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Long-term pancreatic exocrine and endometabolic functionality after pancreaticoduodenectomy. Comparison between pancreaticojejunostomy and pancreatic duct occlusion with fibrin glue

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Abstract. – OBJECTIVE: Even if pancreatic pathologies, residual fibrosis, residual amount of parenchyma, and anastomotic patency are recognized as main causes of exocrine and glycemic impairment after pancreaticoduodenectomy (PD), few data are reported concerning the role of the different pancreatic remnant treatment techniques. The objective of the study is to assess and compare exocrine functionality, glycemic pattern, nutritional status, and quality of life (QoL) after PD between pancreaticojejunostomy (PJ) and pancreatic duct occlusion (PDO), both in an objective and a subjective manner.

PATIENTS AND METHODS: Thirty-two patients (16 PJ and 16 PDO) were evaluated after a mean follow-up of 21 months after surgery. Exocrine insufficiency was objectively evaluated through the 13C-labelled mixed triglyceride breath test. Fasting glucose, fasting insulin, HbA1c and HOMA-IR values were used to assess glucose metabolism. For these two outcomes, anamnestic data were also collected. QoL was assessed with GIQLI, SF-36, EORTC-QLQ-C30, and EORTC-PAN-26 questionnaires.

RESULTS: The ^{13}C-labelled mixed triglyceride breath test detected a lipid digestive insufficiency in 56% of patients after PJ and 100% after PDO respectively ($p = 0.007$). However, no difference was observed between the two groups regarding postoperative necessity of substitutive pancreatic enzymes. Nutritional status, fasting plasma glucose, fasting insulin, HbA1c levels, HOMA-IR values and postoperative necessity of insulin or oral antidiabetic agents were comparable between the two groups. QoL measurements showed similar results. However, in the subdomains analysis, better outcomes were reported regarding digestive symptoms and physical functioning for PJ and PDO respectively.

CONCLUSIONS: Even if an objective exocrine major impairment was evidenced after PDO, this result did not impact the need for a higher rate of postoperative substitutive enzymes. In terms of glycemic pattern, nutritional status, and QoL, the two techniques turn out to be comparable.

Key Words:
Exocrine insufficiency, Glycemic pattern, Long-term, Pancreaticoduodenectomy, Pancreatic duct occlusion, Pancreaticojejunostomy.

Introduction

Despite enormous progress concerning the perioperative and oncological outcomes after pancreaticoduodenectomy (PD)[1-4], nutritional consequences, exocrine and endometabolic functionality have not been properly addressed yet. There have been only a few reports[5-8] in the literature regarding the long-term function assessment of the pancreatic remnant after PD. In addition, the different methods of evaluation used do not allow to draw homogeneous conclusions on this issue. Independently of the extent of pancreatic resection, the loss of 90% of its own function results in an inability to deliver a sufficient quantity of digestive enzymes to the small bowel[9]. This substantiates the occurrence of exocrine insufficien-

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cy in a range comprised between 30 and 100% of all PDs[10-12]. The consequent deficiency in fat-soluble vitamins (vitamins A, D, E, and K), amino acids, and essential fatty absorption[11,13] is at the origin of gastrointestinal symptoms, malnutrition, and weight loss which are generally encountered during patient follow-up[13]. Although it has been demonstrated that extrapancreatic lipases (especially gastric lipases) can make up for fat digestion up to 50 grams of fat per day[14, 15], they are not functionally sufficient to compensate for the mean oral intake of almost 70-90 g/day. As an additional factor, a significant proportion of patients develop pancreatogenic or type 3 diabetes (DM3) after PD. Its prevalence is reported to range from 8 to 23% immediately after surgery and may reach up to 50% at long-term follow-up[16,17]. Considering the current state-of-the-art, no specific guidelines have been established in the treatment of DM3 after PD and its management is usually based on a treatment which can change according to the frequency of glycemic level monitoring. All of these functional issues inevitably originate in a worsening of patient's quality of life (QoL)[18], affecting daily activities at different levels.

So far, multiple factors have been recognized to influence the functional outcomes after PD, and among them, pancreatic disease[6], location of the resection line[19], anastomotic patency[20], and the degree of fibrosis of the pancreatic remnant[21] have been the most investigated ones. Recently, attention has also been paid to the type of anastomotic reconstruction performed.

In this respect, we report a comparison of exocrine functionality and glycemic pattern between pancreaticojejunostomy (PJ) and pancreatic duct occlusion (PDO) after PD. Also, a QoL analysis was reported for both groups in order to better analyze how outcomes obtained could have influenced patients' daily life.

Patients and Methods

After the institution Review Broad approval, a total of 32 out of 105 patients who underwent PD at the Digestive Surgical Unit of the Fondazione Policlinico "A. Gemelli", Catholic University of Sacred Heart of Rome between November 2012 and January 2015 were included in the study. Only patients aged 18 years or older, without preoperative diabetes, who had undergone PD for adenocarcinoma more than 12 months before the study were enrolled. Only patients with an uneventful postoperative course were included. According to the type of pancreatic remnant treatment, patients were divided into two groups: 16 patients who underwent PJ and 16 patients who underwent PDO. In all cases, written informed consent was obtained.

Surgical Procedures

All patients underwent a pylorus-preserving PD. The choice of performing a PJ or PDO was left at the discretion of surgeons.

In case of PDO, after pancreatic resection, a 3/0 suture was placed around the main pancreatic duct and a catheter was inserted into Wirsung duct for glue injection. In all cases, the Glubran-2 glue (n-butyl(2) cyano-acrylate-monomer- + metacryloxy- sulfolane-monomer; GEM, Viareggio, Italy) was used to occlude the pancreatic duct. It is characterized by a rapid solidification (5-10 seconds) after its application. During glue polymerization, the 3/0 suture placed around Wirsung duct was ligated while the catheter inserted into the main pancreatic duct was removed simultaneously.

In all PJ cases, a duct-to-mucosa anastomosis was performed. At the end of the surgery, two abdominal drains were placed close to the pancreatic remnant to allow for adequate monitoring and efficient drainage of the potential pancreatic fistula. An additional drain was placed next to the hepaticojejunostomy.

Pancreatic Remnant Functional Evaluation

Exocrine Function Assessment

The exocrine pancreatic function was assessed both objectively and subjectively. As an objective evaluation, the ^{13}C-labelled mixed triglyceride breath test was performed. All patients were requested to stop oral pancreatic enzyme supplementation 4 days before the exam. Two-hundred-and-fifty milligrams of the 1.3-distearyl-(13C Carbonyl) octanol glycerol substrate was mixed to a test meal. Substrate digestion takes place in the small bowel through lipase, and the percentage of cumulative recovery of $^{13}CO_2$ (%CD) was obtained through the breath test. Patients were asked to harvest breath samples immediately after meal completion and every 30 minutes afterwards. The breaths were then analyzed with isotope ratio mass spectrometry and %CD at 4 hours (defined as %CD 4h) was calculated[22]. Exo-

crine insufficiency was defined when a %CD < 15% was reported after 4 hours from the meal[22,23]. Additionally, nutritional status was also evaluated by means of weight variation, 25-OH-vitamin D levels, international normalized ratio (INR), and blood protein levels (albumin and no-albumin proteins). Patient weight was measured after a mean follow-up of 21 months. A comparison with the preoperative weight was made and the resulting weight variation was expressed as %.

The digestive function was also subjectively evaluated through anamnestic data: substitutive pancreatic enzyme therapy (yes/no), steatorrhea/diarrhea since surgery (yes/no), and worsening of steatorrhea/diarrhea during the 4 days of enzyme therapy washout (yes/no). Steatorrhea was defined as the patient's referral of oily, loose and foul-smelling stools while diarrhea was defined as the passage of 3 or more loose or liquid stools per day.

Endometabolic Evaluation

To assess the glycemic pattern, blood samples for the measurement of HbA1c, plasma glucose, and insulin levels were collected after an overnight (8 hours) fast. The homeostasis model assessment of insulin resistance (HOMA-IR) was also calculated. In addition, an evaluation of the number of patients under insulin or oral antidiabetic agents was made.

HOMA-IR was evaluated using the following formula: fasting insulin μUI/ml x fasting glucose mg/dl/22.5 x 18[24].

QoL Assessment

QoL was assessed through general (SF-36 and GIQLI) and specific (EORTC-QLQ-C30 and EORTC-PAN-26) questionnaires. All questionnaires were previously used to assess QoL in patients with pancreatic diseases requiring surgery[25-28].

The SF-36 questionnaire consists of 8 fields, each ranking between 0 and 100. The GIQLI questionnaire consists of 36 items with a scale ranging from 0 to 4 points for a maximum reachable score of 144. For both the questionnaires, the higher the score, the better the QoL.

The EORTC-QLQ-C30 questionnaire is a multidimensional QoL measurement[29]. It includes five functional measurements (physical, role, emotional, social, cognitive), eight symptoms (fatigue, pain, nausea/vomiting, appetite loss, constipation, diarrhea, insomnia, dyspnea), as well as global health and financial impact. Most items use a 4-item scale. Scores are converted to a 0-100 scale, with higher scores representing better functioning/QoL. The EORTC-PAN-26 questionnaire is made up of 29 items relating to physical and gastrointestinal symptoms, physical status, as well as social, emotional, cognitive, and sexual functioning. Each item has a score ranging from 1 to 4. The score was calculated as a percentile, and 100% was the highest possible score. Higher scores indicate a higher functional status.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation (± SD) and categorical variables as numbers and percentages unless specified otherwise. Ordinal qualitative variables and quantitative variables were compared with a Wilcoxon rank-sum test. A paired comparison of qualitative variables was performed using a Fisher's exact test or chi-square tests. All reported p values are two-tailed, and a p-value < 0.05 was required to conclude statistical significance. SPSS software, version 20.0 (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA), was used for the analysis.

Results

Clinicopathological Data

Patients' characteristics for both groups are reported in Table I. The mean interval between

Table I. Clinicopathological characteristics.

	PJ (n: 16)	PDO (n: 16)	*p*-value
Mean age years (± SD)	58.3 ± 15.1	60.7 ± 12	0.92
Gender n (%)			
Male	9 (56)	12 (75)	0.45
Female	7 (44)	4 (25)	
Mean follow-up months (± SD)	26.6 (± 14.4)	20.4 (± 11.6)	0.25
Adjuvant therapy n (%)	3 (19)	0	0.23
Tumor recurrence n (%)	5 (31)	2 (12.5)	0.39

surgery and pancreatic remnant functional evaluation was 26.6 (± 14.4) months for the PJ group and 20.4 (± 11.6) months for the PDO group (p = 0.25). No difference was found between the groups regarding age, gender, and adjuvant therapy. Even if the recurrence rate was higher in the PJ group (5 patients – 31%), no statistical difference was found.

Exocrine Function Assessment

The results of exocrine/digestive function and of nutritional status are reported in Table II. Sixty-nine *percent* of patients in the PJ group (11 out of 16) were using pancreatic enzymes as compared to 88% (14 out of 16) in the PDO group (p= 0.39). Concerning the symptoms after substitutive therapy was discontinued, steatorrhea and diarrhea were equal for both categories of patients (50% both in the PJ and PDO groups). Even if the worsening of symptoms was more frequent after PDO (31% *vs*. 12% after PJ), no statistical difference was found.

No difference concerning nutritional status resulted from the comparison of all parameters evaluated, except for albumin level, which was found to be higher in the PDO group (p = 0.01).

At the objective evaluation, no difference was found in terms of %CD 4h: 11.2 ± 6.6 *vs*. 7.4 ± 2.9, in the PJ and PDO groups respectively (p = 0.14). However, the best exocrine/digestive function was however reported after PJ: 7 out of 16 (44%) had a %CD 4h > 15% as compared to 0 out of 16 after PDO (p = 0.007) (Figure 1).

Endometabolic Assessment

Thirty-one percent of the entire cohort study (10 patients: 4 after PJ and 6 after PDO respectively, p = 0.5) needed postoperative insulin or oral antidiabetic agents. The HbA1c measurement showed similar results, without any statistical difference between the two groups (6.36% and 6.38% after PJ and PDO respectively, p = 0.38) (Figure 2). Fasting glucose levels were comparable between the two groups (111 ± 9.1 and 102 ± 9.7 mg/dl in the PDO and PJ groups, respectively; p = 0.26). Similarly, no difference was evidenced for fasting insulin (5.73 ± 0.63 and 6.1 ± 1.89 µUI/ml in the PDO and PJ groups, respectively; p = 0.3) and HOMA-IR value (1.6±0.39 and 1.5 ± 1.1 in the PDO and PJ groups, respectively; p = 0.42).

QoL Evaluation

Overall QoL assessment scores are reported in Table III. The mean GIQLI score documented was 101 ±87 *vs*. 97 ± 61 for the PJ and PDO groups, respectively (p = 0.2). Similar results, without any differences between the two techniques, were also found at the SF-36 test for both physical (PCS) and mental (MCS) fields (p = 0.1). A mean value of all fields for both the EORTC-QLQ-30 and EORTC-PAN-26 questionnaires was calculated and no statistical difference was found between the groups (p = 0.1 and 0.09 respectively). However, better outcomes were found after PDO regarding physical functioning at the EORTC-QLQ-30 test (87% *vs*. 60% after PJ – p = 0.03) (Figure 3). Conversely, the EORTC-PAN26 questionnaire evidenced better outcomes in terms of digestive symptoms in the PJ group as compared to the PDO group (p = 0.04) (Figure 4).

Discussion

Even if a significant improvement has been reported after PD regarding short-term outcomes and long-term survival[30-32], only a few reports are present in the literature regarding the long-term

Table II. Exocrine function assessment.

	PJ (n: 16)	PDO (n: 16)	p
Objective evaluation			
Δ Weight (%)	9.3 ± 1.,6	12.6 ± 8.8	0.097
% CD 4h	11.2 ± 6.6	7.4 ± 2.9	0.14
% CD 4h > 15%	7 (44)	0 (0)	0.007
Albumin (g/dL)	4.2 ± 0.42	4.6 ± 0.34	0.01
Non-albumin protein (g/dL)	3.17 ± 0.24	3.18 ± 0.41	0.94
25-OH-vit D (ng/mL)	12.9 ± 13.7	10.7 ± 8.6	0.94
INR	1.04 ± 0.06	1.04 ± 0.07	0.86
Subjective evaluation			
Enzyme therapy (%)	11 (69)	14 (88)	0.39
Steatorrhea/Diarrhea (%)	8 (50)	8 (50)	1
Worsening symptoms (%)	2 (12)	5 (31)	0.11

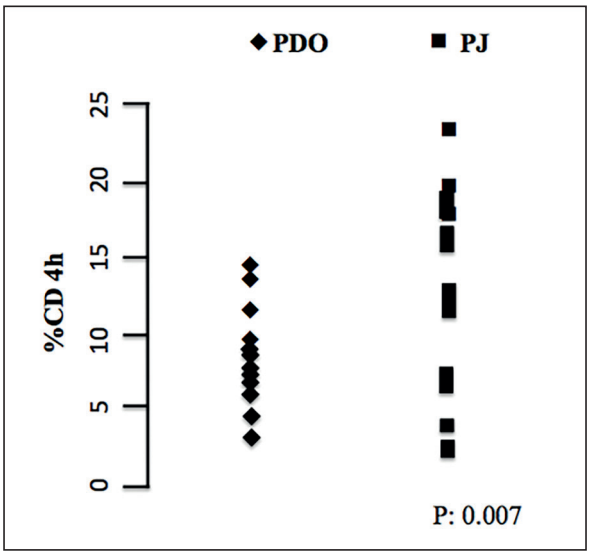

Figure 1. Exocrine insufficiency: %CD 4h evaluation.

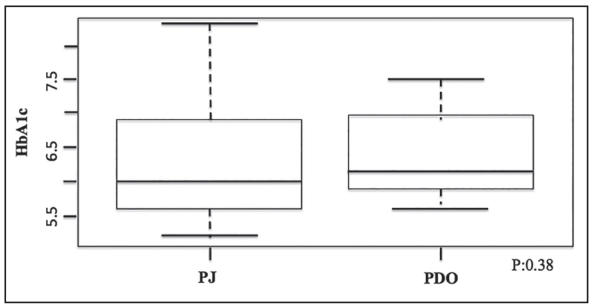

Figure 2. Endocrine insufficiency: HbA1c evaluation.

evaluation of pancreatic remnant function. Fibrosis, atrophy, extent of resection, and anastomotic obstruction were advocated to account for postoperative pancreatic insufficiency[20,33]. However, conclusive studies on post-PD exocrine and glycemic impairment are rare. In addition, they are generally based on different types of evaluation techniques, leading to inhomogeneous results.

So far, only a few reports have focused on the influence of pancreatic remnant treatment in the long term. Regarding pancreatic exocrine insufficiency, most studies[5,11] focused on the comparison between pancreaticogastrostomy (PG) and PJ, including a limited number of patients. Irrespective of the evaluation technique, better functional outcomes were always reported in favor of PJ reconstruction, as lately confirmed in a more extensive recent series by Roeyen et al[34].

In our study, we focused our attention on the differences in functional outcomes between PJ and PDO. PDO could be *de facto* considered as a typical model of complete exocrine insufficiency, due to the induced exocrine atrophy of the pancreatic remnant[35-37]. Its use is particularly recommended in selected patients (soft pancreas, small pancreatic duct, and high-risk patients) with the purpose of preventing and reducing the severity of postoperative complications[38]. In fact, the absence of any anastomosis with the small bowel or the stomach does not lead to the potential pancreatic enzyme activation in case postoperative fistula onset. This results in a more significant incidence of grade A postoperative fistula[38, 39], which is more easily manageable from a clinical standpoint.

The only work which reports a functional evaluation comparison between PJ and PDO was reported by Tran et al[39]. Concerning the exocrine function, the authors observed that only 59% of patients who underwent PDO required an enzyme substitution therapy at 12 months of follow-up[39]. As known, the chemical occlusion of the pancreatic duct should cause a complete parenchymal atrophy. Additionally, the absence of anastomosis with the gastrointestinal tract does not entail any potential digestive enzyme delivery to the gastrointestinal tract. However, the results obtained by Tran et al[39] would assume the presence of potential compensatory mechanisms which would lead to a long-term functional improvement. To better define how significant these compensatory systems are, we evaluated exocrine insufficiency using the ^{13}C-labelled mixed triglyceride breath test and contemporarily analyzed subjective outcomes, namely symptoms and need for substitutive enzyme therapy at fol-

Table III. QoL assessment.

			SF-36						
	GIQLI	*p*	PCS	MCS	*p*	EORTC-QLQ-36	*p*	EORTC-PAN-26	*p*
PJ group	101 ± 87	0.2	41.5 ± 11.1	62.6 ± 15.2	0.1	82.5 ± 32.3	0.1	79.88 ± 34	0.09
PDO group	97 ± 61		46.3 ± 21	50.8 ± 17		80.3 ± 28.1		72.68 ± 36	

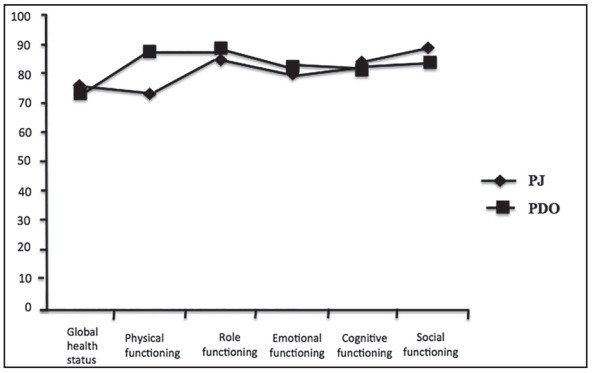

Figure 3. Subfields evaluation of the EORTC-QLQ-30 questionnaire. A significant difference was noted in the physical functioning domain in favor of PDO ($p = 0.03$).

low-up. As compared to all other tests[14,40-42], the ^{13}C-labelled mixed triglyceride breath technique is easy to perform. Additionally, it is not strictly specific to pancreatic lipase activity. It can detect the activity of extrapancreatic lipases[43] and measure lipid digestive function, also during enzyme therapy[13]. In a recent work[44], the ^{13}C-labelled mixed triglyceride breath technique resulted to be comparable to the 72-hour fecal fat quantification for sensitivity, specificity, positive and negative predictive value in assessing pancreas exocrine sufficiency in children. In addition, it has demonstrated a significant correlation with post-operative morphological changes, nutritional status, and endocrine function in patients who underwent pancreaticoduodenectomy[45].

Finally, another research demonstrated a significant correlation between the acinar cell area of the pancreatic stump and the percentage dose ^{13}C cumulative 7 hours[21].

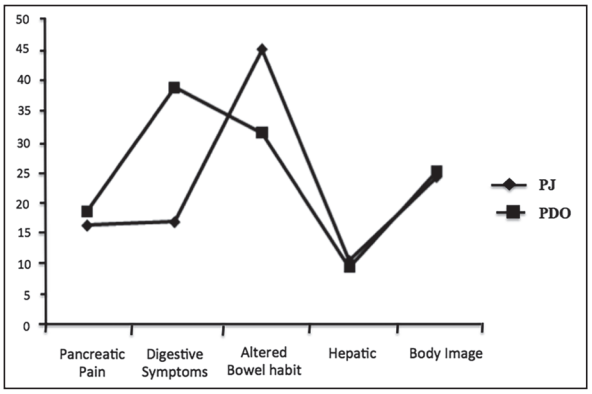

Figure 4. Subfields evaluation of the EORTC-PAN-26 questionnaire. A significant difference was noted in terms of digestive symptoms in favor of PJ ($p = 0.04$).

In addition to these findings, both Laterza et al[23] and Pizzoferrato et al[46] showed the ^{13}C-labelled mixed triglyceride breath test as a reliable technique in the pancreatic exocrine functionality assessment.

According to our data, compensatory mechanisms after PDO have led to achieve similar results as compared to the PJ group in terms of exocrine functionality. In fact, even if the %CD 4h was found to be higher in the PJ group, no statistical difference was evidenced in comparison to the PDO group (11.2 ± 6.6 *vs.* 7.4±2.9 – $p = 014$, respectively). However, 100% of patients could be considered as objectively insufficient after PDO since 100% of them presented a %CD 4h < 15% as compared to only 56% (9 patients) after PJ ($p = 0.007$). In line with Tran et al's results[39], no difference was found at long-term evaluation regarding enzyme therapy necessity between PJ and PDO. In addition, no difference was reported for steatorrhea/diarrhea and worsening of symptoms after pancreatic enzyme suspension. Moreover, with the only exception of albumin levels (statistically superior in the PDO group), no difference was noted for all other objective parameters in the nutritional status evaluation.

The edometabolic remnant function is the other outcome evaluated. It is widely known that an early postoperative DM3 after PD varies between 8 and 23% with a long-term onset in up to 50%[16,17], irrespectively of the reconstruction technique.

Contrasting data are still present in the literature with regards to the potential effect of chemical duct occlusion on the postoperative onset of diabetes. According to some scholars[35,36,47,48], the function of the pancreatic islets of Langerhans is not affected while Konish et al[49] suggested a possible long-term increased risk of diabetes as a consequence of the atrophy induced by occlusion-emulsion. Tran et al[39] documented a higher occurrence of postoperative diabetes in the PDO group at 12 months of follow-up. However, even in endocrine function evaluation, the authors reported only an indirect estimation of pancreatic remnant functionality. In particular, endocrine impairment was defined as the need for postoperative insulin or oral antidiabetic agents therapy. Compared to Tran's work[39], we reported a longer follow-up, and no difference concerning postoperative therapy with insulin or oral antidiabetic agents was evidenced between the two techniques.

To assess post-operative endometabolic function also in an objective manner, we evaluated fasting glycemia, fasting insulin, HOMA-IR and HbA1c levels in both groups of patients.

It has already been demonstrated how glycemia might poorly change after PD, with even a gradual amelioration over time in some cases[50-52]. Two main mechanisms could justify these findings. First, it is possible that the resection of the tumor, and the consequent removal of diabetogenic factors secreted by pancreatic cancer might bring to a glucose metabolism improvement[50, 52]. Second, as reported by Menge et al[50], the potential onset of post-operative delayed gastric emptying may positively influence the post-operative glucose homeostasis. Based on these premises, although we found comparable fasting glycemic values for the two groups, glycemia itself could not be considered sufficient in objectively assessing post-PD glucose homeostasis.

At this regard, HbA1c levels measurement, fasting insulin, and HOMA-IR values yield to a more objective evaluation of the endometabolic function[10, 53]. In our objective assessment, all these three parameters were similar between the two groups, leading to the conclusion that the reconstructive technique after PD does not influence pancreatic endometabolic function.

QoL is the last parameter evaluated. Not many authors report this outcome after PD and so far there is no standardization regarding the specific use of questionnaires[27,54,55]. In our investigation, QoL was evaluated both generically (health status) and specifically (digestive functions), after at least 12 months after surgery. This time period led to avoiding confounding aspects due to immediate post-surgical effects and allowed patients to regain a relative psycho-physical and social balance. It is essential to notice how no difference was found between the two groups regarding general health conditions. The only two differences reported mainly concerned physical functioning (in favor of the PDO group) as well as digestive function (in favor of the PJ group). However, these two aspects could be mainly related to the personal habits of each patient, such as daily activities and tolerance to the diet, which is usually required after PD.

Conclusions

We did not find any significant difference in exocrine and endometabolic functionality between the two different techniques from a clinical standpoint. Even if there was a more frequent objective exocrine insufficiency in the PDO group, this did not result in an increased need for a post-operative substitutive therapy. Likewise, DM3 incidence was similar between the two groups, both in terms of objective evaluation (fasting glycemia, fasting insulin, HbA1c levels and HOMA-IR values) and need for insulin or oral antidiabetic agents therapy.

To our knowledge, this is the only study which compares long-term endocrine and endometabolic functionality between PJ and PDO in both an objective and a subjective manner.

Since no differences in clinical outcomes have been noted, the reconstructive technique to perform should be only based on patients' risk factors, pancreatic stump characteristics (soft or hard) and the experience of the surgeon.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg 2015; 220: 530-536.
2) Schneider EB, Ejaz A, Spolverato G, Hirose K, Makary MA, Wolfgang CL, Ahuja N, Weiss M, Pawlik TM. Hospital volume and patient outcomes in hepato-pancreatico-biliary surgery: is assessing differences in mortality enough? J Gastrointest Surg 2014; 18: 2105-2115.
3) Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 2006; 10: 1199-1210; discussion 210-211.
4) Caruso F, Alessandri G, Cesana G, Castello G, Uccelli M, Ciccarese F, Giorgi R, Villa R, Scotto B, Olmi S. Laparoscopic pancreaticoduodenectomy for tumors of the head of pancreas; 10 cases for a single center experience. Eur Rev Med Pharmacol Sci 2017; 21: 3745-3753.
5) Rault A, SaCunha A, Klopfenstein D, Larroude D, Epoy FN, Collet D, Masson B. Pancreaticojeju-

nal anastomosis is preferable to pancreaticogastrostomy after pancreaticoduodenectomy for longterm outcomes of pancreatic exocrine function. J Am Coll Surg 2005; 201: 239-244.

6) Matsumoto J, Traverso LW. Exocrine function following the whipple operation as assessed by stool elastase. J Gastrointest Surg 2006; 10: 1225-1229.

7) Nakamura H, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T. Predictive factors for exocrine pancreatic insufficiency after pancreatoduodenectomy with pancreaticogastrostomy. J Gastrointest Surg 2009; 13: 1321-1327.

8) Park JW, Jang JY, Kim EJ, Kang MJ, Kwon W, Chang YR, Han IW, Kim SW. Effects of pancreatectomy on nutritional state, pancreatic function and quality of life. Br J Surg 2013; 100: 1064-1070.

9) Kirk RM. General surgical operations: Elsevier Health Sciences, 2006.

10) Lemaire E, O'Toole D, Sauvanet A, Hammel P, Belghiti J, Ruszniewski P. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. Br J Surg 2000; 87: 434-438.

11) Jang JY, Kim SW, Park SJ, Park YH. Comparison of the functional outcome after pylorus-preserving pancreatoduodenectomy: pancreatogastrostomy and pancreatojejunostomy. World J Surg 2002; 26: 366-671.

12) Crucitti F, Doglietto G, Bellantone R, Miggiano GA, Frontera D, Ferrante AM, Castelli A. Digestive and nutritional consequences of pancreatic resections. The classical vs the pylorus-sparing procedure. Int J Pancreatol 1995; 17: 37-45.

13) Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol 2011; 26 Suppl 2: 12-6.

14) Ghaneh P, Neoptolemos JP. Exocrine pancreatic function following pancreatectomy. Ann N Y Acad Sci 1999; 880: 308-318.

15) Abrams CK, Hamosh M, Dutta SK, Hubbard VS, Hamosh P. Role of nonpancreatic lipolytic activity in exocrine pancreatic insufficiency. Gastroenterology 1987; 92: 125-129.

16) Burkhart RA, Gerber SM, Tholey RM, Lamb KM, Somasundaram A, McIntyre CA, Fradkin EC, Ashok AP, Felte RF, Mehta JM, Rosato EL, Lavu H, Jabbour SA, Yeo CJ, Winter JM. Incidence and severity of pancreatogenic diabetes after pancreatic resection. J Gastrointest Surg 2015; 19: 217-225.

17) Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. Pancreatology 2011; 11: 279-294.

18) Gooden HM, White KJ. Pancreatic cancer and supportive care--pancreatic exocrine insufficiency negatively impacts on quality of life. Support Care Cancer 2013; 21: 1835-1841.

19) Falconi M, Mantovani W, Crippa S, Mascetta G, Salvia R, Pederzoli P. Pancreatic insufficiency after different resections for benign tumours. Br J Surg 2008; 95: 85-91.

20) Nordback I, Parviainen M, Piironen A, Raty S, Sand J. Obstructed pancreaticojejunostomy partly explains exocrine insufficiency after pancreatic head resection. Scand J Gastroenterol 2007; 42: 263-270.

21) Yuasa Y, Murakami Y, Nakamura H, Uemura K, Ohge H, Sudo T, Hashimoto Y, Nakashima A, Hiyama E, Sueda T. Histological loss of pancreatic exocrine cells correlates with pancreatic exocrine function after pancreatic surgery. Pancreas 2012; 41: 928-933.

22) Loser C, Brauer C, Aygen S, Hennemann O, Folsch UR. Comparative clinical evaluation of the 13C-mixed triglyceride breath test as an indirect pancreatic function test. Scand J Gastroenterol 1998; 33: 327-334.

23) Laterza L, Scaldaferri F, Bruno G, Agnes A, Boskoski I, Ianiro G, Gerardi V, Ojetti V, Alfieri S, Gasbarrini A. Pancreatic function assessment. Eur Rev Med Pharmacol Sci 2013; 17 Suppl 2: 65-71.

24) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.

25) Bassi C, Johnson C, Fitzsimmons D, Falconi M, Butturini G, Contro C, Frigerio I, Pederzoli P. [Quality of life assessment in pancreatic carcinoma: results of an European multicentric study]. Chir Ital 1999; 51: 359-366.

26) Nieveen van Dijkum EJ, Kuhlmann KF, Terwee CB, Obertop H, de Haes JC, Gouma DJ. Quality of life after curative or palliative surgical treatment of pancreatic and periampullary carcinoma. Br J Surg 2005; 92: 471-477.

27) Scheingraber S, Scheingraber T, Brauckhoff M, Dralle H. Comparison between a general and a disease-specific health-related quality-of-life questionnaire in patients after pancreatic surgery. J Hepatobiliary Pancreat Surg 2005; 12: 290-297.

28) Schmidt U, Simunec D, Piso P, Klempnauer J, Schlitt HJ. Quality of life and functional long-term outcome after partial pancreatoduodenectomy: pancreatogastrostomy versus pancreatojejunostomy. Ann Surg Oncol 2005; 12: 467-472.

29) Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376.

30) Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Kondo N, Nakagawa N, Sueda T. Long-term results of adjuvant gemcitabine plus S-1 chemotherapy after surgical resection for pancreatic carcinoma. J Surg Oncol 2012; 106: 174-180.

31) Serrano PE, Cleary SP, Dhani N, Kim PT, Greig PD, Leung K, Moulton CA, Gallinger S, Wei AC. Improved long-term outcomes after resection of pancreatic adenocarcinoma: a comparison between two time periods. Ann Surg Oncol 2015; 22: 1160-1167.

32) Yoshioka R, Yasunaga H, Hasegawa K, Horiguchi H, Fushimi K, Aoki T, Sakamoto Y, Sugawara Y, Kokudo N. Impact of hospital volume on hospital mortality, length of stay and total costs after pancreaticoduodenectomy. Br J Surg 2014; 101: 523-529.

33) Ohtsuka T, Kitahara K, Matsuyama S, Shimonishi T, Nakafusa Y, Miyazaki K. Significance of pancreatic exocrine function in the perioperative management of pancreatoduodenectomy. Hepatogastroenterology 2006; 53: 788-791.

34) Roeyen G, Jansen M, Ruyssinck L, Chapelle T, Vanlander A, Bracke B, Hartman V, Ysebaert D, Berrevoet F. Pancreatic exocrine insufficiency after pancreaticoduodenectomy is more prevalent with pancreaticogastrostomy than with pancreaticojejunostomy. A retrospective multicentre observational cohort study. HPB (Oxford) 2016; 18: 1017-1022.

35) Gall FP, Zirngibl H, Gebhardt C, Schneider MU. Duodenal pancreatectomy with occlusion of the pancreatic duct. Hepatogastroenterology 1990; 37: 290-294.

36) Gebhardt C. [Pancreaticojejunal anastomosis. Indication, technique and results]. Zentralbl Chir 2001 ;126 Suppl 1: 29-31.

37) Waclawiczek HW, Boeckl O, Lorenz D. [Pancreatic duct occlusion with fibrin (glue) to protect the pancreatico-digestive anastomosis after resection of the head of the pancreas in oncologic surgery]. Langenbecks Arch Chir Suppl Kongressbd 1996; 113: 252-254.

38) Alfieri S, Quero G, Rosa F, Di Miceli D, Tortorelli AP, Doglietto GB. Indications and results of pancreatic stump duct occlusion after duodenopancreatectomy. Updates Surg 2016; 68: 287-293.

39) Tran K, Van Eijck C, Di Carlo V, Hop WC, Zerbi A, Balzano G, Jeekel H. Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. Ann Surg 2002; 236: 422-428; discussion 8.

40) Chowdhury RS, Forsmark CE. Review article: Pancreatic function testing. Aliment Pharmacol Ther 2003; 17: 733-750.

41) Lieb JG, 2nd, Draganov PV. Pancreatic function testing: here to stay for the 21st century. World J Gastroenterol 2008; 14: 3149-3158.

42) Loser C, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut 1996; 39: 580-586.

43) van Dijk-van Aalst K, Van Den Driessche M, van Der Schoor S, Schiffelers S, van't Westeinde T, Ghoos Y, Veereman-Wauters G. 13C mixed triglyceride breath test: a noninvasive method to assess lipase activity in children. J Pediatr Gastroenterol Nutr 2001; 32: 579-585.

44) Wejnarska K, Kolodziejczyk E, Ryzko J, Oracz G. Comparison of 72-hour fecal fat quantification and the 13C-mixed triglyceride breath test in assessing pancreatic exocrine sufficiency in children with chronic pancreatitis. Dev Period Med 2016; 20: 222-227.

45) Hirono S, Murakami Y, Tani M, Kawai M, Okada K, Uemura K, Sudo T, Hashimoto Y, Nakagawa N, Kondo N, Yamaue H. Identification of risk factors for pancreatic exocrine insufficiency after pancreaticoduodenectomy using a 13C-labeled mixed triglyceride breath test. World J Surg 2015; 39: 516-525.

46) Pizzoferrato M, Del Zompo F, Mangiola F, Lopetuso LR, Petito V, Cammarota G, Gasbarrini A, Scaldaferri F. Specific 13C functional pathways as diagnostic targets in gastroenterology breath-tests: tricks for a correct interpretation. Eur Rev Med Pharmacol Sci 2013; 17 Suppl 2: 45-50.

47) Gooszen HG, van der Burg MP, Guicherit OR, Jansen JB, Frolich M, van Schilfgaarde R, Lamers CB. Crossover study on effects of duct obliteration, celiac denervation, and autotransplantation on glucose- and meal-stimulated insulin, glucagon, and pancreatic polypeptide levels. Diabetes 1989; 38 Suppl 1: 114-116.

48) Gooszen HG, van Schilfgaarde R. Pancreatic duct obliteration: clinical application, morphological and functional effects. Neth J Surg 1987; 39: 19-24.

49) Konishi T, Hiraishi M, Kubota K, Bandai Y, Makuuchi M, Idezuki Y. Segmental occlusion of the pancreatic duct with prolamine to prevent fistula formation after distal pancreatectomy. Ann Surg 1995; 221: 165-170.

50) Menge BA, Schrader H, Breuer TG, Dabrowski Y, Uhl W, Schmidt WE, Meier JJ. Metabolic consequences of a 50% partial pancreatectomy in humans. Diabetologia 2009; 52: 306-317.

51) Ohtsuka T, Kitahara K, Kohya N, Miyoshi A, Miyazaki K. Improvement of glucose metabolism after a pancreatoduodenectomy. Pancreas 2009; 38: 700-705.

52) Permert J, Adrian TE, Jacobsson P, Jorfelt L, Fruin AB, Larsson J. Is profound peripheral insulin resistance in patients with pancreatic cancer caused by a tumor-associated factor? Am J Surg 1993; 165: 61-57.

53) Shirakawa S, Matsumoto I, Toyama H, Shinzeki M, Ajiki T, Fukumoto T, Ku Y. Pancreatic volumetric assessment as a predictor of new-onset diabetes following distal pancreatectomy. J Gastrointest Surg 2012; 16: 2212-2219.

54) Pezzilli R, Fantini L, Morselli-Labate AM. Pancreatectomy for pancreatic disease and quality of life. JOP 2007; 8: 118-131.

55) International Expert C. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009; 32: 1327-1234.