Development of Diabetes after Pancreaticoduodenectomy: Results of a 10-Year Series Using Prospective Endocrine Evaluation

Daniel W Maxwell, DO, Mohammad Raheel Jajja, MD, Marvi Tariq, MD, Zayan Mahmooth, MSPH, Rodolfo J Galindo, MD, John F Sweeney, MD, FACS, Juan M Sarmiento, MD, FACS

BACKGROUND: Limited literature is available on the development of impaired glucose tolerance and diabetes mellitus after pancreaticoduodenectomy. The primary aim was to define the diabetic phenotype and correlate preoperative glycemic laboratory results to new-onset diabetes after pancreaticoduodenectomy.

STUDY DESIGN: In this prospective study, perioperative fasting and postprandial (oral glucose tolerance test) plasma glucose, glycated hemoglobin, insulin, and c-peptide were measured in consecutive patients undergoing pancreaticoduodenectomy by the senior author from 2006 to 2017. American Diabetes Association definitions were used for glycemic classifications. Multivariate risk factor analysis was performed.

RESULTS: Of 774 identified patients, 371 diabetics were excluded and 403 patients were included: 167 and 236 were preoperatively classified as nondiabetic and prediabetic, respectively. The incidence rates of diabetes at 120 months post pancreaticoduodenectomy were 9.0% (nondiabetics), 22.0% (prediabetics), and 16.6% (overall). Patients in whom diabetes developed demonstrated a 3-fold larger difference between oral glucose tolerance test and fasting glucose (Δ), and 2-fold larger Δinsulin and Δc-peptide values. Tiered multivariate analysis identified glycated hemoglobin >5.4% with a relative risk (RR) of 2.944 ($p = 0.047$) as an independent predictor of impaired glucose tolerance and diabetes mellitus. Analysis of patients stratified by preoperative classification identified fasting glucose >95 mg/dL (nondiabetics, RR 1.925; $p = 0.002$), and glycated hemoglobin ≥5.4% (prediabetics, RR 3.125; $p = 0.040$) as independent risk factors for diabetes. Compared with nondiabetics, prediabetics classified by any laboratory results demonstrated an RR of 2.471 ($p = 0.001$) for diabetes developing postoperatively. There was no association between primary pathology, advancing age, or BMI and increased risk of diabetes development.

CONCLUSIONS: Diabetes will develop after pancreaticoduodenectomy in approximately 16.6% of patients. A preoperative glycated hemoglobin >5.4% independently predicts new-onset diabetes. Pre- and postoperative endocrine analysis remains paramount for proper patient risk stratification. (J Am Coll Surg 2019;228:400–414. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Disclosure Information: Nothing to disclose.

Presented at the Southern Surgical Association 130th Annual Meeting, Palm Beach, FL, December 2018.

Received December 15, 2018; Accepted December 17, 2018.

From the Department of Surgery (Maxwell, Jajja, Tariq, Sweeney, Sarmiento), Winship Cancer Institute (Jajja, Sarmiento), Division of Endocrinology (Galindo), Emory University, and Emory University School of Medicine (Mahmooth), Atlanta, GA.

Correspondence address: Juan M Sarmiento, MD, FACS, Department of Surgery, Emory University Hospital, Room B206, 1364 Clifton Road, NE, Atlanta, GA 30322. email: jsarmie@emory.edu

The incidence and prevalence of type 2 diabetes mellitus continues to increase in the US, with treatment and care costs estimated at $327 billion in 2017 alone.[1-5] It continues to be an immutable burden on the healthcare system and has been repeatedly identified as an independent risk factor for postoperative complications[6] in multiple surgical specialties, contributing to economic stress. The prevalence of diabetes after pancreatectomy has also increased, comprising 8% to 10% of all diabetes.[7] The American Diabetes Association and WHO have even

https://doi.org/10.1016/j.jamcollsurg.2018.12.042
ISSN 1072-7515/19

Abbreviations and Acronyms

A1c	= glycated hemoglobin
CP	= chronic pancreatitis
eA1c	= estimated glycated hemoglobin
FG	= fasting glucose
GCM	= glycemic control medication
HOMA-β	= Homeostatic Model Assessment of β-cell function
HOMA-IR	= Homeostatic Model Assessment of insulin resistance
OGTT	= oral glucose tolerance test
OR	= odds ratio
PD	= pancreaticoduodenectomy
PDAC	= pancreatic ductal adenocarcinoma
RR	= relative risk

classified diabetes caused by diseases of the pancreas as type 3c diabetes mellitus.[8,9]

The association with new-onset impaired glucose tolerance (or pre-diabetes) and diabetes has been observed since the inception[10] of and subsequent popularization[11] of pancreaticoduodenectomy (PD)—the gold-standard surgical treatment for resectable pancreatic head pathologies. Standardization of surgical techniques, advancements in perioperative care, and improved understanding of inflicting pathologies have led to drastic reductions in mortality and morbidity across all indications.[12-16] Despite these advancements, the relationship between diabetes development and parenchymal resection, pathology, and comorbid states remains understudied.

The previous dogma that functional endocrine preservation was attainable with 20% parenchymal-sparing resections has been discredited previously by both procedural[17-20] and volumetric studies.[21,22] These studies are in turn confounded by the distribution of pancreatic islets[23] in the head of the pancreas, suggesting that the shift from endocrine homeostasis is more complex than parenchymal resection alone. Anatomic changes mandated by the procedure resemble that of the Roux-en-Y gastric bypass, which has attenuating effects on type 2 diabetes.[24-27] Specific pathologies, including pancreatic ductal adenocarcinoma (PDAC) and chronic pancreatitis (CP) have strong associations with impaired glucose tolerance/diabetes, and extrapancreatic insulin regulation[28,29] and endocrinopathies[30] can alter pancreatic endocrine function. The true incidence of diabetes after PD is multifactorial and remains unknown. The primary aim of this study was to define the developing diabetic phenotype and correlate preoperative endocrine evaluation laboratories with new-onset diabetes in nondiabetic and prediabetic patients after PD.

METHODS

Approval was obtained from Emory University Hospital's IRB. Consecutive normoglycemic patients (nondiabetics and prediabetics) undergoing evaluation for PD between January 1, 2007 and December 31, 2017 were prospectively enrolled into this observational study. Pre- and postoperative fasting and 2-hour post-oral glucose tolerance test (OGTT) laboratory results were collected, including glucose, glycated hemoglobin (A1c), insulin, and c-peptide. Demographic data, pre- and postoperative glycemic laboratory results, and procedural data were collected. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used in the drafting of this article.[31]

The primary aim was to define the diabetic phenotype and correlate preoperative glycemic laboratory results to new-onset diabetes in nondiabetic and prediabetic patients after PD. The primary end point was development of postoperative diabetes. Secondary outcomes included development of prediabetes, returning to euglycemia for preoperative prediabetics and diabetics, and associations of postoperative diabetic classifications with the following: race, BMI, advancing age, and pathologic type. Inclusion criteria included nondiabetics and prediabetics by diagnosis and confirmed with preoperative glycemic evaluation, age 18 years or older and younger than 90 years, elective PD, and any pathologic indication in the head of the pancreas. Exclusion criteria included non-PD pancreatectomies, pre-existing diabetes by diagnosis or by preoperative endocrine laboratory testing in the previously nondiabetic, age younger than 18 years or 90 years and older, patients requiring urgent or emergent operation, patients transferred from outside hospitals in extremis or requiring substantial presurgical care that might have altered glycemic response (including infections or sepsis), and vulnerable patient populations.

Endocrine analysis was planned to be performed 1 month before and 1 month post operation and surveillance for diabetic diagnoses and medications prescribed by outside physicians was performed out to the last clinic date or appointment at our Winship Cancer Institute. The OGTT studies were obtained 2 hours after a 75-mg oral glucose load. Patients experiencing mortality before 30-day postoperative endocrine evaluation were not included in survival analysis.

Definitions

The American Diabetes Association's definitions and laboratory ranges for diabetic classifications were used.[8] Institutional averages were used for abnormal fasting insulin (≥25 μIU/mL) and c-peptide (≥3.5 ng/mL).

Postprandial values of ≥166 μIU/mL for insulin and ≥4.5 ng/mL for c-peptide were used. Homeostatic Model Assessment[32,33] of insulin resistance (HOMA-IR), insulin sensitivity, and β-cell function (HOMA-β), as well as estimated glycated hemoglobin (eA1c)[34] were calculated according to their published formulas. The difference between OGTT and fasting values was defined as the delta or change (Δ) value (eg Δinsulin). The CDC's adult BMI classifications were used.[35]

Standardization of operative technique

All PDs were performed by the senior author (JMS) through an upper midline incision. Pylorus preservation was preferred when possible. The bowel anastomosis is primarily performed through a mesenteric defect in a retro-colic orientation. All anastomoses are performed end to side with the following suture configurations: pancreatojejunostomy—duct to mucosa in 2 layers with 1 interrupted 6-0 polydioxanone internally and 3-0 silk externally; hepaticojejunostomy—running, interlocking 4-0 polydioxanone; and duodenojejunostomy—running, interlocking 3-0 polydioxanone. A 5-French pediatric feeding tube is routinely placed within the pancreatic duct for stenting when probe patent. Drains are not routinely placed.

Statistical analysis

Data analysis was performed using SPSS, version 24 (IBM Corp). Comparisons of proportions between 2 groups were made using chi-square or Fisher's exact test. Continuous data were analyzed using 2-sample *t*-tests for means, and nonparametric continuous data were analyzed with Mann-Whitney tests. Differences among 3 groups were determined by ANOVA. Binary logistic regression models were used to assess associations and possible risk factors for the development of postoperative diabetes. Pearson's ρ was used for correlations while area under the receiver operating curve analysis was used for predictive ability via c-statistics for specific strata. Data are presented as means and SDs, medians and ranges, or numbers and percentages. All statistical tests were 2-sided with significance at $p < 0.050$. Comparisons made within text with parentheses use the following orders: (nondiabetics vs prediabetics; p value) or (nondiabetics vs prediabetics vs diabetes; p value).

For patients without a full set of endocrine laboratories results, a single fasting glucose (FG) was used in place of mean glucose concentration in the formula for eA1c,[34] as FG and A1c are commonly used in national health surveys.[36,37] Correlations were performed and eA1c demonstrated a predictive ability for postoperative diabetes between A1c and FG (Fig. 1). Estimated A1c values were not included in risk factor analysis.[8]

RESULTS

Demographics and baseline characteristics

Of 774 identified patients, 371 patients were classified as diabetics on evaluation and were excluded. The 403 remaining patients were included in the analysis: 167 and 236 were preoperatively classified as nondiabetics and prediabetics, respectively (Fig. 2). Demographics and baseline characteristics are located in Table 1. Mean demographic characteristics were: age 59.93 ± 13.61 years, Caucasian (74.69%), BMI 25.90 ± 5.38 kg/m^2, with hypertension (45.16%), American Society of Anesthesiologists class[38] 3 (57.82%), and malignant surgical indication (65.01%).

With respect to preoperative classification, there was a trend of increasing prediabetic patients but decreasing nondiabetic patients with advancing age (Fig. 3). The distribution of postoperative prediabetic and nondiabetic patients in the 65 years and older age group was significantly different compared with the distribution of other age groups ($p = 0.012$). Patients classified as nondiabetic preoperatively were more likely to experience a decrease in BMI in the postoperative period (79.1% vs 72.9%; $p = 0.183$) and prediabetic patients were more likely to experience an increase in BMI (17.7% vs 24.7%; $p = 0.129$). There were no differences between the percent change (-4.89% ± 15.87% vs -4.40% ± 13.63%) or absolute percent change (11.16% ± 12.27% vs 10.50% ± 9.81%) in BMI between preoperative groups. No significant difference were seen in the distribution of BMI classes pre- or postoperatively (Fig. 2C, 2D).

Endocrine analysis

Preoperative and postoperative endocrine laboratories stratified by preoperative and postoperative diabetic statuses are located in Table 2. Graphical trends of these data are available in eFigure 1. In total, 252 (62.5%) patients had complete pre- and postoperative endocrine laboratories. The remaining 151 (37.5%) patients had preoperative FG alone: 76 (18.9%) patients had complete postoperative endocrine laboratory tests and 75 (18.6%) had FG only.

Glucose values

Compared with preoperative values, both groups experienced an overall increase in postoperative fasting ($p < 0.001$ vs $p = 0.196$) and OGTT glucose ($p < 0.001$ vs $p = 0.035$) values on postoperative evaluation. However, A1c did not change significantly for the preoperative

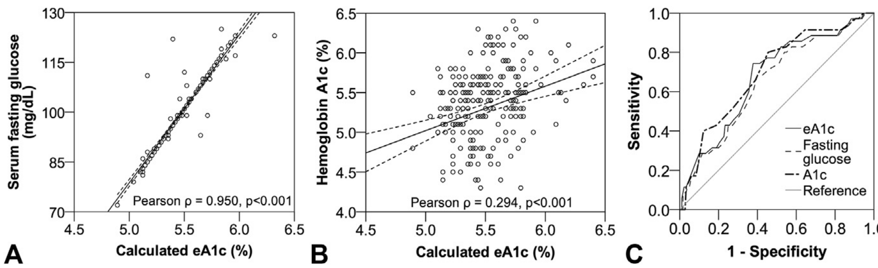


Figure 1. Correlations between (A) fasting glucose (FG) and estimated glycated hemoglobin (eA1c) and (B) measured serum glycated hemoglobin (A1c) and eA1c. (C) Area under the receiver operating curve analysis predicting postoperative diabetic status (diabetes vs no diabetes) with the following continuous predictors: FG (area 0.650; 95% CI 0.553 to 0.747; $p = 0.005$; sensitivity 0.714, specificity 0.639), eA1c (area 0.677; 95% CI 0.582 to 0.771; $p < 0.001$; sensitivity 0.743, specificity 0.622), and A1c (area 0.696; 95% CI 0.604 to 0.789; $p < 0.001$; sensitivity 0.800, specificity 0.544) demonstrating eA1c with a predictive ability that falls between measured serum FG and A1c values. Significance determined at $p < 0.50$.

prediabetics group ($p < 0.001$ vs $p = 0.555$), and eA1c increased for both groups ($p < 0.001$ vs $p < 0.001$). Glucose values stratified by postoperative diabetic status demonstrated increase fasting and OGTT glucose values with worsening diabetic classification that only reached significance in postoperative laboratories between groups.

The Δglucose values differed significantly on preoperative evaluation (10.0 ± 21.53 mg/dL vs 31.56 ± 37.08

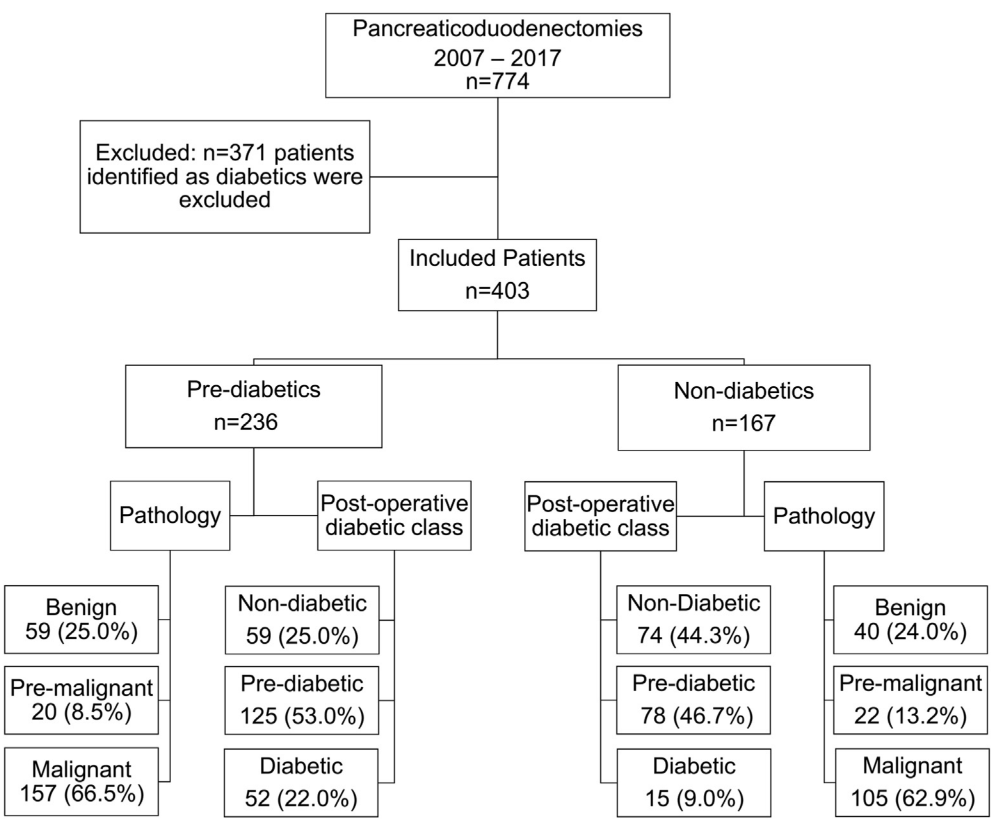


Figure 2. Flowchart depicting exclusion criteria and patient breakdown stratified by preoperative diabetic classifications with final pathologic categories and postoperative diabetic classifications. Postoperative diabetic classifications between respective diabetic classifications are all significantly different at $p < 0.001$.

Table 1. Demographics and Baseline Characteristics

Variable	Nondiabetic (n = 167)	Prediabetic (n = 236)	p Value*
Age, y, mean ± SD	58.44 ± 12.80	60.99 ± 14.09	0.059
18–44 y, n (%)	20 (12.0)	27 (11.4)	0.869
45–64 y, n (%)	91 (54.5)	108 (45.8)	0.087
65 y and older, n (%)	56 (33.5)	101 (42.8)	0.063
Sex, female, n (%)	79 (47.3)	120 (50.8)	0.484
Race, n (%)			
Caucasian	118 (70.7)	182 (77.1)	0.143
African American	41 (24.6)	40 (16.9)	0.077
Asian	3 (1.8)	11 (4.7)	0.120
Hispanic	4 (2.4)	3 (1.3)	0.398
American Indian/Alaskan Native	1 (0.6)	0 (0.0)	0.235
BMI,† kg/m^2, mean ± SD	25.80 ± 5.54	25.98 ± 5.26	0.758
Underweight, n (%)	7 (4.2)	11 (4.7)	0.798
Normal, n (%)	74 (44.3)	93 (39.4)	0.378
Overweight, n (%)	46 (27.5)	71 (30.1)	0.512
Obese, class 1, n (%)	21 (12.6)	32 (13.6)	0.729
Obese, class 2, n (%)	6 (3.6)	10 (4.2)	0.722
Obese, class 3, n (%)	4 (2.4)	3 (1.3)	0.406
Comorbidity, n (%)			
Smoker	37 (22.2)	54 (22.9)	0.940
Hypothyroid	25 (15.0)	28 (11.9)	0.323
Hypertension	68 (40.7)	114 (48.3)	0.177
CVA	6 (3.6)	5 (2.1)	0.354
Coronary artery disease	17 (10.2)	30 (12.7)	0.474
Chronic kidney disease	3 (1.8)	3 (1.3)	0.652
COPD	8 (4.8)	15 (6.4)	0.532
American Society of Anesthesiology physical status classification, n (%)			
1	0 (0.0)	1 (0.4)	0.397
2	48 (28.7)	70 (29.7)	0.790
3	99 (59.3)	134 (56.8)	0.668
4	3 (1.8)	5 (2.1)	0.809
Indication, n (%)			
Benign	39 (23.4)	59 (25.0)	0.704
Premalignant	23 (13.8)	20 (8.5)	0.102
Malignant	105 (62.9)	157 (66.5)	0.449

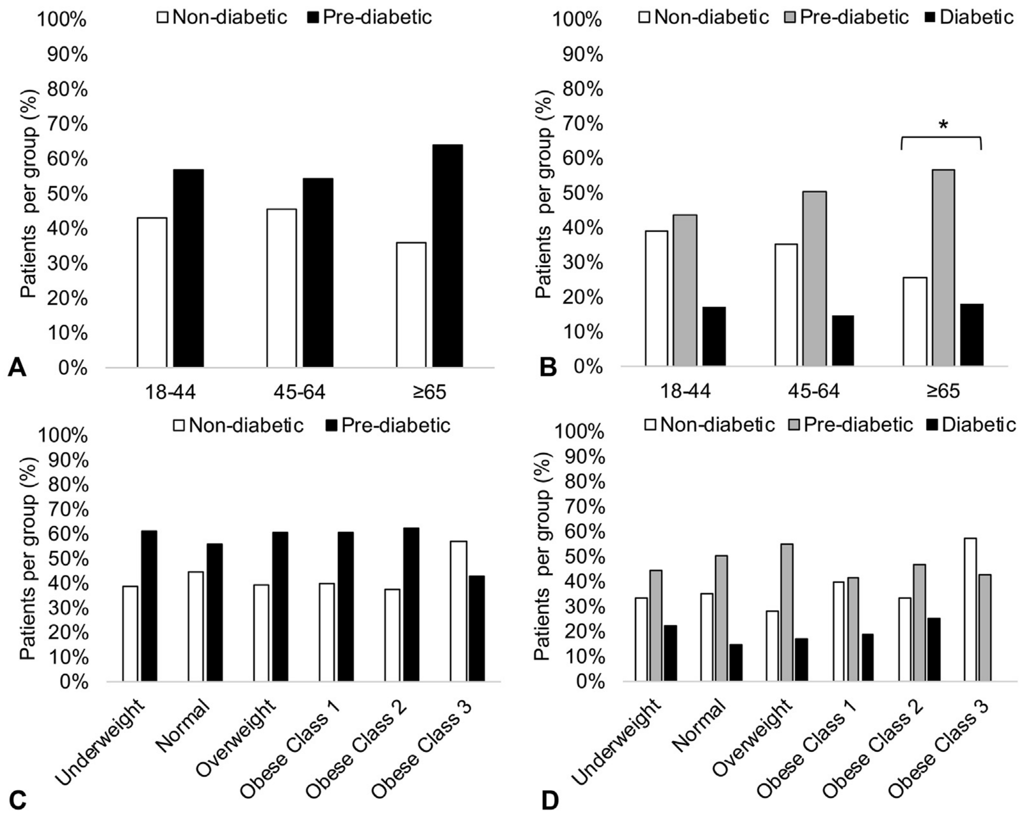
*Significance determined at $p < 0.050$.
†BMI classifications: underweight ≤18.5 kg/m^2; normal 18.5–24.9 kg/m^2; overweight 25.0–29.9 kg/m^2; class 1 obese 30.0–34.9 kg/m^2; class 2 obese 35.0–39.9 kg/m^2; class 3 obese ≥40.0 kg/m^2.

mg/dL; $p < 0.001$), but not postoperatively (32.59 ± 38.65 mg/dL vs 43.04 ± 49.33 mg/dL, $p = 0.120$) (Table 2). When stratified by postoperative diabetic status, an increasing preoperative Δglucose was observed with worsening diabetic classification (21.25 ± 31.61 mg/dL vs 26.58 ± 34.76 mg/dL vs 30.74 ± 34.98 mg/dL; $p = 0.279$). Only in postoperative laboratories did Δglucose values differ significantly between groups (7.89 ± 21.20 mg/dL vs 43.64 ± 30.08 mg/dL vs 94.00 ± 69.37 mg/dL; $p < 0.001$) (Table 2).

Insulin and c-peptide values

Compared with preoperative values, postoperative fasting insulin increased for the nondiabetes group ($p = 0.577$), but decreased for prediabetes group ($p = 0.032$), and OGTT insulin values followed a similar trend ($p = 0.657$ vs $p < 0.001$). Both fasting c-peptide ($p = 0.173$ vs $p = 0.034$) and OGTT c-peptide ($p = 0.657$ vs $p < 0.001$) decreased for both groups.

With respect to preoperative diabetic status, Δinsulin differed significantly preoperatively (29.18 ± 30.72



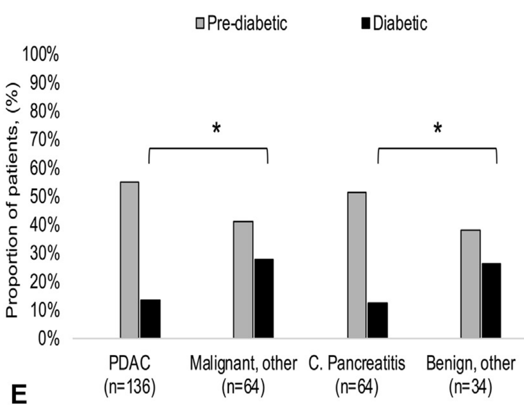


Figure 3. Distribution of age groups in years stratified by (A) preoperative diabetic status and (B) postoperative diabetic status; of BMI classification groups (BMI, kg/m^2) by (C) preoperative and (D) postoperative diabetic status; and of (E) select pathologies with respect to postoperative diabetic status. *Significant at $p < 0.050$. PDAC, pancreatic ductal adenocarcinoma. BMI classifications: underweight $\leq$18.5 kg/m^2; normal 18.5 to 24.9 kg/m^2; overweight 25.0 to 29.9 kg/m^2; class 1 obese 30.0 to 34.9 kg/m^2; class 2 obese 35.0 to 39.9 kg/m^2; and class 3 obese $\geq$40.0 kg/m^2.

μIU/mL vs 63.90 ± 79.49 μIU/mL; $p < 0.001$), but not postoperatively (41.06 ± 40.19 μIU/mL vs 32.57 ± 34.62 μIU/mL; $p = 0.120$). A similar trend was observed for preoperative Δc-peptide (4.51 ± 4.20 ng/mL vs 7.07 ± 4.95 ng/mL; $p < 0.001$) compared with postoperative Δc-peptide (4.84 ± 4.07 vs 4.23 ± 3.51 ng/mL; $p = 0.268$). Stratified by postoperative diabetic status, there were no significant differences observed between preoperative Δinsulin (51.25 ± 54.74 μIU/mL vs 70.87 ± 78.07 μIU/mL vs 55.08 ± 72.66 μIU/mL; $p = 0.177$) and Δc-peptide (5.92 ± 4.72 ng/mL vs 6.32 ± 4.82 ng/mL vs 5.61 ± 5.10 ng/mL; $p = 0.752$), and postoperative Δinsulin (28.21 ± 38.72 μIU/mL vs 38.58 ± 33.52 μIU/mL vs 43.72 ± 42.75 μIU/mL; $p = 0.085$) and Δc-peptide (3.66 ± 3.50 ng/mL vs 4.90 ± 3.57 ng/mL vs 4.63 ± 4.67 ng/mL; $p = 0.099$) approached significance. A trend of increasing Δinsulin, but not Δc-peptide, with worsening postoperative diabetic status was observed.

Table 2. Pre- and Postoperative Endocrine Evaluation Stratified by Diabetic Classification

Variable	Nondiabetic	Prediabetic	Diabetic	p Value
Preoperative diabetic classification				
n	167	236	—	—
Preoperative				
Fasting glucose, mg/dL, mean (SD)	91.70 (5.28)	106.78 (14.00)	—	<0.001*
Glucose, post OGTT, mg/dL, mean (SD)	101.89 (21.53)	139.79 (35.05)	—	<0.001*
A1c, % (SD)	5.09 (0.40)	5.46 (0.51)	—	<0.001*
eA1c, % (SD)	5.40 (0.25)	5.75 (0.31)	—	<0.001*
Insulin, μIU/mL, mean (SD)	7.36 (4.96)	10.93 (7.49)	—	<0.001
C-peptide, ng/mL, mean (SD)	2.33 (3.19)	2.56 (1.94)	—	0.526
Insulin, post OGTT, μIU/mL, mean (SD)	42.75 (32.59)	87.08 (83.83)	—	<0.001*
C-peptide, post OGTT, ng/mL, mean (SD)	6.78 (3.17)	9.62 (4.66)	—	<0.001*
HOMA index, mean (SD)				
IR	1.67 (1.17)	2.92 (2.05)	—	<0.001*
IS	0.92 (0.61)	0.63 (0.84)	—	0.004*
β	93.78 (64.02)	94.59 (67.54)	—	0.931
Postoperative				
Fasting glucose, mg/dL, mean (SD)	104.36 (14.37)	109.74 (17.61)	—	0.013*
Glucose, post OGTT, mg/dL, mean (SD)	136.33 (43.60)	152.39 (55.02)	—	0.018*
A1c, % (SD)	5.38 (0.53)	5.49 (0.63)	—	0.110
eA1c, % (SD)	5.96 (0.62)	6.02 (0.50)	—	0.286
Insulin, μIU/mL, mean (SD)	7.91 (6.11)	8.96 (7.32)	—	0.243
C-peptide, ng/mL, mean (SD)	1.80 (1.50)	2.08 (1.73)	—	0.201
Insulin, post OGTT, μIU/mL, mean (SD)	48.22 (41.77)	41.60 (38.44)	—	0.249
C-peptide, post OGTT, ng/mL, mean (SD)	6.63 (3.91)	6.19 (3.61)	—	0.409
HOMA index, mean (SD)				
IR	2.09 (1.68)	2.55 (2.32)	—	0.094
IS	0.89 (1.20)	0.85 (1.09)	—	0.809
β	75.58 (69.79)	71.52 (59.73)	—	0.659
Postoperative diabetic classification				
n	133	203	67	—
Preoperative				
Fasting glucose, mg/dL, mean (SD)	98.39 (13.84)	102.49 (13.88)	105.64 (11.62)	0.833
Glucose, post OGTT, mg/dL, mean (SD)	118.87 (33.47)	128.42 (35.11)	136.09 (40.25)	0.119
A1c, % (SD)	5.10 (0.51)	5.38 (0.45)	5.55 (0.45)	0.150
eA1c, % (SD)	5.48 (0.33)	5.64 (0.33)	5.73 (0.29)	0.285
Insulin, μIU/mL, mean (SD)	8.98 (7.39)	10.03 (6.72)	10.13 (6.13)	0.988
C-peptide, ng/mL, mean (SD)	2.41 (2.88)	2.36 (2.04)	2.94 (2.56)	0.594
Insulin, post OGTT, μIU/mL, mean (SD)	60.20 (56.70)	79.95 (81.77)	64.48 (73.43)	0.020*
C-peptide, post OGTT, ng/mL, mean (SD)	8.39 (4.12)	8.57 (4.57)	8.65 (4.47)	0.598
HOMA index, mean (SD)				
IR	2.27 (1.99)	2.59 (1.85)	2.67 (1.69)	0.433
IS	0.80 (0.64)	0.72 (0.96)	0.60 (0.45)	0.406
β	94.03 (68.16)	96.09 (67.46)	89.99 (58.77)	0.899
Postoperative				
Fasting glucose, mg/dL, mean (SD)	98.92 (12.17)	109.32 (13.23)	115.79 (27.93)	<0.001*
Glucose, post OGTT, mg/dL, mean (SD)	108.86 (19.04)	152.73 (29.48)	210.19 (82.86)	<0.001*
A1c, % (SD)	5.10 (0.37)	5.58 (0.47)	5.91 (0.91)	<0.001*
eA1c, % (SD)	5.80 (0.55)	5.98 (0.40)	6.43 (0.69)	<0.001*

(Continued)

Table 2. Continued

Variable	Nondiabetic	Prediabetic	Diabetic	p Value
Insulin, μIU/mL, mean (SD)	6.98 (5.15)	9.57 (8.01)	9.06 (5.95)	0.008*
C-peptide, ng/mL, mean (SD)	1.63 (1.03)	2.22 (1.99)	1.95 (1.42)	0.018*
Insulin, post OGTT, μIU/mL, mean (SD)	35.15 (40.83)	47.75 (37.32)	51.74 (43.57)	0.550
C-peptide, post OGTT, ng/mL, mean (SD)	5.33 (3.46)	6.99 (3.55)	6.45 (4.46)	0.207
HOMA index, mean (SD)				
IR	1.78 (1.47)	2.66 (2.37)	2.72 (2.11)	0.012*
IS	1.02 (1.19)	0.81 (1.16)	0.71 (0.85)	0.324
β	70.45 (52.61)	76.31 (74.61)	68.40 (45.41)	0.747

*Significance determined at $p < 0.050$.

A1c, serum glycated hemoglobin concentration; β, β-cell function; eA1c, estimated glycated hemoglobin concentration; HOMA, Homeostatic Model Assessment; IR, insulin resistance; IS, insulin sensitivity; OGTT, oral glucose tolerance test (values drawn 2 h after OGTT).

Homeostatic Model Assessment metrics

Postoperative HOMA-IR increased for nondiabetics ($p = 0.073$) but decreased for prediabetics ($p = 0.167$) when stratified by preoperative classification. The HOMA-insulin sensitivity demonstrated a decrease for nondiabetics ($p = 0.835$), but an increase for prediabetics ($p = 0.057$) patients. The HOMA-β decreased for both groups ($p = 0.087$ vs $p = 0.003$).

Diagnoses and follow-up

Median follow-up period was 17.3 (range 0 to 126.9) months. With diagnoses of pancreatic ductal adenocarcinoma excluded, the median follow-up period was 19.2 (range 0 to 126.9) months. The overall incidence of postoperative diabetes stratified by 1, 3, 5, and 10 years was 39 of 403 (9.7%), 55 of 403 (13.6%), 61 of 403 (15.1%), and 67 of 403 (16.6%). Kaplan-Meier survival analysis with an end point of diabetes vs no diabetes stratified by preoperative diabetic classification is found in Figure 4. Incidence of each diabetic classification made in the postoperative period is found in Table 3. Median time to diagnosis in each group was 13.3 (range 0 to 126.9) months and 10.7 (range 0 to 122.3) months, respectively.

In total, 35 (8.7%) patients were placed on glycemic control medications (GCM): 11 (2.7%) at the time of discharge (3 vs 8; $p = 0.375$) and 24 (6.0%) by their primary care physicians on follow-up (3 vs 21; $p = 0.004$). Of the 35 patients, insulin-dependent diabetes developed in 14 and non-insulin-dependent diabetes developed in 21. The remaining 32 patients meeting criteria for diabetes classification were not using GCMs and included 21 malignant and 4 benign indications with a median survival of 11.7 (range 0.8 to 64.2) months. All patients placed on GCMs at the time of discharge continued to require these medications throughout the follow-up period. Alternatively, patients with postoperative laboratory results demonstrating euglycemia at 1 month did not require GCMs through follow-up. Diabetes developed by 12 months in 56% of patients in this cohort and by 24 months in 70%.

Procedural and pathologic details

Overall, 369 (91.5%) patients underwent pylorus-preserving PD, 9 (2.2%) had extrapancreatic organ resections and 11 (2.7%) had vascular resections (8 venous, 3 arterial). In total, 22.6% of patients underwent chemotherapy: 60 (14.9%) patients underwent neoadjuvant or adjuvant chemotherapy alone and 31 (7.7%) patients underwent combined chemoradiation therapy. However, this was not different between groups (21.7% vs 29.9%; $p = 0.150$).

A list of all included pathology can be found in eTable 1 and distributions of PDAC and CP in Figure 3E. There were no differences between groups among benign (23.4% vs 25.0%; $p = 0.704$), premalignant (13.8% vs 8.5%; $p = 0.090$), and malignant lesions

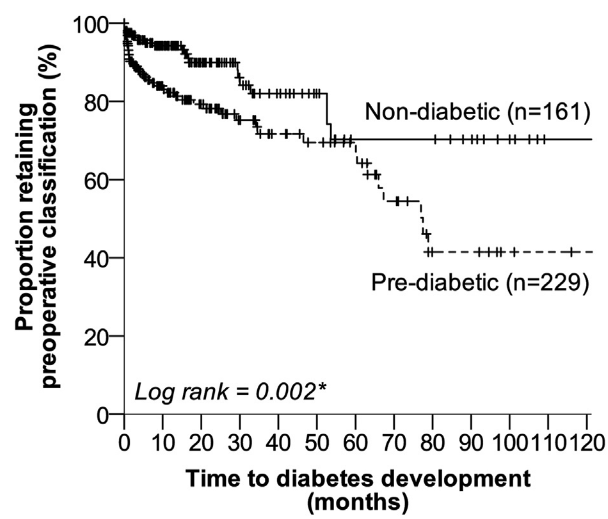


Figure 4. Kaplan-Meier survival analysis demonstrating the time to onset of diabetic diagnosis and those retaining their preoperative diabetic classification. Significance determined by log-rank test at $p < 0.050$.

Table 3. Postoperative Diabetic Classifications by Preoperative Diabetic Classification

	Preoperative, nondiabetic (n = 167)		Preoperative, prediabetic (n = 236)		
Variable	**n**	**%**	**n**	**%**	**p Value**
Nondiabetic	74	44.3	59	25.0	<0.001*
Prediabetic	78	46.7	125	53.0	<0.001*
Diabetic	15	9.0	52	22.0	<0.001*

*Significance determined at $p \leq 0.050$.

(62.9% vs 66.5%; $p = 0.449$) but primary pathologies of PDAC and CP had significantly lower development of new-onset diabetes ($p < 0.001$) postoperatively. Pancreatic gland consistency (out of 10, with increasing value indicating increasing firmness), was significantly lower in the preoperative nondiabetic group (5.79 ± 2.00 vs 6.25 ± 1.90; $p = 0.027$). Excluding patients with a diagnosis of CP, the presence of background pancreatitis

Table 4. Tier 1: Baseline Characteristics Predicting Postoperative Diabetes in All Patients

	Univariate						
Variable	**OR**	**95% CI**	**p Value**	**OR**	**Relative risk**	**95% CI**	**p Value**
Age							
18−44 y	1.063	—	0.882	—	—	—	—
45−64 y	0.861	—	0.577	—	—	—	—
65 y and older	1.152	—	0.603	—	—	—	—
Sex, male	2.067	1.201−3.560	0.009*	2.47	2.273	1.380−4.420	0.002*
Race							
African American	0.569	—	0.140	—	—	—	—
American Indian/Alaskan Native	1.001	—	0.999	—	—	—	—
Asian	2.930	—	0.061	3.669	2.59	1.124−11.974	0.031*
Caucasian	1.230	—	0.515	—	—	—	—
Hispanic	0.833	—	0.867	—	—	—	—
BMI classification†							
Underweight	1.488	—	0.497	—	—	—	—
Normal weight	0.764	—	0.344	—	—	—	—
Overweight	1.075	—	0.808	—	—	—	—
Obese class 1	1.221	—	0.602	—	—	—	—
Obese class 2	1.747	—	0.348	—	—	—	—
Obese class 3	1.012	—	0.999	—	—	—	—
Comorbidity							
Smoker	1.204	—	0.550	—	—	—	—
Hypothyroid	0.484	—	0.139	—	—	—	—
Hypertension	1.625	—	0.071	—	—	—	—
CVA	0.494	—	0.505	—	—	—	—
Coronary artery disease	1.637	—	0.188	—	—	—	—
Chronic kidney disease	1.003	—	0.998	—	—	—	—
COPD	1.059	—	0.919	—	—	—	—
American Society of Anesthesiology physical status classification							
1	0.899	—	0.999	—	—	—	—
2	1.125	—	0.685	—	—	—	—
≥3	0.660	—	0.122	—	—	—	—

*Significance determined at a $p \leq 0.050$.
†BMI classifications: underweight ≤18.5 kg/m^2; normal 18.5−24.9 kg/m^2; overweight 25.0−29.9 kg/m^2; class 1 obese 30.0−34.9 kg/m^2; class 2 obese 35.0−39.9 kg/m^2; class 3 obese ≥40.0 kg/m^2.
OR, odds ratio.

Table 5. Tier 1: Pathologic Factors Predicting Postoperative Diabetes in All Patients

	Univariate			Multivariate			
Variable	**OR**	**95% CI**	**p Value**	**OR**	**Relative risk**	**95% CI**	**p Value**
Malignant indication	0.957	—	0.876	—	—	—	—
Pancreatic ductal adenocarcinoma	0.679	—	0.194	—	—	—	—
Ampullary adenocarcinoma	0.846	—	0.718	—	—	—	—
Cholangiocarcinoma	1.613	—	0.368	—	—	—	—
Neuroendocrine tumor	1.059	—	0.919	—	—	—	—
Benign indication	1.070	—	0.825	—	—	—	—
Chronic pancreatitis	0.829	—	0.628	—	—	—	—
Other benign	0.803	—	0.744	—	—	—	—
Premalignant indication	0.972	—	0.949	—	—	—	—
Background pancreatitis	1.106	—	0.744	—	—	—	—
Background pancreatic intraepithelial neoplasia	1.593	—	0.104	1.855	1.363	1.042−3.300	0.036*
Pancreatic gland consistency ≥6	1.695	—	0.067	—	—	—	—
Chemotherapy or chemoradiation	1.533	—	0.150	—	—	—	—

*Significance determined at $p < 0.050$.
OR, odds ratio.

(6.0% vs 14.8%; p = 0.006), but not pancreatic intraepithelial neoplasia (24.0% vs 28.0%) was significantly lower in the preoperative nondiabetic group.

Risk factor analysis

A tiered multivariate logistic regression analysis was performed overall and for individual data groups to assess baseline characteristics, pathology, and laboratory values for risk factors (Tables 4,5, and 6). Tiers were controlled for their respective factors. Tier 2, consisting of baseline, demographic, and pathologic data (Table 4 and 5, respectively), identified background pancreatitis on pathology, but not a primary diagnosis of chronic pancreatitis, as an independent risk factor for developing diabetes (odds ratio [OR] 2.513; RR 2.103; 95% CI 1.196 to 5.291; p = 0.015). The final multivariate model consisting of all tiers (Tables 4,5, and 6), additionally included surgical factors (extrapancreatic organ resections, vascular resections, pylorus preservation vs classic PD, chemotherapy, and radiation history), and was controlled for the need of intraoperative or postoperative transfusion of blood products, identified A1c ≥5.4% (OR 3.233; RR 2.944; 95% CI 1.004 to 10.386; p = 0.047) as an independent risk factor for the development of diabetes.

On separate analysis of preoperative nondiabetic patients only, unadjusted analysis identified male sex (OR 8.475; 95% CI 1.848 to 38.462; p = 0.006) and FG 95 to 99 mg/dL (OR 2.457; 95% CI 1.387 to 4.348; p = 0.002) as risk factors for diabetes development. In the adjusted model, FG 95 to 99 mg/dL was identified as the only independent predictor for diabetes development (OR 2.415; RR 1.925; 95% CI 1.377 to 4.215; p = 0.002). Analysis of preoperative prediabetic patients identified an A1c ≥5.4% (OR 3.378; RR 3.125; 95% CI 1.058 to 10.753; p = 0.040) as an independent risk factor for diabetes development.

Overall, the RR (controlled for age and BMI) of postoperative diabetes developing in a patient with preoperative prediabetes classified by any laboratory study was 2.471 (95% CI 1.431 to 4.206; p = 0.001). The RRs for those individual endocrine laboratory results (controlled for age and BMI) predicting an end point of diabetes were FG ≥100 mg/dL: RR 2.2 (95% CI 1.14 to 4.25; p = 0.005); glucose, post OGTT ≥140 mg/dL: RR 1.99 (95% CI 1.09 to 3.62; p = 0.028); and A1c ≥5.7%: RR 2.56 (95% CI 1.49 to 4.40; p = 0.001).

DISCUSSION

The current incidence of post-pancreatectomy diabetes is unknown but is estimated to encompass approximately 10% of all type 2 diabetes in the US.[7] Literature pertaining to the incidence of diabetes post-pancreatectomy varies widely between 4.0% and 60.0% and is influenced by pathology, operative factors, and preoperative diabetic status.[20,39-41] A recent meta-analysis reported an adjusted rate of 15.0%, closer to our own incidence.[20] Diabetes development in our cohort closely follows that of the US incidence (9.4%; 4.0% to 25.0% by age group) and period prevalence (12.2% to 14.0% from 2011 to 2016) of the most recent National Diabetic Statistics report and National Health and Nutrition Examination Surveys.[4,37] Many studies use antecedent diagnoses in lieu of preoperative

Table 6. Tier 1: Preoperative Laboratories Predicting Postoperative Diabetes in All Patients

	Univariate			Multivariate			
Variable	**OR**	**95% CI**	**p Value**	**OR**	**Relative risk**	**95% CI**	**p Value**
Fasting glucose ≥100 mg/dL	3.356	1.398–8.057	0.007*	—	—	—	—
Glucose, OGTT ≥150	2.397	1.147–5.012	0.020*	—	—	—	—
Glycated hemoglobin ≥5.4%	5.812	1.922–17.576	0.002*	3.375	3.056	1.058–10.769	0.040*
Insulin ≥13.0 mIU/mL	1.871	—	0.111	—	—	—	—
C-peptide ≥2.1 ng/mL	2.213	1.033–4.742	0.041*	—	—	—	—
Insulin, OGTT ≥45 mIU/mL	1.231	—	0.640	—	—	—	—
C-peptide, OGTT ≥8.2 ng/mL	1.250	—	0.615	—	—	—	—
ΔGlucose ≥20.0 mg/dL	0.703	—	0.358	—	—	—	—
ΔInsulin ≥19.0 mIU/mL	1.246	—	0.582	—	—	—	—
ΔC-peptide ≥6.0 ng/mL	0.596	—	0.211	—	—	—	—
HOMA-IR ≥1	1.627	—	0.346	—	—	—	—
HOMA-β <0.075	1.058	—	0.882	—	—	—	—

*Significance determined at $p < 0.050$.
β, index of β cell function; Δ, difference between OGTT and fasting values; HOMA, Homeostatic Model Assessment; IR, index of insulin resistance; OGTT, oral glucose tolerance test; values drawn 1 h after OGTT; OR, odds ratio.

endocrine evaluation for classification,[18,39,42-44] which can confound the number of diabetics both pre- and postoperatively, as many patients are unaware of their insidiously developing dysglycemia and might be identified as newly diabetic postoperatively.

Historically, the time period at which diabetes develops postoperatively varies from within 30 days[39] to 3.5 years postoperatively.[41] Diabetes developed within the first month in only 13 patients in our cohort, most requiring GCMs before discharge. Patients in whom diabetes would have developed regardless of operation would likely have had diabetes develop within the first 24 months. Kaplan-Meier survival analysis (Fig. 4) demonstrated no additional diabetes development at 60 and 80 months for nondiabetics and prediabetics, respectively.

The phenotype for preoperative nondiabetic patients included small Δ changes and retained insulin sensitivity in the pre- and postoperative phases except when evaluated with HOMA-IR (Table 2). Conversely, preoperative prediabetic patients demonstrated a 3-fold larger Δglucose, and 2-fold larger Δinsulin and Δc-peptide values, with insulin values demonstrating sensitivity alone. This trend was not present when comparing HOMA-IR and HOMA-insulin sensitivity in this group, which demonstrated insulin resistance in both phases but with postoperative improvement and decreasing Δglucose, Δinsulin, and Δc-peptide values. Preoperative prediabetic patients seem to have comparatively blunted postoperative response to operations, with improved insulin sensitivity after resection. This might be an effect of stress attenuation secondary to elevated blood glucose and insulin levels[45] preoperatively, or simply an effect of resection of an inflammatory source from the pancreatic head, allowing β-islets to return to homeostasis.[27]

The HOMA-β did not differ significantly in pre- and postoperative phases when stratified by preoperative diabetic classification, but decreased significantly, by approximately 25%, after resection across all postoperative classifications. This coincides with reduction of approximately 30% of the β-cell mass, which is located in the head of the pancreas.[23] When stratified by postoperative diabetic status, HOMA-β reflects resection but also the natural progression of islet cell failure with worsening classification—postoperative nondiabetics demonstrating the new baseline (70.0%), postoperative prediabetics demonstrating an increase in function, and postoperative diabetics demonstrating β-islet failure. This trend is also noted by impaired fasting glucose and insulin resistance with progressively worsening postoperative diabetic status (nondiabetic < pre-diabetic < diabetic) (Table 2). For patients with borderline endocrine laboratory results and low reserve, PD might be the deciding factor converting prediabetics into diabetics.

Interestingly, 25.0% of preoperative prediabetic patients returned to euglycemia and more than half retained their preoperative classification after resection, supporting the return of β-islet function after PD. These patients had borderline endocrine tests demonstrating prediabetes by American Diabetes Association classifications and small Δs for fasting and OGTT glucose. As with β-islet function, these patients might have been experiencing mild or new pancreatic inflammation caused by ductal obstruction, which resolved after pancreaticojejunostomy, allowing for a return to homeostasis.

Figure 3E demonstrates that PDAC and CP, pathologies classically associated with diabetes development, had a lower proportion of patients with diabetes developing compared with other malignant and benign indications, respectively. This indicates that early surgical intervention can prevent, or at least attenuate, the onset of dysglycemia and preserve β-islet function in nondiabetics and certain prediabetics. It is also interesting to note that pancreatic intraepithelial neoplasm, but not PDAC, and background pancreatitis, but not a primary diagnosis of CP, were identified as risk factors in tier 1 and tier 2 of the multivariate analysis.

We additionally investigated common factors that influence dysglycemia in the general population—age, race, and BMI. Interestingly, only advancing age and Asian race demonstrated a significant effect on outcomes. Body mass index likely did have an effect because diabetics were excluded from analysis. When diabetes developed postoperatively, patients demonstrated greater total weight loss overall, but fewer patients lost weight. Conversely, euglycemic patients lost less total weight but a higher number of patients demonstrated weight loss. Overall, weight loss in this cohort is likely an effect of altered intestinal anatomy, which resembles Roux-en-Y configurations and are known for attenuating diabetes and insulin resistance.[46] Diabetics were purposefully excluded from this analysis, which might explain why BMI did not reach significance in the final model. It was hypothesized that this might change with the inclusion of diabetic patients.

The strengths of this study are its prospective design, standardized surgical technique, and inclusion of a broad variety of pathologies, ultimately demonstrating outcomes that rely on preoperative glycemic status rather than pathologic or demographic data. The results of this study are generalizable and include risk factors that many surgeons and internists can readily evaluate. Endocrine analysis is essential for all patients undergoing PD, as antecedent diagnoses can confound postoperative results and lead to inappropriate risk stratification during consultation.

CONCLUSIONS

The development of diabetes after PD is multifactorial and pancreatic endocrine function is paramount for proper patient consultation and risk stratification. Diabetes develops primarily before 24 months in approximately 16.6% of patients undergoing PD. Pancreaticoduodenectomy has minimal effect on nondiabetics, but prediabetics are at increased risk for diabetes developing following resection. An A1c $\geq$5.4% was identified as an independent risk factor for the development of postoperative diabetes. Early intervention in nondiabetics and some prediabetics can attenuate or reverse dysglycemia after PD.

Author Contributions

Study conception and design: Maxwell, Jajja, Sarmiento
Acquisition of data: Maxwell, Jajja, Tariq, Mahmooth
Analysis and interpretation of data: Maxwell, Jajja, Tariq, Mahmooth, Galindo, Sarmiento
Drafting of manuscript: Maxwell, Jajja, Tariq, Mahmooth, Galindo, Sarmiento
Critical revision: Sweeney, Galindo, Sarmiento

REFERENCES

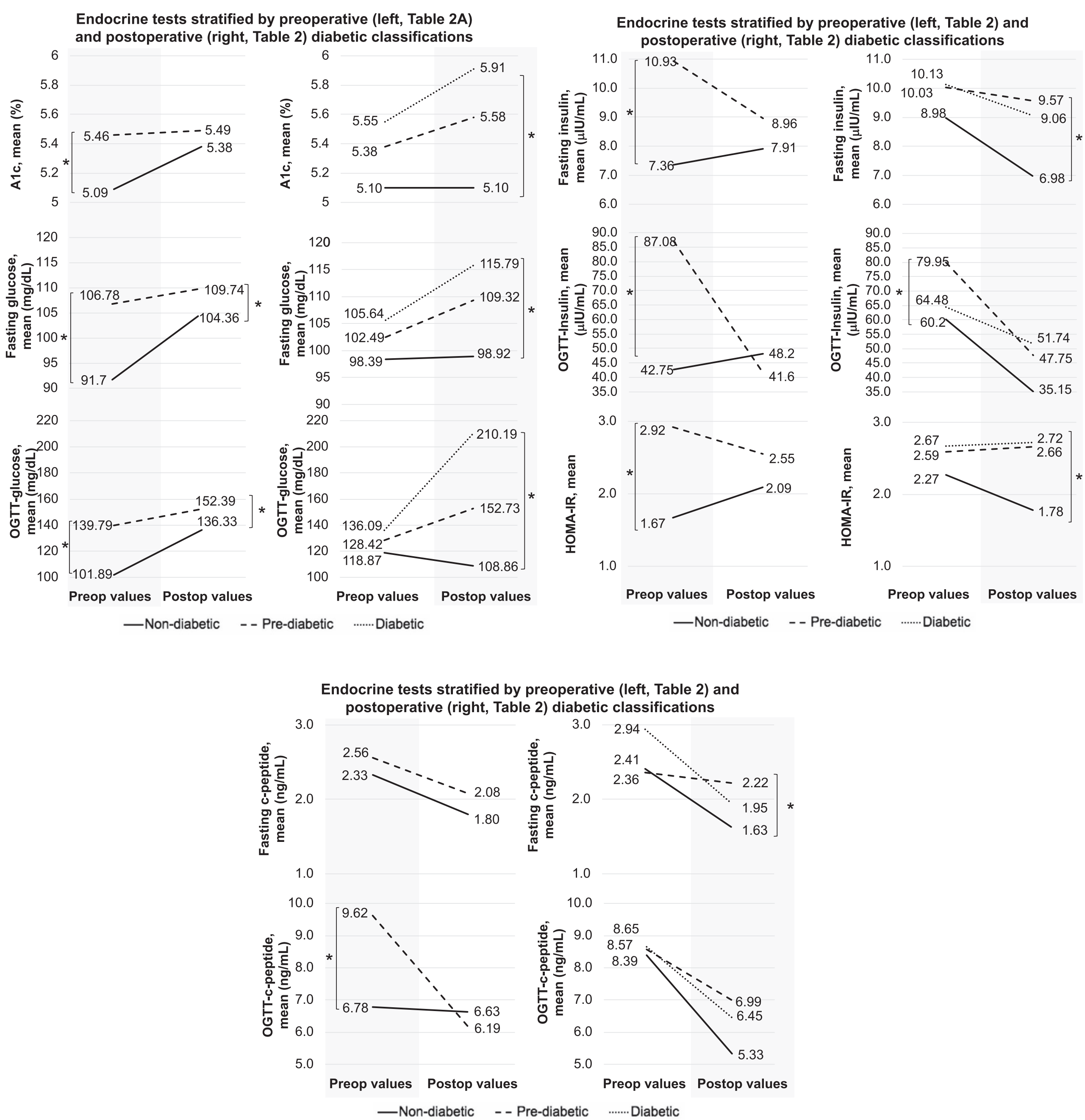
1. Burke JP, Williams K, Gaskill SP, et al. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. Arch Intern Med 1999;159:1450−1456.
2. Geiss LS, Pan L, Cadwell B, et al. Changes in incidence of diabetes in U.S. adults, 1997−2003. Am J Prev Med 2006;30:371−377.
3. CDC. Increasing prevalence of diagnosed diabetes—United States and Puerto Rico, 1995−2010. MMWR Morb Mortal Wkly Rep 2012;61:918−921.
4. CDC. National Diabetes Statistics Report, 2017 Estimates of Diabetes and its Burden in the United States Background. Atlanta, GA: CDC; 2017. Available at: http://www.diabetes.org/assets/pdfs/basics/cdc-statistics-report-2017.pdf. Accessed August 20, 2018.
5. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917−928.
6. Martin ET, Kaye KS, Knott C, et al. Diabetes and risk of surgical site infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016;37:88−99.
7. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes Care 2008;31:S165−S169.
8. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care 2015;38:S8−S16.
9. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. Diabet Med 1998;15:539−553.
10. Kausch W. Das carcinom der papilla duodeni und seine radikale Entfernung. Beitr Z Klin Chir 1912;78:439−486.
11. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935;102:763−779.
12. Beger HG, Gansauge F, Schwarz M, Poch B. Pancreatic head resection: the risk for local and systemic complications in 1315 patients—a monoinstitutional experience. Am J Surg 2007;194:S16−S19.
13. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg 2015;220:530−536.
14. Winter J, Cameron J, Campbell K, et al. 1423 Pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 2006;10:1199−1211.
15. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg 1990;211:447−458.

16. Schneider EB, Ejaz A, Spolverato G, et al. Hospital volume and patient outcomes in hepato-pancreatico-biliary surgery: is assessing differences in mortality enough? J Gastrointest Surg 2014;18:2105–2115.
17. Kumar AF, Gruessner RWG, Seaquist ER. Risk of glucose intolerance and diabetes in hemipancreatectomized donors selected for normal preoperative glucose metabolism. Diabetes Care 2008;31:1639–1643.
18. Burkhart RA, Gerber SM, Tholey RM, et al. Incidence and severity of pancreatogenic diabetes after pancreatic resection. J Gastrointest Surg 2015;19:217–225.
19. De Bruijn KMJ, van Eijck CHJ. New-onset diabetes after distal pancreatectomy. Ann Surg 2015;261:854–861.
20. Beger HG, Poch B, Mayer B, Siech M. New onset of diabetes and pancreatic exocrine insufficiency after pancreaticoduodenectomy for benign and malignant tumors. Ann Surg 2018; 267:259–270.
21. Sakata N, Egawa S, Rikiyama T, et al. Computed tomography reflected endocrine function of the pancreas. J Gastrointest Surg 2011;15:525–532.
22. Okano K, Murakami Y, Nakagawa N, et al. Remnant pancreatic parenchymal volume predicts postoperative pancreatic exocrine insufficiency after pancreatectomy. Surgery 2016;159:885–892.
23. Ionescu-Tirgoviste C, Gagniuc PA, Gubceac E, et al. A 3D map of the islet routes throughout the healthy human pancreas. Sci Rep 2015;5:14634.
24. Ikramuddin S, Billington CJ, Lee W-J, et al. Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomised, controlled trial. lancet Diabetes Endocrinol 2015;3:413–422.
25. Goldfine AB, Patti ME. Diabetes improvement following Roux-en-Y gastric bypass: understanding dynamic changes in insulin secretion and action. Diabetes 2014;63:1454–1456.
26. Lin E, Davis SS, Srinivasan J, et al. Dual mechanism for type-2 diabetes resolution after Roux-en-Y gastric bypass. Am Surg 2009;75:498–502; discussion 502–503.
27. Lin E, Liang Z, Frediani J, et al. Improvement in β-cell function in patients with normal and hyperglycemia following Roux-en-Y gastric bypass surgery. Am J Physiol Metab 2010; 299:E706–E712.
28. DeFronzo RA, Simonson D, Ferrannini E. Hepatic and peripheral insulin resistance: a common feature of type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1982;23:313–319.
29. Ferris HA, Kahn CR. Unraveling the paradox of selective insulin resistance in the liver: the brain-liver connection. Diabetes 2016;65:1481–1483.
30. Pendharkar SA, Walia M, Drury M, Petrov MS. Calcitonin gene-related peptide: neuroendocrine communication between the pancreas, gut, and brain in regulation of blood glucose. Ann Transl Med 2017;5. 419–419.
31. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–349.
32. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419.
33. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–1495.
34. Beck RW, Connor CG, Mullen DM, et al. The fallacy of average: how using HbA1c Alone to assess glycemic control can be misleading. Diabetes Care 2017;40: 994–999.
35. CDC. Defining Adult Overweight and Obesity. Available at. https://www.cdc.gov/obesity/adult/defining.html. Accessed November 1, 2018.
36. Menke A, Casagrande S, Cowie CC. Contributions of A1c, fasting plasma glucose, and 2-hour plasma glucose to prediabetes prevalence: NHANES 2011–2014. Ann Epidemiol 2018; 28:681–685.
37. Mendola ND, Chen T-C, Gu Q, et al. Prevalence of total, diagnosed, and undiagnosed diabetes among adults: United States, 2013-2016 key findings data from the National Health and Nutrition Examination Survey (NHANES). 2018. https://www.cdc.gov/nchs/data/databriefs/db319_table.pdf#3. Accessed November 6, 2018.
38. Owens WD, Felts JA, Spitznagel EL. ASA physical status classifications: a study of consistency of ratings. Anesthesiology 1978;49:239–243.
39. Ferrara MJ, Lohse C, Kudva YC, et al. Immediate post-resection diabetes mellitus after pancreaticoduodenectomy: incidence and risk factors. HPB (Oxford) 2013;15: 170–174.
40. Jimenez RE, Fernandez-del Castillo C, Rattner DW, et al. Outcome of pancreaticoduodenectomy with pylorus preservation or with antrectomy in the treatment of chronic pancreatitis. Ann Surg 2000;231:293–300.
41. Ishikawa O, Ohigashi H, Eguchi H, et al. Long-term follow-up of glucose tolerance function after pancreaticoduodenectomy: comparison between pancreaticogastrostomy and pancreaticojejunostomy. Surgery 2004;136:617–623.
42. Maignan A, Ouaïssi M, Turrini O, et al. Risk factors of exocrine and endocrine pancreatic insufficiency after pancreatic resection: a multi-center prospective study. J Visc Surg 2018;155:173–181.
43. Lim P-W, Dinh KH, Sullivan M, et al. Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. HPB (Oxford) 2016;18:360–366.
44. Huang JJ, Yeo CJ, Sohn TA, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 2000;231: 890–898.
45. Morgan KA, Lancaster WP, Walters ML, et al. Enhanced Recovery After Surgery protocols are valuable in pancreas surgery patients. J Am Coll Surg 2016;222:658–664.
46. Wu J-M, Kuo T-C, Yang C-Y, et al. Resolution of diabetes after pancreaticoduodenectomy in patients with and without pancreatic ductal cell adenocarcinoma. Ann Surg Oncol 2013;20:242–249.

eTable 1. Operative Pathology Stratified by Preoperative Diabetic Status

	Nondiabetic (n = 167)		Prediabetic (n = 236)		
Variable	**n**	**%**	**n**	**%**	**p Value***
Pancreas					
Pancreatic ductal adenocarcinoma	49	29.3	87	36.9	0.134
Chronic pancreatitis	24	14.4	40	16.9	0.494
Neuroendocrine tumor	15	9.0	15	6.4	0.341
Intraductal papillary mucinous neoplasm	10	6.0	13	5.5	0.999
Gastrointestinal stromal tumor	4	2.4	2	0.8	0.237
Serous cystadenoma	3	1.8	5	2.1	0.999
Pseudopapillary tumor	3	1.8	3	1.3	0.695
Metastatic colorectal cancer	2	1.2	0	0.0	0.171
No primary pathology	2	1.2	0	0.0	0.171
Mucinous cystadenoma	2	1.2	0	0.0	0.171
Pseudoaneurysm	2	1.2	0	0.0	0.171
Pseudocyst	2	1.2	1	0.4	0.572
Chronic pancreatitis, autoimmune type	1	0.6	1	0.4	0.999
Colloid carcinoma	1	0.6	1	0.4	0.999
Osteoclastic giant cell carcinoma	1	0.6	0	0.0	0.414
Xanthogranulomatous inflammation	1	0.6	0	0.0	0.414
Acinar cell carcinoma	0	0.0	2	0.8	0.513
Arteriovenous malformation	0	0.0	1	0.4	0.999
Intraductal oncocytic papillary neoplasm	0	0.0	1	0.4	0.999
Intraductal papillary mucinous adenocarcinoma	0	0.0	1	0.4	0.999
Lymphoepithelial cyst	0	0.0	2	0.8	0.513
Duodenum/ampulla					
Ampullary adenocarcinoma	16	9.6	25	10.6	0.867
Duodenal adenocarcinoma	7	4.2	5	2.1	0.248
Ampullary adenoma	4	2.4	1	0.4	0.165
Adenomatous ampullary hyperplasia	4	2.4	2	0.8	0.236
Duodenal adenoma	2	1.2	3	1.3	0.999
Ampullary abscess	0	0.0	1	0.4	0.999
Brunner's gland hamartoma	0	0.0	1	0.4	0.999
Duodenal infarction	0	0.0	1	0.4	0.999
Ectatic duodenal vasculature	0	0.0	1	0.4	0.999
Biliary tree					
Cholangiocarcinoma	5	3.0	16	6.8	0.113
Choledochal cyst	3	1.8	2	0.8	0.653
Medullary biliary carcinoma	1	0.6	0	0.0	0.414
Biliary pseudotumor	1	0.6	0	0.0	0.414
Intrad	0	0.0	1	0.4	0.999
Primary sclerosing cholangitis	0	0.0	1	0.4	0.999
Stomach					
Gastric adenocarcinoma	1	0.6	1	0.4	0.999
Other					
Gastroduodenal artery aneurysm	1	0.6	0	0.0	0.414

*Significance determined at a $p \leq 0.050$.



efigure 1. Pre- and postoperative endocrine evaluation laboratories stratified by diabetic status. Under each heading are laboratories strafied by preoperative diabetic status (left) and postoperative diabetic status (right). Diabetic patients only appear in postoperative trends (right) as these patients developed diabetes following pancreaticoduodenectomy. Preoperative diabetics were excluded from this manuscript. Significance denoted by * at a $p < 0.050$.