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Metabolic consequences of the occlusion of the main pancreatic duct with acrylic glue after pancreaticoduodenectomy

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Metabolic evaluation;
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Abstract

BACKGROUND: Pancreaticoduodenectomy represents the major treatment for pancreatic and periampullary neoplasms. Complications related to pancreaticojejunostomy are still the leading cause of morbidity and mortality. A solution proposed by some surgeons is the occlusion of main pancreatic duct by acrylic glue, avoiding pancreaticojejunostomy. Nevertheless, the consequences of this procedure on glucose metabolism are not well-defined.

METHODS: We retrospectively analyzed a cohort of 50 patients who underwent pancreaticoduodenectomy and had metabolic assessments available. The metabolic evaluation included the following: body composition and clinical evaluation, an oral glucose tolerance test, and an hyperinsulinemic euglycemic clamp procedure.

RESULTS: Twenty-three patients underwent pancreatic duct occlusion and were compared with 27 patients, well-matched controls, who underwent pancreaticojejunostomy. Pancreatic duct occlusion leads to a greater impairment in insulin secretion compared with classic pancreaticojeunostomy.

CONCLUSION: Pancreatic duct occlusion is associated with a greater reduction in insulin secretion but does not lead to meaningful differences in the management of patients with diabetes.

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Whipple's procedure represents the standard treatment of the tumors of the head of the pancreas and other periampullary neoplasms (cancers of the ampulla, distal common bile duct, or duodenum). Despite notable improvements in mortality, currently reported with an incidence of less than 5%,[1,2] morbidity remains a significant problem, being reported in up to 50% of cases.[3] Complications related to pancreatic anastomosis are still the leading cause of morbidity and mortality associated

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with this procedure, and pancreatic postoperative fistula (POPF) is the most dreaded complication and the major potential cause of mortality.[4] A number of alternative techniques have been developed over the years in an attempt to reduce the incidence of POPF, including end-to-end or end-to-side pancreaticojejunostomy (PJ), duct-to-mucosal anastomosis, pancreaticogastrostomy, wider distance between PJ and hepaticojejunostomy, and administration of somatostatin or analogs.[4] Nevertheless, to date, there is no consensus on the best technique for pancreatic anastomosis, and the issue seems to be far from being resolved.[4] A solution adopted by different groups is to avoid the anastomosis and to perform a pancreatic duct occlusion (PDO) with different types of glue. This procedure has led to a marked reduction in mortality in some experiences,[5–7] but has been criticized for favoring the occurrence of postoperative complications and even for resulting in a major impairment of endocrine function of the pancreas.[4,8] Contrasting findings have been published on the effects of PDO on endocrine function and the risk of developing postoperative diabetes in humans,[6] and whether the Wirsung occlusion has a negative effect on endocrine function is still a matter of debate.

Therefore, in this study, we aimed to determine the endocrine effects of these procedures on endocrine function and to define the metabolic outcomes in nondiabetic patients. To pursue this aim, we retrospectively analyzed metabolic changes in insulin secretion and glucose metabolism in a cohort of patients who underwent PDO or classic PJ after pancreaticoduodenectomy, and who had undergone thorough metabolic assessments.

Patients and Methods

Patients and study design

Fifty patients (27 women and 23 men; mean age 63 ± 13 years, body mass index 24.9 ± 1.6 kg/m^2) who underwent pancreaticoduodenectomy for periampullary neoplasms and had metabolic assessments available were considered for the present analysis. Indications for surgery were only periampullary neoplasms: Vater's ampulla (27 cases), distal common bile duct (21 cases), and cancer of the duodenum (2 cases). Patients with pancreatic cancer were excluded from the study. We specifically selected patients with pancreatic texture presumptively "soft" and not dilated main pancreatic duct. Pancreatic texture and duct size were evaluated with preoperative magnetic resonance imaging by an experienced radiologist. As previously described,[9] pancreatic fat infiltration was quantified, and pancreata displaying elevated degrees of intralobular, interlobular, and total fat were considered as having soft pancreatic texture.[10]

All patients had normal cardiopulmonary and kidney function and no family history of diabetes. Patients with preoperative diabetes, as assessed by a 2-hour 75 g oral glucose tolerance test (OGTT) and measurement of glycated hemoglobin (HbA1c) according to the American Diabetes Association criteria,[11] were excluded from the present analysis. Pancreatitis, as determined by altered serum lipase and amylase levels before surgery and/or magnetic resonance imaging morphologic criteria, was considered as an exclusion criterion. In addition, patients who had severe obesity (body mass index > 40), uncontrolled hypertension, and/or hypercholesterolemia were excluded. The study protocol was approved by the local Ethics Committee. All participants provided written informed consent.

Surgical procedures

All patients underwent standard pylorus-preserving pancreaticoduodenectomy.[12] The pancreatic resection margin was the pancreatic neck, in correspondence with portal vein and the amount of the pancreatic head resection was similar in all patients. At the beginning of reconstruction time, in some patients the pancreatic stump was treated by injection in the main pancreatic duct of 3 or 4 mL of acrylic glue (Glubran 2; GEM Srl, Viareggio, Italy) and it was left "free" within the abdominal cavity. Subsequently, a hepaticojejunostomy and a duodenojejunostomy were performed on the same loop, whereas other patients were treated according to the Child[13] classic procedure, including end-to-side PJ with "stump invagination technique,"[14] hepaticojejunostomy, and then duodenojejunostomy on the same loop. All the anastomoses were performed using long-term absorbable sutures. During operation, the surgeons performed PDO or PJ according to their personal evaluation of local conditions. Postoperative morbidity and mortality were recorded. Complications such as POPF, delayed gastric emptying, and postoperative hemorrhage were defined according to the International Study Group of Pancreatic Fistula criteria.[15–17] Postoperative hospital stay was also recorded. All patients undergoing PDO received pancreas enzyme replacement after surgery (80,000 UI pancrelipase per day).

Metabolic evaluation

The metabolic evaluation was performed 1 week before surgery and 40 ± 10 days after surgery. One year after surgery, patients underwent an additional clinical evaluation and HbA1c measurement. The metabolic evaluation was performed at the Division of Endocrinology and Metabolic Diseases of the Catholic University of the Sacred Heart on 3 consecutive days.

Day 1: body composition and clinical evaluation. Patients underwent clinical evaluation and anthropometric assessments according to standard procedures. All patients had blood samples drawn for serum lipid assays (total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol) and HbA1c in the morning after an overnight (8 hours) fast. All the procedures were performed with the subjects in a supine position throughout the experiments.

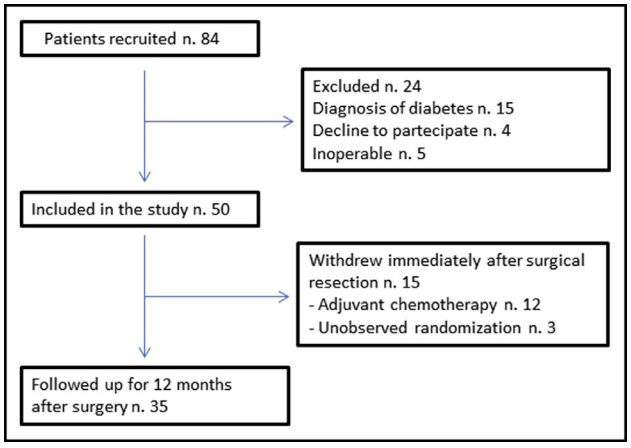

Figure 1 Study enrolment and exclusions.

Day 2: oral glucose tolerance test. All patients underwent a standard OGTT (75 g glucose in 300 mL) at baseline and 1 month postsurgery. Blood samples for the measurement of plasma glucose and insulin levels were collected at 0, 30, 60, 90, and 120 minutes. The American Diabetes Association criteria were used for interpreting the results.[11] Total insulin secretion was assessed as the area under the curve of insulin (AUC INS), calculated using the trapezoidal rule.

Day 3: hyperinsulinemic euglycemic clamp procedure. Hyperinsulinemic euglycemic clamp procedure (HEPC) is well documented as a reference method for direct measurement of whole-body insulin sensitivity and therefore considered the "gold standard."[18]

Peripheral insulin sensitivity was measured with the HECP, at baseline and after surgery. After an overnight fast, insulin (Actrapid HM; Novo Nordisk, Copenhagen, Denmark) was infused at 40 mU/m^2 body surface area (BSA) per minute (initiated with a priming dose of 160 mU/m^2 BSA per minute for 5 minutes and then 80 mU/m^2 BSA per minute for 5 minutes) for 2 hours, as described by DeFronzo et al.[18] Meanwhile, a variable infusion of 20% dextrose was started via a separate infusion pump to maintain the plasma glucose concentration at each participant's fasting plasma glucose level. The infusion rate of dextrose was adjusted based on plasma glucose values determined every 5 minutes. Insulin sensitivity was determined during the last 30 minutes of the HECP by computing the whole-body peripheral glucose utilization (mg/kg/min).

Statistics

The incidence of complications was calculated using descriptive statistics. Comparisons between the 2 groups were made using the Pearson's chi-square test, two-by-two cross-tables or Fisher's exact test. All data are expressed as mean ± standard error, unless otherwise indicated. Because samples were normally distributed, differences in means were tested by 2-tailed Student *t* test for unpaired data using SPSS version 20 (SPSS, Inc, Chicago, IL). A *P* value of less than .05 was considered statistically significant.

Results

During surgical procedure, surgeons performed PDO in 23 patients (PDO group) and PJ in 27 patients (PJ group). Fifteen patients were excluded from follow-up investigations because of prolonged postoperative complications, adjuvant chemoradiotherapy, or patient's refusal. Therefore, postoperative metabolic evaluation was available only for 35 patients, 16 of the PDO group and 19 of the PJ group (Fig. 1). A sufficient recovery period was judged on normalization of inflammatory parameters such as C-reactive protein, erythrocyte sedimentation rate and resolution of POPF, when present.

Postoperative course

There were no deaths in the entire cohort. Postoperative complications are summarized in Table 1. The overall morbidity was 48% (24 patients). A POPF occurred in 13 patients (26%) and delayed gastric empting in 22 patients (44%), with no significant differences between the 2 groups. One single case of postoperative hemorrhage was observed in the PJ group. The mean length of stay was 11.3 ± 3 days (9.5 ± 1.5 in the PDO group vs 13.1 ± 2.8 the PJ group, $P < .0001$). In the PDO group, most of the occurred pancreatic fistulas were subclinical (grade A), while in the PJ group most of them were clinically apparent (grade B) and 2 patients displayed severe pancreatic fistula (grade C) requiring an additional surgical procedure. All the pancreatic fistulas resolved within 40 days after surgery.

Table 1 Postoperative complications

	PDO	PJ	*P* value
No. of cases	24	26	
POPF	6 (25%)	7 (26.9%)	.86
Grade A	5	1	
Grade B	1	4	
Grade C	0	2	
DGE	10 (41.6%)	12 (46.1%)	.97
Grade A	7	7	
Grade B	3	4	
Grade C	0	1	
PPH	0	1 (3.8%)	.96
POHosp-stay (days)	9.5 ± 1.5	13.1 ± 2.8	<.001
PO diabetes	4/16	2/19	.49
IR-Diabetes	2	0	.32

Metabolic evaluation was ascertained postoperatively only in 35 patients. Significance value set at $P < .05$.

DGE = delayed gastric emptying; IR-Diabetes = insulin requiring diabetes; PDO = pancreatic duct occlusion; PJ = pancreaticojejunostomy; POHosp-stay = postoperative hospital stay; POPF = postoperative pancreatic fistula; PPH = postoperative hemorrhage.

Table 2 Anthropometric and metabolic characteristics

Subject characteristics	PDO		PJ	
	Before surgery	After surgery	Before surgery	After surgery
BMI (kg/m^2)	27.7 ± 3.22	26.4 ± 2.54	28.1 ± 3.7	26.8 ± 3.0
Waist-to-hip ratio	.93 ± .05	.73 ± .30	.95 ± .04	.70 ± .24
Fasting glucose (mg/dL)	91.8 ± 2.1	117 ± 9.1*	93.9 ± 4.5	102 ± 9.7
Fasting insulin (μUI/mL)	9.34 ± 1.38	4.13 ± .63*	7.94 ± .94	6.07 ± 5.89
Glucose AUC (mg/dL × 120′ × 10^3)	148 ± 10.2	188 ± 14.2*	134 ± 12.7	144 ± 12.4
Insulin AUC (μUI/ml × 120′ × 10^3)	45.6 ± 10.2	14.1 ± 5.24†	49.5 ± 5.62	24.0 ± 6.23†
HbA1c (%)	5.58 ± .58	7.78 ± .68*	5.6 ± .63	5.98 ± .49
Triglycerides (mg/dL)	152 ± 38	87.7 ± 8.54	143 ± 21	106 ± 16
HDL cholesterol (mg/dL)	48.4 ± 3.95	34.2 ± 3.80	42.7 ± 11.9	43.0 ± 4.40
LDL cholesterol (mg/dL)	146 ± 13.7	65.2 ± 3.72†	141 ± 20.6	72.2 ± 8.4
Total cholesterol (mg/dL)	196 ± 13.8	113 ± 4.72†	217 ± 20.1	137 ± 9.33†

AUC = area under the curve; BMI = body mass index; HbA1c = hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PDO = pancreatic duct occlusion; PJ = pancreaticojejunostomy.

*$P < .05$ before versus after surgery.

†$P < .001$.

Comparison of metabolic variables between the 2 groups

Clinical and hormonal characteristics of all subjects are summarized in Table 2. At baseline, no significant difference between the 2 groups was evident with regard to insulin secretion during OGTT (AUC INS: PJ group 5,951.2 ± 1,023 μIU/mL min vs PDO group 5,483.3 ± 1,105 μIU/mL min, $P = .97$) and insulin sensitivity evaluated during the HECP (glucose uptake: PJ group 4.99 ±

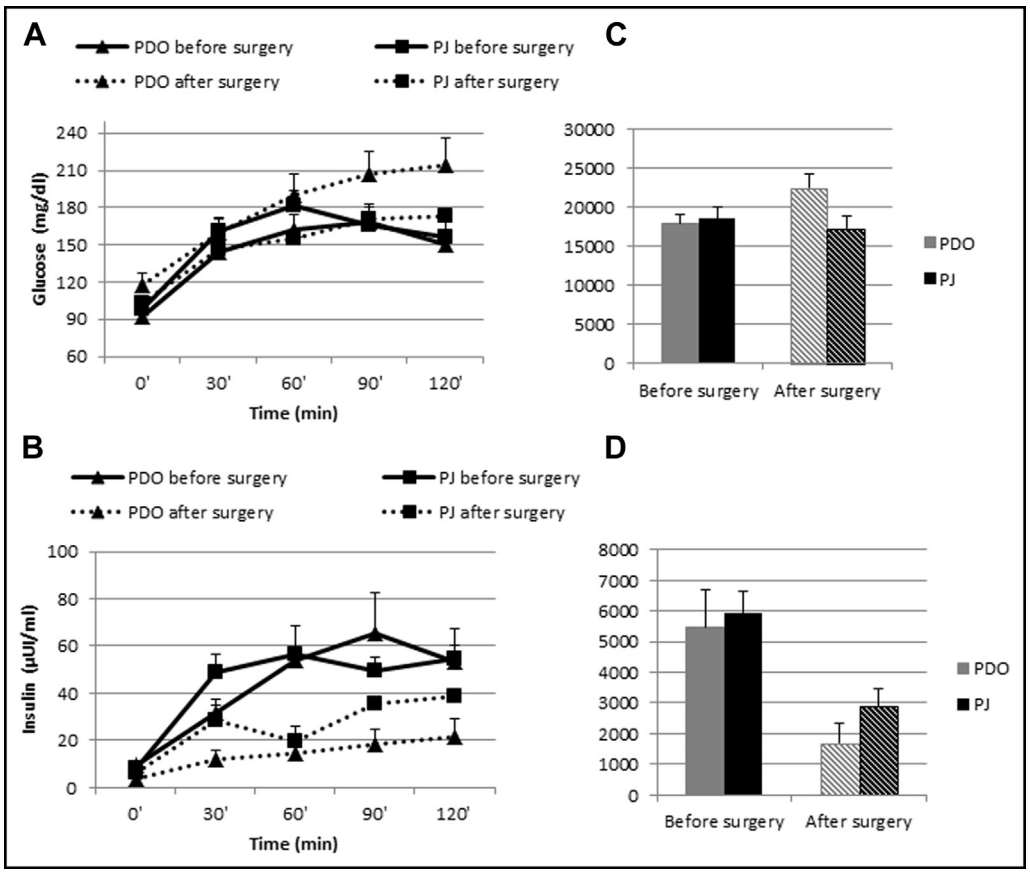

Figure 2 Glucose and insulin concentration during OGTT. Glucose (A) and insulin (B) concentration before (solid line) and after (dotted line) pancreaticoduodenectomy in the PDO group (triangles) and the PJ group (square) (mean ± SEM). Changes in the AUC of glucose (C) and insulin (D) detected during OGTT. SEM = standard error of the mean.

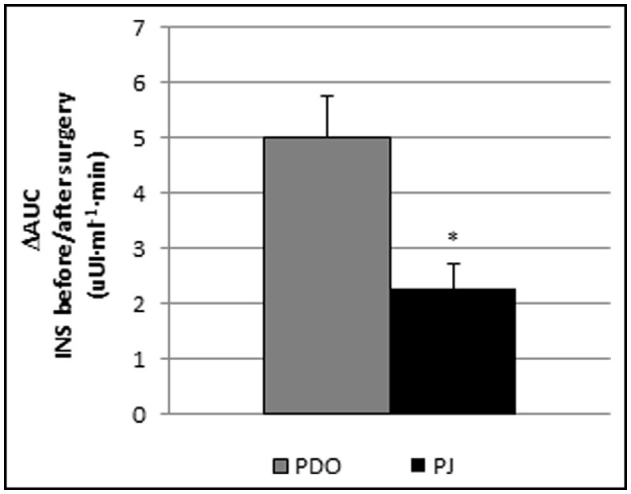

Figure 3 Reductions in the AUCs of insulin secretion during OGTT after surgery. Data are the same of Fig. 1 panel D, here expressed as delta of AUCs of insulin secretion during OGTT before surgery versus after the surgery (mean ± SEM). SEM = standard error of the mean. * $P = .01$.

1.77 mg/kg/min vs PDO 4.85 ± 1.48 mg/kg/min, P = nonsignificant).

Fasting glucose concentration as well as postchallenge glucose excursion increased after surgery ($P = .0001$) in the 2 groups (Fig. 2, panels A and C). As expected, a significant reduction in postchallenge insulin levels was observed ($P = .001$) (Fig. 2, panels B and D).

The AUC INS evaluated in the 2 groups after surgery showed a significant reduction in insulin secretion after surgery (PJ group before surgery 5,951.2 ± 1,023 μU/mL min vs after surgery 2,888.1 ± 745.3 μU/mL min, $P = .001$; PDO group before surgery 5,483.3 ± 1,105 μU/mL min vs after surgery 1,698.6 ± 567.3 μU/mL min, $P = .009$) (Fig. 2, panel D). The mean percentage of reduction in insulin secretion was 51% in the PJ group versus 69% in the PDO group. A significant change was found in the ΔAUC INS between the 2 groups (ΔAUC INS PJ group: 2.25 ± 1.46 vs ΔAUC INS PDO group: 5.02 ± 2.36, $P = .01$) (Fig. 3), that is, in patients who undergone PDO the reduction in insulin secretion after surgery was greater as compared with patients who undergone PJ. Comparing the insulin sensitivity of the 2 groups after surgery, we did not find any significant change after surgery between the 2 groups (PJ before surgery 4.78 ± .48 vs after surgery 5.08 ± .34 mg/kg/; PDO before surgery 4.37 ± .37 vs after surgery 3.95 ± .45 mg/kg/min, P = nonsignificant) (Fig. 4).

After surgery, 2 patients in the PJ group and 4 patients in the PDO group became diabetic. Only 2 patients, both from the PDO group, were initiated on multiple basal-bolus insulin injection; 4 patients reached optimal glucose control (HbA1c <7%) with oral hypoglycemic medications (metformin and dipeptidyl-peptidase IV inhibitors) for at least 1 year. One year after surgery, patients who had not developed diabetes after surgery were reassessed through clinical evaluation and HbA1c measurement. We found that normal glucose tolerance was still preserved in all patients (HbA1c 5.4 ± .5%). The diabetic patients were also well controlled (HbA1c 6.6 ± .7%) with the initially prescribed antidiabetic medications, and only small adjustments in the doses were deemed necessary to maintain glycemic control.

Comments

This study specifically aimed at evaluating changes in glucose tolerance and insulin secretion in patients undergoing PDO after pancreaticoduodenectomy compared with patients undergoing PJ, to investigate the effects of this procedure on postoperative endocrine function. As expected, insulin secretion significantly declined in both groups because of pancreatectomy. The degree of reduction in insulin secretion after surgery was significantly greater in patients in the PDO group compared with the PJ group. These findings are consistent with previous reports in humans,[13,17] wherein PDO has been shown to determine negative effects on pancreatic endocrine function acutely after pancreatectomy. Rovati et al[13] analyzed a cohort of 47 patients who underwent pancreaticoduodenectomy with Wirsung occlusion by neoprene, and reported incident diabetes after surgery in 39 patients and 3 cases at 1 year. This may be because of progressive fibrosis of the gland involving pancreatic islets, or to a direct adverse effect of neoprene on the endocrine pancreas. Furthermore, in a randomized clinical trial conducted at the Erasmus Medical Center of Rotterdam,[19] duct occlusion without PJ significantly increased the risk of endocrine pancreatic insufficiency.

Few studies have specifically investigated the endocrine function of remnant pancreas; however, several reports have described an increased incidence of endocrine insufficiency and diabetes after Wirsung occlusion. In our experience, the 2 different procedures have a different impact on the insulin secretion during OGTT evaluated shortly after the surgery, but clinical outcomes in terms of

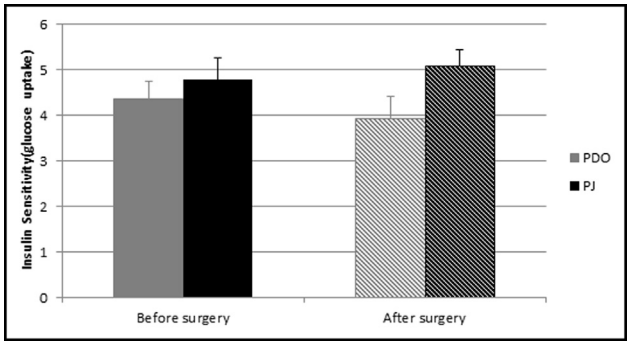

Figure 4 Insulin sensitivity evaluated by hyperinsulinemic euglycemic clamp before (solid bar) and after (striped bar) surgery in the PDO group (grey bar) and the PJ group (dark bar) (mean ± SEM). SEM = standard error of the mean.

therapeutic choice and management have not been affected. Park et al[20] prospectively assessed nutritional status and quality of life (QoL) of patients after pancreatectomy, suggesting that patients recovered QoL and other functional scales within 3 months after surgery. Consistent with previous reports, all patients in our cohort did not report any particular changes in their QoL, even those with newly diagnosed diabetes who were initiated on antidiabetic treatments. In most cases, only oral hypoglycemic agents were prescribed to treat hyperglycemia. Park et al[20] also suggested that endocrine function displays a pattern of recovery by 12 months. Conversely, we did not find any recovery in glucose metabolism following up patients throughout 1 year, despite the different techniques used in the management of pancreatic stump. This suggests that the PDO by acrylic glue could affect the acute insulin secretion response to pancreatectomy, which appears to remain stable over 1 year.

Insulin resistance, along with insulin deficiency, represents the key features in the pathogenesis of type 2 diabetes, and it is generally accepted that both are essential for the full manifestation of the disease. Because insulin resistance itself represents a major underlying cause for hyperglycemia and it has been recognized as a cause for complications in major abdominal surgery[21,22], we measured insulin sensitivity by HECP to rule out any underlying differences in insulin sensitivity between the groups. Furthermore, we also previously showed that insulin resistance itself could directly affect pancreatic endocrine function.[23] It is unlikely that the observed changes in endocrine function were dependent on differences in preoperative insulin sensitivity, because this was comparable in the 2 groups. It is worth noticing that, despite the weight loss following the surgical procedure, there was no significant improvement in insulin sensitivity in either group. Nevertheless, the occurrence of diabetes was not different between the 2 groups and a larger cohort is needed to ascertain whether PDO is associated with an increased incidence of diabetes. Furthermore, it should be acknowledged that, among diabetic patients, only 2 subjects required multiinjection insulin treatment, whereas oral antidiabetic therapy was sufficient to achieve glycemic control in the other patients.

In our single-center limited cohort, we found that the Wirsung occlusion is not associated with a reduction in the overall rate of POPF. However, in most cases these fistulas had a mild clinical impact (A-type fistulas). Postoperative hospital stay was also significantly reduced. Indeed, Wirsung occlusion does not result in a reduction in the overall rate of POPF, but it is mainly responsible for "pure" pancreatic fistulas, which usually have better clinical outcomes, in contrast to those that develop after PJ.

The accurate metabolic evaluation generates important findings in the field of evaluating diabetes risk after PDO. Thus, to the best of our knowledge, this is the first report specifically investigating the endocrine effect of Wirsung occlusion before and after surgery and addressing to substantial clinical implications of endocrine dysfunction after pancreaticoduodenectomy.

Nevertheless, the limited number of patients may represent a limitation, and a randomized study in a larger cohort of patients would be needed to confirm our findings. The observational design of this study represents the main limitation of our work. However, it is unlikely to obtain Ethical committee approval for a randomized control trial comparing reconstructive procedures not comparable in terms of applicability, outcome, and metabolic effects.

The limited cohort recruited in the study may also represent a limitation, but it is worth to notice that we specifically selected patients with specific pancreatic characteristics and because of postoperative complications (POPF) or adjuvant therapy few patients were available at follow-up evaluation. Furthermore, because it has been described the association between diabetes and pancreatic cancer in 20% to 80% of patients at the time of diagnosis suggesting that intrapancreatic tumor and/or other preoperative features could directly affect endocrine function, we specifically selected patients without pancreatic carcinoma to overcome potential bias in evaluating of postoperative metabolic outcomes.

In conclusion, in our experience, the occlusion of pancreatic duct by acrylic glue after pancreaticoduodenectomy reduces insulin secretion but does not determine a significant difference in the occurrence of postoperative diabetes. We report that both procedures determine a reduction in insulin secretion, which is expected because of the acute reduction in beta cell mass. The data highlight the unequal impact of different procedures on endocrine function; however, the greater impairment determined by pancreatic duct occlusion does not lead to significant impact on clinical management.

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