

Diabetes and Pancreatic Anastomosis: Friend or Foe?

Awaj Kafle,¹ Vikas Gupta²

¹Senior Resident, B. P. Koirala Institute of Health Sciences, Dharan, Nepal, ²Professor, General Surgery, PGIMER, Chandigarh

Correspondence

Dr. Awaj Kafle, Senior Resident
Department of General Surgery
BPKIHS, Dharan

Email:

awaj.kafle.ak@gmail.com

DOI: <http://dx.doi.org/10.3126/jcmsn.v14i1.19323>

Orcid ID: orcid.org/0000-0003-0481-4039

Article received: Mar 3rd 2018

Article accepted: Mar 25th 2018

ABSTRACT

Background & Objectives: Pancreaticoduodenectomy (PD) has become a standard operative procedure for both benign and malignant lesions of pancreatic head and periampullary region. Pancreatic Fistula (PF) is the most troublesome complication and heralds the development of other complications. The procedure was associated with high morbidity and mortality in the past but with the identification of various risk factors associated with the development of PF, the management has changed dramatically. Similarly, Diabetes mellitus (DM) and poor glycemic control is associated with various adverse postoperative events. So, the objective of this study was to identify the association between DM and postoperative occurrence of PF. **Materials & Methods:** This was a prospective cross-sectional study enrolling a total of 72 patients. Patients were screened for the presence or absence of DM based on guidelines by American Diabetes Association in January 2009. After surgery, patients were observed for the development of PF. The association between these two was assessed using Chi-Square test. **Results:** Out of 72 patients, 12 had DM. All the patients who had DM did not develop PF; in contrast 15 patients who developed PF were non-diabetic. **Conclusion:** Diabetes Mellitus was found to be protective in preventing the occurrence of PF postoperatively.

Key words: Diabetes Mellitus; Pancreatic Anastomotic Failure; Pancreatic Leak; Pancreaticoduodenectomy.

Citation: Kafle A, Gupta V. Diabetes and Pancreatic Anastomosis: Friend or Foe? JCMS Nepal. 2018;14(1):49-52.

INTRODUCTION

There are various causes for adverse postoperative events, diabetes mellitus (DM) and hyperglycemia are among the leading ones.¹⁻⁴ Increased morbidity and mortality has been seen in patients with DM after certain gastrointestinal resections.^{5,6} The prevalence of DM in general population is 7% whereas it is exceedingly high in patients with pancreatic adenocarcinoma, which is 40 to 65%.⁷⁻⁹ Pancreaticoduodenectomy (PD) has become a standard operative procedure for both benign and malignant lesions of pancreatic head and periampullary region.¹⁰ Although PD was associated with high morbidity and mortality rates in the past, the management has changed significantly during the last twenty years with regard to operative technique as well as care.^{11,12} Delayed Gastric Emptying (DGE) (14 to 18%) and

Pancreatic Fistula (PF) (10 to 25%) are the main morbidities associated with PD.¹³⁻¹⁵ Various attempts, both surgical and non-surgical have been extensively investigated in an attempt to decrease the rate of PF and analyzed by meta-analyses.^{16,17} It is attractive to identify various perioperative risk factors which may promote PF formation. This will significantly change the morbidity and mortality associated with the disease.

Despite common-organ pathology, the impact of comorbid DM on pancreatectomy outcomes is not well defined. Impaired tissue healing and gastroparesis are well-recognized diabetic sequelae. Given these relations with DM, the role of DM in pancreatic surgical outcomes deserves further evaluation.¹⁸

In pancreatic resection, some studies have shown that DM is a significant risk factor for PF after

PD.^{18,19} On the contrary, other studies have revealed that patients with DM did not show a greater risk of development of PF as compared to patients without DM.²⁰⁻²²

Because of the contradictory results of various studies, we decided to perform a study focusing on the relationship between DM and PF in patients undergoing PD. Thus, the objective of the current study was to find the association between preoperative DM and pancreatic leak after PD.

MATERIALS AND METHODS

The current study was performed after ethical approval was obtained from institutional ethical review board of PGIMER, Chandigarh, India. It was a prospective, observational study. All total sampling technique was used for the study (i.e, all the patients who were indicated and fit for the procedure were included in the study) and the total sample size was 72. The study was conducted from January 2014 to June 2015 in the department of General Surgery, PGIMER, Chandigarh, India.

All patients undergoing PD for benign and malignant diseases were included in the study. Following groups of patients were excluded: Locally advanced disease not amenable for resection, patient not giving consent and patient unfit for resection.

These exclusion criteria were for PD rather than for the study per se.

Methodology and study design

All patients meeting the above mentioned criteria underwent routine evaluation with biochemical, hematological and coagulation parameters and were taken up for surgery as per the routine protocol followed in the department. Extent of surgical resection and method of reconstruction was left to the choice of operating surgeon. All patients underwent a detailed history and clinical examination. Patients were monitored for postoperative complications with special attention towards early detection of postoperative pancreatic fistula (POPF).

For each patient, diagnosis of preoperative DM was made based on authentic, documented clinical history or retrospective review of laboratory findings of the patients. The diagnostic criteria which was followed was as outlined by the American Diabetes Association in January 2009. Specifically, those patients with a known history of DM, a preoperative fasting blood glucose level

≥ 126 mg/dL, or 2 or more outpatient random blood glucose levels ≥ 200 mg/dL were classified into the DM group and were included in the study. 23

The occurrence of pancreatic fistula was identified based on the definition given by the International Study Group of Pancreatic Surgery (ISGPS) as output via an intra-operatively placed drain or percutaneous drain of any measurable volume of drain fluid on or after postoperative day 3, with amylase >3 times normal serum value. Pancreatic anastomotic failure was graded into three grades (A, B, C) according to ISGPS scheme.¹⁵

Data was entered in Microsoft Excel sheet and transferred to Statistical Package for Social Sciences (SPSS for Windows, Version 11.3) for statistical analysis. Chi-Square test and Fischer's exact test were used where relevant. 'P' value of <0.05 was considered statistically significant.

RESULTS

In A total of 72 patients were enrolled in the study and underwent surgery.

Age and Sex distribution:

The mean age of study population was 54.54 ± 14.12 years (range from 18 to 80 years). There were 26 (36.11%) females and 46 (63.89%) males in study population. The most common symptoms included jaundice and loss of weight and each of the symptoms were seen in 51 (70.8%) patients (Table 1).

In the present study, we found that 15 (20.8%) patients developed Pancreatic anastomotic failure (PAF) of any type in a total of 72 patients. Out of 15 patients; 12 had Type A fistula whereas Type B fistula was found in one patient and Type C Fistula in two patients.

Twelve patients were diagnosed as diabetic. Of those 12 patients, none developed pancreatic leak. However, 15 patients who developed Pancreatic leak were non-diabetic.

Thus, the overall result which was obtained was, diabetes had a protective role in preventing PAF ($p=0.052$, borderline significance).

DISCUSSION

The Pancreatic fistula is considered to be pacemaker of all complications. Various studies have identified risk factors associated with pancreatic leak.^{24,25} The association of diabetes with pancreatic leak has been studied by many with various contradictory results.^{7,18,21}

Table 1: Symptomatology of the study population

Symptomatology	Number of Patients (Percentage)
Jaundice	51 (70.8%)
Loss of weight	51 (70.8%)
Abdominal pain	37 (51.4%)
Fever/ cholangitis	21 (29.2%)

In a meta-analysis conducted by Xia et al,²⁶ patients without DM were found to be at a higher risk of PF. Databases were searched systematically for relevant articles from January 2005 to June 2013. Ten out of 16 observational clinical studies revealed that DM was associated with a decreased risk of PF (P=0.01). Patients without DM have more fatty tissue and the pancreas is soft in these patients, so have higher incidence of PF.

Nakata et al²² reviewed published literature regarding the impact of preoperative diabetes mellitus in patients undergoing pancreatectomy and found that the occurrence rates of postoperative mortality and morbidities including pancreatic fistula were almost same between patients with and without preoperative DM.

Malleo et al²¹ studied 602 consecutive patients undergoing partial pancreatic resections and found decreased incidence of clinically relevant PF in diabetics. They concluded it to be a consequence of a decreased frequency of high-risk features of the pancreatic gland (soft texture and/or small duct).

Mathur et al.²⁷ conducted a matched analysis of 40 PD patients with and without PF. On histologic evaluation, it showed increased pancreatic fat, reduced duct size and decreased fibrosis. On biochemical assessment, lower rates of DM were found in patients with fistula than those patients who had not developed fistula (13% in fistula patients, 33% in non-fistula patients, $p < 0.05$). Subsequent review showed that those with DM also had less pancreatic fat and increased pancreatic fibrosis. This study correlates the finding of increased "firm" pancreatic quality among DM patients compared with those patients without DM. In our study, all of the 15 patients who developed pancreatic fistula did not have diabetes. Conversely, among 12 patients who were diagnosed as diabetic, none developed pancreatic fistula. Statistically, with

this result, diabetes was found to be protective for the development of pancreatic fistula ($p = 0.052$, borderline significance).

In our study, all confounding factors could not be ruled out and our sample size was limited due to the paucity of number of cases available. This was the limitation of our study and thus we recommend further randomized clinical trials, with larger sample size in future.

CONCLUSION

Diabetes Mellitus was found to have borderline significance in preventing the occurrence of post-operative Pancreatic Fistula. With this finding we can imply that, though DM is considered a risk factor for various adverse post-operative outcomes in different surgeries, it has protective role in preventing the occurrence of PF after PD.

Funding

None

Conflict of Interest Statement:

None Declared

REFERENCES

- Ramos M, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, et al. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. *Ann Surg.* 2008 Oct;248(4):585-91. <https://doi.org/10.1097/SLA.0b013e31818990d1>.
- Browne JA, Cook C, Pietrobon R, Bethel MA, Richardson WJ. Diabetes and early postoperative outcomes following lumbar fusion. *Spine.* 2007 Sep;32(20):2214-9. <https://doi.org/10.1097/BRS.0b013e31814b1bc0>. PMID: 17873813.
- Frisch A, Lin E, Gatcliffe C. Perioperative hyperglycemia and mortality in non-cardiac surgical patients. American Diabetes Association 69th Scientific Sessions. New Orleans, LA, 2009.
- Neumayer L, Hosokawa P, Itani K, El-Tamer M, Henderson WG, Khuri SF. Multivariable predictors of postoperative surgical site infection after general and vascular surgery: results from the patient safety in surgery study. *J Am Coll Surg.* 2007 Jun;204(6):1178-87. <https://doi.org/10.1016/j.jamcollsurg.2007.03.022>. PMID: 17544076.
- Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. *J Gastrointest Surg.* 2002 Jan;6(1):88-94. [https://doi.org/10.1016/S1091-255X\(01\)00019-1](https://doi.org/10.1016/S1091-255X(01)00019-1).
- Wright CD, Kucharczuk JC, O'brien SM, Grab JD, Allen MS. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic

- Surgery Database risk adjustment model. *J Thorac Cardiovasc Surg.* 2009 Mar;137(3):587-96. <https://doi.org/10.1016/j.jtcvs.2008.11.042>. PMID: 19258071.
7. Huxley R, Ansary-Moghaddam A, De González AB, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer.* 2005 Jun;92(11):2076-2083. <https://doi.org/10.1038/sj.bjc.6602619>. PMID: 15886696.
 8. Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, De Andrade M, Petersen GM. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology.* 2008 Jan;134(1):95-101. <https://doi.org/10.1053/j.gastro.2007.10.040>. PMID: 18061176.
 9. Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2007. Available at: <http://www.cdc.gov/diabetes/pubs/pdf/ndfs> Accessed February 12, 2009.
 10. Barends SA, Lillemole KD, Kaufman HS, Souter PK, Yeo CJ, Talamini MA, et al. Pancreaticoduodenectomy for benign disease. *Am J Surg.* 1996;171:131-134. [https://doi.org/10.1016/S0002-9610\(99\)80087-7](https://doi.org/10.1016/S0002-9610(99)80087-7).
 11. Ho CK, Kleeff J, Friess H, Büchler MW. Complications of pancreatic surgery. *HPB Oxford.* 2005;7:99-101. <https://doi.org/10.1080/13651820510028936>. PMID: 18333171.
 12. Beger HG, Rau B, Gansauge F, Poch B, Link KH. Treatment of pancreatic cancer: challenge of the facts. *World J Surg.* 2003;27:1075-1084. <https://doi.org/10.1007/s00268-003-7165-7>. PMID: 12925907.
 13. Lermite E, Sommacale D, Piardi T, Arnaud JP, Sauvanet A, Dejong CHC, et al. Complications after pancreatic resection: Diagnosis, prevention and management. *Clin Res Hepatol Gastroenterology.* 2013;37:230-9. <https://doi.org/10.1016/j.clinre.2013.01.003>. PMID: 23415988.
 14. Strasberg SM, Drebin JA, Soper NJ. Evolution and current status of whipples procedure: an update for gastroenterologists. *Gastroenterol.* 1997;113:983-994. [https://doi.org/10.1016/S0016-5085\(97\)70195-1](https://doi.org/10.1016/S0016-5085(97)70195-1).
 15. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. International study Group on pancreatic fistula definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery.* 2005;138:8-13. <https://doi.org/10.1016/j.surg.2005.05.001>. PMID: 16003309.
 16. Pratt WB, Callery MP, Vollmer CM. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World J Surg.* 2008;32:419-28. <https://doi.org/10.1007/s00268-007-9388-5>. PMID: 18175170.
 17. Molinari E, Bassi C, Salvia R, Butturini G, Crippa S, Talamini G, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula. Results of a prospective study in 137 patients. *Ann Surg.* 2007;246:281-287. <https://doi.org/10.1097/SLA.0b013e3180caa42f>. PMID: 17667507.
 18. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, et al. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. *J Am Coll Surg.* 2010;210:463-473. <https://doi.org/10.1016/j.jamcollsurg.2009.12.029>. PMID: 20347739.
 19. Addeo P, Delperio JR, Paye F, Oussoultzoglou E, Fuchshuber PR, Sauvanet A, et al. Pancreatic stula after a pancreatico-duodenectomy for ductal adenocarcinoma and its association with morbidity: a multicentre study of the French Surgical Association. *HPB (Oxford).* 2014;16:46-55. <https://doi.org/10.1111/hpb.12063>. PMID: 23461663.
 20. Hiyoshi M, Chijiwa K, Fujii Y, Imamura N, Nagano M, Ohuchida J. Usefulness of drain amylase, serum C-reactive protein levels and body temperature to predict postoperative pancreatic stula after pancreaticoduodenectomy. *World J Surg.* 2013;37:2436-42. <https://doi.org/10.1007/s00268-013-2149-8>. PMID: 23838932.
 21. Malleo G, Mazarella F, Malpaga A, Marchegiani G, Salvia R, Bassi C, et al. Diabetes mellitus does not impact on clinically relevant pancreatic stula after partial pancreatic resection for ductal adenocarcinoma. *Surgery.* 2013;153:641-50. <https://doi.org/10.1016/j.surg.2012.10.015>. PMID: 23276391.
 22. Nakata B, Ishikawa T, Amano R, Kimura K, Hirakawa K. Impact of preoperative diabetes mellitus on clinical outcome after pancreatectomy. *Int J Surg.* 2013;11:757-61. <https://doi.org/10.1016/j.ijsu.2013.07.008>. PMID: 23891775.
 23. Standards of medical care in diabetes-2009. *Diabetes Care.* 2009;32:S13-61. <https://doi.org/10.2337/dc09-S013>. PMID: 19118286.
 24. Akamatsu N, Sugawara Y, Komagome M, Shin N, Cho N, Ishida T, et al. Risk factors for postoperative pancreatic fistula after pancreaticoduodenectomy: the significance of the ratio of the main pancreatic duct to the pancreas body as a predictor of leakage. *J Hepatobiliary Pancreat Sci.* 2010;17:322-8. <https://doi.org/10.1007/s00534-009-0248-6>. PMID: 20464562.
 25. El Nakeeb A, Salah T, Sultan A, El Hemaly M, Askr W, Ezzat H, et al. Pancreatic Anastomotic Leakage after Pancreaticoduodenectomy. Risk factors, Clinical predictors, and Management (Single Center Experience). *World J Surg.* 2013;37: 1405-1418. <https://doi.org/10.1007/s00268-013-1998-5>. PMID: 23494109.
 26. Xia X, Huang C, Cen G, Qiu ZJ. Preoperative diabetes as a protective factor for pancreatic fistula after pancreaticoduodenectomy: a meta-analysis. *Hepatobiliary Pancreat Dis Int.* 2015;14:132-138. [https://doi.org/10.1016/S1499-3872\(15\)60330-7](https://doi.org/10.1016/S1499-3872(15)60330-7).
 27. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg.* 2007 Dec;246(6):1058-64. <https://doi.org/10.1097/SLA.0b013e31814a6906>. PMID: 18043111.