Impact of Diabetes Mellitus on the Outcomes After Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma: A Single Center Experience

Ayman El Nakeeb, Ahmed Shehta, Rami Said, Mohamed El Dosoky, Ahmed Moneer, Mohamed Elrefai, Hosam Hamed, Talaat Abd Allah

Corresponding author:

Ayman El Nakeeb, MD
Professor of general surgery,
hepatobiliary and pancreatic surgery
Gastroenterology Surgical Center
Mansoura University, Egypt
E-mail: elnakeebayman@yahoo.com

Gastroenterology Surgical Center, Mansoura University, Egypt

ABSTRACT

Purpose: Pancreatic ductal adenocarcinoma is a life-threatening health problem. Surgical excision is the principal step of multimodal treatment, but it is associated with poor outcomes. At the time of diagnosis, up to 80% of those patients have impaired glucose tolerance or diabetes mellitus. The role of pre-operative diabetes mellitus on the outcomes after pancreaticoduodenectomy is still unclear.

Method: We reviewed the data of patients who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. Patients were divided into 2 groups according to presence or absence of preoperative diabetes mellitus.

Results: Our study included 451 patients. Diabetes mellitus group included 113 patients (25.1%), and non-diabetes mellitus group included 338 patients (74.9%). More firm pancreas was found in diabetes mellitus group, and more clinically relevant postoperative pancreatic fistula was found in non-diabetes mellitus group. There was more delayed gastric emptying, and wound infection in diabetes mellitus group. The long-term outcomes were comparable between groups regarding the overall ($p=0.55$) and disease-free survival rates ($p=0.972$).

Conclusion: Preoperative diabetes mellitus did not affect the perioperative outcomes after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. Preoperative diabetes mellitus is not associated with postoperative pancreatic fistula; however, it is significantly associated with delayed gastric emptying and wound infection.

Key words: diabetes mellitus, pancreaticoduodenectomy, pancreaticogastrostomy, pancreaticojejunostomy, pancreatic fistula

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a life-threatening health problem/condition that poses substantial challenges in its management. It is the 10th most common cancer worldwide, and the 4th main cause of cancer-related death (1).

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Although many patients have an unresectable disease at the time of diagnosis, radical surgical excision is the principal step of multimodal treatment to achieve adequate long-term outcomes (2).

Post-operative morbidity after pancreatic resection still high with poor survival outcomes even with advancement in perioperative care (3, 4).

Several risk factors have been identified to be associated with the development of post-operative morbidity and poor long term outcomes, but the role of pre-operative diabetic status in this setting is still unclear. At the time of diagnosis, up to 80% of PDAC cases have either impaired glucose tolerance or clinically manifest diabetes mellitus (DM) (5, 6). On the other hand, it is unclear whether preoperative DM is a predisposing factor or a possible consequence of PDAC, or both.

Few studies have evaluated the impact of preoperative DM on perioperative and long term outcomes after pancreatic resection for PDAC. The results of these studies are very controversial, and most of them included tumors that are located in all parts of the pancreas (7-10). We aimed to evaluate the impact of preoperative DM on the perioperative and long term outcomes of patients who underwent pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma of the pancreatic head in a tertiary high volume center.

PATIENTS AND METHODS

Study Design

We retrospectively reviewed the data of all patients who underwent PD for periampullary tumors at Gastroenterology Surgical Center, Mansoura University, Egypt during the period between January 1993 and December 2016. Patient data were reviewed from a prospectively maintained database for all patients undergoing PD since 2000 and before 2000, the data were reviewed from the archive files of the patients. A written informed consent for the surgical procedures was obtained from each patient.

Patients with pathologically confirmed PDAC were only included in this study, while other periampullary tumors were excluded. Patients were divided into two groups according to the presence or absence of pre-operative DM. Faculty of Medicine, Mansoura University review board approved this study.

Preoperative assessment

Preoperative assessment included clinical, laboratory and radiological evaluation as described in previous studies (11, 12).

Surgical procedures

The surgical technique including dissection and reconstructions is described in previous studies (12, 13).

Postoperative care and follow up

Post-operatively, all patients received intra-venous antibiotics and proton pump inhibitors. Somatostatin analogues were administered in some selected cases (100 µg subcutaneously every 8 hours). Clinical and radiological follow up were performed postoperatively.

In patients with smooth post-operative course oral intake was resumed on the 4th post-operative day then oral solid food afterwards.

After discharge, patients were followed up after 1 week in outpatient clinic. They were scheduled for routine follow up visits at 1, 3, 6 month after surgery, then every 6 month. Follow up visits included complete clinical evaluation, laboratory evaluation including tumor markers (CA 19-9), and radiological evaluation (abdominal ultrasonography and/or triphasic computed tomography).

Clinical outcomes

Diagnosis of DM was made according to clinical history and past laboratory tests based on the 2010 American Diabetes Association criteria (14). Patients with a known history of DM, a preoperative fasting blood glucose level ≥ 126 mg/dL, or two or more outpatient random blood glucose levels ≥ 200 mg/dL were included into the DM group. For patients with only inpatient preoperative laboratory results, those with two or more serum measurements ≥ 200 mg/dL obtained before 7:00 AM were also included into the DM group. Only laboratory analyzed blood samples were considered. Blood glucose measurements by routine glucose meters were not considered.

Postoperative morbidity was defined and graded according to the Clavien-Dindo classification (15).

Post-operative pancreatic fistula (POPF), delayed gastric emptying (DGE), biliary leakage were defined according to the International Study Group for Pancreatic Fistula (ISGPF) (16-18).

Postoperative mortality was defined as death within 90 days after liver resection.

Overall survival (OS) is calculated from the day of surgery to the day of death or last follow up.

Disease free survival (DFS) is calculated from the day of surgery to the day of tumor recurrence or the day of death or last follow up.

Outcomes of the study

The primary outcome was the rate of POPF.

Secondary outcomes included length of postoperative stay, time to resume oral intake, total postoperative morbidity according to Clavien-Dindo classification, delayed gastric emptying, biliary leakage, wound infection, hospital mortality, and survival outcomes (OS and DFS).

Statistical analysis

Statistical analysis of the data is performed using SPSS software version 20. For continuous variables are reported as median and compared by independent sample t-test or Mann-Whitney for continuous variables when appropriate. Categorical variables are described using frequency distributions and compared by Chi-square test. Survival rates were calculated by Kaplan-Meier method and were compared by log rank test. A p values < 0.05 is considered to be significant.

RESULTS

During the study period, 980 patients underwent PD for periampullary tumors at our center. Of them 451 patients had pathologically confirmed PDAC and were only included in this study, while other periampullary tumors were excluded. Patients were divided into two groups according to the presence or absence of preoperative DM. DM group included 113 patients (25.1%), and Non-DM group included 338 patients (74.9%).

Baseline characteristics

Baseline characteristics of the patients are shown in *table 1*. There were significant differences between the two groups regarding preoperative fever, and abdominal pain, and random blood glucose.

Surgical outcomes

Operative data of the patients are also shown in

table 1. There was more firm pancreas in DM group, and this was statistically significant.

The postoperative data of the patients are shown in *table 2*. There was more clinically relevant POPF in Non-DM group. There were more DGE, especially grade C, in DM group which required longer nasogastric tube decompression. Also, there were more wound infection rate in DM group.

The median follow up period for all patients was 24 month (4 – 120 month). The OS and DFS curves of all patients are shown in *figs. 1a, 1b*.

Recurrence occurred in 53 patients (11.8%), 10 patients (8.8%) in DM group and 43 patients (12.7%) in Non-DM group, with no statistically significant difference between the groups ($p = 0.269$).

Mortality occurred in 306 patients (67.8%), 56 patients (49.6%) in DM group and 250 patients (74%) in Non-DM group, and this was statistically significant ($p < 0.001$).

The long-term oncological outcomes were comparable between groups regarding the OS rates ($p = 0.55$) and DFS ($p = 0.972$). The 1-, 3-, and 5- year OS rates were 80.4%, 35.5%, and 0%, respectively, in DM group, and 83.2%, 35.2%, and 7.3%, respectively, in Non-DM group (*fig. 1c*). The 1-, 3-, and 5-year DFS rates were 70%, 0%, and 0%, respectively, in the DM group, and 53.5%, 4.7%, and 0%, respectively, in Non-DM group (*fig. 1d*).

Predictors of POPF

On univariate analysis, significant factors associated with POPF included preoperative loss of weight, preoperative body mass index [weight (kg)/height (m²)], presence of soft pancreas, and pancreatic stent as shown in *table 3*.

On multivariate analysis, significant factors associated with POPF included preoperative loss of weight, presence of soft pancreas, and pancreatic stent as shown in *table 3*.

DISCUSSION

DM and poor glycemic control have been shown to be significant predictors for adverse postoperative and long term outcomes after different surgical operations, including digestive tract operations (19-21).

The association between DM and PDAC is demonstrated by previous studies (6, 22-24). At the time of diagnosis of PDAC, about 20-65% of patients have coexisting DM, and up to 80% of patients have impaired glucose tolerance exceeding the disease prevalence in

Table 1 - Baseline characteristics of the study patients

Variables	All 451	DM 113 (25.1%)	Non-DM 338 (74.9%)	P value
Age (years)	55 (12 - 88)	55 (12 - 88)	55 (25 - 79)	0.186
Sex				0.836
Male	291 (64.5%)	72 (63.7%)	219 (64.8%)	
Female	160 (35.5%)	41 (36.3%)	119 (35.2%)	
BMI (kg/m ²)				0.095
Less than 25	323 (71.6%)	74 (65.5%)	249 (73.7%)	
More than 25	128 (28.4%)	39 (34.5%)	89 (26.3%)	
Presentation				
Jaundice	428 (94.9%)	110 (97.3%)	318 (94.1%)	0.173
Fever	103 (22.8%)	18 (15.9%)	85 (25.1%)	0.044
Abdominal pain	337 (74.4%)	74 (65.5%)	263 (77.8%)	0.009
Vomiting	48 (10.6%)	16 (14.2%)	32 (9.5%)	0.162
Preoperative labs				
Albumin (g/dl)	4 (2.4 - 5.8)	4 (3 - 5.8)	4 (2.4 - 5.1)	0.939
Bilirubin (mg/dl)	5.5 (0.4 - 38)	5.5 (0.4 - 36)	5.5 (0.5 - 38)	0.754
Blood glucose (mg/dl)	110 (70 - 520)	165 (70 - 520)	95 (72 - 140)	0.000
Preoperative ERCP	224 (49.7%)	60 (53.1%)	164 (48.5%)	0.4
Liver				0.235
Normal	398 (88.2%)	103 (91.2%)	295 (87.3%)	
Cirrhotic	53 (11.8%)	10 (8.8%)	43 (12.7%)	
Pancreatic texture				0.001
Soft	258 (57.2%)	49 (43.4%)	209 (61.8%)	
Firm	193 (42.8%)	64 (56.6%)	129 (38.2%)	
PD diameter (mm)	5 (1 - 15)	5 (1 - 12)	5 (1 - 15)	0.157
PD diameter groups				0.57
Less than 3 mm	121 (26.8%)	28 (24.8%)	93 (27.5%)	
More than 3 mm	330 (73.2%)	85 (75.2%)	245 (72.5%)	
Operation time (hours)	5 (3.5 - 10)	5 (3.5 - 10)	5 (3.5 - 9)	0.2
Blood loss (ml)	500 (50 - 3000)	400 (100 - 3000)	500 (50 - 3000)	0.847
Blood transfusion				0.114
No	201 (44.6%)	55 (48.7%)	146 (43.2%)	
Yes	250 (55.4%)	58 (51.3%)	192 (56.8%)	

the general population (5, 6). It remains unclear whether preoperative DM is a predisposing factor or a consequence of PDAC development, or both. In the current study, the overall incidence of DM among PDAC patients was 25.1%.

The impact of preoperative DM on the perioperative and long term outcome of after pancreatic resections, especially PD, for PDAC patients is of great importance. Few previous studies had evaluated the impact of preoperative DM on the outcomes of pancreatic resections for PDAC (9, 10, 25, 26). The outcomes of such studies had been controversial, and many of these studies included all types of pancreatic resections.

POPF is the commonest and most feared major morbidity after PD. It is associated with longer hospitalization, abdominal collections, and sepsis. Also, it can

lead to life-threatening events, such as secondary hemorrhage, multi-organ failure, and mortality (27). Previous studies tried to identify different predictive factors for POPF after PD. They identified several preoperative factors as old age, unintended weight loss, and malnutrition, and operative factors as soft pancreas, excess parenchymal fat, small pancreatic duct, longer operation time as predictive factors for POPF formation (28-30).

The impact of preoperative DM on POPF had been controversial between different studies. Chu et al found a significant higher POPF rate in DM patients than non-DM patients. They also found that preoperative DM was an independent predictor of increased POPF rate, but it did not significantly compromise the postoperative outcomes (7). Malleo et al found that preoperative

Table 2 - Postoperative outcomes of the study patients

Variables	All 451	DM 113 (25.1%)	Non-DM 338 (74.9%)	P value
Hospital stay	8 (5 - 71)	9 (1 - 51)	8 (5 - 71)	0.599
Start oral intake	5 (3 - 51)	5 (3 - 51)	5 (3 - 40)	0.966
Drain removal	8 (4 - 71)	9 (4 - 51)	8 (4 - 71)	0.933
Somatostatin use	316 (70.1%)	77 (68.1%)	239 (70.7%)	0.24
Complications				
Overall	142 (31.5%)	39 (34.5%)	103 (30.5%)	0.424
1	47 (10.4%)	14 (12.4%)	33 (9.8%)	0.456
2	44 (9.8%)	12 (10.6%)	32 (9.5%)	
3	33 (7.3%)	6 (5.3%)	27 (8%)	
4	0	0	0 (%)	
5	18 (4%)	7 (6.2%)	11 (3.3%)	
Pancreatic fistula				
Any	70 (15.5%)	13 (11.5%)	57 (16.9%)	0.174
A	28 (6.2%)	8 (7.1%)	29 (5.9%)	0.212
B	24 (5.3%)	2 (1.8%)	22 (6.5%)	
C	18 (4%)	3 (2.7%)	15 (4.4%)	
Clinically relevant pancreatic fistula	42 (9.3%)	5 (4.5%)	37 (10.9%)	0.018
Biliary leakage	35 (7.8%)	12 (10.6%)	23 (6.8%)	0.193
Delayed gastric emptying				
Any	77 (17.1%)	23 (20.4%)	54 (16%)	0.02
A	22 (4.9%)	9 (8%)	13 (3.8%)	0.03
B	47 (10.4%)	9 (8%)	38 (11.2%)	
C	8 (1.8%)	5 (4.4%)	3 (0.9%)	
Types:				0.07
Primary	13 (2.9%)	7 (6.2%)	6 (1.8%)	
Secondary	64 (14.2%)	16 (14.2%)	48 (14.2%)	
Pancreatitis	7 (1.6%)	3 (2.7%)	4 (1.2%)	0.274
Bleeding PG	6 (1.3%)	0	6 (1.8%)	0.154
Bleeding GJ	13 (2.9%)	2 (1.8%)	11 (3.3%)	0.415
GJ leakage	5 (1.1%)	3 (2.7%)	2 (0.6%)	0.07
Obstructed GJ	11 (2.4%)	1 (0.9%)	10 (3%)	0.215
Wound infection	27 (6%)	15 (13.3%)	12 (3.6%)	0.000
Respiratory complications	20 (4.4%)	4 (3.5%)	16 (4.7%)	0.594
Re-exploration	32 (7.1%)	8 (7.1%)	24 (7.1%)	0.994
Perioperative mortality	17 (3.8%)	6 (5.3%)	11 (3.3%)	0.321
Disease-free survival				Log-Rank 0.972
1 year	56.6%	70%	53.5%	
3 year	5.7%	0	4.7%	
5 year	0	0	0	
Overall survival				Log-Rank 0.55
1 year	82.5%	80.4%	83.2%	
3 year	35%	35.5%	35.2%	
5 year	7.2%	0%	7.3%	

DM is not a predictive factor for POPF after resection of PDAC. They also found that all grade "C" POPFs occurred only in non-DM patients (8).

In our study, POPF rate was higher in Non-DM group (57 patients – 16.9%) than DM group (13 patients – 11.5%), and this was statistically non-significant ($p =$

0.174). Clinically relevant POPF was significantly higher in Non-DM group (Non-DM: 37 (10.9%), DM: 5 (4.5%), p value = 0.018). When we analyzed the predictive factors of POPF, preoperative DM was not a significant predictor of POPF ($p = 0.176$). This can be attributed to significant higher incidence of firm pancreatic

Figure 1 - (a) Overall survival of all study patients. (b) Disease-free survival of all study patients. (c) Overall survival rates of DM and Non-DM groups ($p = 0.55$, Log-Rank test). (d) Disease-free survival rates of DM and Non-DM groups ($p = 0.972$, Log-Rank test)

Table 3 - Univariate and multivariate analysis of predictors of postoperative pancreatic fistula

	Univariate	Multivariate
Age	0.266	
Sex	0.556	
Diabetes Mellitus	0.176	
Body mass index	0.03	0.07
Carbohydrate antigen 19—9	0.429	
Preoperative hemoglobin	0.427	
Preoperative WBCs	0.558	
Preoperative albumin	0.119	
Preoperative creatinine	0.475	
Preoperative amylase	0.187	
Preoperative ERCP	0.646	
Liver cirrhosis	0.181	
Mass size	0.721	
Soft pancreas	0.006	0.03
Mobilized part of pancreatic stump	0.754	
Pancreatic duct diameter	0.819	
Pancreatic duct to posterior border	0.508	
Blood loss	0.644	
Blood transfusion	0.813	
Operation time	0.577	
Somatostatin use	0.963	

parenchyma in DM group (64 patients – 56.6%) than Non-DM (129 patients – 38.2%), $p = 0.001$. This association had been addressed by previous studies which found that DM patients had less pancreatic parenchymal fat and increased pancreatic parenchymal fibrosis (8, 29). This is addressed as higher degree "intrinsic gland fibrosis" by Malleo et al (8).

DGE is one of the most annoying morbidities after PD, with overall reported incidence of 13% to 42% (28-30). The underlying pathophysiologic mechanism of DGE is still unclear. Previous studies had identified several underlying mechanisms such as lack of duodenal hormones, oedema of duodenojejunostomy, local ischaemia of the antrum, and gastric atony due to vagotomy (1-5).

On the other hand, DM is the most common cause of gastroparesis, related to vagal neuropathy, and hyperglycemia induced reduction of gastric emptying time (27). So, DM patients are expected to have a higher rate of DGE after PD.

Previous studies demonstrated that there was no association between preoperative DM and DGE rate

after PD (18, 19).

In our study, we found significantly higher DGE rates in DM group (23 patients – 20.4%) than Non-DM group (54 patients – 16%), ($p = 0.02$). This required prolonged use of nasogastric tube in DM group than Non-DM group, and this was also statistically significant ($p = 0.005$). We also found that significantly higher wound infection rate in DM group (15 patients – 13.3%) than Non-DM group (12 patients – 3.6%), ($p < 0.001$).

Regarding the long-term outcomes, the outcomes of previous studies were heterogeneous. Canon et al found that preoperative DM was a significant predictor of OS and DFS after pancreatic resection (10). Similar findings had been addressed by Cahgpar et al (9). In our study, there was statistically significant difference between DM and Non-DM groups regarding OS and DFS (Log-Rank: 0.55 and 0.972 respectively).

Limitations of this study includes that it is retrospective study over a long duration. The diagnosis of pre-operative DM was made based on documented past history and laboratory glucose levels. It was not possible to differentiate between type I and type II DM. Hemoglobin A1c evaluation was not routinely done and so not available for all patients.

CONCLUSIONS

In conclusion, we found that preoperative DM did not significantly affect the perioperative outcomes after PD for PDAC patients, however, certain morbidities are affected by preoperative DM. Preoperative DM is not associated with POPF, and higher incidence of clinically relevant POPF occurred in non-diabetics. Preoperative DM was significantly associated with higher incidence of DGE and wound infection. Finally, preoperative DM did not compromise the OS and DFS rates.

Conflict of interest

No conflict of interest for any author.

Author contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; by Ayman El Nakeeb, Ahmed Shehta, Rami Said, Mohamed El Dosoky, Ahmed Moneer, Hosam Hamed, Mohamed Elrefai, Talaat Abd Allah. Drafting the work or revising it critically for important intellectual content; by Ayman El Nakeeb,

Ahmed Shehta. Final approval of the version to be published; by Ayman El Nakeeb, Ahmed Shehta. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved by Ayman El Nakeeb, Ahmed Shehta.

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