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New Onset Diabetes in Patients Undergoing Pancreatic Resection at Two Academic Institutions

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Abstract

Objectives: Pancreatic surgeries are commonly performed for benign and malignant lesions; however, the incidence of New-Onset Diabetes (NODM) post-pancreatectomy is unknown.

Design and Setting: A retrospective data review was performed on patients who underwent pancreatectomy from 1/1/2004 to 12/31/2015 at North Shore University Hospital and Long Island Jewish Hospital using ICD-9 codes. Patients who had preoperative and postoperative Hemoglobin A1c (HbA1c) values were included in our analysis.

Participants: 383 pancreatic resections were performed at North Shore University Hospital and Long Island Jewish Hospital.

Primary and Secondary Outcomes: Of the 383 patients, all but two patients had a pancreatectomy, 60% of which were malignant. Only 52 patients without diabetes had their Hemoglobin A1c (HbA1c) checked both pre and post-operatively. Of these patients, 20 patients (38.5%) had an HbA1c $\geq$ 6·5% and developed new onset diabetes. There was no association with new onset diabetes and risk factors such as gender, ethnicity, smoking, alcohol use, benign versus malignant conditions or type of pancreatic surgery. However, when patients were compared on age, significantly younger patients developed new onset diabetes compared to patients who did not develop new onset diabetes (56 vs. 70, respectively; p=0.0451).

Interpretation: Post-pancreatectomy patients are at significant risk for developing new onset diabetes, and the incidence in this study cohort was similar to other published studies. Younger patients had a higher risk of developing new onset diabetes but there were no other risk factors that could be risk stratified for developing pancreatogenic diabetes.

Keywords: New onset diabetes; Pancreatectomy; Pancreatogenic diabetes; Pancreatic surgery

Background

Historically, diabetes has been defined as autoimmune destruction of the pancreas (Type 1 Diabetes) or insulin resistance (Type 2 diabetes), however, this dichotomy no longer exists. Diabetes Type 3c or pancreatogenic diabetes has been observed in persons with loss or destruction of the endocrine parenchyma; interestingly enough, the endocrine portion of pancreas comprises less than 5% of total pancreas volume [1].

Conditions such as pancreatitis, cystic fibrosis, trauma, hemochromatosis or malignancy have been implicated in Type 3c Diabetes; also through surgical interventions like pancreatectomy and other procedures used to treat these disorders [2]. Pancreatic surgery is the standard procedure for most benign and malignant lesions of the pancreas, and can be performed with low morbidity and mortality rates, especially when performed by experienced surgeons with high operative volumes and through less invasive techniques such as laparoscopic and robotic surgery [3]. A majority of pancreatic surgeries are performed for benign diseases, most patients have prolonged survival, which puts them at risk to develop pancreatogenic diabetes or worsening of their pre-existing diabetes [4]. The rate of post-pancreatectomy diabetes can vary depending on the portion and percentage of the pancreas resected, and the risk increases over time [1,5-7]. The minimum amount of residual pancreas needed to preserve normal glucose homeostasis

is unknown. Rates of post-operative pancreatogenic diabetes can vary from 5% to 9% in patients with presumably normal pancreatic parenchyma, to 25% to 50% in patients undergoing distal pancreatectomy for chronic pancreatitis [8].

Some surgeons have performed a so-called 'central pancreatectomy' to preserve the normal pancreatic tissue in the body and tail of the pancreas that would normally be respected. The proposed benefit under this approach is the preservation of pancreatic function and the spleen, making the patient less likely to develop postoperative diabetes mellitus. The limitations, however, are that these patients are more likely to develop *anastomotic* leaks and fistulas [1,9].

Therefore, understanding the incidence of post-operative diabetes for patients undergoing distal pancreatectomy and pancreaticoduodenectomy are important; however, it is challenging to determine since reported rates of diabetes vary, even among patients undergoing the same procedure (i.e., pancreaticoduodenectomy) where there is minimal variation in the proportion of gland removed [1]. Small sample sizes are also a limiting factor in the majority of studies reporting on the long-term incidence of pancreatogenic diabetes. The severity of diabetes, the type of pancreatic resection and length of follow-up are often missing in published reports as well [10-13].

The goal was to fill these holes in the literature with this retrospective study. The goal of this study was to examine the incidence of post-pancreatectomy diabetes, as well as determine the rate of post-pancreatectomy diabetes and look for associated risks factors.

Materials and Methods

Study Design and Setting

The study was approved by the Institutional Review Board (IRB) at North well Health, Hofstra University School of Medicine. A retrospective review was performed on patients who underwent pancreatectomy from 1/1/2004 to 12/31/2015. Patients who underwent pancreatectomy at North Shore University Hospital and Long Island Jewish Hospital were identified using ICD-9 codes. The incidence of new onset postoperative diabetes was the primary outcome measured. Hemoglobin A1c (HbA1c) ≥ 6.5%. defined New Onset Diabetes Mellitus (NODM). The other standard diagnostic criteria: fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) following a 75-gram oral glucose tolerance test and patients with symptoms of hyperglycemia with a random glucose level ≥ 200 mg/dL (11.1 mmol/L) were not used [14].

Secondary outcome data was included: patient demographics (age, ethnicity, sex, BMI), smoking and alcohol use, history of pre-operative diabetes, co-morbidities, type of pancreatic resection, operative indication (malignant disease vs. benign disease, and chronic pancreatitis), perioperative transfusion requirements, perioperative complications, chemotherapy or radiation use, disease recurrence, mortality, and new need for diabetes medications within 30 days of surgery. Of note, the HbA1c values were obtained only in patients undergoing pre-surgical laboratory analysis within our institution.

Patients were required to have preoperative and postoperative HbA1c values to be included in our core analysis. Patients who had preoperative diabetes were placed in another category and analyzed separately. Results after pancreaticoduodenectomy and distal pancreatectomy were examined collectively. All patients who underwent total pancreatectomy and who developed insulin-dependent diabetes were removed from the final analysis.

Statistical Analysis

Continuous data were reported as mean ± standard deviation or median and interquartile range (25^{th},75^{th} percentiles). Categorical data were reported as frequency and percentages. Fisher's Exact test was used to examine the association between categorical demographic and operative variables and group (operationalized as partial vs. complete removal of pancreatic tissue). The Mann-Whitney Wilcoxon test was used to compare continuous demographic variables, operative data and length of hospitalization with respect to group status. Statistical significance was achieved at $p<0.05$. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

From January 1, 2004, to December 31, 2015, 383 pancreatic resections were performed at North Shore University Hospital (71%) and Long Island Jewish Hospital (29%). Of the 383 patients, 2 patients had total pancreatectomy and 380 patients had partial pancreatectomy (1 patient was missing). As expected, both patients who had total pancreatectomy developed insulin dependent diabetes.

Demographics, Co-morbidities and Pathology

Demographic data were collected for all patients who underwent pancreatic surgery (Table 1). Out of 383 patients, 164 (43%) were male and 219 (57%) were female; mean age (SD) was 64 (13.5). The bulk of the patients identified as Caucasian, followed by African-American, Hispanic, East Asian, multiracial, and other. The average pre-operative body mass index was 27.0 (ranging from 14 to 56.7). Nearly half (46%) of the sample reported a history of alcohol use, or a history of smoking (52.2%). Together, more than 80% of the sample had a tumor either in the head of the pancreas (46.9%) or in the tail (33.9%) (Table 2). Among 381 patients, malignancy (60.6%) was diagnosed more than benign pathology (39.4%) (Tables 3,4). Of 380 patients who had partial

pancreatectomy, most patients had a *pancreatoduodenectomy* (38.3%) or distal pancreatectomy (39.8%); the remaining patients underwent either subtotal pancreatectomy, other surgeries, or had data missing (Table 5). With regard to treatment, 83 out of 325 patients reported a history of chemotherapy (26%, 58 were missing) and 55 out of 325 patients with radiation (17%, 58 were missing).

Patient Data, Total Study Population	
Demographics, Comorbidities and Pathology	
Male Gender	164/383 (43%)
Caucasian/White*	239 (62.4%)
African-American/Black	61 (16%)
Hispanic	33 (8.6%)
Eastern Asian	23 (6%)
Multiracial	11 (2.9%)
Indian/South Asia	7 (1.8%)
Arab/Middle Eastern	2 (0.5%)
Other Race/Ethnicity	19 (5%)
Mean BMI	27 ± 6.1
History of Diabetes Mellitus - Yes	119/383 (31%)
Presence of Hepatic Steatosis	54/336 (16%)**
History of Alcohol - Yes	166/362 (46%)**
History of Smoking- Yes	191/366 (52.2%)**
History of Chemotherapy - Yes	83/325 (25.5%)**
History of Radiotherapy - Yes	55/325 (17%)**
Disease Recurrence Post-Resection	84/324 (26%)**

Table 1: Baseline Characteristics

*Note: Racial/Ethnic categories are mutually inclusive and will not add to 100%.

**Denotes missing data

Site of Pancreatic Tumor (total n=354, 29 missing)	
Head	166 (46.9%)
Tail	120 (33.9%)
Body	40 (11.3%)
Multifocal	25 (7.1%)
Neck	3 (0.8%)

Table 2: Site of Pancreatic Tumor.

Disease Type (total n=162)*	Frequency
Pancreatitis	28
Intraductal Papillary Mucinous Neoplasm (IPMN)	26
Mucinous Cystic Neoplasm (MCN)	26
Serous cystadenoma	24
Pseudocyst	16
Benign neuroendocrine tumor	10
Benign islet cell tumor	6
Other	26

Table 3: Frequency of Benign Pancreatic Disease

*Note: Some patients may have had multiple benign lesions

Disease Type (total n=235)*	Frequency
Adenocarcinoma	150
Malignant neuroendocrine tumor	31
Metastases	16
Malignant islet cell tumor	6
Lymphoma	3
Cystadenocarcinoma	3
Other	26

Table 4: Frequency of Malignant Pancreatic Disease

*Note: Some patients may have had multiple malignancies

Type of Pancreatic Surgery (total n=379, 4 missing)	
Distal	151 (39.8%)
Whipple	145 (38.3%)
Subtotal	11 (2.9%)
Other*	72 (19.0%)

Table 5: Type of Pancreatic Surgery

*Other including cystgastrotomies, enucleation and necrosectomies

Hemoglobin A1c (HbA1c) testing

Out of 383 patients, 26 patients had their HbA1c checked on admission while 357 patients did not. Because HbA1c was not listed as a diagnostic criterion for diabetes until 2010, it was acknowledged that checking HbA1c may not have been standard of care prior to 2010 [15]. After 2010, 10 patients had their HbA1c checked, while 134 patients did not. There were also many patients without HbA1c checked post-operatively. After 2010, 62 patients (42%) had their HbA1c checked and 87 patients (58%) did not.

Outcomes in Patients without a Preoperative Diagnosis of Diabetes

Data were collected from 52 patients who had no history of diabetes and had their HbA1c checked after surgery. Twenty patients (38%) had a HbA1c ≥ 6.5% while 32 patients (62%) did not. Analysis of the association of NODM with any of the demographic variables, pancreatic disease or type of resection yielded no significant relationships. There was no association with new onset diabetes and gender (p=0.77), ethnicity (p=0.69), presence of hepatic steatosis (p=0.71), smoking history (p=0.25), or alcohol history (p=0.54). There was also no significant association between benign versus malignant disease with new onset diabetes (p=0.26), or type of pancreatic resection (p=0.14) (Table 6). Another analysis was performed to see if there was an association with NODM and mortality rate, and found that there was no significance (p=0.74). There was however a significant difference in the age distributions between the patients who developed NODM. The results indicate that the median age of patients with NODM is significantly younger than patients without new onset diabetes (55.5 vs. 69.5, respectively; p=0.045).

Type of Pancreatic Surgery	New Onset Diabetes		
Frequency Col (Pct)	**No**	**Yes**	**Total**
Whipple	12 (37.50%)	2 (10.00%)	14
Subtotal	1 (3.13%)	1 (5.00%)	2
Distal	14 (43.75%)	13 (65.00%)	27
Other*	5 (15.60%)	4 (20.00%)	9
Total	32	20	52

Table 6: Association of Type of Partial Pancreatic Resection and New Onset Diabetes.

Outcomes in Patients with a Preoperative Diagnosis of Diabetes Mellitus

One hundred and nineteen patients out of 383 (31%) had a history of diabetes before pancreatic surgery. There was a significant association between mortality and history of diabetes; a higher percentage of patients with a history of diabetes died compared to those who lived (38.5% vs. 25%; p=0.007).

Discussion

An increasing number of patients are undergoing pancreatic surgeries as the prevalence of pancreatic cancer increases, [16] and although the perioperative outcomes of patients undergoing these procedures are improving, the risk of developing NODM should be considered. Pancreatogenic diabetes is distinct from type 1 and type 2 diabetes since there is both a reduction in alpha, beta, delta and pancreatic polypeptide cells, not simply the beta cells. Decreased pancreatic polypeptide levels, whose impact is relatively unknown, and alpha cells that produce glucagon, can lead to a diminished response to hypoglycemia and subsequent "brittle diabetes" [8,17].

In a review of the literature, the percentage of patients who developed NODM post-pancreatectomy varied between 4 to 73% [1]. A recent systematic review evaluated the incidence of NODM after distal pancreatectomy, and included twenty-six studies which comprised 1,731 patients who underwent distal pancreatectomy. Authors found that the average cumulative incidence of new onset diabetes after distal pancreatectomies performed for chronic pancreatitis was 39%, and for benign or potentially malignant lesions, 14%. The average percentage of insulin-dependent diabetes among patients with new onset diabetes was 77% [18].

In this study, it was recognized that HbA1c was not measured frequently enough, especially in the subgroup of patients who underwent pancreatic surgery. The hospitals have since changed our approach with these patients and require pre-surgical testing, which includes measuring HbA1c levels. Also, a considerable number of patients did not have their HbA1c checked post-operatively, which is alarming. All providers should be aware of the implications of pancreatic surgery, and require HbA1c measurements post-operatively as well.

In the cohort of patients in two academic institutions, NODM occurred in 38% of our patients who underwent partial pancreatectomy, which is consistent with other published studies [5,19-21]. These results indicated that patients who developed new onset diabetes after their surgery were significantly younger than those who did not. It is unclear why this occurred, but we hypothesize that younger patients may have been followed for a longer time period. There was no association with new onset diabetes and mortality and/or other risk factors (i.e., BMI, type of pancreatic disease, ethnicity, etc.).

There was a significant association between mortality and history of diabetes, which is consistent with multiple studies published in the literature [22,23]. This subgroup of patients should be counseled on the importance of diabetes management.

Limitations

The reported findings should be interpreted with caution as there were several limitations in the study. Although there was a large group of patients undergoing pancreatic resections, due to the spotty availability of both operative and postoperative HbA1c measurements, only a small subset of patients (n=52) could be included in the core analysis. There was no indicator of time in

patients who developed new onset diabetes. HbA1c was the only diagnostic criterion for diabetes, which, as mentioned before, was not part of the diagnostic criteria until 2010. Some of the patients may have been treated outside of our institution, which limited data collection. The review was unable to quantify the amount of the pancreas that was resected, or the actual mass (weight) of the pancreatic parenchyma removed. It was unclear if the patients had any hemoglobinopathies or blood transfusions, which may influence the HbA1c values. Lastly, the study was not able to differentiate between patients who developed pancreatogenic diabetes due to pancreatic resection versus the development of type 2 diabetes due to systemic disease.

Conclusion

Post-pancreatectomy patients are at significant risk for developing NODM, and the incidence in our study cohort was similar to other studies published in the literature. Preoperative and postoperative HbA1c values need to be evaluated routinely. The study demonstrated that all patients undergoing a pancreatectomy who reported having had a history of diabetes were at a higher risk for death and that younger patients were at a higher risk of developing new onset diabetes. Given this high risk, all patients, particularly younger patients, should be counseled on the long-term risks of pancreatectomy as it relates to the development of diabetes.

References

1. King J, Kazanjian K, Matsumoto J, Reber HA, Yeh MW, et al. (2008) Distal pancreatectomy: incidence of postoperative diabetes. J Gastrointest Surg 12: 1548-1553.
2. Association AD (2014) Standards of Medical Care in Diabetes-2014. Diabetes Care 37: S14-S80.
3. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, et al. (2007) Perioperative mortality for pancreatectomy: a national perspective. Ann Surg 246: 246-253.
4. Burkhart RA, Gerber SM, Tholey RM, Lamb KM, Somasundaram A, et al. (2015) Incidence and severity of pancreatogenic diabetes after pancreatic resection. J Gastrointest Surg 19: 217-225.
5. Lillemoe KD, Kaushal S, Cameron JL, Sohn TA, Pitt HA, et al. (1999) Distal pancreatectomy: indications and outcomes in 235 patients. Ann Surg 229: 693-698.
6. Ishikawa O, Ohigashi H, Eguchi H, Yokoyama S, Yamada T, et al. (2004) Long-term follow-up of glucose tolerance function after pancreaticoduodenectomy: comparison between pancreaticogastrostomy and pancreaticojejunostomy. Surgery 136: 617-623.
7. Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, et al. (2000) Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 231: 890-898.
8. Maeda H, Hanazaki K (2011) Pancreatogenic diabetes after pancreatic resection. Pancreatol 11: 268-276.
9. Hines OJ, Reber HA (2000) Median pancreatectomy: do the risks justify the effort? J Am Coll Surg 190: 715-716.
10. Berney T, Rüdisühli T, Oberholzer J, Caulfield A, Morel P (2000) Long-term metabolic results after pancreatic resection for severe chronic pancreatitis. Arch Surg 135: 1106-1111.
11. Slezak LA, Andersen DK (2001) Pancreatic resection: effects on glucose metabolism. World J Surg 25: 452-460.
12. Parra Membrives P, Díaz Gómez D, Martínez Baena D, Lorente Herce JM (2011) [Blood glucose control and risk of progressing to a diabetic state during clinical follow up after cephalic duodenopancreatectomy]. Cirugia Espanola 89: 218-222.
13. Litwin J, Dobrowolski S, Orłowska-Kunikowska E, Sledziński Z (2008) Changes in glucose metabolism after Kausch-Whipple pancreatectomy in pancreatic cancer and chronic pancreatitis patients. Pancreas 36: 26-30.
14. Association AD (2018) 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care 41: S13-S27.
15. Standards of Medical Care in Diabetes-2010 | Diabetes Care [Internet]. [cited 2018 Jul 6]. Available from: http://care.diabetesjournals.org/content/33/Supplement_1/S1116. 1.
16. USCS Data Visualizations [Internet]. [cited 2018 Aug 26]. Available from: https://gis.cdc.gov/grasp/USCS/DataViz.html
17. Cui Y, Andersen DK (2011) Pancreatogenic Diabetes: Special Considerations for Management. Pancreatology 11: 279-294.
18. De Bruijn KMJ, van Eijck CHJ (2015) New-onset diabetes after distal pancreatectomy: a systematic review. Ann Surg 261: 854-861.
19. Adam U, Makowiec F, Riediger H, Trzeczak S, Benz S, et al (2001) [Distal pancreatic resection--indications, techniques and complications]. Zentralbl Chir 126: 908-912.
20. Balzano G, Zerbi A, Veronesi P, Cristallo M, Di Carlo V (2003) Surgical treatment of benign and borderline neoplasms of the pancreatic body. Dig Surg 20: 506-510.
21. Belyaev O, Herzog T, Chromik AM, Meurer K, Uhl W (2013) Early and late postoperative changes in the quality of life after pancreatic surgery. Langenbecks Arch Surg 398: 547-555.
22. Brown RE, Riddell MC, Macpherson AK, Canning KL, Kuk JL (2014) All-cause and cardiovascular mortality risk in U.S. adults with and without type 2 diabetes: Influence of physical activity, pharmacological treatment and glycemic control. J Diabetes Complications 28: 311-315.
23. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, et al. (2014) Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA Intern Med 174: 251-258.