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Considerations on pancreatic exocrine function after pancreaticoduodenectomy

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Abstract

The pancreaticoduodenectomy (PD) procedure may lead to pancreatic exocrine and endocrine insufficiency. There are several types of reconstruction for this kind of operation. Pancreaticogastrostomy (PG) was introduced to reduce the rate of postoperative pancreatic fistula. Although some randomized control trials have shown no differences regarding pancreatic leakage between PG and pancreaticojejunostomy (PJ), recently some reports reveal benefits from the PG over the PJ. Some surgeons concern about the performing of the PG and inactivation of pancreatic enzymes being in contact with the gastric juice, and the detrimental results over the exocrine pancreatic function. The pancreatic exocrine function can be measured with direct and indirect tests. Direct tests have the highest sensitivity and specificity for detection of exocrine insufficiency but require tube placement. Among the tubeless indirect tests, the van de Kamer stool fat analysis remains the standard

to diagnose fat malabsorption. The patient compliance and time consuming makes it not so suitable for its clinical use. Fecal immunoreactive elastase test is employed for screening of exocrine insufficiency, is not cumbersome, and has been used to study pancreatic function after resection. We analyze the FE1 levels in our patients after the PD with two types of reconstruction, PG and PJ, and we discuss some considerations about the pancreaticointestinal drainage method after pancreaticoduodenectomy.

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Key words: Pancreaticoduodenectomy; Pancreaticogastrostomy; Pancreaticojejunostomy; Pancreatic exocrine function; Fecal elastase

Core tip: Many patients present pancreatic exocrine insufficiency after pancreatic resection. Exocrine insufficiency leads to steatorrhea, flatulence, abdominal pain, weight loss and malnutrition. Extent of resection will determine the severity of insufficiency, but also changes in anatomy may be determining factors. Pancreatogastrostomy is deemed detrimental over the pancreatic function because of the hypothetical inactivation of pancreatic enzymes due to the acid juice of the stomach. In this review we discuss the physiological aspects of the changes in exocrine pancreatic function focusing on the pancreaticoenterostomy after a pancreaticoduodenectomy.

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INTRODUCTION

After a pancreaticoduodenectomy (PD) procedure the patient has an altered upper gastrointestinal and pancreatic anatomy with potential pancreatic exocrine and endocrine insufficiency. The first known pancreaticoduodenectomy was performed by Alessandro Codivilla on february 1898 in Italy^[1], followed by Kausch^[2] 11 years later. There are two operation techniques performed predominantly: the classic Whipple operation, developed and modified by Whipple^[3], and the pylorus-preserving procedure inaugurated by Watson^[4] and popularized by Traverso *et al.*^[5]. In the classic PD, an antrectomy or distal gastrectomy is associated to the resected specimen. Gastric resection is avoided in the pylorus-preserving modification. Mortality and morbidity are not significantly different between both techniques^[6], but the pylorus-preserving procedure improve postoperative weight gain^[7-9].

The majority of authors consider pancreatic anastomotic leakage as the primary cause of morbidity and mortality after PD^[10-13]. Pancreaticogastrostomy (PG) was introduced to reduce pancreatic leakage. Waugh and Clagett at the Mayo Clinic were the first to use this anastomosis in the clinical setting. Mackie *et al.*^[14] from the University of Pennsylvania reported their experience and observed lower operative mortality in their institution with implantation of PG. Initially infrequently used, PG is becoming more commonly performed clinically as gastrointestinal pancreatic drainage after PD. Three randomized control trials have shown PG and pancreaticojejunostomy (PJ) to be similar regarding pancreatic fistula rates^[15-17] and a meta-analysis concluded that PG and PJ were not different in terms of pancreatic fistula or overall morbidity rate^[18]. Nevertheless, McKay *et al.*^[19] using meta-analytical techniques found that the results suggested that PG rather than PJ for reconstruction of the pancreatic remnant after PD resulted in a significant decrease in pancreatic fistula or leakage. Recently, Shen *et al.*^[20] showed similar results in their own meta-analysis.

Many surgeons are worried about the inactivation of pancreatic enzymes and deterioration of pancreatic exocrine function due to the reflux of gastric juice into the pancreatic main duct when PG is used as the reconstruction procedure.

The aim of this article is to review the repercussion on exocrine pancreatic function according to the type of pancreatic anastomosis performed after PD. We also report our results in pancreatic exocrine function evaluated by fecal elastase test in a series of patients undergoing PD.

THEORETICAL CONSIDERATIONS OF PANCREATICODUODENECTOMY RESECTION

In a PD the possibilities regarding gastric resection are antrectomy (distal gastrectomy), or gastric-sparing techniques such as pylorus-preserving procedure, or pylorus

resection with the cutting line just before the pylorus ring preserving the most part of the stomach. A greater weight loss can be expected when gastric resection is performed rather than with pylorus-preserving procedure or pylorus resection PD^[2-4].

A soft, non-fibrotic gland with a small pancreatic duct increases significantly the risk of subsequent pancreatic leakage. Several techniques have been described to deal with this kind of pancreatic remnant^[21]. We consider the PG anastomosis in which the pancreatic remnant is telescoped into the gastric lumen^[22] as the first choice in those situations (Figures 1 and 2).

Pros and cons may be argued for each kind of anastomosis. Some groups report worse functional results with PG than PJ after PD. Their explanation for this feature is that reflux of gastric juices in the main pancreatic duct causes inactivation of the pancreatic enzymes and insufficiency of the remnant pancreas. This is a theoretical argument. In contrast, in PJ anastomosis the activation of pancreatic exocrine secretion can occur more easily in the presence of intestinal enterokinase and bile, which may irritate the remnant pancreas *via* the activation of trypsinogen and chymotrypsinogen^[9,23]. The activated enzymes may breakdown the anastomosis. This is also another theoretical argument without evidence-based clinical data.

Unless clinical consequences of the PG reconstruction result in greater deterioration than the potential benefits of this technique, PG is a safer anastomosis when dealing with a soft pancreatic parenchyma.

CLINICAL CONSIDERATIONS OF PANCREATIC EXOCRINE INSUFFICIENCY

Classical studies^[24,25] have demonstrated that the defective digestion of protein, fat, and starch is not observed until the secretion of lipase, trypsin, and amylase is less than 10% of its normal values. The most frequently described sign of pancreatic exocrine insufficiency after resectional surgery is steatorrhea^[26], *i.e.*, stool fat content of more than 7 g/d, which may associate abdominal pain, flatus, and mostly weight loss. Fat malabsorption occurs when pancreatic lipase and trypsin decrease below 5% of normal values^[27].

Halloran *et al.*^[28] considered that the high rate of impaired fat absorption in some series using PG, could be largely attributed to pancreatic enzyme degradation by gastric juice and acid. On the other hand, Johnson^[29] studied gastric and pancreatic function after a Whipple operation with duct-to-mucosa PG in six out of 50 patients who agreed to undergo endoscopy and gastric intubation test. All patients had normal gastric secretion and all but one patient had demonstrable amylase and lipase activity in the gastric aspirate. The patient with no detectable enzyme activity had no clinical pancreatic insufficiency and had very high basal values of gastric secretion and a very high peak acid output (22 mmol/h). The explanation from the author is that although pancreatic enzymes are inactivated at low pH, the conditions found

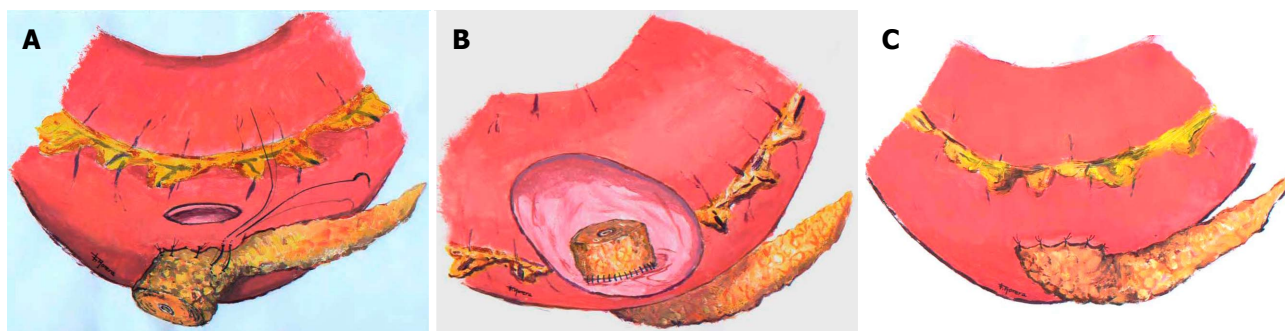


Figure 1 Pancreaticogastrostomy. A: A gastrotomy is performed in the posterior wall of the stomach, and a first layer of stitches are applied approximating gastric serosa to the pancreatic stump; B: The pancreas is telescoped into the gastric lumen, and two pancreato-mucosa running sutures complete the second layer of the anastomosis; C: The final step of the anastomosis is concluded applying the last sero-pancreatic outer stitches.



Figure 2 A scanner of the pancreaticogastrostomy in the early postoperative term. In enlarged view. p: Pancreatic stump throw the gastric wall; s: Gastric lumen containing oral contrast media; v: Splenic vein draining to the portal vein on the right side of the patient; j: High density image corresponding to the staplers of the cutting edge of the jejuna limb used in the hepatico-jejunostomy.

in the stomach immediately after a meal will be favorable for normal activity of the pancreatic enzymes. Therefore, the buffering capacity of the food may protect the pancreatic enzymes from denaturation at the time when they are required for digestion, and the PG may not be detrimental in the exocrine pancreatic function. When a PJ is performed, there is no concern about the acid pH, but the changing anatomy may provide a negative feedback following a high-caloric jejunal load which results in reduced exocrine secretion^[30].

Regardless of the type of reconstruction, PD survivors should be carefully followed up for evidence of pancreatic endocrine and exocrine insufficiency^[31]. When the clinical evolution of the patient demonstrates signs of pancreatic insufficiency, pancreatic enzyme replacement therapy should be routinely considered^[21].

Direct pancreatic function tests have the highest sensitivity and specificity for detection of exocrine pancreatic insufficiency and are subsequently the “gold standard” for testing pancreatic function. Nevertheless, because they are cumbersome, time-consuming, and require tube placement, tubeless indirect tests of pancreatic function

have been introduced. Among them, the 72-h stool fat analysis (van de Kamer test) remains the standard test to diagnose and quantify fat malabsorption^[32,33]. This test requires patient compliance that is rarely obtained, and therefore its clinical use is limited.

Fecal immunoreactive elastase test is considered one of the most satisfactory pancreatic function tests for screening of pancreatic insufficiency^[34]. Fecal elastase-1 measurement has been suggested to support exocrine insufficiency after pancreatic resection^[19,35]. Elastase does not interfere with pancreatic enzyme supplements, and therefore the results are not affected by pancreatic enzyme replacement therapy when patients are under oral pancreatic enzyme treatment.

We have reviewed the data on fecal elastase from a series of PD performed at our centre by using both types of pancreatic anastomosis, PG and PJ. The pancreaticogastrostomy was performed in two layers, with intussusception of the pancreatic stump into the gastric lumen, an inner layer suturing the pancreatic stump to the gastric mucosa, and an outer layer approximating the pancreas to the gastric serosa. Elastase was measured by ELISA

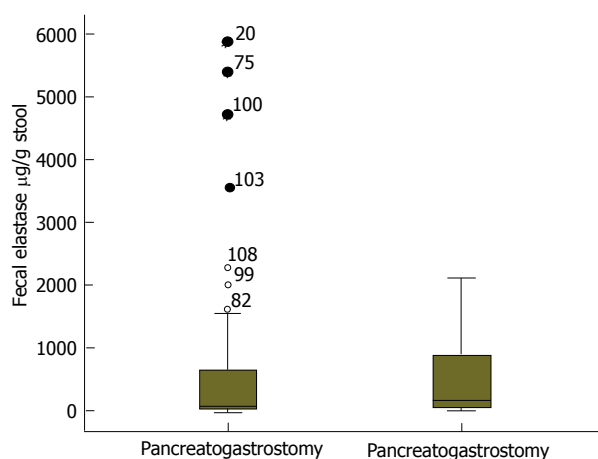


Figure 3 Fecal elastase levels in pancreatico-gastrostomy group and pancreatico-jejunostomy group. Means are depicted with horizontal bars.

to estimate the postoperative pancreatic exocrine function. Stool elastase levels were available in 108 patients, 76 PG and 32 PJ. The average age was $62.7 \text{ years} \pm 10.9$, mostly men (64.8%). Malignancy was the most predominant pathological diagnosis (pancreatic adenocarcinoma, ampuloma, or cholangiocarcinoma) and no histology of chronic pancreatitis was found in the specimens. Fecal elastase levels are considered normal when they are above $200 \text{ } \mu\text{g/g}$ stool. The mean fecal elastase after PD in our series was of $57.9 \text{ } \mu\text{g/g} \pm 104.3$. The mean fecal elastase in the PG group was $61.1 \text{ } \mu\text{g/g} \pm 116.4$; and it was $50.20 \text{ } \mu\text{g/g} \pm 68.5$ in the PY group (Figure 3). The statistical analysis did not show significant difference between elastase levels in both groups ($P = 0.622$). There is an evident decrease in stool elastase levels of patients after PD. This decrease is not influenced by the type of pancreatic drainage used.

Non-alcoholic fatty liver disease has been described after pancreaticoduodenectomy^[36-38] as a late-phase complication. This was not assessed in our patients; nevertheless this topic may be of concern in patients with long-term survival with chronic pancreatitis and it may deserve special interest in future studies.

In summary, we consider PG as the elective pancreatico-intestinal drainage method after pancreaticoduodenectomy when dealing with the soft parenchyma. Pancreatic functional concerns about this kind of reconstruction do not support its rejection. Regardless the type of pancreatic anastomosis performed in the PD, the pancreatic exocrine function after pancreatic resection should be surveyed.

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