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REVIEW ARTICLE

Assessment of Exocrine Function of Pancreas Following Pancreaticoduodenectomy

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Abstract

Pancreatic exocrine insufficiency (PEI) is a common long-term complication after pancreaticoduodenectomy (PD) and is observed in 23–80% of patients. As the postoperative mortality after PD has substantially decreased, it warrants more attention on the diagnosis and treatment of functional long-term consequences after PD. These include PEI and endocrine insufficiency that can result in significant nutritional impairment and often adversely impacts quality of life (QOL) of the patient. A PubMed search was performed for articles using key words "pancreatic exocrine insufficiency"; "pancreaticoduodenectomy"; "quality of life after pancreaticoduodenectomy"; "stool elastase"; "direct, indirect tests for pancreatic exocrine insufficiency"; "pancreatic enzyme replacement therapy." Relevant studies were shortlisted and analyzed. This review summarizes relevant studies addressing PEI following PD. We also discuss functional changes after PD, risk factors and predictive factors for postoperative PEI, clinical symptoms, direct and indirect tests for estimation of PEI, pancreatic enzyme replacement therapy (PERT), and QOL after pancreatic resection for malignancy. It was found that significant PEI occurs in most patients following PD. Fecal elastase 1 is an easy indirect test and should be performed routinely in both symptomatic and asymptomatic patients after PD. PERT should be considered in every patient after PD with the aim to improve the QOL and perhaps even their long time survival.

Keywords Pancreatic exocrine insufficiency · Pancreatic cancer · Periampullary cancer · Pancreaticoduodenectomy · Stool elastase

Introduction

Pancreatic exocrine insufficiency (PEI) is defined as inadequate pancreatic enzyme activity for digestion caused by insufficient pancreatic enzyme production, insufficient activation, or disturbed enzyme deactivation [1]. PEI is a known complication of malignant diseases, pancreatic resection, and post-surgical alteration of the anatomy of the foregut [1, 2]. The available data indicate that PEI occurs in 46–100% of patients with resectable pancreatic and ampullary cancers [3].

The pancreatic secretion is a clear fluid liquid, 97% of water and electrolytes [4], and 3% of proteins. These 3% of proteins are mainly represented by proteases (80%), amylase (7%), lipase (4%), and nucleases (1%) [5]. Normal absorption of nutrients involves a complex mixture of digestive enzymes and bile salts, and an intact intestinal mucosa to enable the uptake of these hydrophobic complexes. Under normal condition, pancreatic enzyme release occurs in response to nutritional intake. The initial stimulus is seeing, smelling, and tasting of food which is vagal mediated and termed cephalic phase [6]. Next, gastric distension increases pancreatic enzyme secretion via the gastropancreatic reflex (gastric phase) [7]. The passage of chime through the duodenum provides the most robust stimulation of exocrine pancreatic secretion, particularly the passage of hydrolyzed triglycerides. This is termed as intestinal phase mostly mediated by cholecystokinin [8–10].

In patients following pancreaticoduodenectomy (PD), a duodenal resection, which is the strongest pancreatic exocrine

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stimulator, contributes to decreased postprandial enzyme secretion. This decreased pancreatic exocrine secretion shifts the site of maximal nutrient absorption from the proximal to distal small intestine [3]. Mechanisms of PEI include reduction of glandular tissue following pancreatic resection, impending postoperative pancreatic duct occlusion, extensive denervation following lymph node dissection, and surgically altered anatomy [11].

Functional Changes After Pancreaticoduodenectomy

Incidence of delayed gastric emptying (DGE) after PD is between 15 to 40% [12]. DGE is defined as gastric stasis requiring nasogastric intubation for 10 days or more or inability to tolerate a regular diet on 14th postoperative day. Preserving or resection of pylorus does not have a great impact in the occurrence of delayed gastric emptying [13]. Causes of DGE are decrease in the subjective perception of the occurrence of belching and nausea after PD due to absence of mechanoreceptors [14], presence of peritonitis as a result of postoperative complications such as intraabdominal abscesses, leakage of pancreaticojejunostomy, ischemia of the antropyloric muscle [15, 16]. Gastric scintigraphy is the preferred method to determine delayed gastric emptying. In general, gastric emptying function gradually recovers spontaneously to the preoperative level by 6 months after PD. Prokinetics can be used for clinical relief of symptoms.

With the resection of duodenum, the major digestive processes are disturbed and the delicately controlled digestive chain between the stomach, duodenum, and pancreatobiliary secretions is disrupted. A reduced production of pancreas-stimulating hormones such as gastrin, cholecystokinin, and secretin leads to an inadequate pancreatic secretion of bicarbonate. As a result, the gastric content is not neutralized to an optimal pH. Furthermore, reduced production of enterokinase by the duodenum leads to an inadequate activation of pancreatic proteolytic, amylolytic, and lipolytic enzymes [17].

The pathophysiology is complex and comprises of factors such as preoperative exocrine pancreatic function and the chosen surgical procedure of resection and restoration of gastrointestinal tract continuity. Up to 90–95% of the pancreatic enzyme output may be lost before clinical signs of exocrine insufficiency develop [18]. The most frequently described change in exocrine pancreatic function after PD is reduced digestion of fat [19]. Deterioration of the exocrine function occurs after pancreatic surgery depending on the extensiveness of resection. Another important factor regarding the exocrine function is whether the PD is combined with a partial resection of the stomach. First of all, there is an inadequate grinding of food particles. Secondly, a reduced secretion of secretin and cholecystokinin results in a reduced production of bicarbonate-rich fluid and digestive enzymes, such as amylase, lipase, and trypsinogen, which are important for the continuation of the digestion. Finally, the resection of the pancreatic parenchyma also contributes to a decreased production of pancreatic juices, leading to maldigestion and malabsorption of nutrients postoperatively [17].

Predictive Factors for Postoperative Exocrine Insufficiency

Male gender, malignant pathology, presence of a partial gastrectomy, neoadjuvant chemotherapy, adjuvant chemotherapy, and adjuvant radiation therapy were associated with development of postoperative PEI [20, 21]. Body mass index, pathologic pancreatitis, and neoadjuvant radiation therapy were not associated with development of PEI [20].

On multivariate analysis of study by Pei-wen Lim et al. [20], the presence of adjuvant therapy and the presence of a PD were associated with the development of postoperative PEI. Relative risk of developing postoperative PEI is 2.3 in patients undergoing PD and 2.2 in patients undergoing adjuvant chemotherapy [20]. Multiple authors [22] used the pancreatic main duct diameter, the pancreatic glandular diameter, and the degree of pancreatic fibrosis as predictors for postoperative PEI [22]. Focusing on the main pancreatic duct diameter, Sato et al. reported in 44 patients that a preoperative duct diameter > 10 mm was associated with a lower postoperative para-aminobenzoic acid (PABA) excretion at 2 months in comparison with normal preoperative duct diameter < 3 mm (53% versus 89%) [23]. Addressing postoperative pancreatic main duct dilatation, Matsumoto et al. failed to prove a correlation between postoperative duct dilation (> 3 mm) and fecal elastase 1 excretion [24]. Assuming anastomotic structuring to be the culprit of duct dilation in this study, the authors concluded that a reduction of pancreatic tissue contributed more than an anastomotic stricture to postoperative PEI [24]. Nakamura et al. compared postoperative 13C-labeled mixed triglyceride breath testing in 52 patients who underwent pylorus-preserving PD for intraductal papillary mucinous neoplasms, ampullary cancer, pancreatic cancer, and cholangiocarcinoma with pancreatic parenchymal thickness on computer tomography imaging. A postoperative pancreatic parenchymal thickness cutoff of 13 mm identified PEI with a sensitivity and specificity of 88.2% and 88.9% respectively [25].

Clinical Symptoms

Typical symptoms of PEI are abdominal discomfort, weight loss, steatorrhoea, malnutrition, and vitamin deficiency [26, 27]. Steatorrhoea and azotorrhoea, an excessive discharge of nitrogenous substances in the feces, occur when secretion of lipase and trypsin fall below 5–10% of normal levels. Typical features of steatorrhoea are voluminous fatty (shiny and

sticky) stools [28, 29]. Steatorrhoea is conventionally diagnosed when daily stool fat excretion exceeds 7 g during ingestion of a diet containing 100 g fat per day [30]. Often, steatorrhoea is accompanied by diarrhea. This is partly caused by accelerated gastric emptying and intestinal transit in patients with PEI that can also reversed by enzyme supplementation [31].

As a consequence of fat malabsorption, fat-soluble vitamins are insufficiently absorbed so that patients may exhibit low vitamin D levels and develop osteopathy, i.e., osteopenia, osteoporosis, and osteomalacia [32–35]. Vitamin A deficiency can occur causing night blindness, visual impairment, and other ocular infections. As a consequence of vitamin E and K deficiency, neurologic symptoms or coagulopathy can occur [26].

Pancreatic Function Tests

How frequent is exocrine insufficiency present in patients who undergo PD? This question has not been addressed to any degree in the literature. The function of the exocrine pancreas is difficult to assess because of its anatomic inaccessibility and large reserve capacity. The diagnosis and treatment of PEI is of increasing importance to maintain patients in an optimal condition to withstand treatment and to improve outcome.

There are direct and indirect methods for estimation of PEI. Direct measurements, in general, require duodenal intubation and aspiration of pancreatic secretion after administration of secretagogues [36, 37]. The direct methods of identification of PEI though very sensitive and specific are invasive, time-consuming, and expensive [38, 39]. The indirect tests on the other hand are relatively simple to perform and measure either the pancreatic enzyme or the by-products of enzyme activity (Table 1).

Table 1 Various tests for determining pancreatic exocrine insufficiency

Direct	Indirect (all are tubeless)
Invasive	
Secretin test	Pancreolauryl test
Secretin-cholecystokinin test	Bentiromide test
Secretin-caerulein test	Dual-label Schilling test
Secretin-bombesin test	Quantitative fecal fat excretion
Intraductal secretin test	Triglyceride breath test
Serum pancreatic polypeptide	Fecal fat analysis
Lundh test	Serum glucose level
Noninvasive test (tubeless)	
Serum trypsin levels	
Fecal chymotrypsin	
Amino acid consumption test	
Fecal elastase 1	

Direct Tests

The fecal excretion of pancreatic enzymes correlates with duodenal enzyme secretion [40]. Tests requiring duodenal intubation (secretin and Lundh test) cannot be applied for post-PD patients and hence are not being discussed hereunder [41–44]. Pancreatic enzymes are inactivated to different degrees during gastrointestinal transit. Chymotrypsin and elastase 1 are more stable enzymes and are therefore suitable for stool testing.

Fecal Chymotrypsin

The activity of chymotrypsin in stool can be tested photometrically. To improve the sensitivity of the test, three different stool samples are necessary and this partly explains why chymotrypsin measurements have been largely replaced by measurement fecal elastase 1 which only requires a single stool sample. Moreover, since a differentiation between human and substituted chymotrypsin is not possible, the test results are influenced by pancreatin supplementation. Thus, it is important that these enzyme supplements are discontinued at least 5 days before the examination. On the other hand, the chymotrypsin test can also be used to monitor a patient's compliance with enzyme supplementation in refractory cases. The main drawbacks of this test are its low sensitivity and specificity in patients with mild or moderate pancreatic exocrine insufficiency [45].

Fecal Elastase 1

Estimation of fecal elastase 1 in stool by ELISA (enzyme-linked immunosorbent assay) is a relatively inexpensive, non-invasive, and simpler test. Testing for elastase 1 in the stool has several advantages over testing for fecal fat, trypsin, or chymotrypsin. The test does not require a timed stool collection or special diet and has a 99% negative predictive value for pancreatic insufficiency [46].

Elastase 1, a serine endopeptidase produced by the pancreas, is composed of 240 amino acids and its molecular weight is 26 kD. Elastase 1 remains bound to bile acids during its passage through the intestine and is concentrated further in the large intestine. Human pancreatic elastase 1 remains undegraded during intestinal transit and absolutely pancreatic specific. Therefore, its concentration in feces reflects exocrine pancreatic function. Stool elastase test became commercially available at the end of 2001.

It has several advantages namely:

1. It is stable at a wide range of pH and temperature and is resistant to proteolytic cleavage [47].
2. Intraindividual variation of pancreatic elastase 1 concentration is low [47].

3. The measurement of stool elastase 1 is not affected by exocrine pancreatic supplements [47].
4. It can be measured on a spot sample of stool by sandwich ELISA [47].

Values > 200 μg elastase/gm stool indicate normal exocrine pancreatic function, between 100 and 200 μg elastase/gm stool indicate mild to moderate PEI, and < 200 μg elastase/gm stool indicate severe PEI [24].

The diagnostic efficiency of pancreatic elastase 1 determination in stool has been evaluated in many clinical studies. Laser et al. reported 93% sensitivity and 93% specificity for the diagnosis of PEI [48]. Stein et al., Laser et al., and Katschinski et al. have demonstrated a good correlation between elastase 1 and invasive intubation tests (i.e., the secretin-pancreozymin test and the secretin-caerulein test) [48–50]. Pancreatic elastase 1 stool test has been shown to be more sensitive than the fecal chymotrypsin test, especially in mild to moderate PEI [51]. Laser et al., Katschinski et al., Glasbrenner et al., and Gullo et al. showed that elastase 1 determination is more specific than the pancreolauryl test at a comparable sensitivity [48, 50, 52, 53].

Basic Principle of the Assay

The ELISA plate is coated with a monoclonal antibody which only recognizes human pancreatic elastase 1. Elastase 1 samples and standards bind to the antibody and are immobilized on the plate. A complex of monoclonal anti-elastase 1 biotin and peroxidase streptavidin binds to elastase 1 during the next incubation.

Indirect Tests

Pancreolauryl Test

The pancreolauryl test (fluorescein dilaurate test) is no longer commercially available in many countries. The patient ingests a substrate that is metabolized by pancreatic enzymes. The metabolite is absorbed from the gut, conjugated, and excreted in urine, where it can be measured. Increased fecal excretion of the unsplit molecule and decreased absorption, blood levels, and urinary excretion of metabolite will occur in patients with PEI. To account for interindividual variability of intestinal absorption and renal function, the fluorescein dilaurate test includes application of the absorbable metabolite (fluorescein) on a second day and the results are expressed as the ratio of excreted fluorescein on the test and control day in percent. A ratio of less than 20% is clearly abnormal. A modified serum test eliminates the need for a second test day but does not increase sensitivity and specificity [54].

Breath Tests

Several breath tests using 13C-labeled substrates for measurement of pancreatic function have been developed during the recent years [53]. Of these, tests using 13C-labeled lipids are most promising. The labeled lipids are ingested orally together with a test meal and need to be digested to monoglycerides and free fatty acids by pancreatic lipase prior to absorption. Hepatic metabolism of the absorbed lipids leads to production of 13CO2 which is transported to the lung and exhaled. Thus, the ratio of breath 13CO2/12CO2 over time reflects intestinal lipolysis by pancreatic lipase as the rate-limiting step of lipid absorption. Available substrates include 1,3 distearyl-2[13C]-octanoate, called 13C-mixed triglyceride, which has several advantages over other lipid markers and is most commonly used. Other potential lipid markers are uniformly labeled Hiolein and cholesteryl-13C-octanoate [54]. Sensitivity and specificity of certain test modifications have been reported to exceed 90% [55]. Moreover, a modified version of the 13C-mixed triglyceride breath test has been shown to also detect mild to moderate PEI [56]. A major disadvantage of the test is the need for prolonged breath sampling. Retrospective comparison of test results in a large group of patients has shown that an abbreviated version requiring breath sample for 4 h still provides a high accuracy but that shorter tests lack specificity [57]. Apart from diagnosis of PEI, 13C-breath tests can also be used to monitor the effect of enzyme replacement therapy [58].

Fecal Fat Analysis

The 72 h stool for fecal fat estimation is considered the "gold standard" indirect test for estimation of PEI [59–61]. However, the test is cumbersome for patients as well as for laboratory personnel. The study requires the patient to be on a higher fat diet (600 g per day) and collect all stools produced in the last 72 h of the study period. For laboratory personnel, the test entails handling of large volume of stool.

Pancreaticoduodenectomy and PEI

PD has been performed to treat malignant and benign diseases of the pancreas and periampullary area [62, 63]. Quality of life (QOL) decreases if there is an impairment of the pancreatic exocrine function during the postoperative period [64]. PEI is common in those patients about to undergo PD, particularly those with adenocarcinoma [65]. The development of PEI after pancreatic surgery is an understudied topic even though it has been reported as a common clinical manifestation after surgery.

Alessandro Codivilla performed the first known PD in 1898 in Italy [66], followed by Kausch 11 years later. There

are two operation techniques performed predominantly: the classic Whipple operation developed and modified by Whipple [67], and the pylorus-preserving procedure inaugurated by Watson [68] and popularized by Traverso et al. [69]. In the classic PD, an antrectomy or distal gastrectomy is associated to the resected specimen. Gastric resection is avoided in the pylorus-preserving modification.

Following PD, prevalence of PEI remains at a high rate of 70–100% irrespective of whether patients undergo Whipple or pylorus-preserving PD and whether pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ) is performed [3]. Yamaguchi et al. compared postoperative prevalence of PEI in patients undergoing PD ($n = 10$) and pylorus-preserving PD ($n = 44$) [70]. Patients in the PD cohort had mostly pancreatic cancer, ampullary cancer, and cystic neoplasms, whereas only half of pylorus-preserving PD were performed for pancreatic malignancy. Within 3 months postoperatively, mean PABA excretion decreased in both cohorts from 61.6 to 41.3% and 69 to 48.8% respectively [70].

PJ is the most common pancreaticoenteric anastomosis followed by PG in the setting of PD and pylorus-preserving PD [71, 72]. The initial study by Lemaire et al. detected PEI in 94% of patients based on a 72-h fecal fat excretion (median 28 g/24 h) and in 100% of patients based on fecal elastase 1 at 32 months (median) following PD with PG [73]. Nakamura et al. found PEI utilizing 13C-labeled mixed triglyceride breath testing 62.3% of 61 patients with a PG following PD or pylorus-preserving PD with a postoperative follow-up range of 3–108 months [74]. Lastly, Jang et al. compared the prevalence of PEI in 20 patients undergoing PJ with 14 patients undergoing PG in the setting of pylorus-preserving PD [75]. Based on fecal elastase 1 testing, 95% patients in PJ cohort and 100% in the PG cohort had PEI at 21.9 and 26.5 months, respectively, although most patients remained asymptomatic [75].

In those with normal exocrine function preoperatively, the pancreatic parenchymal loss with PD will result in a reduction to abnormal secretory capacity in two-thirds of cases. Pancreatic enzyme supplementation should be considered preoperatively in many patients and in almost all cases postoperatively because of the parenchymal reduction associated with PD.

Classical studies [30, 76] 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 PEI after resectional surgery is steatorrhoea [17], i.e., stool fat content of more than 7 g/dl, which may associate abdominal pain, flatus, and mostly weight loss. Fat malabsorption occurs when pancreatic lipase and trypsin decrease below 5% of normal values.

Christopher M. Halloran et al. [77] analyzed 40 patients following resection for pancreatic malignancy and examined the coefficient of fat absorption, symptoms, QOL, and accuracy of fecal elastase 1 measurement to predict PEI. They concluded that PEI was common and sustained following resection and not associated with significant symptoms. These patients had a tendency toward poorer quality of life. Postoperative pancreatic enzyme replacement should be considered more routinely. Morera-ocon FJ et al. [78] reviewed the data on fecal elastase in a series of PD performed by using both types of pancreatic anastomosis, PG and PJ. Elastase was measured by ELISA to estimate the postoperative pancreatic exocrine function. Stool elastase levels were available in 108 patients, 76 PG, and 32 PJ. Average age was 62.7 years ± 10.9, mostly men (64.8%). Malignancy was the most predominant pathological diagnosis. Mean fecal elastase levels after PD in their series was 57.9 μg ± 104.3. The mean fecal elastase in the PG group was 61.1 μg ± 116.4 and it was 50.2 ± 68.5 in the PJ group. The statistical analysis did not show significant difference between elastase levels in both groups ($p = 0.6222$). They found an evident decrease in stool elastase levels of patients after PD. This decrease is not influenced by the type of pancreatic drainage used. They concluded that regardless of the type of pancreatic anastomosis performed after PD, pancreatic exocrine function after pancreatic resection should be surveyed.

Lemaire et al. [73] evaluated pancreatic exocrine and endocrine function, pancreatic atrophy, and main pancreatic dilatation in the pancreatic remnant following PD in 19 patients with median interval between operation and evaluation was 32 (range 12–120) months. PEI was assessed by measuring 72 h fecal fat concentrations and fecal elastase 1. They found 16 of 17 patients had raised fecal fat excretion and fecal fat elastase was reduced in all 17 patients analyzed, with a median concentration of 12 μg per gm stool. Pei-wen Lim et al. [20] analyzed the long-term risks of PEI in patients who underwent pancreatectomy from 2002 to 2012. They found 94 (43%) of 214 subjects without preoperative exocrine insufficiency developed exocrine insufficiency. Twenty (21%) did so within 30 days, 29 (31%) between 30 and 90 days, and 45 (48%) after 90 days. They also concluded that reporting 30-day functional outcomes for pancreatic resection is insufficient, as nearly 45% of subjects who develop disease do so after 90 days. Reporting of at least 90-day outcomes may more reliably assess risk for postoperative endocrine and exocrine insufficiency.

Satti Bebarry et al. [46] evaluated the role of fecal elastase 1 as a marker of exocrine pancreatic insufficiency and concluded fecal elastase 1 as a useful noninvasive screening test of pancreatic insufficiency. Similarly, E.C.M Sikkens et al. [79] evaluated the course of pancreatic function, before and after pancreatic resection. Exocrine function was determined before and after surgery by measuring monthly fecal elastase 1 concentration. Twenty-nine patients were included, 12 with pancreatic cancer, 14 with ampullary carcinoma, and three with

Table 2 A summary of reports measuring stool elastase after pancreaticoduodenectomy

Author	Number of patients	Postoperative period	Mean or median stool elastase μg/g stool
Lemaire et al. [73]	19	32 (12–70) months	12 (1–34)
Lyubimova et al. [81]	24	14 days–20 years	29 (16–85)
Pessaux et al. [82]	18	40 (3–104) months	74 (0–32)
Mariani et al. [83]	13	21 (11–44) day	50
Christopher M. H et al. [77]	40	6 weeks	101 (59–144)
		3 months	88 (46–129)
		6 months	104 (56–152)
		12 months	92 (39–145)
Morera-Ocon FJ et al. [78]	108		57.9 ± 104.3
E.C.M Sikkens et al. [79]	57	6 months	30 (20–46)

bile duct carcinoma. Thirteen patients had exocrine insufficiency at preoperative diagnosis. After a median follow-up of 6 months, this had increased to 24 patients and concluded that most patients with tumors in pancreatic region requiring pancreatic resection either had PEI at diagnosis or became exocrine insufficient soon after surgical resection. Hans G. Beger et al. [80] conducted a systematic review and a meta-analysis to assess the frequency and severity of new onset of diabetes mellitus and PEI after PD. They concluded that there was a significant decrease in exocrine function after PD (Table 2).

Pancreatic Enzyme Replacement Therapy

In order to avoid maldigestion and ameliorate the nutritional status of patients with PEI, the cornerstone of treatment is pancreatic enzyme replacement therapy (PERT) [84–86]. Available formulations contain pancreatic enzymes encapsulated in microgranules or minimicrospheres with a pH-sensitive coating in order to either prevent the release and the subsequent inactivation of enzymes by gastric acidity or to release the enzymes into the intestinal lumen where the pH is higher and optimal for the digestion and absorption of food. Currently, the Italian guidelines also suggest minimicrospheres to be the ideal pancreatin formulation [87].

The initial recommended dose of pancreatic extract which should be given is 40,000–50,000 units of lipase per meal and 25,000 units per snack, and this dose should be progressively increased until the steatorrhea is totally or sufficiently reduced [1, 88]; this dosage should be maintained over time. It has been reported that in patients undergoing a pylorus-preserving PD for malignancy, gastro-protected microspheres were less effective than those in patients who had undergone a classic Whipple technique probably because microspheres are retained in the stomach [89]. Anatomical changes secondary to reconstruction after a PD lead to important physiological alterations which frequently correlate with the severity of postoperative PEI. PD (either Whipple or pylorus preserving) is associated with several and complex pathophysiological events such as (1) disturbance of gastric fundus relaxation caused by the disappearance of antro-fundic and duodenal-fundic reflexes, (2) the absence of neutrally stimulated pancreatic excretion caused by the lack of fundus relaxation, (3) the reduction of cholecystokinin-mediated stimulation of pancreatic secretion secondary to duodenal resection, (4) large and hard to digest nutrient particles reaching the jejuna lumen due to resection of the distal stomach, (5) reduction in exocrine pancreatic secretion due to pancreatic head resection, and (6) asynchrony between the gastric emptying of nutrients and biliopancreatic secretion as a result of anatomical reconstruction [90–92].

For these reasons, every patient who is candidate for a PD should be considered at increased risk for PEI regardless of the underlying disease [24, 91]. Therefore, it has been suggested that, after PD, PERT be given to all patients with malignancy, especially those with impending adjuvant therapy [24, 93, 94].

In Fig. 1, an algorithm is suggested for diagnosis and treatment of PEI.

Quality of Life

QOL is an important outcome measure after pancreatic resection for malignancy because various surgical approaches aimed at prolonged survival can have a great impact on patient performance. Although many studies have addressed the QOL issue, it is difficult to compare results because of difference in methods, study designs, and patient characteristics in these studies. The instruments used for QOL assessment range from visual analogue scales, standardized health care-related questionnaires in combination with a standard functional assessment of Cancer Therapy Hepatobiliary quality of life survey [95] to an EORTC (European Organisation for Research and Treatment of Cancer) quality of life questionnaire C30 core questionnaire [96] in combination with a disease-specific

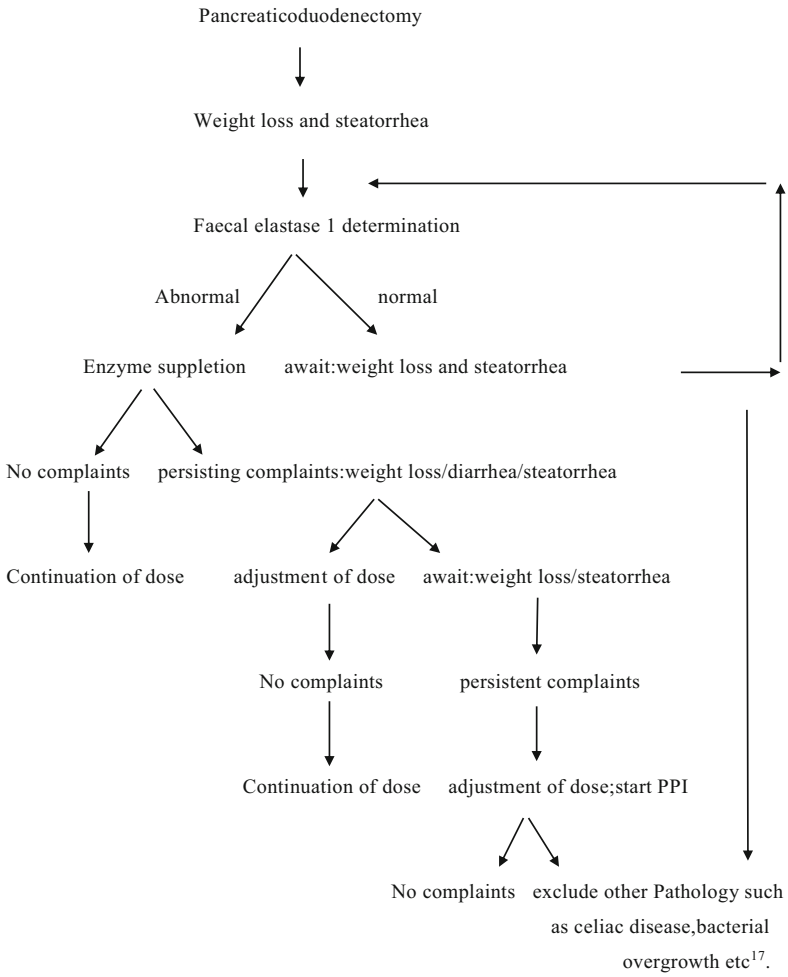

Fig. 1 Algorithm suggested for diagnosis and treatment of PEI

Gastrointestinal Quality of Life Index [97, 98]. Most studies revealed a large decrease in most QOL scales immediately after surgery followed by a slow recovery to preoperative level by 12–24 months after surgery. The surgical techniques of resection and reconstruction do not seem to affect QOL.

Conclusions

PEI is a known complication of PD. The resulting symptoms have a substantial impact on the patient's QOL. Now that the postoperative mortality after PD has substantially decreased, more attention should be focused on the diagnosis and treatment of the functional consequences after PD. Though direct methods of identification of PEI are very sensitive and specific, noninvasive tests are relatively simple to perform. Estimation of fecal elastase 1 in stool by ELISA is a relatively inexpensive noninvasive and simpler test. Evident decrease in stool elastase level of patients after PD is found which is not influenced by type of pancreatic anastomosis used. Postoperative pancreatic enzyme replacement should be considered more routinely. Stool for elastase should be periodically monitored to guide this therapy.

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