Population-Level Incidence and Predictors of Surgically Induced Diabetes and Exocrine Insufficiency after Partial Pancreatic Resection

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ABSTRACT

Context: Endocrine and exocrine insufficiency after partial pancreatectomy affect quality of life, cardiovascular health, and nutritional status. However, their incidence and predictors are unknown.

Objective: To identify the incidence and predictors of new-onset diabetes and exocrine insufficiency after partial pancreatectomy.

Design: We retrospectively reviewed 1165 cases of partial pancreatectomy, performed from 1998 to 2010, from a large population-based database.

Main Outcome Measures: Incidence of new onset diabetes and exocrine insufficiency

Results: Of 1165 patients undergoing partial pancreatectomy, 41.8% had preexisting diabetes. In the remaining 678 patients, at a median 3.6 months, diabetes developed in 274 (40.4%) and pancreatic insufficiency developed in 235 (34.7%) patients. Independent predictors of new-onset diabetes were higher Charlson Comorbidity Index (CCI; hazard ratio [HR] = 1.62 for CCI of 1, $p = 0.02$; HR = 1.95 for CCI ≥ 2, $p < 0.01$) and pancreatitis (HR = 1.51, $p = 0.03$). There was no difference in diabetes after Whipple procedure vs distal pancreatic resections, or malignant vs benign pathologic findings. Independent predictors of exocrine insufficiency were female sex (HR = 1.32, $p = 0.002$) and higher CCI (HR = 1.85 for CCI of 1, $p < 0.01$; HR = 2.05 for CCI ≥ 2, $p < 0.01$). Distal resection and Asian race predicted decreased exocrine insufficiency (HR = 0.35, $p < 0.01$; HR = 0.54, $p < 0.01$, respectively).

Conclusion: In a large population-based database, the rates of postpancreatectomy endocrine and exocrine insufficiency were 40% and 35%, respectively. These data are critical for informing patients' and physicians' expectations.

INTRODUCTION

Pancreatic resection is performed for various indications, including malignant and premalignant lesions of the pancreas, duodenum, and adjacent structures; intractable pain in the setting of pancreatitis; and trauma. The most commonly performed pancreatectomy operation is the Whipple procedure, or pancreaticoduodenectomy, in which the head of the pancreas and the duodenum are resected, followed by reconstruction of the intestinal tract. The second most common is the distal pancreatectomy, in which the tail of the pancreas, with or without the spleen, is removed. Loss of pancreatic parenchyma can lead to new-onset endocrine and exocrine insufficiency, conditions that greatly affect postoperative quality of life, cardiovascular health, and nutritional status. Understanding the natural history of postpancreatectomy insufficiency can assist patients and physicians with postoperative expectations and management. However, there are limited data describing the incidence and predictors of postsurgical pancreatic insufficiency.[1,2]

It is generally held that the likelihood of developing pancreatic insufficiency depends on the volume of parenchyma resected and the health of the remaining parenchyma.[1,2] Existing studies are limited to small, single-center reviews. Their interpretation is limited by inconsistent definitions of diabetes and a lack of long-term follow-up, and none are sufficiently powered to stratify outcomes by resection type and patient and disease characteristics. Thus, the reported incidence of postpancreatectomy diabetes varies widely in the literature; for example, reported rates of diabetes after Whipple procedures range from 0% to 50%,[1-4] and after distal pancreatectomy range from 5% to 42%.[4-6]

We performed the first population-based study of the incidence and natural history of postpancreatectomy endocrine and exocrine insufficiency in a large database with long follow-up and a precise and uniform definition of disease, and stratified postpancreatectomy insufficiency risk by patient, disease, and resection characteristics.

METHODS

This study was approved by the Kaiser Permanente Southern California (KPSC) institutional review board (no. 6330) and complies with the Health Information Portability and Accountability Act. We retrospectively queried the KPSC patient data repository to identify all patients who underwent pancreatic resection from 1998 to 2010, as indicated by Current Procedural Terminology (CPT) codes.

The KPSC database contains health information, including billing and diagnosis codes as well as laboratory results and prescription drug information. Because KPSC is a closed system, we expect all patient health information during the period of coverage

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to be included in the database. Patients who were younger than age 18 years or pregnant were excluded, as were patients who had prior pancreatic surgery, and those with less than 6 months of postoperative follow-up within KPSC.

We collected patient demographic information and the reason for resection as indicated by International Classification of Diseases, Ninth Revision (ICD-9) code. Pancreatic resection was dichotomized into Whipple procedure or distal resection. We defined *diabetes* as the presence of any of the following: abnormal laboratory values, including abnormal fasting blood glucose level (> 125 mg/dL) and hemoglobin A_{1C} (≥ 6.5%), or new prescriptions for diabetic medications, including both oral hypoglycemic medications and insulin. We defined *exocrine insufficiency* by the use of pancreatic enzyme replacement. We defined the *date of onset of either outcome* as the date of the first abnormal laboratory value or date of first prescription in the patient's medical record.

In the patients without a preoperative diagnosis of diabetes, univariable and multivariable Cox proportional hazards models were created to assess the effect of patient demographics, pathologic findings, and operation type on the time to development of postpancreatectomy diabetes and exocrine insufficiency. Individuals in whom postpancreatectomy insufficiency did not develop were censored at last known follow-up. All p values were two sided, and p values lower than 0.05 were considered statistically significant. Analyses were performed using SAS software (SAS Institute Inc, Cary, NC).

Table 1. Characteristics of 1165 patients who underwent partial pancreatectomy from 1998 to 2010

Characteristic	Number (%)[a]
Age, median years (interquartile range)	62.5 (52.5-70.9)
Sex	
Women	634 (54.4)
Men	531 (45.6)
Body mass index, kg/m²	
Mean	27.2
< 18.5	15 (1.3)
18.5-24.9	199 (17.1)
25-29.9	200 (17.2)
≥ 30	144 (12.4)
Unknown	607 (52.1)
Race/ethnicity	
White	596 (51.2)
Hispanic	284 (24.4)
Black	171 (14.7)
Asian/Pacific Islander	94 (8.1)
Unknown	20 (1.7)
Charlson Comorbidity Index	
0	139 (11.9)
1	282 (24.2)
≥ 2	744 (63.9)
Operation	
Whipple procedure	692 (59.4)
Distal pancreatic resection	473 (40.6)
Pathologic finding	
Malignant lesion	696 (59.7)
Benign lesion	131 (11.2)
Pancreatitis	187 (16.1)
Other	151 (13.0)

[a] Data are number (%) except for age and mean body mass index.

Table 2. Outcomes in 678 patients without preoperative diabetes undergoing partial pancreatectomy

Outcome	Value
Incidence of diabetes, no. (%)	274 (40.4)
Median time to diabetes, months	3.6
Incidence of enzyme use, no. (%)	235 (34.7)
Median time to enzyme use, months	3.6
Median follow-up time, months	19.6

Table 3. Cox proportional hazards model of likelihood of diabetes developing after partial pancreatectomy (n = 678)

Characteristic	Hazard ratio	Adjusted 95% CI	p value[a]
Age, years			
18-59	1.00	—	—
≥ 60	1.02	0.8-1.3	0.86
Sex			
Women	1.00	—	—
Men	1.17	0.9-1.5	0.21
Body mass index, kg/m²			
< 18.5	1.92	0.7-4.9	0.18
18.5-24.9	1.00	—	—
25-29.9	0.95	0.6-1.5	0.82
≥ 30	1.44	0.9-2.3	0.13
Unknown	1.20	0.8-1.7	0.31
Race/ethnicity			
White	1.00	—	—
Hispanic	1.30	1.0-1.7	0.09
Black	1.34	0.9-1.9	0.10
Asian/Pacific Islander	1.02	0.6-1.7	0.95
Unknown	0.22	0.0-1.6	0.14
Charlson Comorbidity Index			
0	1.00	—	—
1	1.62	1.1-2.4	**0.02**
≥ 2	1.95	1.3-3.0	**< 0.01**
Operation			
Whipple procedure	1.00	—	—
Distal pancreatic resection	0.98	0.7-1.3	0.87
Pathologic finding			
Malignant lesion	1.00	—	—
Benign lesion	0.79	0.5-1.2	0.30
Pancreatitis	1.51	1.0-2.2	**0.03**
Other	0.92	0.6-1.4	0.67

[a] Boldface indicates statistical significance (p < 0.05).
— = referent values; CI = confidence interval.

RESULTS

A total of 1165 patients underwent partial pancreatectomy between 1998 and 2010 at KPSC; their demographics, histologic diagnoses, and operation types are shown in Table 1. The patients' median age was 62.5 years, most patients (59.4%) underwent Whipple procedures, and most resections were performed because of malignancy (59.7%).

Of the 1165 patients undergoing partial pancreatectomy, 487 (41.8%) had preexisting diabetes. For the remaining 678 patients, we had postoperative health information for a median of 19.6 months. During this time, diabetes developed in 274 (40.4%) patients at a median 3.6 months, and pancreatic insufficiency developed in 235 (34.7%) at a median 3.6 months (Table 2).

As shown in Table 3, independent predictors of new-onset diabetes were as follows: increasing Charlson Comorbidity Index (CCI; hazard ratio [HR] = 1.62 for CCI of 1, p = 0.02, and HR = 1.95 for CCI ≥ 2, p < 0.01) and pancreatitis histologic findings (HR = 1.51, p = 0.03). There was no difference when we compared malignant and benign pathologic findings, or Whipple and distal pancreatic resections. This is also shown in Figure 1, which illustrates diabetes-free survival, stratified by Whipple procedure vs distal resection.

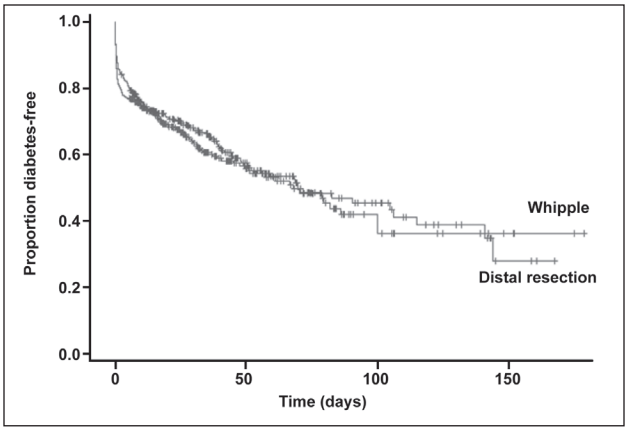

Figure 1. Kaplan-Meier curve of diabetes-free postoperative survival, stratified by Whipple procedure vs distal pancreatic resection (n = 678).

Table 4. Cox proportional hazards model of likelihood of exocrine insufficiency developing after partial pancreatectomy (n = 678)

Characteristic	Hazard ratio	Adjusted 95% CI	p value[a]
Age, years			
18-59	1	—	—
≥ 60	0.94	0.8-1.2	0.54
Sex			
Women	1	—	—
Men	.76	0.6-0.9	**< 0.01**
Body mass index, kg/m²			
< 18.5	1.06	0.5-2.4	0.89
18.5-24.9	1	—	—
25-29.9	0.95	0.7-1.3	0.73
≥ 30	0.72	0.5-1.1	0.10
Unknown	0.92	0.7-1.2	0.52
Race/ethnicity			
White	1.00	—	—
Hispanic	0.80	0.6-1.0	0.07
Black	0.87	0.7-1.1	0.31
Asian/Pacific Islander	0.54	0.4-0.8	**< 0.01**
Unknown	0.47	0.2-1.3	0.13
Charlson Comorbidity Index			
0	1.00	—	—
1	1.85	1.2-3.0	**< 0.01**
≥ 2	2.05	1.3-3.2	**< 0.01**
Operation			
Whipple procedure	1	—	—
Distal pancreatic resection	0.35	0.3-0.5	**< 0.01**
Pathologic finding			
Malignant lesion	1	—	—
Benign lesion	0.77	0.5-1.1	0.18
Pancreatitis	1.08	0.8-1.5	0.64
Other	0.16	0.1-0.3	**< 0.01**

[a] Boldface indicates statistical significance (p < 0.05) .
— = referent value; CI = confidence interval.

As shown in Table 4, independent predictors of exocrine insufficiency were female sex (HR = 1.32, p < 0.01) and increasing CCI (HR = 1.85 for CCI of 1, p < 0.01; HR 2.0 for CCI ≥ 2, p < .01). Compared with the Whipple procedure, distal pancreatic resection was associated with decreased enzyme use (HR = 0.35, p < 0.01). Asian race also predicted decreased likelihood of exocrine insufficiency (HR = 0.54, p < 0.01).

DISCUSSION

The risk of new-onset diabetes developing after partial pancreatic resection is often a source of anxiety for both patients and surgeons. Patient counseling and establishing expectations for recovery are important elements in perioperative care. Little to no data exist to guide patients' and physicians' expectations, however. Ours is the first study of which we are aware that helps address this gap in knowledge by comprehensively characterizing pancreatic function after resection using a large population-based database with long-term follow-up and specific, reliable, and reproducible criteria for defining endocrine and exocrine insufficiency. We found a 40% incidence of new-onset diabetes and a 35% incidence of exocrine insufficiency after pancreas surgery. This rate significantly exceeds the incidence of diabetes generally reported in the literature. Although we did identify some predictors of postoperative diabetes, such as a higher comorbidity index, we did not observe a difference between Whipple procedures and distal resections or between benign and malignant pathologic findings.

Our study is unique in that our methods relied on analysis of a large, closed-patient database that contains linked operative, pathologic, laboratory, and pharmacy records in a multiracial population. This database allowed us to use a precise definition of diabetes and to accurately assess our outcome of interest in a significantly higher number of patients than has previously

been examined during an extensive follow-up period. As surgical techniques and perioperative care continue to improve, data on long-term outcomes after pancreas surgery, such as those presented here, are invaluable to informing patients' and physicians' expectations.

Our study has several limitations. Our findings may be limited by the bias contained in any retrospective study. Additionally, although the use of administrative data such as ICD-9 and CPT codes allows analysis of much larger numbers of patients, individual patient records were not able to be reviewed to confirm accuracy of coding. Our definition of exocrine insufficiency is also limited in that patients may be prescribed enzyme replacement on the basis of clinical suspicion or nonspecific complaints (or even prophylactically depending on physician preference), and the diagnosis is rarely confirmed with laboratory studies such as fecal fat testing. Thus, we may have overestimated the true incidence of postoperative exocrine insufficiency.

Our findings are critical for informing patients' and surgeons' expectations after partial pancreatectomy. In a climate of increasingly standardized clinical pathways and patient education protocols, and emphasis on quality of care, lowering costs, and decreasing readmissions, our data suggest that education regarding diabetes is an important component of perioperative postpancreatectomy care. Possible interventions might include increased diabetes teaching and earlier involvement of endocrinologists, closer blood glucose monitoring in the postoperative inpatient setting, and additional routine screening in the postoperative outpatient setting.

Perhaps less clear are the implications for patients with pancreatic cystic disease, for whom appropriate indications for resection continue to evolve. Understanding the true rate of postoperative diabetes and exocrine insufficiency could affect the discussion of risks and benefits of operative intervention in these patients.

CONCLUSION

Our population-based study finds the incidence of diabetes and exocrine insufficiency after partial pancreatectomy to be much higher than previously reported. This information should improve patients' and physicians' expectations after pancreatic surgery. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Postoperative Treatment

It cannot be too often emphasized, however, that the postoperative treatment is as essential as the operation, and the surgeon is as much responsible for the postoperative treatment as for the operation.

— Roscoe C Giles, MD, 1890-1970, first African American to be certified by the American Board of Surgery