

Nutritional Status, Fecal Elastase-1, and ^{13}C -labeled Mixed Triglyceride Breath Test in the Long-term After Pancreaticoduodenectomy

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Objective: This study aimed to compare the body composition, dietary intake and serum levels of vitamins and minerals, and exocrine pancreatic function in patients late after pancreaticoduodenectomy (PD) and healthy subjects.

Methods: Fifteen patients (PD group) who had undergone PD over 1 year before the study and 15 health volunteers (control group) were included in the study. All volunteers underwent dietary intake evaluation, body composition, laboratory data, exocrine pancreatic function by elastase-1, and ^{13}C -labeled triglycerides in breath tests. The PD group subjects also underwent upper gastrointestinal endoscopy and small intestinal bacterial overgrowth analysis.

Results: Nutrient intake was adequate, and there were no differences in body mass index and mineral serum levels between the groups. The PD group showed lower serum levels of retinol, α -tocopherol, and ascorbic acid. Small intestinal bacterial overgrowth occurred in 39% of the patients. Fecal elastase-1 was lower in the PD group. The PD group had a higher ^{13}C peak time; the cumulative label ^{13}C recovery in 7 hours was similar in both groups.

Conclusions: Fecal elastase-1 decreased, and the excretion of ^{13}C in breath was similar to healthy controls. Although the data point toward an adaptation in the absorptive capacity of fats, A, C, and E hypovitaminosis indicate that some absorptive insufficiency persists late after PD.

Key Words: pancreaticoduodenectomy, pancreatic function, fecal elastase, ^{13}C -breath test, nutritional status

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Pancreaticoduodenectomy (PD) has been performed to treat malignant and benign diseases.^{1,2} Mortality rates after pancreatic resection have reduced gradually³ because of improvements in surgical techniques, as well as in postoperative care and centralization of surgery to high-volume centers.^{4,5} Quality of life decreases if there is an impairment of the pancreatic exocrine function during the postoperative period.⁶ Pancreaticoduodenectomy may result in pancreatic insufficiency, manifested clinically as an increased frequency of bowel movements with increased fat in 72-hour stool collection,⁷ as well as a necessity of pancreatic enzyme replacement.⁸ Although a huge variety of tests for the assessment of

pancreatic function is available, the diagnosis of pancreatic exocrine insufficiency can be difficult because there are methodological limitations of direct and indirect tests.

Direct tests such as secretin-caerulein remain as the criterion standard, but they require gastroduodenal intubation to collect pancreatic juice, an invasive, time-consuming, and expensive procedure.⁹ Among the different indirect tests to assess the pancreatic function, measurements of *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid, plasma pancreatic polypeptide, and amino acid consumption tests were abandoned over time.¹⁰ However, fecal elastase-1 or ^{13}C -labeled mixed triglyceride tests are being endorsed by a growing number of studies published in recent years.¹⁰

The fecal elastase-1 is a human-specific protease synthesized by the pancreatic acinar cells,¹¹ whose secretion has a good correlation with amylase, lipase, and trypsin.¹² The breath test using mixed triglyceride labeled with the stable ^{13}C isotope is based on the principle that intestinal triglyceride absorption requires prior hydrolysis by lipase to produce free fatty acids and monoacylglycerol.¹³ After intestinal absorption, the ^{13}C -marked fatty acids are metabolized in the liver producing $^{13}\text{CO}_2$, which is released in breath. Therefore, the increase in $^{13}\text{CO}_2$ concentrations in breath is correlated to intestinal lipid digestion and absorption.¹³ Some investigations assessed pancreatic secretion by fecal elastase-1^{11,14,15} and the absorptive function by ^{13}C -labeled mixed triglyceride breath test in patients undergoing different types of pancreatic resection.¹¹

Most studies conducted with patients who underwent PD emphasized body composition.^{16–18} In cases in which the outcome is satisfactory, the weight returns to previous values in late postoperative.^{16–18} On the other hand, although the patients did not present any evidence of severe nutritional risk, there was a deficiency of micronutrients such as iron, selenium, carotene, and vitamins A and D.^{8,14}

To our knowledge, there have been no reports on the evaluation of the pancreatic function simultaneously with different approaches to nutritional assessment in patients who had undergone PD with pancreaticojejunostomy and standard techniques of duct-to-mucosa anastomosis with internal stenting. The purpose of this study was to compare the body composition, dietary intake, vitamin and mineral serum levels, and exocrine pancreatic function by elastase-1 and ^{13}C -labeled triglyceride breath tests in patients late after PD and healthy control subjects.

2000 to 2010. Subjects who had undergone surgery over 1 year before the study and with no clinical evidence of tumor recurrence were eligible for this study. Twenty-five patients were deceased, and 17 individuals had inconsistent registration data and/or were impossible to contact. Eight patients were excluded because they were receiving postoperative adjuvant chemotherapy. Two subjects refused to participate, and 4 individuals had residual or recurrent neoplastic disease. The control subjects were selected among the employees of the institution or among healthy individuals who attended a public program of physical activity.

The final casuistic included 15 patients (PD group) who had undergone PD (Table 1) and 15 health volunteers (control group), which presented mean (SD) of 61 (13) versus 55 (14) years ($P = 0.23$) and 87% versus 71% of males ($P = 0.36$), respectively. Upper gastrointestinal endoscopy was performed by the same endoscopist. In 8 patients, it was possible to reach the pancreaticojejunal anastomosis, and none of the patients presented obstructions in the pancreaticojejunal and hepaticojejunal anastomoses. We performed an assessment of body composition and food intake and analysis of routine laboratorial data in all volunteers. The evaluation of pancreatic fecal elastase-1 and absorption of ^{13}C was made in all patients (PD group); 7 healthy volunteers (control group) were randomly chosen for these tests.

Surgical Procedures

The PD was performed by a single team, using the standard techniques. All patients who underwent PD had undergone the resection of the pancreatic head, duodenum, biliary duct, and gallbladder. According to an individual evaluation performed during surgery, the antrum and pylorus were preserved ($n = 9$) or resected ($n = 6$). The same procedures were performed in all patients who included the following: (a) single-loop pancreatic and biliary reconstruction, (b) pancreatojejunostomy, (c) duct-to-mucosa anastomosis using interrupted suturing with polypropylene 5-0 suture, and (d) internal pancreatic duct silicone stent (6 to 10 french, around 10 cm). When the subjects were analyzed according to the digestive tract reconstruction technique, we could not find any differences in the evaluated parameters. Because of this, posterior statistical analysis was conducted on all individuals who underwent PD, regardless of antrum and pylorus preservation.

Body Composition and Dietary Intake

The analysis of the composition of the habitual diet was based on the Semi-Quantitative Food Frequency Questionnaire, which assesses the food intake for the previous 6 months. The dietetic data were processed by specific software (NutWin 1.5 Professional Software; Federal University of São Paulo, São Paulo, Brazil). None of the patients used vitamin or mineral supplements during the 6 months before the study.

The individuals were questioned about the changes in their body weight between the perisurgical period and at the time of the study. Anthropometric measurements were done using standard techniques. Body impedance analysis was performed using a bioelectrical impedance analyzer (Biodynamics BIA 450 Bioimpedance Analyzer; Biodynamics Corporation, Shoreline, WA). A single researcher collected these data to minimize interobserver variation.

Nutritional and Routine Clinical Laboratorial Assessment

Blood samples were taken from all the volunteers after a 12-hour fasting period. Routine tests included serum glucose, hemoglobin level, mean corpuscular volume, total lymphocyte counts, liver enzymes, total protein, albumin, transferrin, plasmatic lipids, and C-reactive protein. Iron, zinc, and copper were analyzed by atomic absorption flame spectrophotometry (Perkin Elmer 3110; Perkin-Elmer, Waltham, MA). Folic acid and cyanocobalamin were determined by chemiluminescent enzyme immunoassay (IMMULITE kit; Siemens Healthcare Diagnostics Products Ltd, Gwynedd, North Wales, United Kingdom). Ascorbic acid was measured by colorimetric reaction with 2,4-dinitrophenylhydrazine and spectrophotometric detection. Determination of retinol and α -tocopherol was accomplished by ultraviolet high-performance liquid chromatography.

Hydrogen Breath Tests

After fasting overnight and being on a low-fiber diet for at least 1 day, the individuals from the PD group underwent the test. Hydrogen concentrations were measured in parts per million (ppm) with a gas chromatograph (Model microlyzer; QuinTron, Milwaukee, WI). A hydrogen breath sample was obtained at baseline before the intake of a solution containing 80 g glucose dissolved in 300 mL

TABLE 1. Characteristics of Patients Who had Undergone PD Surgery

Case	Sex	Age, y	Time Elapsed After Surgery, mo	Histopathologic Diagnosis	TNM* Classification
1	Male	69	30	Pancreatic head carcinoma	pT3N0Mx
2	Male	57	65	Carcinoma of papilla of Vater	pT1N1Mx
3	Male	80	119	Carcinoma of papilla of Vater	pT3N0Mx
4	Male	58	20	Carcinoma of papilla of Vater	pT2N0M0
5	Male	61	120	Carcinoma of papilla of Vater	pT2N0M0
6	Male	79	108	Carcinoma of papilla of Vater	pT1N1M0
7	Male	60	52	Neuroendocrine tumor	Not applicable

water. Hydrogen in end-expiratory breath samples was analyzed every 10 minutes for 180 minutes. The breath tests indicated small intestinal bacterial overgrowth when there was at least 1 H₂ peak (>20 ppm increase) above the baseline value.

Fecal Elastase-1 Test

Stool samples were frozen at -20°C until analysis. Fecal elastase-1 levels were determined with an enzyme-linked immunosorbent assay by elastase-1 ELISA kit (Bioserv Analytics and Medical Devices Ltd, Rostock, Germany). The results were expressed as fecal elastase-1 concentration in microgram per gram of stool. Fecal elastase-1 levels of less than 100 µg/g stool were indicative of severe exocrine pancreatic insufficiency, from 100 to 200 µg/g of moderate pancreatic insufficiency, and greater than 200 µg/g of normal exocrine pancreatic.¹⁹

¹³C-labeled Mixed Triglyceride Breath Test

The pancreatic enzymes were withdrawn for at least 5 days before testing in 2 patients who previously used this substitution therapy (27,000 and 36,000 U/d). The ¹³C-mixed triglyceride test had been performed after a 12-hour overnight fasting. The subjects received a test meal, which consisted of 200 mL tea, 60 g toast with 18 mL olive oil, and 200 mg ¹³C-mixed triglycerides (Cambridge Isotope Laboratories, Andover, MA). This test meal contained approximately 20 g fat, and no other drinks or foods were allowed during the experiment. Breath samples were collected via a straw in 10-mL breath sample containers (Vacutainer; Becton Dickinson UK Ltd, Oxford, United Kingdom). Basal breath samples were obtained before the meal, and postprandial breath samples were collected every hour for 7 hours. The ¹³C/¹²C ratio of carbon dioxide was analyzed with an isotope ratio mass spectrometer (Europa Scientific Isotope Ratio Mass Spectrometers 20-20; Sercon, Crewe, England) and calculated as Δ value with regard to Pee Dee Belemnite international limestone standard. The increase in ¹³C content with regard to the baseline value of the initial breath sample was expressed as atom percentage in excess. We noted the time when percentage maximum was reached (time of peak), and we calculated the cumulative percentage of label recovered in the breath over 7 hours (percentage dose ¹³C cum 7 hours).¹⁷ Pancreatic insufficiency was considered when cumulative percentage of label recovered was lower than 5% 7 hours after ingesting ¹³C-mixed triglycerides.¹¹

Statistical Analysis

Data analyses were performed with the Statistica software (version 8.0; StatSoft Inc, Tulsa, OK). Variables with normal distribution were analyzed by Student *t* test and reported as mean (SDs). Variables with nonnormal distribution were analyzed by Mann-Whitney *U* test and reported as median values and range. The level of significance (α) was set at 0.05

RESULTS

Body Composition and Dietary Intake

The patients who underwent PD presented weight loss of 20 (range, 7–35) kg when compared with the habitual weight in perisurgical period. However, at the moment of evaluation, they recovered a mean (SD) of 91% (11%) of the patients who underwent PD lost weight. There was no statistical difference in body mass index (mean [SD], 25 [4] vs 27 [4.0] kg/m², *P* = 0.09) and in fat body mass (19 [4] vs 21 [5] kg, *P* = 0.34). On the other hand, the PD group presented lower lean mass (mean [SD], 45 [11] vs 55 [10] kg, *P* = 0.03) than the control group. The patients who underwent PD presented a higher intake of energy, iron, zinc, copper, vitamin B₁₂, and folate than the healthy controls (Table 2).

Routine Laboratory Evaluation and Nutritional Status Laboratory Assessment

The routine laboratory examinations were within the reference values, except for higher serum alkaline phosphatase (mean [SD], 295 [150] U/L) and C-reactive protein (median, 0.26 [range, 0.06–2.61] mg/dL) in the PD group. Iron, copper, and zinc serum levels were similar among the study groups and within the reference range, whereas serum retinol, α -tocopherol, and ascorbic acid levels were lower in the patients who underwent PD in comparison with the controls (Table 3). Regarding the reference range, serum vitamin A levels were normal in all patients, whereas serum vitamin E and C levels were low in 12 and 13 patients, respectively.

Hydrogen Breath Tests

It was not possible to perform hydrogen breath tests in 2 patients because 1 of them had diabetes mellitus and the other had dumping syndrome immediately after ingesting the glucose solution. Among the 13 patients, 5 presented excessive expiratory H₂, which was indicative of small intestinal bacterial overgrowth.

TABLE 2. Nutrient Intake in Patients Who had Undergone PD (PD Group) and Healthy Volunteers (Control Group)

	PD Group (n = 15)	Control Group (n = 15)	P
Total energy, kcal	2676 (477)	2109 (602)	<0.01
Protein, % ED	16 (2)	16 (3)	0.53
Lipid, % ED	31 (5)	31 (7)	0.80
Carbohydrate, % ED	54 (6)	51 (6)	0.13
Iron, mg	20 (5)	14 (5)	<0.01
Zinc, mg	13 (3)	9 (3)	<0.01

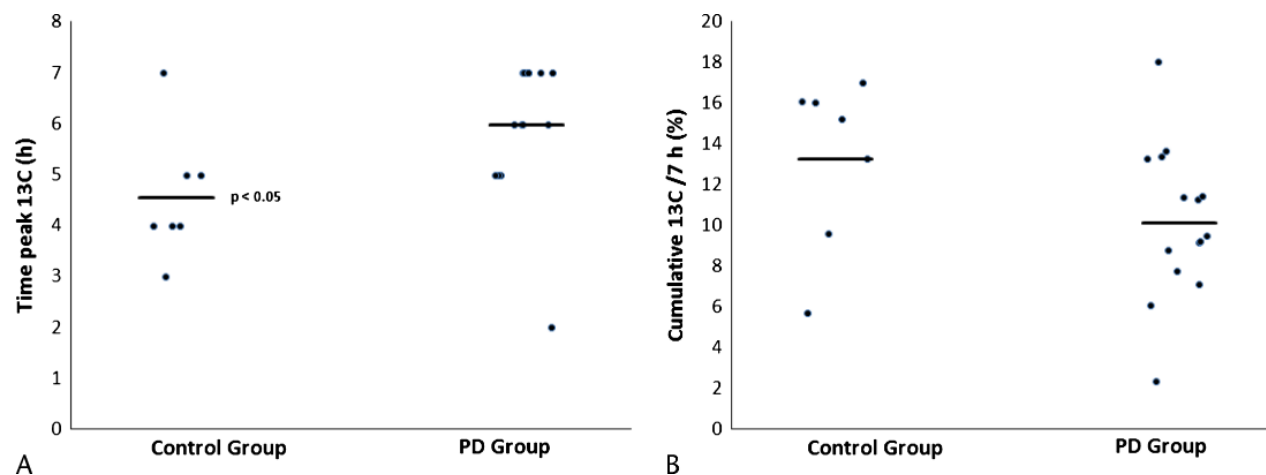


FIGURE 2. A, Time to reach ¹³C peak values in the control group and PD group. B, Seven hours after ingesting the ¹³C, the cumulative recovered ¹³C in the control group and PD group.

These hypotheses explain the normal anthropometric values.^{8,16,18} The intestinal adaptive response to pancreatic insufficiency may differ from nutrient to nutrient, justifying the punctual biochemical deficiencies, such as low serum vitamin B₁₂, folate, and iron in patients who underwent PD.^{27,30} Liposoluble vitamin deficiency is a predictable consequence when absorptive capacity of lipids is compromised,¹⁴ and abnormal serum vitamin E levels have been documented after PD,⁸ even after routine multivitamin supplementation.³¹ It is possible that the small intestinal bacterial overgrowth observed in the 5 patients may have contributed to reduce serum vitamins C and E, apart from retarding ¹³C peak values.

In PD, the loss of the biliopancreatic sphincter and the possible retrograde and slow contraction movement in the excluded loop³² may result in enteric reflux into the biliary tract, liver, and pancreas. These mechanisms can lead to bacterial contamination and inflammation in the liver and biliary tract,^{33–36} which justify the elevated alkaline phosphatase and C-reactive protein in this study. Regardless of a possible decrease in the absorptive capacity of nutrients, the inflammatory and oxidative stress could justify the deficiency of antioxidant vitamins C and E in patients who underwent PD.³⁷

The limitation of this study was the small sample size, justified by the strict inclusion criteria and survival rate of patients who had undergone PD, once high local recurrence rates in combination with the early metastatic spread lead to low survival rates after resection.³⁸ In this context, our study's sample size is similar to that in works, which included only late postoperative patients who underwent PD.^{14,15,27} We were cautious enough to exclude patients with recurrent tumor activity and those with short elapsed time after surgery, which may compromise the critical analysis of the results.

Among the strengths of this study, we may point out the standardization of surgical techniques, including pancreaticojejunal

clinical and nutritional status. This consideration is valid for minimally invasive surgery for PD,⁴¹ where the limitations of the surgical approach may require changes in the surgical technique that may result in a greater loss of pancreatic function.

In conclusion, after 12 months or more after PD, the patients had their body composition preserved but presented low serum α -tocopherol and ascorbic acid levels. Although fecal elastase-1 excretion is reduced in almost half of the patients, the absorptive capacity of lipids (as evaluated by ¹³C-labeled mixed triglyceride breath test) was satisfactory in most of them. It is possible that mild/moderate insufficiency is not detected by the ¹³C-labeled mixed triglyceride breath test, but it may be enough to lead to vitamin deficiency. Clinical and research priorities should be focused on a deeper understanding of the adaptive mechanisms of absorptive capacity after PD. It would also be interesting to evaluate the impact of venous vitamin supplementation on the health and quality of life of patients who undergo PD. Regardless of the absorptive capacity of lipids in late postoperative period, the obtained data point out that the patients need specific vitamin supplementation.

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