Hemoglobin A1c as a marker to stratify diabetes risk following pancreaticoduodenectomy

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INTRODUCTION

The association between pancreatic ductal adenocarcinoma (PDAC) and diabetes mellitus (DM) has been studied dating back to 1973 [1]. Over the following decades, reports suggested that patients with type 2 DM had a nearly 200% increased risk for development of PDAC [2–4]. More recent evidence suggests at least some evidence of glucose intolerance at the time of PDAC diagnosis in up to 80% of patients [5]. This is likely an overestimate, however, as PDAC may cause a paraneoplastic reaction leading to DM [6,7]. In fact, new-onset DM can be an early marker of pancreatic malignancy [8–10].

Patients with PDAC are treated with aggressive surgery when possible, with pancreaticoduodenectomy (PD) being the standard of care for patients with lesions in the head of the pancreas. With a significant reduction in pancreatic volume, this may lead to a significant decrease in the number of insulin-secreting β cells, causing concern that this operation could lead to new-onset or worsening DM [11]. For benign disease, studies show that up to 18% of patients undergoing PD and 14–31% undergoing distal pancreatectomy develop DM postoperatively [12,13]. Other studies, which include both benign and malignant indications, note a 4%–40.4% incidence of new-onset DM postoperatively [14,15]. The mechanism behind this increase is unclear, as many patients have improved insulin resistance following surgery [16].

The objective of this study is to evaluate whether preoperative hemoglobin A1c (HbA1c) values in patients undergoing PD can help predict the incidence of new-onset or worsening DM. Patients are stratified by HbA1c to determine the effect of preoperative diabetes risk on development of DM postoperatively. We hypothesize that higher preoperative HbA1c will place patients at higher risk for postoperative development of DM.

MATERIAL AND METHODS

We performed a retrospective review of all patients who underwent a PD from January 2011 to December 2017 at a single academic center. Patients with both benign and malignant indications for PD were included. Patients who did not have documented follow-up within the hospital system within 6 months from the date of operation were excluded, as determination of change in DM status was impossible. Patients who underwent total pancreatectomy based on intraoperative margin status were also excluded. Information on patient demographics, DM status, surgical indications, and perioperative outcomes was also obtained through medical record review.
DM was defined by the following criteria: HbA1c value of ≥6.5%, documentation of DM diagnosis in preoperative history and physical examination, or treatment with insulin or oral antihyperglycemic agents preoperatively. Patients without a preoperative diagnosis of diabetes but with an HbA1c of 5.7%–6.4% were considered at risk for diabetes in accordance with the American Diabetes Association recommended classification [17]. Worsening DM was defined by an increase in HbA1c level of at least 0.5% or by an escalation in treatment (eg, initiation of oral antihyperglycemic therapy or transition from oral medications to insulin). Improvement was defined as decrease in HbA1c or cessation of need for insulin or oral medications. Diabetes in the postoperative period was defined similarly. Patients were not considered to have postoperative DM unless this diagnosis was made greater than 30 days from the date of operation. Blood glucose and use of insulin in the immediate postoperative period were not recorded, as hyperglycemia in the immediate postoperative period is common and not associated with long-term development of DM [18].

Descriptive statistics were calculated to describe new diagnosis of or worsening DM postoperatively. Categorical variables were analyzed with the χ² test unless the expected cell frequency was less than 5. In these scenarios, the Fisher exact test was used. Relative risk was also calculated for pairwise group comparisons. The P values for pairwise group comparisons were adjusted for multiplicity using Holm-Bonferroni multiple comparison procedure [19]. Patients were stratified based on diagnosis and preoperative HbA1c. This study was approved by the Institutional Review Board of the University of Utah.

RESULTS

A total of 173 PDs were performed during this study period. Eighty-three patients (48.0%) were excluded for lack of 6-month follow-up (n = 46), lack of preoperative HbA1c value (n = 32), death within 30 days (n = 4), or intraoperative conversion to total pancreatectomy (n = 1). A total of 90 patients met the study inclusion criteria. Median patient age at time of resection was 63 (interquartile range 56–69). Twenty-one patients (23.3%) had a known diagnosis of DM prior to evaluation. Of these, 12 patients (57.1%) were prescribed insulin, 8 patients (38.1%) were using oral antihyperglycemic agents, and 1 patient (4.8%) was not taking medications for DM. There were 7 patients (7.8%) with an HbA1c of 5.6% preoperatively with no known diagnosis of DM. Another 23 patients (25.6%) were at risk for DM preoperatively. Most of the PDs (66.7%) were performed for a malignant diagnosis. Median follow-up time for all patients was 613 days (interquartile range 395–1,079 days).

In the group of patients with DM (either known or based on HbA1c) prior to evaluation, 14 (50.0%, standard error [SE] 9.4%) had worse DM postoperatively. Of the 23 patients at risk for DM preoperatively, 7 (30.4%, SE 9.6%) were diagnosed with DM postoperatively. Only 3 patients (7.7%, SE 4.3%) of the 39 patients with preoperative HbA1c ≤5.6% were diagnosed with DM following resection (Table 1). This diagnosis was made for 1 patient 22 months following resection by a rise in HbA1c from 5.3 to 10.8. This patient underwent PD for a benign cystic lesion of the pancreas. The new DM diagnosis was made for 1 patient 22 months following resection. The median time to diagnosis of worsening DM was 18 months (Figure).

Table 1

| Risk of new-onset or worsening DM, stratified by preoperative DM status | Patients | Known DM preoperatively | New DM postoperatively | Worsening DM postoperatively |
|--------------------------------------------------------------|---------|------------------------|------------------------|-----------------------------|
| No risk (HbA1c ≤ 5.6%)                                         | 39      | 0                      | 3 (7.7%, 4.3%)          | –                           |
| At risk (HbA1c 5.7%–6.4%)                                     | 23      | 0                      | 7 (30.4%, 9.6%)         | –                           |
| DM (HbA1c ≥ 6.5% or known diagnosis)                          | 28      | 21                     | –                      | 14 (50.0%, 9.4%)             |

Reported as total number of patients (percent of patients, SE).

Figure. Risk of new or worsening DM, stratified by preoperative DM status. Error bars represent standard errors.

DISCUSSION

This study demonstrates the utility of preoperative HbA1c values in predicting development of new-onset or worsening DM following PD. Few prior studies used HbA1c to stratify patient cohorts by presence and severity of preoperative DM despite this marker being the criterion standard for diagnosis of DM [20]. This cohort had similar rates of DM development following PD compared to other published reports (11.1%) [12–15]. Patients at risk for DM were 4.0 times more likely to develop DM postoperatively than patients with preoperative HbA1c ≥6.5%.
≤ 5.6%, and patients with known DM were 6.5 times more likely to develop worsening glycemic control following PD. Patients with preoperative HbA1c ≤ 5.6% were very unlikely to develop DM following PD (7.7% of patients). No other variables in this study were helpful for predicting DM within 4 years of the diagnosis of malignancy [8]. Another study being diagnosed with PDAC is 50% greater in patients diagnosed with PD. Although the duration of DM ≤ 2 years of the PDAC diagnosis [21].

This study was limited by a small sample size. HbA1c was not available preoperatively for all patients, requiring many patients to engage in healthy behaviors including weight loss, exercise, and dietary modification postoperatively. This knowledge can also help surgeons more accurately discuss the risks of PD with patients undergoing an operation.

**Author contribution**

CS and JB conceived of the project idea. JB and HS were responsible for data collection. JB performed the data analysis and wrote the initial draft of the manuscript. All authors contributed to revisions and completion of the final manuscript.

**Conflict of interest**

None of the authors have any financial disclosures or conflicts of interest.

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**References**

[1] Wynder E, Mabuchi K, Maruchi N, Fornier J. Epidemiology of cancer of the pancreas. J Natl Cancer Inst 1973;50(3):645–67.
[2] Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. JAMA 1995;272(20):1605–9.
[3] Ragozzino M, Melton L, Chu C, Palumbo P. Subsequent cancer risk in the incidence cohort of Rochester, Minnesota, residents with diabetes mellitus. J Chronic Dis 1982;35(1):13–9.
[4] Friedman G, Eeden S van. Risk factors for pancreatic cancer: an exploratory study. Int J Epidemiol 1993;22(1):30–7.
[5] Wang F, Herrington M, Larsson J, Perrett J. The relationship between diabetes and pancreatic cancer. Mol Med 2003;2:1–5.
[6] Pamulla R, Leiriness JB, Ramlet WR, Basu A, Gloria M, Prevalence CST. Clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology 2008;134(4):981–7.
[7] Sah RP, Nagpal JSB, Mulbhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. Nat Rev Gastroenterol Hepatol 2013;10(7):423–33. https://doi.org/10.1038/nrgastro.2013.49.
[8] Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M, Type II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2015;112:2076–83. https://doi.org/10.1038/bjc.2015.219.
[9] Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. Pancreas 2013;42(2):198–201. https://doi.org/10.1097/MPA.0b013e3182550296.
[10] Li D. Diabetes and pancreatic cancer. Mol Carcinog 2012;51(1):54–74. https://doi.org/10.1002/mc.20771.
[11] Singh AN, Pal S, Kilambi R, et al. Diabetes after pancreaticoduodenectomy: can we predict it? J Surg Res 2018;227:211–9. https://doi.org/10.1016/j.jss.2018.02.010.
[12] Falcom M, Mantovani W, Crippa S, Mascetta G, Salvia R, Pedezzoli P. Pancreatic insufficiency after different resections for benign tumours. Br J Surg 2008;95:84–9. https://doi.org/10.1002/bjs.5552.
[13] Kwon JH, Kim SC, Shin IK, et al. Factors affecting the development of diabetes mellitus after pancreatic resection. Pancreas 2015;44(8):1296–303. https://doi.org/10.1097/MPA.0000000000000404.
[14] Elliott IA, Epelboym J, Winner M, Allendorf JD, Haigh PT. Population-level incidence and predictors of surgically induced diabetes and exocrine insufficiency after partial pancreatic resection. Pern J 2017;21:1–4.
[15] Ferrara MJ, Lohse C, Kudva YC, et al. Immediate post-resection diabetes mellitus after pancreatoduodenectomy: incidence and risk factors. HPB 2013;15:170–4. https://doi.org/10.1111/j.1477-2574.2012.00520.x.
[16] Sohn SY, Lee EK, Han SS, et al. Favorable glycemic response after pancreatoduodenectomy in both patients with pancreatic cancer and patients with non-pancreatic cancer. Med (United States) 2018;97(18).https://doi.org/10.1097/MD.0000000000010590.
[17] Association AD. Classification and diagnosis of diabetes. Diabetes Care 2015;38 (Suppl. 1):58–516. https://doi.org/10.2337/dc15-5005.

**Table 2**

| Preop | Postop | Change |
|-------|--------|--------|
| 4.8   | 5.4    | 0.6    | 12.5%  |
| 5.0   | 5.6    | 0.6    | 12.0%  |
| 5.3   | 10.8   | 5.5    | 103.8% |
| 5.3   | 5.8    | 0.5    | 9.4%   |
| 5.4   | 5.3    | –0.1   | –1.9%  |
| 5.4   | 5     | –0.4   | –7.4%  |
| 5.5   | 5.4    | –0.1   | –1.8%  |
| 5.6   | 5.7    | 0.1    | 1.8%   |
| 5.6   | 5.9    | 0.3    | 5.4%   |
| 5.6   | 6.0    | 0.4    | 7.1%   |
| 5.7   | 6.5    | 0.8    | 14.0%  |
| 5.8   | 4.5    | –1.3   | –22.4% |
| 5.8   | 5.1    | –0.7   | –12.1% |
| 6.0   | 5.5    | –0.5   | –8.3%  |
| 6.1   | 7.5    | 1.4    | 23.0%  |
| 6.2   | 6.2    | 0      | 0.0%   |
| 6.2   | 7.1    | 0.9    | 14.5%  |
| 6.2   | 5.8    | –0.4   | –6.5%  |
| 6.2   | 8.0    | 1.8    | 29.0%  |
| 6.7   | 5.6    | –1.1   | –16.4% |
| 6.7   | 7.7    | 1      | 14.9%  |
| 6.8   | 7.7    | 0.9    | 13.2%  |
| 6.9   | 6.6    | –0.3   | –4.3%  |
| 6.9   | 7.6    | 0.7    | 10.1%  |
| 6.9   | 8.3    | 1.4    | 20.3%  |
| 7.3   | 9.3    | 2      | 27.4%  |
| 7.6   | 7.2    | –0.4   | –5.3%  |
| 9.7   | 13.2   | 3.5    | 36.1%  |
| 10.7  | 15.4   | 4.7    | 43.9%  |
[18] Hu Q, Ren J, Li G, et al. Clinical significance of post-operative hyperglycemia in nondiabetic patients undergoing definitive surgery for gastrointestinal fistula. Surg Infect (Larchmt) 2016;17(4):491–7. https://doi.org/10.1089/sur.2016.050.

[19] Sankoh AJ, Huque MF, Dubey SD. Some comments on frequently used multiple end-point adjustment methods in clinical trials. Stat Med 1997;16(22):2529–42.

[20] Hamilton L, Jeyarajah DR. Hemoglobin A1c can be helpful in predicting progression to diabetes after Whipple procedure. HPB 2007;9(1):26–8.

[21] Chari S, Klee G, Miller L, Raimondo M, DiMagno E. Islet amyloid polypeptide is not a satisfactory marker for detecting pancreatic cancer. Gastroenterology 2001;121(3):640–5.

[22] Lim P, Dinh KH, Sullivan M, et al. Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. Int Hepato-Pancreato-Biliary Assoc 2016;18(4):360–6. https://doi.org/10.1016/j.ihpb.2015.11.003.

[23] Gallagher JM, Erich RA, Gattermeyer R, Beam KK. Postoperative hyperglycemia can be safely and effectively controlled in both diabetic and subcutaneous insulin protocol. J Bone Jt Surg 2017:e0008:1–8.