Received: 1 August 2022 | Accepted: 20 October 2022

DOI: 10.1002/ueg2.12344

ORIGINAL ARTICLE

ueg journal WILEY

Post-pancreatitis diabetes mellitus is common in chronic pancreatitis and is associated with adverse outcomes

Ana Dugic[1] | Hannes Hagström[1,2,3] | Ingrid Dahlman[1] | Wiktor Rutkowski[1] | Diana Daou[1] | Paula Kulinski[1] | J.-Matthias Löhr[2,4] | Miroslav Vujasinovic[1,2]

[1]Department of Medicine, Huddinge, Karolinska Institute, Stockholm, Sweden

[2]Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden

[3]Clinical Epidemiology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden

[4]Department of Clinical Science, Intervention, and Technology (CLINTEC), Karolinska Institute, Stockholm, Sweden

Correspondence

Ana Dugic, Department of Medicine, Huddinge Karolinska Institute Hälsovägen, Huddinge C1:77, 14186 Stockholm, Sweden.
Email: ana.dugic@ki.se

Abstract

Background: Post-pancreatitis diabetes mellitus (PPDM) is a common consequence of chronic pancreatitis (CP). We aimed to determine the incidence and predictors of PPDM after CP onset, as well as complications and antidiabetic therapy requirements, in a high-volume tertiary center.

Methods: We did a cohort study with retrospectively collected data from patients with definite CP seen at the Karolinska University Hospital between January 1999 and December 2020. Cause-specific Cox regression analysis was used to assess PPDM predictors. To estimate risk of complications and need for therapy the Fine-Gray subdistribution hazard model was employed, accounting for death as a competing risk.

Results: We identified 481 patients with CP. The cumulative incidence of PPDM was 5.1%, 13.2%, 27.5% and 38.9% at 5, 10, 15 and 20 years, respectively. Compared to CP patients without diabetes, patients with PPDM were predominantly male (55% vs. 75%), had more frequently alcoholic etiology (44% vs. 62%) and previous acute pancreatitis. The only independent predictor of PPDM was presence of pancreatic calcifications (aHR = 2.45, 95% CI 1.30–4.63). Patients with PPDM had higher rates of microangiopathy (aSHR = 1.59, 95% CI 1.02–2.52) and infection (aSHR = 4.53, 95% CI 2.60–9.09) compared to CP patients who had type 2 diabetes (T2DM). The rate of insulin use was three-fold higher, whereas metformin use rate was two-fold higher in the same comparison.

Conclusions: Patients with PPDM have a higher frequency of clinically significant complications and were more commonly prescribed insulin and metformin, suggesting a more aggressive phenotype than that of T2DM. Greater PPDM awareness is needed to optimize disease management.

KEYWORDS

chronic pancreatitis, complications, diabetes mellitus, insulin, post-pancreatitis

INTRODUCTION

Chronic pancreatitis (CP) can have a severe impact on quality of life in addition to life-threatening long-term sequelae.[1,2] CP is characterized by inflammation, progressive fibrotic destruction of glandular tissue, or duct obstruction, leading to irreversible impairment of both exocrine and endocrine functions.[3] Long-term complications include abdominal pain, pancreatic exocrine insufficiency, malnutrition, low bone mineral density, pseudocysts, splanchnic vascular complications, diabetes mellitus and pancreatic cancer.[4–6]

Diabetes is a common complication of CP, although its occurrence varies widely from 5% to >80%, depending largely on etiology, geographical location, and duration of follow-up.[1] Diabetes in diseases of the exocrine pancreas has been classified under different names during the 20th century, mostly as "pancreatogenic diabetes", a term commonly used by surgeons to denote diabetes that occurred after pancreas resections.[7] In the first decade of the 21st century, the misnomer "type 3c diabetes" was introduced to denote diabetes of the exocrine pancreas.[8] This term has also been used in European guidelines on chronic pancreatitis.[1] Contrary to popular belief, neither the World Health Organization (WHO) nor the American Diabetes Association (ADA)[9] have endorsed the term "type 3c diabetes".[10] Instead, diabetes in diseases of the exocrine pancreas has consistently been classified under "other specific types of diabetes"; hence, it has always been semantically indistinguishable from entities such as monogenic diabetes, drug-induced diabetes, or infection-related diabetes.[8] However, semantic evolution continued, and in 2017 the term "diabetes of the exocrine pancreas" (DEP) was proposed and has been increasingly used since then. Given that the pancreatitis is by far the most common cause of DEP, term "post-pancreatitis diabetes mellitus" (PPDM) was coined.[11]

To date, there are no standardized diagnostic criteria for diabetes secondary to pancreatitis. Ewald and Hardt[12] outlined several criteria that might help to make the diagnosis, yet many of the proposed tests have limited feasibility in daily clinical practice. The recently proposed PPDM definition[13] tried to simplify its distinction from other diabetes types (mainly type 1 and type 2 diabetes), which might help improve PPDM recognition by medical practitioners of different specialties who often meet these patients. According to this concept, PPDM should be suspected in all adults with a history of pancreatitis who fulfill the diagnostic criteria for diabetes by the ADA. Confirmed type 1 diabetes, or type 2 diabetes prior to first attack of pancreatitis, or stress hyperglycemia during (or within 3 months after) pancreatitis rules out the diagnosis of PPDM.[14]

Due to a poor disease awareness, patients with PPDM are commonly misclassified as having type 2 diabetes mellitus (T2DM). This may be worrisome, as recent data indicate that PPDM exhibits worse glycemic control and earlier insulin requirements compared to T2DM. Patients with PPDM can develop potential life-threatening acute complications due to "brittle diabetes", with rapid swings of glucose levels from hyperglycemia to severe hypoglycemia after administration of exogenous insulin due to the lack of a counter-regulatory hormone response.[15] Consequently, the therapeutic approach in terms of glucose-lowering agents requires special considerations that differ from those in other diabetes types.[16] In addition, chronic diabetes complications such as microangiopathy (nephropathy, neuropathy, retinopathy) are generally considered to be as common in PPDM as in typical diabetes.[17] However, due to the scarcity of evidence it remains unclear whether these assumptions translate into clinically relevant adverse outcomes. Therefore, the aim of the present study was to determine the incidence, predictive factors, complications, and antidiabetic therapy requirements in patients with PPDM in a high-volume tertiary center.

Key summary

Summarize the established knowledge on this subject

- Post-pancreatitis diabetes mellitus (PPDM) is a common complication of chronic pancreatitis. However, due to a poor disease awareness and lack of clear diagnostic criteria, patients with PPDM are commonly misclassified as having type 2 diabetes.
- Diabetic complications are thought to be more pronounced in PPDM than in type 2 diabetes, but due to scarcity of evidence it has remained unclear whether these assumptions translate into clinically relevant adverse outcomes.
- We therefore aimed to assess incidence, predictive factors, complications, and antidiabetic therapy requirements in patients with PPDM and chronic pancreatitis in a high-volume tertiary center.

What are the significant and/or new findings of this study?

- At the time of chronic pancreatitis diagnosis about 20% of patients have had type 2 diabetes, whereas further 13% went on to develop PPDM after 10 years of follow-up.
- PPDM has a more aggressive phenotype that type 2 diabetes in chronic pancreatitis, with higher rate of clinically relevant complications (microangiopathy and infection) and higher need for glucose-lowering therapy.
- Pancreatic calcifications are strong predictor of PPDM, and such patients may need more thorough follow-up.

PATIENTS AND METHODS

Study cohort

We initially assessed 1055 patients with an International Classification of Diseases (ICD)-based code for CP (K86 or K86.1) who presented at the Department of Upper Abdominal Diseases at Karolinska University Hospital between January 1999 and December 2020. A flowchart of patient selection and study design is presented in Figure 1. The definite diagnosis of CP was determined according to

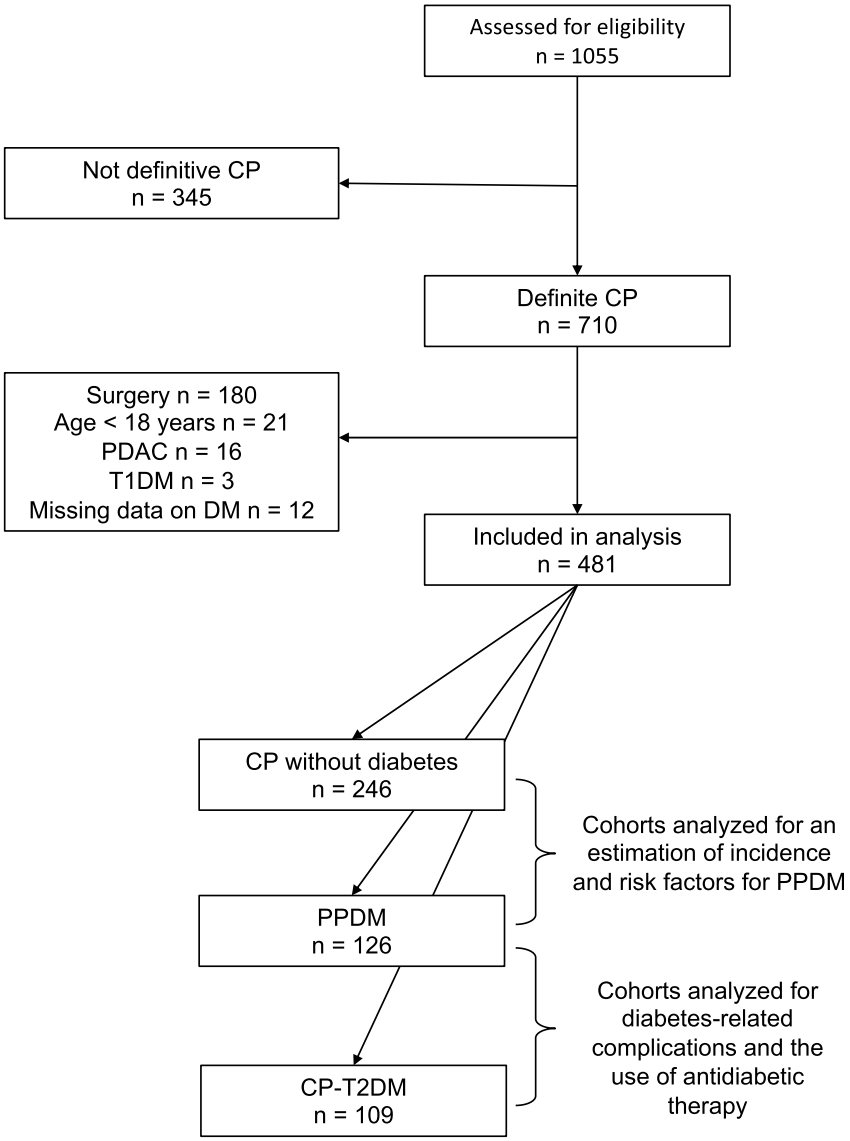

FIGURE 1 Flowchart of patient selection and study design. CP, chronic pancreatitis; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; PDAC, pancreatic ductal adenocarcinoma; CP-T2DM, chronic pancreatitis and type 2 diabetes mellitus; PPDM, post-pancreatitis diabetes mellitus.

M–ANNHEIM criteria.[18] We excluded patients without a Swedish personal identification number (a unique 12-digit number issued to all Swedish residents), patients with missing or insufficient data in medical charts related to this study, patients with probable CP according to M–ANNHEIM criteria, patients <18 years of age, patients who had undergone pancreatic surgery, patients with pancreatic cancer, and patients who were diagnosed with type 1 diabetes mellitus (T1DM) according to patient records.

Diagnosis and classification of diabetes

Patients were identified using ICD-10 codes for diabetes (E10, E11, E13). Diabetes was diagnosed by recording either fasting plasma glucose levels ≥7.0 mmol/L, plasma glucose ≥11.1 mmol/L two hours after a 75 g oral glucose load, or casual plasma glucose ≥11.1 mmol/L accompanied by diabetes symptoms or glycated hemoglobin (HbA1c) ≥6.5% (48 mmol/mol).[10] The CP-T2DM group was defined as individuals who were diagnosed with diabetes prior to pancreatitis or ≤ 90 days after the first pancreatitis diagnosis.[13,14] The PPDM group was defined as patients who were diagnosed with diabetes >90 days after the date of first pancreatitis diagnosis. The 90-day threshold was used because glycated hemoglobin (HbA1c) reflects average plasma glucose over the previous 8–12 weeks. In addition, a 90-day lag was applied to prevent the misclassification of patients with preexisting T2DM or transient stress-induced hyperglycemia (commonly seen after a bout of pancreatitis) as PPDM. The T1DM group, excluded from the analysis, comprised patients with CP and diabetes who had positive diabetes autoantibody panel. These definitions are in line with a recently published diagnostic algorithm for diabetes in CP.[14,19] Based

on these criteria, two investigators (Ana Dugic and Miroslav Vujasinovic) independently classified patients into different categories, and the potential discrepancies were consensually solved by re-analyzing patients' charts. As a result, three mutually exclusive cohorts were created: CP without diabetes, PPDM and CP-T2DM.

Baseline characteristics and outcome measures

The following baseline characteristics were extracted from the patients' charts: age, sex (female or male), body mass index (BMI), occupation (white- or blue-collar workers), family history of pancreatic disease in first-degree relatives, etiology of CP (alcoholic or non-alcoholic), smoking status (ever or never), comorbidities (none, one or ≥ 2), pancreatic calcifications on imaging, PEI, and a history of acute pancreatitis (AP). Patients' occupation was designated by collar color. Blue-collar workers are those who perform a greater degree of physically-taxing or manual labor (industrial, agricultural, construction and manufacturing sectors), whereas white-collar workers typically work in office settings in clerical, administrative, and management roles. Diagnosis of PEI was based upon values of fecal-elastase 1 (FE-1) expressed in μg/g of stools, with levels <200 μg/g being categorized as PEI. Patients were routinely asked to classify their feces according to the Bristol stool scale[20] and only feces type 1–5 was used for FE-1 assessment (to avoid false-negative test results of FE-1 in liquid stools). The baseline comorbidities we assessed from patients' charts were hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), low bone mineral density, liver disease, splanchnic venous thrombosis, and thyroid disease.

Microvascular complications that occurred after diabetes diagnosis comprised nephropathy, neuropathy, retinopathy, and diabetic foot. Neuropathy was confirmed either by presence of senso-motoric and autonomic neuropathic symptoms, typical senso-motoric deficits on physical examination or a formal diagnosis from a specialist physician. Nephropathy was defined by elevated creatinine (>90 μmol/L for women, >100 μmol/L for men) or presence of proteinuria (albumin to creatinine ratio ≥3 mg/mmol in a spot urine sample or albumin >20 mg/L in 24-h urine specimen), or a formal diagnosis made by a specialist physician. Retinopathy at any stage was recorded at a visit to ophthalmology outpatient clinic. Diabetic foot was verified by presence of foot ulcers, or a formal diagnosis made by a specialist physician.

Infection was defined as occurrence of bacterial infections that required either inpatient or outpatient antibiotic therapy, with onset between diabetes diagnosis and last contact. Infections are categorized into the following groups in accordance with ICD-10: pneumonia, abdominal infection, orthopedic infection, skin/subcutaneous tissue infection, urinary tract infection (Supplemental Table 1). In individuals who had more than one infection during the follow-up, the index infection is taken as an outcome. Hypoglycemia was defined as any hypoglycemic episode during the follow-up that required hospitalization.

The first prescription of antidiabetic medication was taken as a proxy for drug use. Any first prescription of insulin during the study period after diabetes diagnosis was classified as “ever use”, whereas if there was no prescription, it was classified as “never use” of insulin. The identical approach was used for categorization of metformin use.

Follow-up

The primary analysis investigated risk for PPDM. For this, follow-up time started at the date of CP diagnosis. Patients could however have had a first diagnosis of CP prior to their initial visit at our institution. In patients with a history of acute pancreatitis the date of the first acute pancreatitis bout was taken as the baseline. We initially estimated the incidence and risk factors associated with PPDM, with death considered as a competing event. Because T2DM and PPDM are mutually exclusive, the cohort was constrained to CP patients without T2DM.

Secondary analysis included estimation of diabetic complications and antidiabetic therapy requirements among patients with PPDM and CP-T2DM. For this purpose, the start of follow up was reset to the date of first diabetes diagnosis (diabetes diagnosis could also have been made before first presentation at our center). Accordingly, CP patients without diabetes were excluded from the analysis.

The patients were followed up until the occurrence of death, loss to follow-up, or the end of the study period (24 November 2021).

Statistical analyses

Descriptive analyses were presented as proportions for categorical data, whereas continuous data were presented as medians with interquartile range (IQR).

Cause-specific Cox proportional hazard models were fitted to investigate factors predictive of PPDM. The association between baseline characteristics and PPDM (age, sex, BMI, etiology of CP, smoking, pancreatic calcifications, PEI, previous acute pancreatitis, and comorbidity) were explored in univariate models. The selection of variables for inclusion in a multivariable model was based on clinical relevance and the Akaike information criterion (AIC)-based stepwise backward variable elimination. The proportional hazards assumption was assessed graphically and tested with scaled Schoenfeld residuals, and no violation was detected. The cumulative incidence of PPDM with death unrelated to diabetes considered as a competing event was plotted using the competing risk function.

In the secondary analysis, PPDM patients and CP-T2DM patients were identified to estimate the differences in the rate of diabetic complications (microangiopathy, infection, and hypoglycemia requiring hospitalization) and the need for antidiabetic therapy. For this purpose, patients with CP without diabetes were excluded and the follow-up was reset to that of the first diabetes diagnosis. Rates were calculated as the number of incidence cases during the study period

(numerator) divided by the time at risk (in 100 person-years) accumulated in the specific subgroup. To estimate differences in risk rates among groups, we performed competing risk regression analyses using Fine-Gray subdistribution hazard models, with death as a competing risk event. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CIs) were calculated. Based on clinical relevance and taking the small number of events into account (respecting the "rule of thumb" with employing at least 10 uncensored events per variable in the model to avoid its overfitting), the adjusted model included age at diabetes onset and history of acute pancreatitis as covariates. Statistical analyses were performed in R software (RStudio, Version 1.4.1717, RStudio Inc). Two-sided $p < 0.05$ was set as the threshold for statistical significance.

Ethics

The study was approved by the regional board of ethics (Dnr: 2020–02209). The committee waived the requirement for individual informed patient consent because of the retrospective nature of the study.

RESULTS

Characteristics of study individuals

We identified 1055 individuals with a diagnosis of CP. After application of exclusion criteria, a total of 481 patients with definite CP were included: 246 (51%) patients without diabetes, an additional 126 (26%) patients who later went on to develop PPDM, and 109 (23%) patients with preexisting T2DM. Figure 1 presents the flowchart of study enrollment. Patients with PPDM were predominantly male (75% vs. 55%), with more frequent alcoholic etiology (62% vs. 44%), and a history of acute pancreatitis (79% vs. 60%) compared to patients with CP alone (Table 1). Median time to PPDM was 4.2 (IQR 1.9–7.7) years. PPDM patients had been followed for a median of 5.2 (IQR 2.5–9.0) years, whereas a median follow-up for those with CP-

TABLE 1 Difference between patients at the time of chronic pancreatitis (CP) diagnosis

Variable	Overall	CP without diabetes	PPDM	CP-T2DM
Cohort size	481	246	126	109
Age (years)	58 (47–67)	56 (44–70)	54 (44–63)	56 (45–64)
Sex (male)	313/481 (65.1)	135/246 (54.9)	95/126 (75.4)	83/109 (76.1)
BMI (kg/m^2)	23.8 (21.1–26.8)	23.6 (20.6–26.3)	24.6 (21.1–27.2)	23.8 (21.5–26.4)
BMI (kg/m^2)				
<18.5	17 (3.5)	10 (4.1)	5 (4.0)	2 (1.8)
18.5–24.9	163 (33.9)	81 (32.9)	37 (29.4)	45 (41.3)
25–29.9	86 (17.9)	38 (15.4)	23 (18.3)	25 (23.0)
30–39.9	26 (5.4)	13 (5.3)	9 (7.1)	4 (3.7)
Family history	32/380 (6.7)	23/192 (9.3)	6/103 (4.8)	3/85 (2.8)
Collar (blue)	200/363 (41.6)	91/177 (37.0)	58/96 (46.0)	51/90 (46.8)
Etiology				
Nonalcoholic	243/481 (50.5)	139/246 (56.5)	48/126 (38.1)	56/109 (51.4)
Alcoholic	238/481 (49.5)	107/246 (43.5)	78/126 (61.9)	53/109 (48.6)
Smoking (ever)	317/462 (65.9)	155/233 (63.0)	87/123 (69.0)	75/106 (68.8)
Calcifications	286/456 (59.5)	133/239 (54.1)	73/111 (57.9)	80/106 (73.4)
PEI	190/405 (39.5)	92/206 (37.4)	48/104 (38.1)	50/95 (45.9)
Previous AP	307/475 (63.8)	149/242 (61.6)	99/125 (78.6)	59/108 (54.1)
Comorbidity				
0	196/450 (40.7)	110/221 (44.7)	54/123 (42.9)	32/106 (29.4)
1	134/450 (27.8)	60/221 (24.4)	40/123 (31.7)	34/106 (31.2)
≥2	120/450 (24.9)	51/221 (20.7)	29/123 (23.0)	40/106 (36.7)

Note: Data are expressed as median (IQR) or *n* (%). Percentages do not add-up to 100 because information is missing for some patients.

Abbreviations: AP, acute pancreatitis; CP-T2DM, chronic pancreatitis and type 2 diabetes mellitus; PEI, pancreatic exocrine insufficiency; PPDM, CP patients who will later develop post-pancreatitis diabetes mellitus.

T2DM was 12.5 (IQR 7.1–20.8) years. Of patients who died, 68 (28%) individuals had CP alone, 35 (32%) individuals had PPDM and 40 (32%) had CP-T2DM.

Incidence and factors predictive of PPDM

After accounting for death as a competing risk, the cumulative incidence for PPDM was 5.1%, 13.2%, 27.5% and 38.9% at 5, 10, 15 and 20 years, respectively (Figure 2). Univariate analysis revealed older age at CP onset (HR = 1.18, 95% CI = 1.01–1.37), male sex (HR = 1.92, 95% CI 1.18–3.16), BMI (HR per one unit increase = 1.09, 95% CI 1.02–1.17) and pancreatic calcifications (HR = 2.03, 95% CI 1.24–3.31) as risk factors for PPDM. For multivariable analysis, the following variables were included in the model: age, sex, alcoholic etiology, smoking, calcifications, BMI, PEI, comorbidities, and a history of acute pancreatitis. Finally, pancreatic calcifications were found to be the only independent predictor of future PPDM (adjusted HR = 2.45, 95% CI 1.30–4.63) (Table 2).

Diabetes-related complications and use of antidiabetic medication

Secondary analysis was performed after identification of PPDM and CP-T2DM cohorts. Compared to CP-T2DM, patients with PPDM had higher incidence rate of hypoglycemia, infection, and microvascular complications (nephropathy, neuropathy, retinopathy, and diabetic foot) (Table 3). Multivariable competing risk regression analysis revealed an increase in rate of microvascular complications (adjusted SHR = 1.59, 95% CI 1.02–2.52) and infection (adjusted SHR = 4.53, 95% CI 2.60–9.09) in the PPDM versus CP-T2DM patients. The rate of insulin use was three times higher (adjusted SHR = 3.01, 95% CI 1.93–4.70), whereas rate of metformin use was two times higher (adjusted SHR = 2.00, 95% CI 1.20–3.34) in patients with PPDM than in the CP-T2DM cohort (Table 3).

DISCUSSION

Post-pancreatitis diabetes mellitus is a common consequence of pancreatic inflammation that can occur both after acute and chronic pancreatitis. Although dwarfed by type 2 diabetes (which makes up >95% of diabetes cases), PPDM is the second most common diabetes type in adults (1.8%), surpassing type 1 diabetes (1.1%).[11,21,22] In our cohort, 23% of patients had type 2 diabetes at the time of CP diagnosis, whereas an additional 13% developed PPDM after 10 years. After 15 and 20 years the cumulative incidence of PPDM was 28% and 39%, respectively. The cumulative incidence estimates in our cohort are difficult to compare with the estimates from other studies which have reported cumulative incidence ranging from 12% to 50% at 10 years (Table 4).[23–26] First, there was significant heterogeneity of the population comprising diabetic patients in these reports, and in the current study there were strong inclusion criteria, as we clearly defined diabetes subgroups and excluded patients with pancreatic cancer and those who underwent pancreatic surgery. Second, these studies used the Kaplan-Maier method to calculate cumulative incidence, which might have led to its overestimation. This commonly encountered bias was mitigated in our study by accounting for death as a competing risk, yielding the more precise estimates. Briefly,

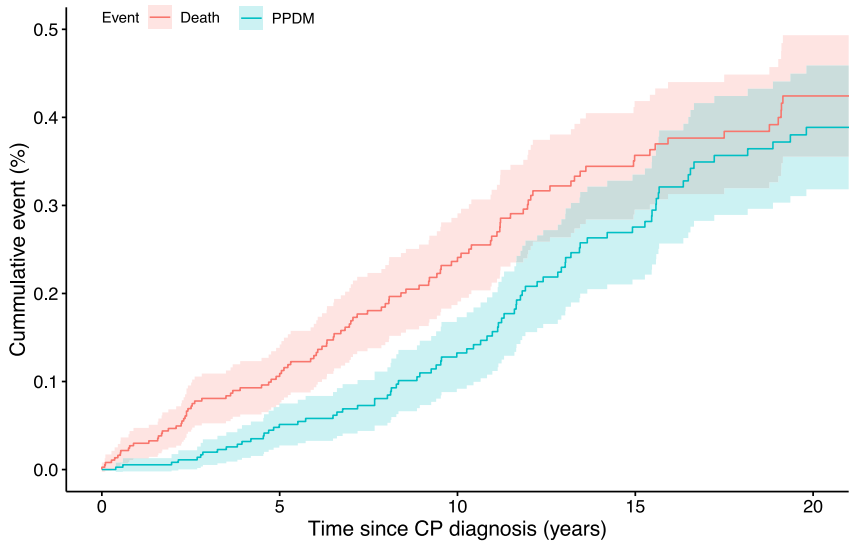

FIGURE 2 Cumulative incidence of post-pancreatitis diabetes mellitus (PPDM) in patients with chronic pancreatitis (CP) derived from the cumulative incidence function. The green line shows cumulative incidence of PPDM after accounting for competing risk events (i.e., death occurring prior to the event of interest, indicated with the red line). Accounted cumulative incidence for PPDM was 5.1%, 13.2%, 27.5%, and 38.9% at 5, 10, 15, and 20 years, respectively, after CP diagnosis. PPDM, post-pancreatitis diabetes mellitus.

TABLE 2 Risk factors predictive of PPDM

Variable	Univariate model HR (95% CI)	*p*-value	Multivariable model HR (95% CI)	*p*-value
Age	**1.18 (1.01–1.37)**	**0.04**	1.10 (0.91–1.36)	0.32
Sex				
Female	1.00	–	1.00	–
Male	**1.92 (1.18–3.16)**	**0.01**	1.45 (0.77–2.72)	0.25
BMI (kg/m^2)	**1.09 (1.02–1.17)**	**0.02**	–	–
Collar				
White	1.00	–	–	–
Blue	1.23 (0.75–2.00)	0.42	–	–
Etiology				
Nonalcoholic	1.00	–	1.00	–
Alcoholic	1.48 (0.95–2.28)	0.08	1.20 (0.64–2.28)	0.57
Smoking				
Never	1.00	–	1.00	–
Ever	1.09 (0.70–1.73)	0.40	0.64 (0.35–1.17)	0.15
Calcifications				
No	1.00	–	1.00	–
Yes	**2.03 (1.24–3.31)**	**0.004**	**2.45 (1.30–4.63)**	**0.005**
PEI				
No	1.00	–	1.00	–
Yes	1.30 (0.81–2.08)	0.27	1.58 (0.95–2.64)	0.08
Previous AP				
No	1.00	–	1.00	–
Yes	0.98 (0.55–1.72)	0.94	1.25 (0.66–2.38)	0.47
Comorbidities				
0	1.00	–	1.00	–
1	1.21 (0.74–1.98)	0.45	1.22 (0.65–2.30)	0.53
≥2	1.34 (0.77–2.36)	0.30	1.16 (0.96–2.27)	0.64

Note: Hazard ratios were calculated using cause-specific hazard regression models. Age was analyzed as a 10-year interval scale. Bold represent statistically significant results.

Abbreviations: AP, acute pancreatitis; BMI, body mass index; CI, confidence interval; HR, cause-specific hazard ratio; PEI, pancreatic exocrine insufficiency.

competing risks are events that preclude the outcome of interest, and the patients who experience a competing event have an outcome risk of zero. Because Kaplan-Meier estimates assume that censored patients have an outcome risk similar to subjects who remain in the study, patients who are censored because of a competing risk will overestimate Kaplan-Meier outcome risk (i.e., the outcome risk estimated from the Kaplan-Meier analysis will exceed the true risk).[27,28]

Patients with PPDM were predominantly male, with more frequent alcoholic etiology and they had more acute pancreatitis episodes compared to patients with CP alone; however, pancreatic calcifications were the only independent predictor of PPDM. These findings are in keeping with large nationwide epidemiological studies from Taiwan,[29] New Zealand,[22] and the UK[21] that highlight a higher risk of developing PPDM in males, with the working and aging population being most affected. Nearly 80% of our patients with PPDM experienced at least one previous episode of acute pancreatitis, compared to 62% patients with CP only and 57% with CP and type 2 diabetes. Interestingly, concordant with findings from Olesen at al.[30] after performing multivariable analysis we observed no association between previous attacks of acute pancreatitis and PPDM risk in CP patients. This indicates the mechanism underlying the two-fold increased risk of diabetes in patients with acute pancreatitis (but without CP) described in population-based studies does not seem to be applicable to most patients with CP.[30–32] Therefore, it may be speculated that diabetes in the context of acute pancreatitis is

TABLE 3 Differences in diabetes complications and the need for therapy among PPDM and CP-T2DM patients

	T2DM (n = 109)			PPDM (n = 126)			FG sub-distribution hazard SHR (95% CI)	
Outcome	Events; n (%)	Person-years	IR (95% CI)	Events; n (%)	Person-years	IR (95% CI)	Crude model	Adjusted model
Complications								
Infection	32/106 (29.4)	1576.8	2.0 (1.4–2.9)	53/126 (42.1)	776.9	6.8 (5.1–8.9)	4.66 (2.55–8.51)**	**4.53 (2.60–9.09)****
Hypoglycemia	19/106 (17.4)	1576.8	1.2 (0.7–1.9)	18/122 (14.3)	776.7	2.3 (1.4–3.7)	1.61 (0.68–3.8)	–
Microangiopathy	74/102 (67.9)	1554.4	4.8 (3.7–6.0)	70/121 (55.6)	769.0	9.1 (7.1–11.5)	1.47 (0.98–2.22)	**1.59 (1.02–2.52)***
Nephropathy	49/100 (45)	1513.7	3.2 (2.4–4.3)	41/119 (32.5)	741.5	5.5 (4.0–7.5)	–	–
Neuropathy	46/100 (42.2)	1527.0	3.0 (2.2–4.0)	39/116 (31)	754.4	5.2 (3.7–7.1)	–	–
Retinopathy	27/100 (24.8)	1545.3	1.7 (1.2–2.5)	15/117 (12.8)	757.2	2.0 (1.1–3.3)	–	–
Diabetic foot	15/101 (13.8)	1548.4	1.0 (0.5–1.6)	12/116 (9.5)	750.1	1.6 (0.8–2.8)	–	–
Therapy								
Insulin	89/106 (81.7)	1548.8	5.7 (4.6–7.1)	99/123 (78.5)	753.4	13.1 (10.7–16.0)	2.94 (1.96–4.41)**	**3.01 (1.93–4.70)****
Metformin	49/106 (45)	1548.8	3.2 (2.3–4.3)	47/123 (37.3)	753.4	6.2 (4.6–8.3)	1.51 (0.99–2.32)	**2.00 (1.20–3.34)***

Note: Hazard ratios were derived from Fine-Gray subdistribution regression models. Model was adjusted for previous episode of acute pancreatitis and age at diabetes onset. CP-T2DM was set as a reference group. Microangiopathy is presented as a composite outcome comprising neuropathy, nephropathy, retinopathy, and diabetic foot. Bold represent statistically significant results.

Abbreviations: CI, confidence interval; CP-T2DM, chronic pancreatitis and type 2 diabetes mellitus; IR, incidence rate per 100 person-years; PPDM, post-pancreatitis diabetes mellitus; SHR, sub-distribution hazard ratio.

*$p < 0.05$, **$p < 0.001$.

mediated through different mechanisms compared to those involved in the development of diabetes in patients with CP. Generally, in the latter setting, PPDM is interpreted as a function of the duration of pancreatitis, as the increased risk of diabetes over time reflects accumulation of damage to the pancreatic parenchyma caused by chronic inflammation.[33] Since pancreatic calcifications are expression of an chronic inflammatory tissue injury, it is not surprising that our study identified them as an independent predictor of PPDM, which is in line with previous reports (Table 4).[24,30,34] Interestingly, other entities such as PEI were not identified as risk factors for PPDM in the present study. Indeed, until recently, the extent of PPDM association with PEI was a topic of considerable ambiguity, with reported prevalence of PEI varying between 29% and 64% in CP patients with diabetes.[23,30] However, there is an emerging body of evidence that PEI represents one the risk factors for PPDM,[30,34] which highlights the need to further understand the mechanistic underpinnings of the endocrine-exocrine interactions of the pancreas.[33]

Diabetes-related microvascular complications such as neuropathy, nephropathy, and retinopathy are generally thought to occur as frequently in PPDM as in typical type 2 diabetes.[35] However, due to the scarcity of data there is yet no sufficient evidence that would corroborate this hypothesis. Our study is the first to examine microvascular complications in PPDM, evidencing an increase in rate of clinically significant complications in patients with PPDM compared to CP patients who had type 2 diabetes (adjusted SHR = 1.59, 95% CI 1.02–2.52). In addition, when comparing the two groups the rate of infection was 4.5 times higher in PPDM (adjusted SHR = 4.53, 95% CI 2.60–9.09). The rate of hospitalization requiring hypoglycemia was also higher in PPDM in our cohort; however, this finding did not reach statistical significance.

Another key finding of our study is that the insulin requirement rate was three times higher among PPDM patients compared to CP patients who had type 2 diabetes (adjusted SHR = 3.01, 95% CI 1.93–4.70). This observation is in alignment with a population-based study from the UK,[21] that found greater insulin use among patients with diabetes following pancreatic disease at 1 year and 5 years, compared to patients with type 2 diabetes. In addition, a nationwide study from Denmark[16] demonstrated a three-fold increase in insulin requirements of PPDM patients compared to those with type 2 diabetes. Recent literature suggests significantly higher risk of hospitalization for infection among patients who were on insulin compared to those not using insulin, which may reflect insulin therapy as a marker of disease severity.[36] Accordingly, the higher rate of insulin use among our patients with PPDM may explain the greater underlying susceptibility to infection.

Collectively, our data emphasize a more aggressive disease phenotype in PPDM with the need for earlier initiation of therapy. Biguanides (metformin) are recommended as a first choice of treatment, and maintained biguanide treatment has been suggested irrespective of patients' requirements for insulin use.[16,37] Here we found that approximately 60% of patients with PPDM were not prescribed metformin, suggesting potential undertreatment. Patients with PPDM, who are often misclassified as having T2DM, are commonly treated with insulin in monotherapy following a short trial of oral glucose-lowering therapy, or started directly on insulin.[16] However,

TABLE 4 Studies published on risk factors and outcomes of diabetes accompanied with CP

Author, country, year	Study type	Cohort size (n)	Results
Malka,[24] France, 2000	Single center	Total: 500 subjects • CP pts with elective pancreatic surgery (n = 231) • CP pts without pancreatic surgery (n = 222)	• The cumulative incidence of DM: 50% ± 3% at 10 years and 85% ± 4% at 25 years after CP. • Independent risk factors for DM: pancreatic calcifications (RR 3.2, 2.2–4.7) and distal pancreatectomy (RR 2.4, 1.6–3.8).
Wang,[25] China, 2011	Single center	Total: 387 subjects • CP pts before invasive therapy (n = 387: pts with DM [n = 46] vs. pts without DM [n = 341]) • CP pts after invasive therapy (n = 317: pts with DM [n = 41] vs. pts without DM [n = 276])	• The cumulative incidence of DM: 51.5% at 20 years after CP onset. • Risk factors for DM before any invasive therapy: Age at CP onset (HR 1.03, 1.01–1.05), smoking (HR 2.86, 1.45–5.65), chronic pain (HR 0.41, 0.18–0.95), and pancreatic calcifications (HR 2.33, 1.20–4.50). • Risk factors for DM after invasive therapy (surgery/endoscopy): Smoking (HR 2.20, 1.15–4.21) and distal pancreatectomy (HR 5.41, 2.51–11.70).
Pan,[26] China, 2016	Single center	Total: 2011subjects • CP with DM (n = 564) • CP without DM (n = 1447)	• cumulative incidence of DM after the onset of CP: 27.9%, 45.8% and 64.1% at 10,20 and 30 years, respectively • Risk factors for DM development after the diagnosis of CP: male sex (HR 1.51, 1.08–2.11), alcohol abuse (HR 2.00, 1.43–2.79), steatorrhea (HR 1.46, 1.01–2.11), biliary stricture (HR 2.25, 1.43–3.52), and distal pancreatomy (HR 3.41, 1,80–6.44).
Bellin,[34] USA, 2017	Nationwide survey	Total: 1171 subjects • CP with DM (n = 383) • CP without DM (n = 788)	• Risk factors for DM regardless of the time of CP diagnosis: - DM before CP diagnosis: Calcifications (OR 2.54, 1.39–4.64) and exocrine pancreas insufficiency (OR 2.50, 1.46–4.26). - DM after CP diagnosis: Calcifications (OR 2.19, 1.15–4.15) and exocrine pancreas insufficiency (OR 3.06, 1.71–5.45).
Woodmansey,[21] UK, 2017	Nationwide survey	Total: 31,789 subjects • T1DM (n = 354) • T2DM (n = 30,876) • Diabetes following pancreatic disease (n = 559: Diabetes following AP [n = 361], diabetes following CP [n = 198])	• The incidence rate of diabetes following pancreatic disease: 2.59 (2.38–2.81) per 100,000 person-years. • Diabetes following pancreatic disease exhibited poor glycemic control (OR 1.7, 1.3–2.2) compared with T2DM. • The use of insulin was greater in pts with diabetes following pancreatic disease at 1 year (OR 9.6, 7.0–13.2) and 5 years (OR 7.4, 5.2–10.4) compared to T2DM pts.
Cho,[44] New Zealand, 2019	Nationwide survey	Total: 10,549 subjects • PPDM (n = 959: PPDM-A [n = 698], PPDM-C [n = 261]) • Age- and sex-matched T2DM (n = 9590)	• All-cause mortality was higher in PPDM pts compared to T2DM (HR 1.13, 1.00–1.29). • compared with T2DM, PPDM was associated with higher risks of mortality from cancer (HR 1.44, 1.13–1.83), infectious disease (HR 2.52, 1.69–3.77), and gastrointestinal disease (HR 2.56, 1.64–4.01). • The risks of hospitalization for COPD (HR 1.36, 1.09–1.70), moderate to severe renal disease (HR 1.33, 1.14–1.54), and infectious disease (HR 1.32, 1.15–1.53) were higher in individuals with PPDM versus T2DM.
Lin,[29] Taiwan, 2020	Nationwide survey	Total: 5566 subjects • Pts with CP and DM (n = 506) • Age- and sex-matched pts with DM alone (n = 5060)	• Pts with CP and DM were at increased risk of DKA (HR 9.51, 6.51–13.91), HHS (HR 4.96, 2.85–8.62), hypoglycemia (HR 3.02, 2.23–4.08) and all-cause mortality (HR 2.43, 1.82–3.27) compared with pts with DM alone.

(Continues)

TABLE 4 (Continued)

Author, country, year	Study type	Cohort size (n)	Results
Liu,[23] China, 2020	Single center	Total: 1633 subjects • Idiopathic CP and DM (n = 168) • Idiopathic CP without DM (n = 1146)	• cumulative incidence of DM after the diagnosis of CP: 7.2%, 8.5% and 11.9% at 3, 5 and 10 years, respectively. • Risk factors for DM development in idiopathic CP: biliary stricture at/before diagnosis of CP (HR 2.52, 1.55–4.08), steatorrhea at/before diagnosis of CP (HR 2.01, 1.32–3.05).
Olesen,[30] Multinational, 2020	Multicentric study	Total: 1117 subjects • Definitive CP and DM (n = 457) • Definitive CP without DM (n = 660)	• Risk factors for DM: age at diagnosis (OR 1.02, 1.01–1.04), duration of CP (OR 1.08, 1.05–1.11), dyslipidaemia (OR 4.42, 2.14–9.13), overweight (OR 1.72, 1.23–2.40) or obese (OR 3.28, 1.88–5.74) BMI categories, pancreatic calcifications (OR 1.53, 1.08–2.16), pancreatic resection (OR 2.21, 1.16–4.22), and PEI (OR 2.33, 1.75–3.10).
Aslam,[46] India, 2021	Single center	Total: 587 subjects • CP with pancreatogenic DM (n = 118) • CP without diabetes (n = 469)	• Risk factors for pancreatogenic DM: older age (OR 1.08, 1.05–1.11), presence of pancreatic parenchymal (OR 2.284, 1.04–5.04) and ductal (OR 2.35,1.06–5.21) calcifications, exocrine insufficiency (OR 6.29, 2.26–17.50), and pancreatic duct stricture (OR 3.36, 1.14–9.91). • Risk factors for earlier pancreatogenic DM onset: Smoking (HR 2.37, 1.29–4.35) and pancreatic ductal calcification (HR 2.03, 1.29–3.21).
Viggers,[16] Denmark, 2021	Nationwide survey	Total: 398,456 subjects • PPDM (n = 5879: PPDM-A [n = 3418], PPDM-C [n = 2461]) • T1DM (n = 9252) • T2DM (n = 383,325)	• The incidence rate of PPDM was 7.9 (7.7–8.1) per 100,000 person-years. • There was an earlier and increased use of insulin in both PPDM-A and PPDM-C compared with T2DM. • CP pts with PPDM had increased insulin requirements compared with T2DM (HR 4.30, 4.01–4.56).
Olesen,[45] Denmark, 2022	Nationwide survey	Total: 389,204 subjects • PPDM-A (n = 3418) • PPDM-C (n = 2461) • T2DM (n = 383,325)	• CP pts with PPDM increased risks of severe hypoglycemia (HR 5.27, 4.62–6.00) and all-cause mortality (HR 1.54, 1.45–1.64) compared to T2DM pts. • compared with T2DM, PPDM-A was associated with an increased risk of severe hypoglycemia (HR 2.95, 2.53–3.45) and all-cause mortality (HR 1.18, 1.11–1.25). • No difference in risk of major cardiovascular events was observed for the PPDM-A or PPDM-C subgroups compared with T2DM.
Present study, Sweden, 2022	Single center	Total: 481 subjects • CP without diabetes (n = 246) • PPDM (n = 126) • CP and T2DM (n = 109)	• The cumulative incidence of PPDM: 5.1%, 13.2%, 27.5%, and 38.9% at 5, 10, 15 and 20 years after CP, respectively. • Independent predictor of PPDM: pancreatic calcifications (HR 2.45, 1.30–4.63). • Pts with PPDM had increased rate of microangiopathy (HR 1.59, 1.02–2.52) and infection (HR 4.53, 2.60–9.09) compared to CP pts with T2DM. • The rate of insulin (HR 3.01, 1.93–4.70) and metformin use (HR 2.00, 1.20–3.34) was higher in PPDM pts than in CP pts with T2DM.

Note: Presented hazard ratios and odds ratios were from adjusted models with 95% confidence intervals.

Abbreviations: AP, acute pancreatitis; CP, chronic pancreatitis; DM, diabetes mellitus; HR, hazard ratio; OR, odds ratio; PEI, pancreatic exocrine insufficiency; PPDM, post-pancreatitis diabetes mellitus; PPDM-A, post-pancreatitis diabetes mellitus after acute pancreatitis; PPDM-C, post-pancreatitis diabetes mellitus after chronic pancreatitis; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

as opposed to insulin, biguanides (metformin) are shown to promote a survival benefit in PPDM patients.[38] Given that the patients with chronic pancreatitis are at increased risk of developing pancreatic cancer[19,37,39]—especially those with high BMI and diabetes[4]—the proposed antineoplastic properties of metformin might be of an additional benefit to PPDM patients. Although guidelines and recommendations for management of PPDM have been underdeveloped, most experts in the field agree that PPDM needs special consideration for management, including maintained treatment with biguanides in all patients with PPDM irrespective of their requirement for insulin, and avoidance of incretin-based treatment (acute pancreatitis is a known side-effect), sulfonylureas (due to their increased risk of inducing hypoglycemia) and sodium-glucose cotransporter 2 (SGLT2) inhibitors (due to increased risk of diabetic ketoacidosis in patients with absolute insulin deficiency).[16,37,40–42] A recently published systematic review and meta-analysis revealed a significant association between pancreatitis and DPP-4 inhibitors; however, no such association was observed for GLP-1 receptor agonists.[43] Therefore, proper and timely diagnosis of PPDM is of high importance in terms of antidiabetic therapy choice.

The current study was designed to give detailed characterization of patients with PPDM, and was performed in a well-defined cohort of patients in a high-volume tertiary center which is the main strength of the study. The large number of patients enabled inclusion of only well characterized individuals who had definite CP, whereas patients with probable CP were excluded. Patients with pancreatic cancer and those who underwent pancreatic surgery were also excluded from the analysis, as they are more prone to diabetes caused by other mechanisms (pancreatic cancer-related diabetes and surgical diabetes, respectively). In comparison with registry-based studies that exclusively rely on ICD codes, we could check the accuracy of diabetes and other diagnoses by looking at patients' clinical charts, thereby decreasing the risk of misclassification bias and increasing the credibility of the study results. Another strength of the study is the use of a competing risk regression analysis expressed by Fine-Gray subdistribution hazard models. This is particularly important in studies of PPDM, as patients with CP have higher rates of mortality compared to the general population and individuals with type 2 diabetes.[16,44,45]

The retrospective nature of the study is a limitation, due to possible loss of some relevant data. Moreover, omitting some CP cases due to its subclinical forms (i.e., minimal-change CP) cannot be excluded. Consequently, this might have led to misclassification of diabetes in some patients. However, if there had been a misclassification, it would have been a nondifferential misclassification, as the study groups were derived from a single cohort with a unitary coding system and the definition of diabetes was applied to all groups equally. Therefore, a prospective large-scale validation of the PPDM definition used in this study would be essential for its implementation in daily clinical practice. Another noteworthy point is the shorter median follow-up of patients with PPDM compared to CP-T2DM individuals, which is in part a consequence of a baseline reset (to the date of diabetes diagnosis) for the purpose of our secondary analysis. Furthermore, by changing the baseline the model assumption has been partially compromised, as patients with type 2 diabetes had to survive until occurrence of pancreatitis to be included in the study. On the other hand, not changing baseline would introduce immortal time bias that would have arisen had the follow-up started at the point of CP diagnosis. In the latter case all outcomes of interest that had happened before the pancreatitis diagnosis would have not been captured in CP patients with type 2 diabetes. Consequently, this would have led to the overestimation of the adverse outcomes in PPDM. As this is a single center study, the present model was limited by the number of outcomes when assessing diabetic complications. It would be of interest to conduct a register-based study on the subject, and thus obtain higher accuracy regarding the rate of PPDM complications. Lastly, in this study we did not investigate how previous endoscopic interventions (that are proxy for pancreatic duct strictures and intraductal stones) might influence the occurrence of endocrine dysfunction, which might be also considered a study limitation. Collectively, the present study highlights the need for more research effort to tailor evidence-based recommendations for diagnosis and treatment of PPDM.

CONCLUSIONS

The cumulative incidence of post-pancreatitis diabetes after a diagnosis of chronic pancreatitis is around 13% at 10 years. Pancreatic calcifications are a strong risk factor for PPDM, and such patients may need more thorough follow-up. Furthermore, compared to CP patients with type 2 diabetes, those with PPDM had a more aggressive phenotype with a higher frequency of clinically significant complications and higher need of glucose-lowering therapy.

AUTHORS' CONTRIBUTIONS

Study conception and design: Ana Dugic, Miroslav Vujasinovic, J.-Matthias Löhr, Hannes Hagström; Acquisition of data: Diana Daou, Paula Kulinski, Wiktor Rutkowski, Ana Dugic, Miroslav Vujasinovic; Statistical analysis: Ana Dugic; Drafting and writing of the manuscript: all authors; Guarantors of the article: Miroslav Vujasinovic, J.-Matthias Löhr. All authors approved the final version of the article, including the authorship list.

ACKNOWLEDGMENTS

The authors would like to thank the Swedish Society for the Development of Pancreatology for their continuous support in development of pancreatology in Sweden.

CONFLICT OF INTEREST

MV: Abbott (lecture fee and support in organization of scientific meetings), Mylan/Viatris (lecture fee and support in organization of scientific meetings); ID: Novo Nordisk (lecture fee), JML: Abbott (lecture fee and support in organization of scientific meetings), Mylan (lecture fee and support in organization of scientific meetings).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ana Dugic https://orcid.org/0000-0002-1893-0754
Hannes Hagström https://orcid.org/0000-0002-8474-1759
Ingrid Dahlman https://orcid.org/0000-0003-3819-5977
Wiktor Rutkowski https://orcid.org/0000-0002-0471-1673
Diana Daou https://orcid.org/0000-0002-1218-3663
Paula Kulinski https://orcid.org/0000-0002-3714-4409
J.-Matthias Löhr https://orcid.org/0000-0002-7647-198X
Miroslav Vujasinovic https://orcid.org/0000-0002-6496-295X

REFERENCES

1. Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J. 2017;5(2):153–99. https://doi.org/10.1177/2050640616684695
2. Levy P, Dominguez-Munoz E, Imrie C, Lohr M, Maisonneuve P. Epidemiology of chronic pancreatitis: burden of the disease and consequences. United Eur Gastroenterol J. 2014;2(5):345–54. https://doi.org/10.1177/2050640614548208
3. Brock C, Nielsen LM, Lelic D, Drewes AM. Pathophysiology of chronic pancreatitis. World J Gastroenterol. 2013;19(42):7231–40. https://doi.org/10.3748/wjg.v19.i42.7231
4. Vujasinovic M, Dugic A, Maisonneuve P, Aljic A, Berggren R, Panic N, et al. Risk of developing pancreatic cancer in patients with chronic pancreatitis. J Clin Med. 2020;9(11):3720. https://doi.org/10.3390/jcm9113720
5. Vujasinovic M, Dugic A, Nouri A, Brismar TB, Baldaque-Silva F, Asplund E, et al. Vascular complications in patients with chronic pancreatitis. J Clin Med. 2021;10(16):3720. https://doi.org/10.3390/jcm10163720
6. Vujasinovic M, Nezirevic Dobrijevic L, Asplund E, Rutkowski W, Dugic A, Kahn M, et al. Low bone mineral density and risk for osteoporotic fractures in patients with chronic pancreatitis. Nutrients. 2021;13(7):2386. https://doi.org/10.3390/nu13072386
7. Deckert T. Late diabetic manifestations in "pancreatogenic" diabetes mellitus. Acta Med Scand. 1960;168(5-6):439–46. https://doi.org/10.1111/j.0954-6820.1960.tb06675.x
8. Petrov MS, Basina M. Diagnosis of endocrine disease: diagnosing and classifying diabetes in diseases of the exocrine pancreas. Eur J Endocrinol. 2021;184(4):R151–R63. https://doi.org/10.1530/eje-20-0974
9. American Diabetes A. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S15–33. https://doi.org/10.2337/dc21-s002
10. American Diabetes A. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S13–28. https://doi.org/10.2337/dc19-s002
11. Petrov MS. Diabetes of the exocrine pancreas: American Diabetes Association-compliant lexicon. Pancreatology. 2017;17(4):523–6. https://doi.org/10.1016/j.pan.2017.06.007
12. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. World J Gastroenterol. 2013;19(42):7276–81. https://doi.org/10.3748/wjg.v19.i42.7276
13. Petrov MS. Diagnosis of endocrine disease: post-pancreatitis diabetes mellitus: prime time for secondary disease. Eur J Endocrinol. 2021;184(4):R137–49. https://doi.org/10.1530/eje-20-0468
14. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol. 2019;16(3):175–84. https://doi.org/10.1038/s41575-018-0087-5
15. Löhr JM, Beuers U, Vujasinovic M, Alvaro D, Frøkjær JB, Buttgereit F, et al. European Guideline on IgG4-related digestive disease - UEG and SGF evidence-based recommendations. United Eur Gastroenterol J. 2020;8(6):637–66. https://doi.org/10.1177/2050640620934911
16. Viggers R, Jensen MH, Laursen HVB, Drewes AM, Vestergaard P, Olesen SS. Glucose-lowering therapy in patients with post-pancreatitis diabetes mellitus: a nationwide population-based cohort study. Diabetes Care. 2021;44(9):2045–52. https://doi.org/10.2337/dc21-0333
17. Conlon KC, Duggan SN. Pancreatogenic type 3c diabetes: underestimated, underappreciated and poorly managed. Practical Gastroenterol. 2017:15.
18. Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol. 2007;42(2):101–19. https://doi.org/10.1007/s00535-006-1945-4
19. Cho J, Scragg R, Petrov MS. Postpancreatitis diabetes confers higher risk for pancreatic cancer than type 2 diabetes: results from a nationwide cancer registry. Diabetes Care. 2020;43(9):2106–12. https://doi.org/10.2337/dc20-0207
20. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920–4. https://doi.org/10.3109/00365529709011203
21. Woodmansey C, McGovern AP, McCullough KA, Whyte MB, Munro NM, Correa AC, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): a retrospective cohort study. Diabetes Care. 2017;40(11):1486–93. https://doi.org/10.2337/dc17-0542
22. Pendharkar SA, Mathew J, Petrov MS. Age- and sex-specific prevalence of diabetes associated with diseases of the exocrine pancreas: a population-based study. Dig Liver Dis. 2017;49(5):540–4. https://doi.org/10.1016/j.dld.2016.12.010
23. Liu Y, Wang D, Guo HL, Hao L, Wang T, Zhang D, et al. Risk factors and nomogram for diabetes mellitus in idiopathic chronic pancreatitis. J Gastroenterol Hepatol. 2020;35(2):343–52. https://doi.org/10.1111/jgh.14785
24. Malka D, Hammel P, Sauvanet A, Rufat P, O'Toole D, Bardet P, et al. Risk factors for diabetes mellitus in chronic pancreatitis. Gastroenterology. 2000;119(5):1324–32. https://doi.org/10.1053/gast.2000.19286
25. Wang W, Guo Y, Liao Z, Zou DW, Jin ZD, Zou DJ, et al. Occurrence of and risk factors for diabetes mellitus in Chinese patients with chronic pancreatitis. Pancreas. 2011;40(2):206–12. https://doi.org/10.1097/mpa.0b013e31820032ae
26. Pan J, Xin L, Wang D, Liao Z, Lin JH, Li BR, et al. Risk factors for diabetes mellitus in chronic pancreatitis: a cohort of 2, 011 patients. Medicine (Baltim). 2016;95(14):e3251. https://doi.org/10.1097/md.0000000000003251
27. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: the importance of multistate models and competing risks analysis. Hepatology. 2015;62(1):292–302. https://doi.org/10.1002/hep.27598
28. van Walraven C, McAlister FA. Competing risk bias was common in Kaplan-Meier risk estimates published in prominent medical journals. J Clin Epidemiol. 2016;69:170–3 e8. https://doi.org/10.1016/j.jclinepi.2015.07.006
29. Lin CH, Yeh NC, Wang JJ, Ho CH, Her SH, Tsay WI, et al. Effect of chronic pancreatitis on complications and mortality in DM patients: a 10-year nationwide cohort study. J Clin Endocrinol Metab. 2020;105(3):e739–45. https://doi.org/10.1210/clinem/dgaa035

30. Olesen SS, Poulsen JL, Novovic S, Nojgaard C, Kalaitzakis E, Jensen NM, et al. Multiple risk factors for diabetes mellitus in patients with chronic pancreatitis: a multicentre study of 1117 cases. United Eur Gastroenterol J. 2020;8(4):453–61. https://doi.org/10.1177/2050640620901973
31. Shen HN, Yang CC, Chang YH, Lu CL, Li CY. Risk of diabetes mellitus after first-attack acute pancreatitis: a national population-based study. Am J Gastroenterol. 2015;110(12):1698–706. https://doi.org/10.1038/ajg.2015.356
32. Das SL, Singh PP, Phillips AR, Murphy R, Windsor JA, Petrov MS. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut. 2014;63(5):818–31. https://doi.org/10.1136/gutjnl-2013-305062
33. Goodarzi MO, Petrov MS, Andersen DK, Hart PA. Diabetes in chronic pancreatitis: risk factors and natural history. Curr Opin Gastroenterol. 2021;37(5):526–31. https://doi.org/10.1097/mog.0000000000000756
34. Bellin MD, Whitcomb DC, Abberbock J, Sherman S, Sandhu BS, Gardner TB, et al. Patient and disease characteristics associated with the presence of diabetes mellitus in adults with chronic pancreatitis in the United States. Am J Gastroenterol. 2017;112(9):1457–65. https://doi.org/10.1038/ajg.2017.181
35. Duggan SN, Ewald N, Kelleher L, Griffin O, Gibney J, Conlon KC. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. Eur J Clin Nutr. 2017;71(1):3–8. https://doi.org/10.1038/ejcn.2016.127
36. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. Diabetes Care. 2018;41(3):513–21. https://doi.org/10.2337/dc17-2131
37. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. Pancreatology. 2011;11(3):279–94. https://doi.org/10.1159/000329188
38. Cho J, Scragg R, Pandol SJ, Goodarzi MO, Petrov MS. Antidiabetic medications and mortality risk in individuals with pancreatic cancer-related diabetes and postpancreatitis diabetes: a nationwide cohort study. Diabetes Care. 2019;42(9):1675–83. https://doi.org/10.2337/dc19-0145
39. Mellenthin C, Balaban VD, Dugic A, Cullati S. Risk factors for pancreatic cancer in patients with new-onset diabetes: a systematic review and meta-analysis. Cancers. 2022;14(19):4684. https://doi.org/10.3390/cancers14194684
40. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016;1(3):226–37. https://doi.org/10.1016/s2468-1253(16)30106-6
41. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology. 2011;141(1):150–6. https://doi.org/10.1053/j.gastro.2011.02.018
42. Dawwas GK, Flory JH, Hennessy S, Leonard CE, Lewis JD. Comparative safety of sodium-glucose cotransporter 2 inhibitors versus dipeptidyl peptidase 4 inhibitors and sulfonylureas on the risk of diabetic ketoacidosis. Diabetes Care. 2022;45(4):919–27. https://doi.org/10.2337/dc21-2177
43. Singh AK, Gangopadhyay KK, Singh R. Risk of acute pancreatitis with incretin-based therapy: a systematic review and updated meta-analysis of cardiovascular outcomes trials. Expert Rev Clin Pharmacol. 2020;13(4):461–8. https://doi.org/10.1080/17512433.2020.1736041
44. Cho J, Scragg R, Petrov MS. Risk of mortality and hospitalization after post-pancreatitis diabetes mellitus vs type 2 diabetes mellitus: a population-based matched cohort study. Am J Gastroenterol. 2019;114(5):804–12. https://doi.org/10.14309/ajg.0000000000000225
45. Olesen SS, Viggers R, Drewes AM, Vestergaard P, Jensen MH. Risk of major adverse cardiovascular events, severe hypoglycemia, and all-cause mortality in postpancreatitis diabetes mellitus versus type 2 diabetes: a nationwide population-based cohort study. Diabetes Care. 2022;45(6):1326–34. https://doi.org/10.2337/dc21-2531
46. Aslam M, Jagtap N, Karyampudi A, Talukdar R, Reddy DN. Risk factors for development of endocrine insufficiency in chronic pancreatitis. Pancreatology. 2021;21(1):15–20. https://doi.org/10.1016/j.pan.2020.11.011

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Dugic A, Hagström H, Dahlman I, Rutkowski W, Daou D, Kulinski P, et al. Post-pancreatitis diabetes mellitus is common in chronic pancreatitis and is associated with adverse outcomes. United European Gastroenterol J. 2023;11(1):79–91. https://doi.org/10.1002/ueg2.12344