

ORIGINAL ARTICLE

Incidence and Implications of Impaired Glycemic Control Following Distal Pancreatectomy: A 10-Year Experience

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ABSTRACT

Background *De-novo* diabetes mellitus is an important consequence of distal pancreatectomy, and a better understanding of the frequency and risk factors for this outcome may allow alteration of the treatment course. The aim of this study was to define the relationship between the volume of pancreas resected and the development of pancreatic endocrine dysfunction following distal pancreatectomy. **Patients and Methods** We interrogated our prospectively-maintained pancreatic resection database to identify patients who underwent distal pancreatectomy from 2005 through 2015. Data on perioperative endocrine function, histopathology, demographics and pancreas resection volume were extracted and analyzed. **Results** 317 patients underwent distal pancreatectomy between 2005 and 2015. The incidence of *de-novo* diabetes mellitus was 14.7% (n=34). A high baseline body mass index was associated with development of diabetes mellitus (P = 0.017). However, neither patient demographics, the underlying pathology nor the volume of resected pancreas predicted the development of new onset diabetes mellitus. **Conclusions** *De-novo* diabetes mellitus is common following distal pancreatectomy regardless of resection volume or histopathological diagnosis. The presence of a high pre-operative body mass index is a statistically significant risk factor for developing *de-novo* post-operative diabetes mellitus and this is important for the consent process.

INTRODUCTION

The endocrine consequences of distal pancreatectomy (DP) are an evolving phenomenon. The development of *de-novo* DM is a well-documented complication of DP, however, the incidence rate reported is highly variable, ranging between 8% and 57%, depending on the length of follow-up reported [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. Endocrine dysfunction post-pancreatectomy may present as either worsening of pre-existing, or development of *de-novo* diabetes mellitus (DM). The American Diabetic Association (ADA) refers to *de-novo* DM as pancreatogenic or type 3c diabetes [1, 2].

Previous studies have hypothesized demographic and operative risk factors such as gender, body mass index (BMI), and volume of resected pancreas; however,

the results have been inconsistent [9, 12, 13, 14]. The understanding of *de-novo* DM after DP along with the associated perioperative risk factors is imperative, bearing in mind the substantial morbidity associated with DM, which is the seventh leading cause of death in the United States, and those with diabetes have double the overall risk of death than those without [1].

The aim of this study was to approach the question of the relationship between the volume of pancreas resected and the incidence of new onset DM utilizing precise pathological specimens instead of radiological measurements as performed in all prior studies. The secondary goals of this study were to identify significant baseline comorbidities associated with *de-novo* DM, and furthermore to examine the effect of patient demographics and the etiology of pancreatic disease on the incidence of *de-novo* DM following DP.

PATIENTS AND METHODS

The subjects of this study were identified from a prospectively-maintained, pancreatectomy database. The database contains details of all adult patients (≥ 18 years of age) who have undergone elective pancreatectomy at our institution, and for the purposes of this study, the period 2005 through 2015 was chosen for analysis. We only included patients who underwent a distal pancreatectomy \pm splenectomy for a pancreatic pathology. We excluded all patients who had a concomitant resection of other

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Abbreviations CP chronic pancreatitis, DM diabetes mellitus; DP distal pancreatectomy
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organs, and as such patients undergoing DP as part of a gastrectomy or during resection of a retroperitoneal sarcoma were excluded. All patients who met the inclusion criteria regardless of their preoperative diabetic status where included, patients without a preoperative diagnosis of diabetes where analyzed as a subgroup.

The patient's demographic data (gender, age, race, body mass index [BMI]) at the time of operation were documented as was any history of pancreatitis, exocrine pancreas insufficiency (EPI), or prior diagnosis of DM. EPI was defined as the primary or secondary disturbance of the exocrine pancreatic function leading to maldigestion, numerous invasive and noninvasive diagnostic tests are performed [15]. All patients who utilized pancreatic enzyme replacement therapy where identified as having EPI.

The patients BMI was calculated from weight and height measurements performed at the time of hospital admission prior to surgery.

The histopathological diagnosis was extracted from the final pathology report. The volume of resected pancreas was calculated by physician investigators using the three dimensions reported by anatomical pathologists in their report template. The resected pancreas volume was reported in cubic centimeters (cm³).

All available peri-operative random plasma glucose levels were recorded and analyzed. Patients with preoperative impaired glycemic control or DM were identified. Among the patients with normal preoperative plasma glucose levels we analyzed the postoperative levels and stratified them by development of *de-novo* DM postoperatively; i.e. "*de-novo* DM" and "no *de-novo* DM". The American Diabetic Association (ADA) guidelines were used to diagnose patients with DM namely: random plasma glucose levels of ≥ 200 mg/dL (11.1 mmol/L) or post hospital hemoglobin A1C $\geq 6.5\%$ (48 mmol/mol) [2]. Plasma glucose levels used for diagnosis of *de-novo* DM excluded any measurements taken after 72 hours post-operatively to account for physiological stress hyperglycemia secondary to inflammation [16]. If patients were on intravenous fluids at this stage, or were on enteral or parenteral nutrition then the glucose level used to confirm a diagnosis of DM was delayed until the patient was on an oral diet.

Categorical and continuous variables were reported as frequencies (n, %) and median (interquartile range), respectively. Due to the skewness of the variables' distribution we used Wilcoxon rank-sum tests and Kruskal-Wallis equality-of-populations tests to examine the significance of differences in patients who developed *de-novo* DM and who did not. Bivariate linear regression models were fit to examine the contribution of factors found to be significant (P<0.2) in the respective univariate analyses performed. A P<0.05 indicated the presence of a statistically significant association. All analyses were performed using IBM SPSS Statistics for Windows, Version 24 (IBM Corp., Armonk, NY., USA)

RESULTS

We identified a total of 327 patients who underwent DP between 2005 and 2015. We included 317 patients after applying the inclusion and exclusion criteria. There was a female predominance (n=188, 59.3%) in the study population with a median age of 62 (Interquartile Range [IQR] = 50.23 - 68.8) years. The median body mass index was 27 (IQR = 24 - 31) Kg/m².

The most common final pathological diagnoses were: pancreatic ductal adenocarcinoma [PDAC] (n=79, 24.9%); pancreatic neuroendocrine tumor (n=72, 22.7%); intraductal papillary mucinous neoplasm [IPMN] (n=57, 18%); chronic pancreatitis [CP] (n=52, 16.4%); and mucinous cystic neoplasm [MCN] (n=36, 11.4%) (**Table 1**). The median volume of tissue excised during DP was 92.9 cm³ (IQR = 51.9 - 157.7).

Assessing the incidence of *De-novo* DM by pathology, we noted that it was highest in patients with pancreatic ductal adenocarcinoma (n=12, 35.3%) followed by pancreatic neuroendocrine tumors (n=7, 20.6%), chronic pancreatitis (n=6, 17.6%) and mucinous cystic neoplasm (n=5, 14.7%) while none of the patients with serous cyst adenoma developed *de-novo* DM. Development of *de-novo* DM was independent of the histopathology of the pancreas resected (P>0.05).

Assessment of the correlation between the volume of pancreas resected and *de-novo* DM did not demonstrate an increased risk for the development of this complication as although patients with *de-novo* diabetes were noted to have larger volume resections than those who did not develop new diabetes, the difference was not statistically significant (P=0.693).

Neither gender nor age appeared to influence patients' risk of developing DM post-operatively. The median BMI of patients who developed *de-novo* DM post was however significantly greater than those who did not (30 Kg/m² versus 27 Kg/m²; P=0.017).

DISCUSSION

Understanding the true incidence and risk factors for the development of diabetes in the post-operative period should lead to better and more predictable outcomes for patients undergoing distal pancreatectomy. Being able to accurately counsel patients regarding potential post-operative challenges is increasingly important as the number of pancreatic resections performed annually in the USA exceeds 10,000 cases [17]. Postoperative diabetes was found to have the largest negative impact on leisure and physical activities during a study examining quality of life after partial pancreatic resection [18].

The primary finding of the study was the identification of a significant incidence of post-operative *de-novo* DM in our study population at 14.7%. This result is lower than the systematic review of 1,731 patients by De Bruijn *et al.* which reported an incidence of 39% in patients undergoing resection for CP and 14% in patients without CP [18, 19].

Table 1. Patient characteristics be development of *de-novo* diabetes mellitus post-distal pancreatectomy.

	<i>De-novo</i> DM	No <i>de-novo</i> DM	p-value
Median Age, y [IQR]	62 [53 – 67]	61.5 [49.8 - 69]	0.987
Female, n (%)	21 (61.8)	167 (59)	
Median BMI [IQR]	30 [26 – 34.3]	27 [23 - 31]	0.017
Median Resection Volume, cm ³ [IQR]	91.9 [54.4 – 183.7]	92.9 [50 -154.5]	0.693
Final Pathology, n (%)			0.431
PDAC	12 (35.5)	67 (23.7)	
CP	6 (17.6)	46 (16.3)	
IPMN	3 (8.8)	54 (19.1)	
MCN	5 (14.7)	31 (11)	
PNET	7 (20.6)	65 (23)	
SCN	0	15 (5.3)	
SPEN	1 (2.9)	5 (1.8)	
Median Length of Stay [IQR]	6.5 [5 – 8.3]	6 [5 – 7]	0.159

BMI body mass index; CP chronic pancreatitis; IPMN intraductal papillary mucinous neoplasm; IQR interquartile range; MCN mucinous cystic neoplasm; PDAC pancreatic adenocarcinoma; PNET pancreatic neuroendocrine tumors; SCN serous cystadenoma

Table 2. Incidence of *de-novo* diabetes post-distal pancreatectomy in the literature.

Author	Country	Year of publication	Number of patients	Pathology	Incidence of NODM	Length of Follow up
Lillemoe [3]	USA	1999	235	24% CP 75% tumors 1% other	19/235 (8.1%)	NR
Lee [4]	South Korea	2010	188	70% tumor 30% other	20/188 -10.6%	34.5 months (mean)
Irani [5]	USA	2008	171	78% tumor 11% other 11% CP	6/171 (3.5%)	NR
Sakorafas [6]	USA	2001	135	100% CP	65/135 -48.2%	80 month (mean)
King [7]	USA	2008	125	8.8% CP tumors 92%	10/111 (8%)	21 months (median)
Shoup [8]	USA	2002	125	7.2% CP tumors 15.2% Other	6/125 -4.8%	21 months (median)
Kang [9]	South Korea	2015	101	5.9% CP 91.1% tumor 3% other	25/101 (24.8%)	12 months minimum

CP chronic pancreatitis; NR not reported

When isolating all published series that included over 100 patients, we found the mean incidence of *de-novo* DM to be 15.4% (Table 2).

In order to try not to overcall the incidence of DM in the early postoperative period, we excluded plasma glucose levels prior to 72 hours post-operatively. This decision was instituted based on the findings of Davis *et al.* who found the incidence of stress hyperglycemia in the general surgery population increased daily for the first 72 hours. Additionally for patients requiring prolonged intravenous support, or enteral/parenteral nutrition the glucose levels used to define DM were taken once those patients had resumed a solid diet.

Interestingly, we did not see any correlation between the volume of pancreatic resection and risk of developing post-operative *de-novo* DM. This potential relationship has been demonstrated in several studies, although, no relationship has yet been established by gross specimen volume [1, 7, 20]. In the current study we calculated the volume of the resected pancreas whereas prior studies that reported a correlation used percentage of total pancreatic parenchyma [1, 7, 20]. Shirakawa *et al.* and Kang *et al.* both found the volume of pancreatic tissue to be an independent risk factor of *de-*

novo post-operative DM by measuring resection volume by computed tomography volumetry [9, 13].

Our results affirm the findings of Kang *et al.* who reported high BMI is a pre-operative risk factor for *de-novo* DM after DP [9]. High pre-operative BMI can also be implicated in other perioperative complications as established by Tee and colleagues, who investigated the outcomes of elective distal pancreatectomy in patients with metabolic syndrome, their principle findings included a 42% greater odds of major morbidity (P<0.01), 59% greater odds of deep/organ space surgical site infection (P<0.01), and two-fold greater odds of respiratory failure (P<0.01) [21]. The effects of pre-operative obesity are not limited to the consequences of glucose metabolism they also have an association with pancreatic steatosis which is a known risk factor for developing pancreatic fistulas after elective partial pancreatectomy [22, 23, 24, 25].

Although our results determine there is not a statistically significant correlation with the volume of pancreas resected and the incidence of *de-novo* DM there are limitations to this conclusion, most notably the standardization and length of follow up. Requisition of long term outcomes were difficult due to out initiation

being a quaternary referral center where often many of our patients do not follow up with primary care physicians in our health system. Our study analyzed preoperative and post-operative serum plasma glucose levels which are more difficult to establish plasma glucose trends from when compared to serum hemoglobin A1c levels. Future studies may benefit from incorporating pre-operative serum hemoglobin A1c values into their protocols to examine the predictive nature of preoperative plasma glucose control on post-operative outcomes.

The high prevalence of obesity and the associated risk factors of developing *de-novo* DM when entering the operating room with a high BMI give this study important clinical implications, the most notable being the need to diligently monitor patients with high BMI's for *de-novo* DM after distal pancreatectomy. Diabetes has been shown to be a predictor of worse survival in all stages of disease and specifically is associated with negative clinical outcomes in those with pancreatic ductal adenocarcinoma and those undergoing elective distal pancreatectomy [26, 27, 28].

CONCLUSION

De-novo diabetes is common following DP but its development is independent of the size of the resection specimen. Furthermore, patient demographic factors, and the histopathological diagnosis did influence the incidence of *de-novo* DM. It would however appear that a high pre-operative BMI is a significant risk factor for developing *de-novo* post-operative DM, and obese patients should be counseled as to a higher risk for diabetes, and be closely monitored for the development of this important complication. The association of DM and individual pancreatic pathologies of both benign and malignant disease may indicate that there is subclinical DM prior to surgery, possibly due to parenchymal obstruction and destruction that is not appreciated clinically. This important finding requires further evaluation in a detailed prospective study.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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