micro- and macrovascular complications, with inconsis tent results (6,7,16–18). Compared with type 2 diabetes, the prevalence of microvascular complications in DEP was similar for diabetic nephropathy, similar or lower for retinopathy, and similar or higher for neuropathy (6,7,16–18). Among macrovascular complications, coronary heart and cerebrovascular diseases occurred in DEP to a similar or lesser extent than in type 2 diabetes, while peripheral arterial disease occurred to a similar extent (6,7,17,18). There is little evidence on mortality in DEP compared with type 2 diabetes (6,19,20). Furthermore, previous research had limitations such as small sample sizes, inclusion of very few diseases among all DEP causes, and lack of adjustment for confounding factors (6,7,16–20). Therefore, we compared the rates of insulin use, acute and chronic diabetic complications, and mortality between DEP and type 2 diabetes using the Korean National Health Insurance Service (NHIS) database.

RESEARCH DESIGN AND METHODS

Data Source and Study Design

In this population-based retrospective cohort study, we used the Korean NHIS-Health Screening Cohort, which included individuals participating in national health screening programs provided by the NHIS in the Republic of Korea biennially. The data include longitudinal information on demographics, socioeconomic status, medical and pharmaceutical claims, such as diagnosis code (ICD-10 code), drug prescriptions (Anatomical Therapeutic Chemical [ATC] code), and medical procedures, health examination data, such as anthropometric measures, laboratory data, and responses to self-reported questionnaires, and death records (Supplementary Table 1).

We selected patients aged ≥18 with newly diagnosed diabetes from 1 January 2012 to 31 December 2017. Diabetes was determined to be present by both standard diagnosis codes (ICD-10, E11.x) and standard prescription (ATC) codes for antidiabetes medications. The index date was defined as the date of the first diagnosis of diabetes. Patients with at least one diagnostic code for type 1 diabetes (ICD-10, E10.x) or gestational diabetes mellitus (ICD-10, O24) and patients with prescriptions of antidiabetes drugs during the preceding 12 months from the index date were excluded. Among 270,239 new cases of diabetes, we further excluded subjects who did not participate in national health screening programs within 2 years before the index date, had missing data for confounding factors, or underwent pancreatic surgery, had a prior diagnosis of hereditary hemochromatosis, or experienced their first attack of acute pancreatitis during the preceding 12 months of the index date. We categorized persons with diabetes into two groups in accordance with a history of pancreatic diseases for 5 years before the index date: diabetes following pancreatic disease (indicated DEP) and diabetes without prior pancreatic disease (type 2 diabetes). Pancreatic diseases were defined using ICD-10 codes based on the most up-to-date definition of DEP listed in Supplementary Table 2 (2). A flowchart of patient selection is shown in Supplementary Fig. 1. This study was approved by the Ajou University Hospital Institutional Review Board (AJIRB-MED-EXP-19-106), which waived the requirement for informed consent because anonymized and deidentified information was used for analysis.

Study Outcomes

The primary outcome was the incidence of patients initiating insulin treatment, which was defined based on the ATC code (A10A). Secondary outcomes were the cumulative incidences of diabetic complications and all-cause mortality. Diabetic complications include both acute (defined as hypoglycemia, HHS, and DKA) and chronic (defined as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, and coronary heart, cerebrovascular, and peripheral arterial diseases) diabetic complications based on ICD-10 codes (Supplementary Table 3). Each subject was followed from the index date to death or end of the study period (December 31, 2018). We investigated secondary outcomes according to DEP subtypes: postacute pancreatitis diabetes mellitus (PPDM-A), postchronic pancreatitis diabetes mellitus (PPDM-C), pancreatic

cancer-related diabetes (PCRD), and cystic fibrosis-related diabetes (CFRD). We also examined secondary outcomes based on insulin regimen: basal insulin (intermediate, long-acting insulin) alone, prandial insulin (short-acting, rapid-acting insulin) alone, and combination of basal and prandial insulin.

Statistical Analysis

Data were analyzed to produce means (SDs) for continuous variables and numbers (percentages) for categorical variables. To compare the differences betw een two groups, the *t* test for continuous variables and the χ^2 test for categorical variables with the Yates correction were performed. The time to insulin treatment was assessed using Kaplan-Maier plots and compared using the log-rank test. We used a Cox proportional hazards model to calculate the hazard ratios (HR) with 95% CIs for insulin therapy at 1 and 5 years from the index date. In this analysis, a crude model and two adjusted models were calculated. Model 1 adjus ted for sex, age, BMI, fasting plasma glucose (FPG), LDL cholesterol, alcohol consumption, smoking status, and medical coverage. Model 2 adjusted for model 1 plus systolic blood pressure (BP), triglyceride, estimated glomerular filtration rate (eGFR), and Charlson comorbidity index (CCI), which was modified to avoid the duplication of target disease and outcomes (Supplementary Table 4). The cumulative incidence function method was performed to analyze the time to the occurrence of diabetic complications and mortality. Since the initially generated Cox proportional hazard models did not meet the assumption of proportionality of risks, we instead created logistic regression models for the odds ratio (OR) of diabetic complications and all-cause mortality in unadjusted and adjusted for the same covariates shown in models 1 and 2. All statistical results were analyzed using SAS Enterprise Guide 7.1 software (SAS Institute, Cary, NC), and *P* values of <0.05 were considered to be significant.

RESULTS

Baseline Characteristics of the Study Population

The study included 157,523 individuals (59.1% men) with newly diagnosed diabetes, with a mean age of 57.6 ± 11.8 years and a mean BMI of 25.8 ± 3.6 kg/m^2. The median follow-up period was 4.2 years (interquartile range, 2.6–5.7) from the date of diabetes diagnosis (Table 1). Among them, there were 3,629 individuals (2.3%) with DEP, consisting of PPDM-A (28.4%), PPDM-C (62.4%), PCRD (9.0%), and CFRD (0.2%), shown in Supplementary Table 6. At baseline (diagnosis of diabetes), patients with DEP tended to be older and male and to have lower BMI, waist circumference, systolic BP, diastolic BP, FPG, LDL cholesterol, triglyceride, and eGFR than those with type 2 diabetes. They were also more likely to have comorbidities and medical aid, which provides health care benefits to low-income families.

Insulin Use

DEP was associated with a higher risk of insulin use than type 2 diabetes (Fig. 1). The 1- and 5-year cumulative proportions of insulin use were 10.8% and 19.3% in type 2 diabetes, and 17.8% and 32.4% in DEP, respectively (log-rank test, $P < 0.0001$). The crude HRs for insulin requirement of patients with DEP were 1.71 (95% CI 1.58–1.85, $P < 0.0001$) at 1 year and 1.63 (1.54–1.73, $P < 0.0001$) at 5 years compared with those with type 2 diabetes (Supplementary Table 5). After adjusting for sex, age, BMI, FPG, LDL cholesterol, alcohol consumption, smoking status, medical coverage, systolic BP, triglyceride, eGFR, and CCI, patients with DEP had a 1.39-fold higher risk for insulin use at 1 year (HR 1.39, 95% CI 1.29–1.51, $P < 0.0001$) and 1.38-fold higher risk at 5 years (HR 1.38 [1.30–1.47], $P < 0.0001$) than those with type 2 diabetes. We also conducted sensitivity analyses by excluding patients who initiated insulin during the first 6 months following the index date to eliminate transient insulin use for acute hyperglycemic crisis, which showed that patients with DEP still had a higher rate of insulin use than those with type 2 diabetes (log-rank test, $P < 0.0001$) (Supplementary Fig. 2).

Acute Diabetic Complications

Patients with DEP had a higher risk of hypoglycemia than those without (Fig. 2*A* and Table 2). The group with DEP had a crude OR of 2.48 (95% CI 2.08–2.96, $P < 0.0001$) for hypoglycemia compared with the group with type 2 diabetes. This association persisted after further adjustment for baseline characteristics (model 2: OR 1.85, 95% CI 1.54–2.21, $P < 0.0001$). However, the DEP group revealed a trend toward higher risks of HHS and DKA, but this association did not reach statistical significance after full adjustments (model 2: HHS OR 1.34, 95% CI 0.97–1.85, $P = 0.0766$; DKA OR 1.42, 95% CI 0.86–2.35, $P = 0.1761$). In the subgroup analysis by each pancreatic disease, PPDM-A and PPDM-C showed similar results of higher risk of hypoglycemia compared with type 2 diabetes (model 2: OR 1.86 [95% CI 1.34–2.59], $P = 0.0002$ and 1.91 [1.53–2.38], $P < 0.0001$, respectively) (Supplementary Table 7). However, PCRD was associated with a higher risk of HHS (model 2: OR 2.25 [1.00–5.07], $P = 0.0497$). We could not analyze diabetic complications in the CFRD group ($n = 8$) due to the insufficient number of events.

Chronic Diabetic Complications

As for microvascular complications, pat ients with DEP had higher risks of diabetic neuropathy and nephropathy than those with type 2 diabetes (model 2, OR 1.38, 95% CI 1.28–1.49, $P < 0.0001$ and OR 1.38, 95% CI 1.27–1.50, $P < 0.0001$, respectively) (Fig. 2*B*, *C*, and Table 2). Patients with DEP did not have a high risk of diabetic retinopathy in the crude model, but multivariate analysis showed that patients with DEP had a 1.10-fold higher risk of diabetic retinopathy than patients with type 2 diabetes (model 2: OR 1.10, 95% CI 1.01–1.20, $P = 0.0347$) (Fig. 2*D* and Table 2). Similarly, the risk of developing macrovascular complications, such as coronary heart, cerebrovascular, and peripheral arterial diseases, was significantly higher in patients with DEP than in those with type 2 diabetes (OR 1.59, 95% CI 1.48–1.70, $P < 0.0001$; OR 1.38, 95% CI 1.28–1.49, $P < 0.0001$; OR 1.34, 95% CI 1.25–1.44, $P < 0.0001$, respectively) (model 2 in Fig. 2*E–G* and Table 2). In the subgroup analysis by each pancreatic disease, PPDM-C had higher risks of all chronic diabetic complications compared with type 2 diabetes (Suppl ementary Table 7). PPDM-A showed a similar trend, except no higher risk was seen for diabetic retinopathy. The PCRD group had a higher risk of diabetic neph ropathy and coronary heart and cerebrovascular diseases.

Table 1—Baseline characteristics

	All diabetes (*N* = 157,523)	Type 2 diabetes (*n* = 153,894)	DEP (*n* = 3,629)	*P* value
Sex				<0.0001
Male	93,137 (59.1)	90,869 (59.0)	2,268 (62.5)	
Female	64,386 (40.9)	63,025 (41.0)	1,361 (37.5)	
Age, years	57.6 (11.8)	57.6 (11.8)	60.9 (11.7)	<0.0001
18–29	892 (0.6)	887 (0.6)	5 (0.1)	<0.0001
30–39	7,896 (5.0)	7,783 (5.1)	113 (3.1)	
40–49	30,546 (19.4)	30,047 (19.5)	499 (13.8)	
50–59	50,742 (32.2)	49,687 (32.3)	1,055 (29.1)	
60–69	40,055 (25.4)	39,032 (25.4)	1,023 (28.2)	
70–79	22,820 (14.5)	22,066 (14.3)	754 (20.8)	
≥80	4,572 (2.9)	4,392 (2.9)	180 (5.0)	
Medical coverage				<0.0001
NHI	154,482 (98.1)	150,981 (98.1)	3,501 (96.5)	
Medical aid	3,041 (1.9)	2,913 (1.9)	128 (3.5)	
Income quintiles				<0.0001
1 (lowest)	23,774 (15.1)	23,267 (15.1)	507 (14.0)	
2	22,248 (14.1)	21,795 (14.2)	453 (12.5)	
3	27,117 (17.2)	26,493 (17.2)	624 (17.2)	
4	34,439 (21.9)	33,688 (21.9)	751 (20.7)	
5 (highest)	43,688 (27.7)	42,623 (27.7)	1,065 (29.3)	
Missing data	6,257 (4.0)	6,028 (3.9)	229 (6.3)	
CCI, mean (SD)	0.8 (0.9)	0.8 (0.9)	1.3 (1.1)	<0.0001
BMI, mean (SD), kg/m^2	25.8 (3.6)	25.8 (3.6)	24.8 (3.6)	<0.0001
<18.5	1,935 (1.2)	1,817 (1.2)	118 (3.3)	<0.0001
18.5–24.9	66,541 (42.2)	64,719 (42.1)	1,822 (50.2)	
25.0–29.9	70,906 (45.0)	69,481 (45.1)	1,425 (39.3)	
≥30.0	18,141 (11.5)	17,877 (11.6)	264 (7.3)	
Waist circumference, mean (SD), cm	86.6 (9.0)	86.6 (9.0)	85.1 (8.8)	<0.0001
Systolic BP, mean (SD), mmHg	129.3 (15.7)	129.3 (15.7)	128.1 (15.8)	<0.0001
Diastolic BP, mean (SD), mmHg	79.9 (10.4)	80.0 (10.4)	79.0 (10.4)	<0.0001
FPG, mean (SD), mg/dL	142.5 (54.8)	142.9 (55.0)	125.3 (42.2)	<0.0001
Total cholesterol, mean (SD), mg/dL	210.0 (46.9)	210.2 (46.9)	199.7 (45.3)	<0.0001
Triglyceride, mean (SD), mg/dL	195.7 (165.3)	196.0 (165.1)	183.8 (174.4)	<0.0001
HDL cholesterol, mean (SD), mg/dL	51.1 (29.4)	51.0 (29.6)	51.4 (19.3)	0.2218
LDL cholesterol, mean (SD), mg/dL	122.3 (53.3)	122.5 (53.5)	113.4 (40.0)	<0.0001
Serum creatinine, mean (SD), mg/dL	0.9 (0.7)	0.9 (0.7)	1.0 (0.8)	<0.0001
eGFR, mean (SD), mL/min/1.73 m^{2*}	86.4 (18.4)	86.5 (18.4)	82.8 (19.3)	<0.0001
Alcohol consumption				<0.0001
None	86,773 (55.1)	84,627 (55.0)	2,146 (59.1)	
≤13 units/week	53,349 (33.9)	52,301 (34.0)	1,048 (28.9)	
≥14 units/week	17,283 (11.0)	16,849 (10.9)	434 (12.0)	
Unknown	118 (0.1)	117 (0.1)	1 (0.0)	
Smoking status				0.5364
Never smoker	85,326 (54.2)	83,393 (54.2)	1,933 (53.3)	
Former smoker	31,065 (19.7)	30,337 (19.7)	728 (20.1)	
Current smoker	41,058 (26.1)	40,093 (26.1)	965 (26.6)	
Unknown	74 (0.0)	71 (0.0)	3 (0.1)	

Data are *n* (%) unless indicated otherwise. Percentage might not add up to 100% due to rounding. *eGFR was calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation: $eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if Black]. SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

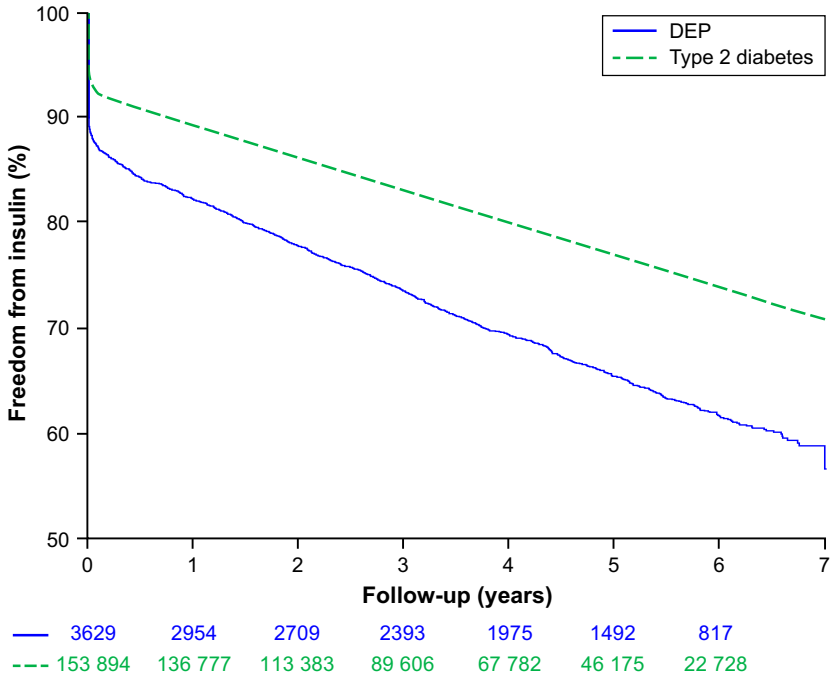

Figure 1—Kaplan-Meier curves of freedom from insulin use for DEP and those with type 2 diabetes. The number and cumulative proportion of patients at risk over time is shown ($P <$ 0.0001 by log-rank test).

All-Cause Mortality

The group with DEP had a higher risk of all-cause mortality than the group with type 2 diabetes ($P < 0.0001$) (Fig. 2*H*). All-cause mortality in DEP had attenuated associations after adjustment, but DEP still exhibited a significantly increased risk of all-cause mortality compared with type 2 diabetes (OR 1.74, 95% CI 1.57–1.93, $P < 0.0001$) (model 2 in Table 2). We found the consistent results for mortality in DEP compared with type 2 diabetes even after matching cardiovascular (CV) or renal disease (OR 1.52 [95% CI 1.25–1.87], $P <$ 0.0001 and 1.84 [1.05–3.22], $P =$ 0.0320, respectively) (model 2 in Supplementary Table 8). Even when analyzed by PPDM-A, PPDM-C, and PCRD, the risk for each of these subgroups with DEP was higher than for type 2 diabetes (OR 1.77 [95% CI 1.46–2.14] 1.47 [1.29–1.69], and 3.85 [2.93–5.05], respectively; all $P < 0.0001$) (model 2 in Supplementary Table 7).

Sensitivity Analyses to Insulin First User and Subgroup Analysis by Insulin Regimen

We performed sensitivity analyses only including patients who were prescribed insulin as the first treatment among patients who had never been prescribed antidiabetic drugs, which showed results consistent with risks observed for all diabetic complications and mortality in the larger sample receiving all treatments (Supplementary Table 9).

In subgroup analysis, patients were divided into basal insulin alone, prandial insulin alone, and combination of basal and prandial insulin, and we analyzed with an as-treated approach until treatment discontinuation, the occurrence of a specific study outcome, death, or end of the study period, whichever came first (Supplementary Fig. 3). Significant interactions were seen for the outcomes coronary heart and cerebrovascular diseases, where odds of these outcomes were higher in DEP compared with type 2 diabetes in the basal only compared with the prandial only and combined basal and prandial insulin regimens.

CONCLUSIONS

In this population-based cohort study, we comprehensively evaluated whether newly diagnosed DEP follows a different clinical course compared with type 2 diabetes. We found that DEP leads to a poorer clinical course, such as a more frequent requirement of insulin treatment, higher risk of hypoglycemia and chronic diabetic complications, and increased mortality compared with type 2 diabetes.

There were 3,629 patients with newly diagnosed DEP. The proportion of DEP among new-onset diabetes was 2.3%. A primary care study from the U.K., which was similar to our study design, found that the majority of cases of DEP were initially misdiagnosed as type 2 diabetes and that 1.5% of cases of type 2 diabetes were actually DEP (4). The incidence of DEP varies by country and clinical care setting, with an estimated worldwide incidence of ~6 per 100,000 general population per year (21). PPDM-C was the most common cause of DEP in our study, which is similar to a previous study in Germany (3). Prospective cohort studies in France (22) and China (23) found that the progression of chronic pancreatitis was a major determinant of DEP. However, PPDM-A was the most common subtype of DEP in the U.K. (4) and New Zealand (5).

In our study population, the proportion of male patients with DEP was 62.5% ($P < 0.0001$). This sex bias confirms previous studies reported in the U.K. (4) and Germany (7). Acute and chronic pancreatitis, usually caused by chronic and heavy alcohol consumption, are some of the common etiologies of DEP (21,24). Therefore, it is possible to predict the male dominance in DEP since binge drinking is five times more common among men than women in Korea (25). Patients with DEP were less obese than those with type 2 diabetes (a median BMI 24.8 kg/m^2 at the time of diagnosis), similar to the U.K. study (4). The low BMI in DEP can be explained as a result of malnutrition due to pancreatic exocrine insufficiency (PEI) (26). There are no previous studies comparing lipid profiles, and we found that serum total cholesterol and LDL cholesterol levels were lower in the group with DEP group than in the group with type 2 diabetes.

The group with DEP had a higher cumulative incidence of insulin therapy initiation than the group with type 2 diabetes, similar to the prior U.K. study (4). We also confirmed this trend with the exception of insulin therapy within 6 months after diagnosis, which can be considered a transient period for glycemic control in acute pancreatitis and acute hyperglycemic crisis (27). In another study comparing daily insulin doses, the daily dose was higher in patients with DEP than in those

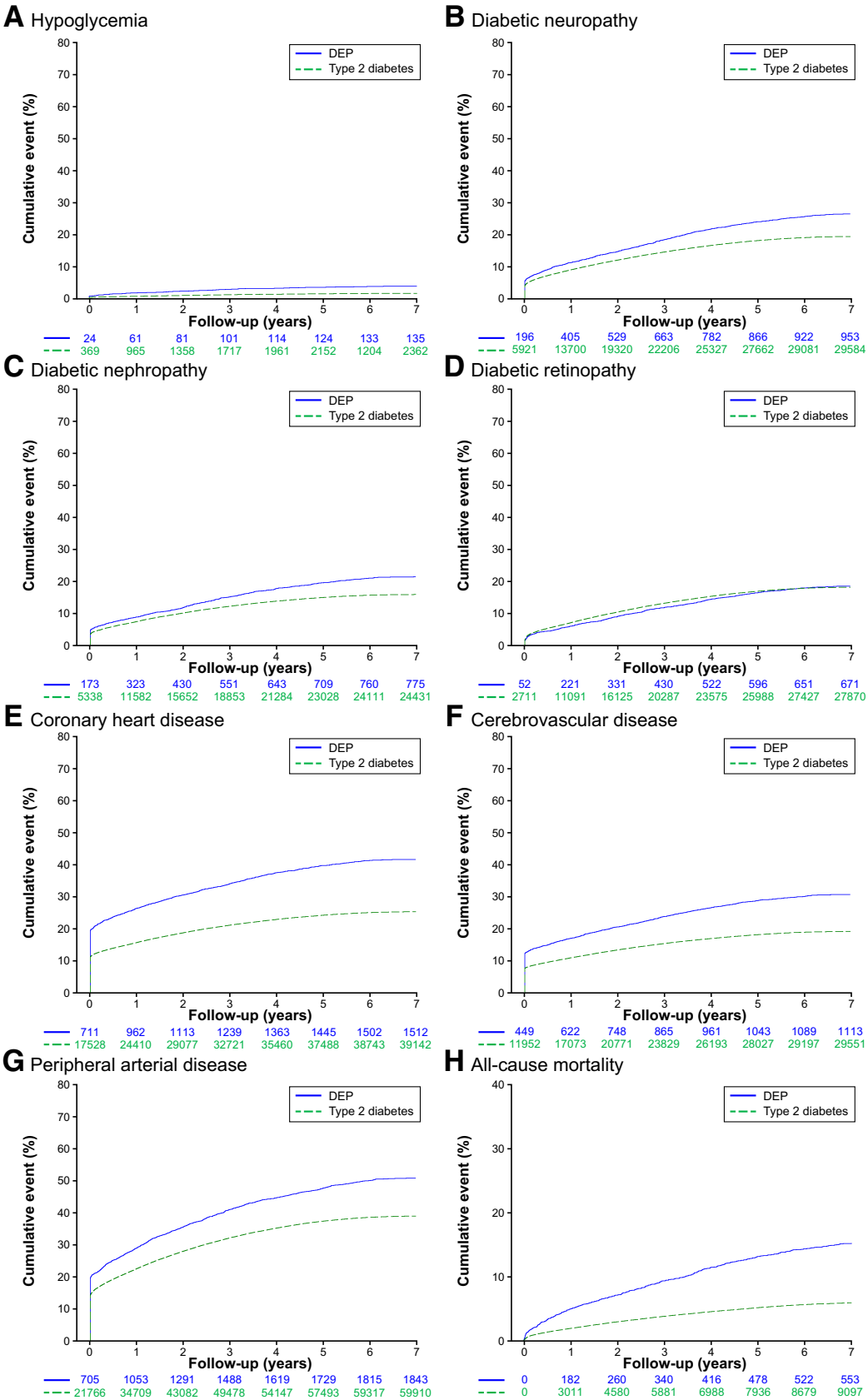

Figure 2—Cumulative proportions of diabetic complications and overall mortality for DEP and type 2 diabetes. *A*: Hypoglycemia is an acute complication of diabetes. Microvascular complications include diabetic neuropathy (*B*), nephropathy (*C*), and retinopathy (*D*). Macrovascular complications consist of coronary heart (*E*), cerebrovascular (*F*), and peripheral arterial diseases (*G*). *H*: All-cause mortality is stratified in patients by diabetes with or without prior pancreatic disease. The tables show the number of patients at risk by year.

Table 2—Relative odds for diabetic complications and all-cause mortality in DEP compared with type 2 diabetes

		DEP	95% CI	*P* value
Acute diabetic complications				
Hypoglycemia	Crude OR	2.48	2.08–2.96	<0.0001
	Model 1 OR	2.06	1.72–2.46	<0.0001
	Model 2 OR	1.85	1.54–2.21	<0.0001
Hyperosmolar hyperglycemic state	Crude OR	1.39	1.01–1.91	0.0461
	Model 1 OR	1.41	1.02–1.94	0.0370
	Model 2 OR	1.34	0.97–1.85	0.0766
Diabetic ketoacidosis	Crude OR	1.60	0.97–2.63	0.0672
	Model 1 OR	1.49	0.90–2.47	0.1178
	Model 2 OR	1.42	0.86–2.35	0.1761
Chronic diabetic complications				
Diabetic neuropathy	Crude OR	1.50	1.39–1.61	<0.0001
	Model 1 OR	1.47	1.36–1.58	<0.0001
	Model 2 OR	1.38	1.28–1.49	<0.0001
Diabetic nephropathy	Crude OR	1.44	1.33–1.56	<0.0001
	Model 1 OR	1.44	1.33–1.56	<0.0001
	Model 2 OR	1.38	1.27–1.50	<0.0001
Diabetic retinopathy	Crude OR	1.03	0.94–1.12	0.5538
	Model 1 OR	1.11	1.02–1.21	0.0186
	Model 2 OR	1.10	1.01–1.20	0.0347
Coronary heart disease	Crude OR	2.10	1.96–2.24	<0.0001
	Model 1 OR	1.74	1.62–1.87	<0.0001
	Model 2 OR	1.59	1.48–1.70	<0.0001
Cerebrovascular disease	Crude OR	1.86	1.73–2.00	<0.0001
	Model 1 OR	1.49	1.38–1.61	<0.0001
	Model 2 OR	1.38	1.28–1.49	<0.0001
Peripheral arterial disease	Crude OR	1.62	1.52–1.73	<0.0001
	Model 1 OR	1.45	1.36–1.56	<0.0001
	Model 2 OR	1.34	1.25–1.44	<0.0001
All-cause mortality	Crude OR	2.86	2.61–3.14	<0.0001
	Model 1 OR	1.94	1.75–2.15	<0.0001
	Model 2 OR	1.74	1.57–1.93	<0.0001

Relative odds for acute, chronic diabetic complications, and all-cause mortality after diagnosis of DEP were analyzed using logistic regression models. Diabetes without prior pancreatic disease, described as type 2 diabetes, was used as a reference group. Model 1 OR is the OR adjusted for sex, age, BMI, FPG, LDL cholesterol, alcohol consumption, smoking status, and medical coverage. Model 2 OR is the OR adjusted for sex, age, BMI, FPG, LDL cholesterol, alcohol consumption, smoking status, medical coverage (same as model 1), systolic BP, triglyceride, eGFR, and CCI.

with type 2 diabetes (7). This suggests that patients with DEP require early insulin therapy to overcome treatment failure of hypoglycemic agents due to insulin insufficiency (28). In addition, the longer the follow-up period, the greater the gap in the proportion of insulin use between the two groups. This tendency could be attributable to insulin deficiency following progressive β-cell injury in the natural clinical course of DEP.

Only a few studies for acute diabetic complications, such as hypoglycemia and hyperglycemic crisis, in DEP have been published to date. We found that patients with DEP had a higher risk of developing hypoglycemia but not DKA or HHS. A Japanese study mentioned that severe hypoglycemia in patients with DEP may be a significant cause of death (6). Since DEP reduces glucagon secretion but preserves peripheral insulin sensitivity, this may explain the vulnerability to hypoglycemia (29). By the same mechanism, DEP is considered less likely to cause ketoacidosis than type 2 diabetes, but the current study showed a similar risk of DKA between the two groups. Conversely, in the German Diabetes Patienten Verlaufsdokumentation (DPV) registry study, the risk of DKA was higher in patients with DEP than in those with type 2 diabetes (7). This discrepancy might be explained by differences in participant characteristics (e.g., ethnicity, study design) and in adjustment for confounding factors.

There are also few data on the chronic diabetic complications of DEP. In previous research, patients with DEP and type 2 diabetes had a similar risk of microvascular complications (6,7,17). The risk of macrovascular complications is thought to be relatively lower than in type 2 diabetes (6,7,17,18). This may be because patients with DEP have relatively few CV risk factors and are more malnourished as a result of PEI (4,7,15). Interestingly, we found a higher risk of diabetic neuropathy (adjusted OR 1.38), nephropathy (1.38), and retinopathy (1.10) in DEP than in type 2 diabetes. Contrary to popular belief, we also demonstrated that patients with DEP had a higher risk of macrovascular complications, such as coronary heart (adjusted OR 1.59), cerebrovascular (1.38), and peripheral arterial diseases (1.34). Unlike the current study, two recent large population-based studies reported that the risk of micro- and macrovascular complications in DEP compared with type 2 diabetes was similar in Japan and lower in Germany (6,7). These inconsistencies may be because

our study adjusted for all possible covariates to minimize the impact and reduce bias from known CV risk factors, in contrast to the unadjusted Japanese study or the partially modified DPV registry study.

In subgroup analyses, the risk of developing diabetic complications of PPDM-A and PPDM-C was similar to that of overall DEP, but PPDM-C had a higher odds than PPDM-A. However, PCRD had only higher risks of HHS, diabetic nephropathy, coronary heart disease, and cerebrovascular disease compared with type 2 diabetes.

Although DEP has been described to cause micro- and macrovascular complications as the disease progresses without the genetic or metabolic traits that accompany type 2 diabetes (6,30,31), the mechanism is still not well known. There are two possible mechanisms that increase the risk of chronic diabetic complications in DEP compared with type 2 diabetes. One postulated mechanism is high glycemic variability in DEP. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial reported that high glycemic variability may lead to a risk of micro- and macrovascular complications in patients with diabetes (32). A recent study using continuous glucose monitoring found that patients with fibrocalculous pancreatic diabetes have higher glucose fluctuations than those with type 2 diabetes (33). Wide glucose fluctuations have been shown to induce overproduction of reactive oxidative species, an increase in inflammatory mediators, and monocyte/macrophage recruitment, which are important factors in the development of atherosclerosis (34,35).

The other hypothesized mechanism is PEI. Patients with PEI due to chronic pancreatitis, with or without diabetes, had more CV events than patients without PEI (36). Patients with PEI are at an increased risk of malnutrition, resulting in lipid, fat-soluble vitamin, and protein deficiencies (37). Malnutrition due to diverse diseases, namely hypoalbuminemia, hypocholesterolemia, and vitamin D deficiency, is a well-known risk factor for CV events (38–40).

We also found a higher all-cause mortality (adjusted OR 1.74) in the group with DEP than in the group with type 2 diabetes. This higher mortality may be attributed to hypoglycemia, diabetic complications, and the underlying pancreatic disorder itself or the conditions that produced it (6,36,39). All subgroups (PCRD, PPDM-A, and PPDM-C) had higher overall mortality compared with type 2 diabetes. The highest mortality from pancreatic cancer can be explained by its poor prognosis (20). Recent studies of mortality from PPDM in New Zealand showed consistent findings; that is, patients with PPDM have a higher risk of all-cause mortality than those with type 2 diabetes (19,20). Cho et al. (19) also demonstrated that the group with PPDM was associated with higher risks of mortality from cancer, infectious disease, and gastrointestinal disease compared with the group with type 2 diabetes, but not vascular disease. Unfortunately, we are not able to analyze the specific cause of death due to the lack of causes of death in the claims database that we accessed for this study. Although our data showed that DEP and its subtypes, PPDM-A and PPDM-C, had a higher risk of coronary heart, cerebrovascular, and peripheral arterial diseases than type 2 diabetes, it does not guarantee a higher risk of CV mortality in DEP due to these conditions than in type 2 diabetes.

This study has several strengths. This is a large comprehensive nationwide cohort study that evaluated the clinical course of DEP compared with type 2 diabetes. We included various etiologies of pancreatic disorders and a complete description of all diabetic complications for many years after diagnosis. We also adjusted for multiple confounding factors, such as laboratory values, anthropometric measures, and comorbidities, as well as demographic characteristics. Therefore, this study will help us understand the natural process of DEP.

Our study has several limitations. First, it was performed using retrospectively collected data and ICD-10 codes to identify diabetic complications in the NHIS claims database. Thus, diagnostic discrepancies in claims data compared with medical diagnoses could have reduced the accuracy of the analysis.

Second, although coding for pancreatic disease prior to type 2 diabetes was defined as consistent with a diagnosis of DEP, it is unclear whether all cases of DEP should be considered as DEP. However, DEP has no generally accepted diagnostic criteria. Although some cases of DEP are coded as E12.x–E14.x, these codes may not reflect all instances of DEP and may rather contain different types of diabetes, including posttransplantation diabetes, drug-induced diabetes, latent autoimmune diabetes in adults, type 1 diabetes, type 2 diabetes, and DEP. Most cases of DEP are known to be misdiagnosed as type 2 diabetes (3,4). Therefore, we included only subjects with type 2 diabetes (E11.x) in the enrollment period, with minimal impact on other causes of diabetes (i.e., we tried to recruit a group with DEP with higher diagnostic specificity and therefore less likely to include patients with forms of diabetes other than DEP).

Third, the follow-up period may be relatively short to evaluate chronic diabetic complications. However, ∼30% patients with newly diagnosed type 2 diabetes were reported to have at least one or more chronic diabetic complications (41). A recent global prospective study has shown a significant occurrence of microvascular and macrovascular complications despite only a median 4.1-year duration for type 2 diabetes, with a similar follow-up period to our research, but with only about one-tenth of our sample size (42). Therefore, we think a follow-up period of 4.2 years with a large sample size in our study can evaluate chronic complications due to prior research having succeeded in doing this with similar follow-up duration to our study but much smaller sample size.

Fourth, although we adjusted for initial FPG levels, we were unable to follow-up FPG or HbA_{1c} levels due to limitations of the claims database.

Fifth, the findings are from Korea, and it is unknown whether these results can be applied to other ethnic groups because the rates of alcohol use and the proportion of causes of DEP may be different in other racial and ethnic groups.

Finally, underreporting of self-reported health behaviors could lead to an underestimation of the effect of health-related behaviors on diabetes and pancreatic diseases.

In summary, DEP is associated with a higher risk of insulin treatment, hypoglycemic episodes, diabetic complications, and mortality. Physicians should keep in mind tailored management, including the best time for insulin therapy and a regular monitoring strategy to reduce diabetic complications and mortality while managing patients with DEP. Further large-scale prospective studies including

different racial and ethnic groups are needed to assess whether these findings are applicable to other populations.

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