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Original article

Metabolic effect of pancreatoduodenectomy: Resolution of diabetes mellitus after surgery☆

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ABSTRACT

Background: It is considered natural that glucose tolerance worsens after pancreatectomy. However, diabetes mellitus (DM) resolves after metabolic bypass surgery and anatomic changes after PD resemble those after metabolic surgery. This study assessed the incidence of DM resolution after pancreatectomy and differences in metabolic parameters following pancreatoduodenectomy (PD) and distal pancreatectomy (DP).

Methods: Between 2007 and 2013, 218 consecutive patients with pancreatic diseases underwent PD (n = 112) or DP (n = 106) at Seoul National University Hospital. Factors associated with changes in glucose homeostasis were evaluated by assaying serum glucose concentrations in prospectively collected samples.

Results: Of the 218 patients, 88 (40.4%) had preoperative DM, with 27 (30.7%) of the latter showing postoperative resolution of DM, a rate significantly higher in patients who had undergone PD than DP (40.4% vs. 12.9%, $p = 0.008$). Fasting blood glucose ($p = 0.001$), PP2 ($p < 0.001$), and HOMA-IR ($p = 0.005$) significantly decreased after PD but not after DP. Multivariate analysis revealed that PD was independently associated with DM resolution (odds ratio 7.790, $p = 0.003$). PD was associated with a significantly higher DM resolution rate than DP among the 37 pancreatic cancer patients with preoperative DM (34.6% vs. 0%, $p = 0.036$). DM resolution rates were similar in pancreatic cancer and other pancreatic diseases ($p = 0.419$).

Conclusion: More than 40% of patients with preoperative DM show resolution after PD. Decreased insulin resistance and suspected enhanced glucose stimulated insulin secretion decreasing PP2 seem to contribute improved glucose homeostasis after PD. BMI was unrelated to DM resolution, indicating that PD-associated physio-anatomical changes may help resolve DM independent of weight.

Introduction

Glucose tolerance worsens after pancreatectomy, with more than 17% of patients without preoperative diabetes mellitus (DM) developing this disease after surgery [1]. Pancreatectomy, however, can also have positive effects on glucose homeostasis by reducing body mass index (BMI), altering life style including dietary habits, or by the physio-anatomical changes resulting from gastrointestinal tract reconstruction. DM has been reported to resolve in 21.8–22.5% of patients after pancreatoduodenectomy (PD) [2] and rates of insulin resistance were found to decrease significantly after PD but not after distal pancreatectomy (DP) [3]. DM has also been found to resolve after bariatric surgery, especially after Roux-en-Y gastric bypass or bilio-pancreatic diversion, in 84–98% of patients [4]. PD associated physio-anatomical changes are similar to those of metabolic surgery, in that the duodenum and proximal jejunum are bypassed and the gastrointestinal tract is reconstructed. The effects of metabolic surgery on glucose and insulin homeostasis have been characterized as weight-independent and

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have been explained by the lower and upper intestinal hypotheses of possible neuroendocrine mechanisms [4]. Manipulation of the gastrointestinal tract, the largest endocrine organ of the human body, may influence metabolic pathways, other than weight loss and diminished caloric intake, with these metabolic alterations being significantly more frequent after bypass than after restrictive surgery [4]. This study evaluated the incidence of DM resolution after PD and DP, as well as determining whether changes in glucose homeostasis were dependent on type of operation or primary disease.

Materials and methods

Patients and serial measures of glucose tolerance

Total of 301 consecutive patients underwent PD or DP for pancreatic diseases between January 2007 and December 2013 at Seoul National University Hospital. Among them, 77 patients who did not completed pre- and postop 12 month testing were excluded. Additional 6 patients who had recurrence before the 1st year were excluded to eliminate any effect of primary disease. Plasma glucose concentrations were measured before (fasting blood sugar [FBS]) and 2 h after (PP2) a 75-g oral glucose tolerance test, both before and 12 months after surgery. BMI (body mass index), hemoglobin A1c (HbA1c), fasting insulin and c-peptide were measured before and 12 months after surgery (Fig. 1). Patients were told not to take any oral hypoglycemic drug or insulin on the night before blood was drawn. Insulin resistance was determined by calculating HOMA-IR scores (Homeostatic model assessment-insulin resistance; [insulin (μIU/ml) x glucose (mg/dL)]/22.5). Diabetes was diagnosed according to the current version of American Diabetes Association guidelines: HbA1c $\geq$ 6.5%, FBS $\geq$ 126 mg/dL or PP2 $\geq$ 200 mg/dL [5]. Because history of DM of each patient was incomplete, patients first diagnosed as having DM during preoperative work-up but who were unaware of having DM previously were classified as having “undetected DM”, rather than “recent onset DM”. This study was approved by our Institutional Review Board.

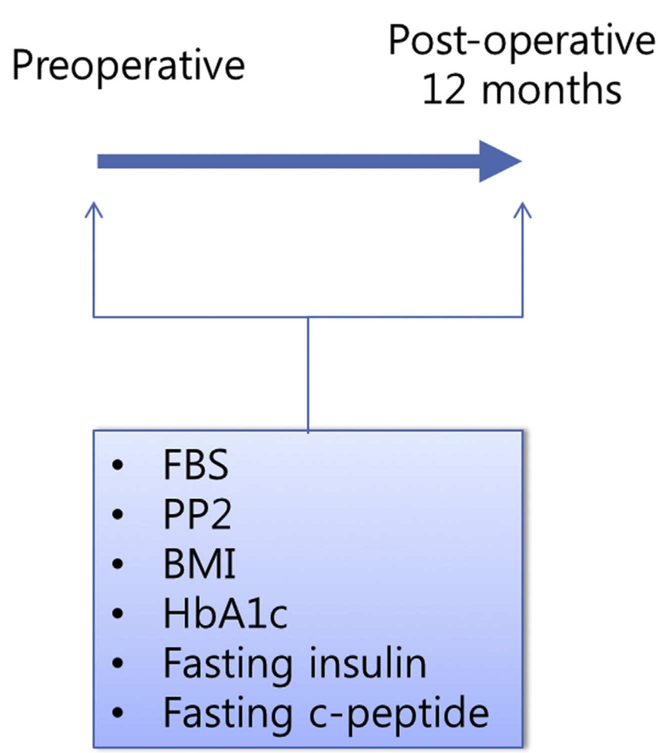

Fig. 1. Biochemical tests performed pre- and postoperative 12 months.

Operative details for pancreatoduodenectomy

Pylorus preservation has been attempted in all pancreatoduodenectomy cases, unless duodenal ischemia, duodenal ulcer, or duodenal tumor infiltration are present. Among the study subjects, 97 patients (86.6%) underwent pylorus-preserving pancreatoduodenectomy and 15 patients (13.4%) underwent Whipple's operation. Antecolic loop duodenojejunostomy or gastrojejunostomy was performed. Lymph node dissection in pancreatoduodenectomy included the removal of regional lymph nodes to the right side of the celiac and superior mesenteric artery and all tissues in the hepatoduodenal ligament, except for the portal vein and hepatic artery [6].

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows Version 21.0 (IBM Corp., Armonk, NY, USA). Nominal variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using Student's t-tests or Mann–Whitney U tests. Serial changes in glucose profiles were tested by paired t tests. Binary variables were included in a multivariate logistic regression model to identify any factors significantly predictive of outcomes and to estimate their odds ratios (ORs). Two-sided p values < 0.05 were considered statistically significant.

Results

Incidence of post-pancreatectomy DM and resolution of preoperative DM according to type of surgery

Of the 218 patients, 112 underwent PD and 106 underwent DP. Age was significantly higher in the PD group, as were the proportions of males, patients undergoing chemotherapy or radiation therapy, and patients with pancreatic cancer (Table 1).

Table 1
Baseline characteristics of total subjects.

	PD (n = 112)	DP (n = 106)	P-value
Age	60.3 ± 11.6	55.3 ± 12.7	0.003
Sex (M:F)	68:44	36:70	<0.001
Body mass index (BMI)	23.5 ± 3.1	24.1 ± 3.4	0.156
FBS (mg/dL)	119.5 ± 45.7	102.6 ± 22.6	0.001
PP2 (mg/dL)	214.8 ± 93.1	167.6 ± 67.3	<0.001
HbA1c (%)	6.3 ± 1.0	5.9 ± 0.7	0.007
HOMA-IR	4.2 ± 6.8	4.3 ± 9.0	0.952
Fasting c-peptide (ng/mL)	3.1 ± 2.8	3.3 ± 2.5	0.452
Pancreatitis	7 (6.3%)	6 (5.7%)	0.854
Alcohol	26 (23.2%)	15 (14.2%)	0.087
Primary disease			<0.001
Pancreatic cancer	43 (38.4%)	30 (28.3%)	0.115
IPMN	51 (45.5%)	22 (20.8%)	
NET	12 (10.7%)	19 (17.9%)	
MCN	3 (2.7%)	18 (17.0%)	
SPT	2 (1.8%)	10 (9.4%)	
SCT	1 (0.9%)	7 (6.6%)	
Chemotherapy	37 (33.0%)	19 (17.9%)	0.011
Radiation therapy	33 (29.5%)	17 (16.0%)	0.018

PD, pancreatoduodenectomy; DP, distal pancreatectomy; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; MCN, mucinous cystic neoplasm; SPT, solid pseudopapillary tumor; SCT, serous cystic tumor; PP2, two-hour postprandial glucose.