Pancreatology 22 (2022) 1020–1027

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Pancreatic exocrine insufficiency following pancreatoduodenectomy: A prospective bi-center study

V.J. Kroon [a, 1], L.A. Daamen [a, b, 1], D.S.J. Tseng [a, 1], A. Roele- de Vreugd [a], L.J.H. Brada [a], O.R. Busch [c], T.C. Derksen [a], A. Gerritsen [a], S.J.E. Rombouts [a], F.J. Smits [a], M.S. Walma [a], R.A.W. Wennink [a], M.G. Besselink [c], H.C. van Santvoort [a, 2], I.Q. Molenaar [a, 2, *]

[a] Dept. of Surgery, Regional Academic Cancer Center Utrecht, University Medical Center Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, the Netherlands
[b] Dept. of Radiation Oncology, UMC Utrecht Cancer Center, Utrecht University, Utrecht, the Netherlands
[c] Dept. of Surgery, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 20 February 2022
Received in revised form
6 June 2022
Accepted 1 August 2022
Available online 5 August 2022

Keywords:
Pancreatic exocrine insufficiency
pancreatic surgery
pancreatic cancer
pancreatic enzyme replacement therapy

ABSTRACT

Background/objectives: Pancreatic exocrine insufficiency (PEI) is a common complication following pancreatoduodenectomy (PD) leading to malnutrition. The course of PEI and related symptoms and vitamin deficiencies is unknown. This study aimed to assess the (long-term) incidence of PEI and vitamin deficiencies after PD.

Methods: A bi-centre prospective observational cohort study was performed, including patients who underwent PD for mainly pancreatic and periampullary (pre)malignancies (2014–2018). Two cohorts were formed to evaluate short and long-term results. Patients were followed for 18 months and clinical symptoms were evaluated by questionnaire. PEI was based on faecal elastase-1 (FE-1) levels and/or clinical symptoms.

Results: In total, 95 patients were included. After three months, all but three patients had developed PEI and 27/29 (93%) patients of whom stool samples were available showed abnormal FE-1 levels, which did not improve during follow-up. After six months, all patients had developed PEI. During follow-up, symptoms resolved in 35%–70% of patients. Vitamin D and K deficiencies were observed in 48%–79% of patients, depending on the moment of follow-up; 0%–50% of the patients with deficiencies received vitamin supplementation.

Discussion: This prospective study found a high incidence of PEI after PD with persisting symptoms in one-to two thirds of all patients. Limited attention was paid to vitamin deficiencies. Improved screening and treatment strategies for PEI and vitamins need to be designed.

1. Introduction

Pancreatic exocrine insufficiency (PEI) is a common complication following pancreatoduodenectomy (PD) for either benign or malignant indications, with a median prevalence of 74% (range 36%–100%) at six months postoperatively [1,2]. PEI results from the both the partial pancreatectomy and duodenectomy [3]. Duodenectomy leads to reduced serum levels of secretin and cholecystokinin, which decreases bicarbonate and pancreatic fluid release [3,4]. The decrease in bicarbonate and pancreatic fluid release results in a suboptimal pH for digestion and less transfer of pancreatic enzymes, respectively [4–6]. In combination with the loss of pancreatic parenchyma, this substantially reduces the pancreatic secretory capacity after PD [3].

The diagnosis of PEI is generally based upon clinical symptoms and can be supported by laboratory faecal testing. Typical manifestations of PEI include steatorrhea, weight loss, muscle wasting, foul smelling stools, malabsorption, and flatulence [2,7,8]. Malabsorption caused by PEI, resulting in malnutrition, can be reflected by the presence of serum vitamin A, D, E and K deficiencies [9].

* Corresponding author. Regional Academic Cancer Center Utrecht, UMC Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, the Netherlands, HP G 04.228, PO Box 85500, 3508 GA, Utrecht, the Netherlands.
E-mail addresses: I.Q.Molenaar@umcutrecht.nl, v.j.kroon@students.uu.nl (I.Q. Molenaar).
[1] authors share first authorship.
[2] authors share senior authorship.

https://doi.org/10.1016/j.pan.2022.08.002

Laboratory tests are direct tests such as 72-h faecal fat excretion, and indirect tests such as faecal elastase-1 (FE-1) [10]. Of these, FE-1 testing is most commonly used, as it is easy, quick and non-invasive. Elastase-1 is an enzyme produced by the pancreas and excreted in the faeces, which gives an approximation of the pancreatic exocrine function [11]. Nevertheless, the diagnostic accuracy of FE-1 is only moderate, given that its correlation with severity of clinical symptoms following resection for (pre)malignancies was found to be mediocre [11–13].

Although PEI can be treated with pancreatic enzyme replacement therapy (PERT), it often remains underdiagnosed and subsequently undertreated [14]. [-16] Moreover, the long-term course of PEI during follow-up after PD is unknown, as prospective studies on this subject are lacking. PERT was found to be associated with improved survival in patients with pancreatic and periampullary malignancies by improving their nutritional status [14,17]. PEI is also known to have a significant impact on quality of life (QoL) of patients, which can be improved with adequate treatment [14–16]. This emphasizes the need for more awareness for the presence of (undertreated) PEI after PD, enabling early diagnosis and treatment optimization.

The aim of this study is twofold: first, to assess the (long-term) incidence and course of PEI in a prospective cohort of patients after PD for pancreatic and periampullary (pre)malignancies, and second, to assess the incidence of vitamin deficiencies in these patients.

2. Methods

2.1. Study design

The prospective observational Exocrine Pancreatic Insufficiency in Pancreatic Surgery (EPIPS) cohort study was performed in two Dutch centres for pancreatic surgery, the University Medical Center Utrecht (UMC Utrecht) and Amsterdam UMC. Two cohorts were followed for 18 months including patients who underwent PD for a suspected or confirmed pancreatic or periampullary (pre)malignancy between 2014 and 2018. The first cohort included patients prior to surgery (cohort A) and the second cohort included patients who survived at least two years after pancreatic surgery, to evaluate the long-term incidence of PEI (cohort B). This distinction was made since long-term survival is relatively uncommon in patients with pancreatic and periampullary malignancies. All participants provided informed consent to participate in the study. Patients were deemed non-eligible for inclusion if they were younger than 18 years or if other causes for fat malabsorption were present (e.g. cancer recurrence, inflammatory bowel disease, celiac disease, cystic fibrosis, major gastrointestinal surgery other than PD). The institutional review board of the UMC Utrecht approved the study (NL43502.041.13).

2.2. Follow-up

Both cohorts were followed over a period of 18 months: for cohort A, follow-up was conducted 3, 6, 12 and 18 months after surgery; for cohort B, follow-up was conducted after 24, 30, 36 and 42 months. If disease recurrence occurred after inclusion in cohort A or B, follow-up was terminated at the date of recurrence diagnosis.

2.3. Data collection

During each visit, a questionnaire regarding symptoms of PEI was completed. This questionnaire was based upon the questionnaires used by the Dutch Pancreatitis Study Group to evaluate PEI in patients with pancreatitis [18]. Questions included occurrence of flatulence, pain, nausea, vomiting and use of PERT. Furthermore, questions regarding frequency of bowel movements, consistency and colour of stool, and steatorrhea were included. Severity of symptoms was scored according to the Common Terminology Criteria for Adverse Events (CTC-AE) score V4.03 [19]. In addition, blood and stool samples were collected. Blood samples were used for evaluation of vitamin A, D, E and K status, as well as blood glucose levels, HbA1c and INR; stool samples were used for FE-1 testing as a diagnostic test for reduced pancreatic secretion. Patients' records were retrospectively reviewed to collect additional data on PEI-related treatment and to determine the vital status of each patient.

2.4. Outcome

The primary outcome was the incidence of PEI before and after PD and the postoperative course of PEI during 42 months of follow-up. PEI was defined as reduced pancreatic exocrine secretion as indexed by FE-1 levels (Table 1) and/or PEI-related symptoms. PEI was considered not to be present in patients without symptoms and normal FE-1 levels. Patients with reduced pancreatic exocrine secretion who did not experience any PEI-related symptoms were deemed subclinical. Patients with PEI-related symptoms who did not receive PERT were deemed untreated. Patients whose symptoms persisted despite PERT were considered undertreated. Patients were considered having their symptoms resolved when receiving PERT and not experiencing symptoms of PEI. We used a combination of FE-1 levels and clinical symptoms for the definition of PEI as FE-1 levels alone can underdiagnose PEI in operated patients [20]. The treatment course was presented using a Sankey-diagram (available online at http://www.sankeymatic.com).

Secondary outcomes were the incidence and severity of symptoms, endocrine pancreatic insufficiency and vitamin A-, D-, E– and K-deficiencies. Vitamin K was tested using High Performance Liquid Chromatography, spectrofluorometry and coulometry with fractioning and pre-extraction. Definitions for the primary and secondary outcomes are presented in Table 1.

2.5. Sample size

Since this is a one-armed, non-comparative study, it is not possible to calculate an unequivocal sample size. In order to estimate a realistic and appropriate sample size we used the standard formula for the calculation of a level of confidence for a single proportion ($P\pm (Z_{\alpha}\cdot\sqrt{}$ (P(1-P)/N), and $d = Z_{\alpha}\cdot\sqrt{}$(P(1-P)/N)). From this formula the sample size (N) can be extracted:

$$N = \frac{Z_{\alpha^2} \cdot P(1-P)}{d^2}$$

N = sample size; Z_{α} = z statistic for level of confidence; P = expected prevalence of proportion; d = precision [21]

Since P (incidence of PEI) is the primary endpoint of this study and the reported incidence varies between 33 and 90%, it is difficult to choose a definite value for P. We therefore based the incidence of PEI after PD on recent publications, and used an estimated incidence of 65% (P = 0.65) [15,22]. With a level of confidence of 95% (z = 1.96) and d = 0.1, the calculated sample size is 87 patients.

2.6. Statistical analysis

Baseline characteristics were summarized descriptively to characterize the study population. Continuous data were presented as mean ± standard deviation (SD) or median with interquartile

Table 1
Definition outcomes.

Pancreatic exocrine secretion as indexed by FE-1 test	
Normal pancreatic exocrine secretion	>200 μg/g
Mild-moderate reduction of pancreatic exocrine secretion	100–200 μg/g
Severe reduction of pancreatic exocrine secretion	<100 μg/g
Secondary outcomes	
Endocrine pancreatic insufficiency	HbA1c > 42 mmol/l and/or use of oral antidiabetics or insulin
Vitamin A deficiency	<0.6 μmol/L
Vitamin D deficiency	<50 nmol/L
Vitamin E deficiency	<12 μmol/L
Vitamin K deficiency	<0.8 nmol/L

PEI, Pancreatic Exocrine Insufficiency; FE-1, Faecal Elastase - 1.

range (IQR), depending on a normal or non-normal distribution. Categorical data were presented as frequencies with percentages.

Univariate analyses were performed to compare symptoms and laboratory measurements between patients with and without PEI as indexed by FE-1 levels. Categorical variables were compared using the Chi-squared or the Fisher exact test, depending on group size. Students' t-test and Mann-Whitney *U* test were used to compare continuous variables. To determine the relation between PEI, as indexed by FE-1 levels, and symptom severity, Spearman coefficients were computed. To compare preoperative FE-1 levels to postoperative levels, the Wilcoxon Signed Rank test was used. A P-value < 0.05 was considered statistically significant.

3. Results

In total, 95 patients were included: 72 patients in cohort A and 23 patients in cohort B (Supplementary Table 2). Baseline characteristics are shown in Table 2.

3.1. Preoperative presence, treatment and symptoms of PEI

PEI, as defined previously, was present in 44/72 patients (61%) preoperatively (Fig. 1). Of these, 11 patients received PERT preoperatively, successfully resolving symptoms in two of them.

In 50/72 patients (69%), FE-1 was obtained preoperatively. Based on baseline FE-1 levels, 28 patients had reduced pancreatic secretion and 22 patients showed normal pancreatic secretion. Of patients with abnormal FE-1, 20 patients had severe reduction in pancreatic secretion and eight patients had mild-moderate reduction (Fig. 2). Baseline symptoms did not differ between patients with abnormal FE-1 levels and patients with normal FE-1 levels (Table 3). Both at baseline and at three months of follow-up, Spearman coefficients showed no significant association between severity of symptoms and FE-1 levels (Table 4). Only one out of eight patients with mild-moderate reduction of pancreatic secretion experienced PEI-related symptoms, resulting in seven out of eight having subclinical PEI, while 16/20 patients with severe reduction of pancreatic secretion had symptoms. Of patients with normal FE-1 levels, six experienced symptoms of PEI. Symptoms that were most frequently reported included weight loss (n = 49) and abdominal pain (n = 37).

Five out of 20 patients with severe reduction of pancreatic function based on FE-1 were receiving PERT preoperatively, which resolved symptoms in one case. There were no patients with mild to moderate reduction of pancreatic secretion receiving PERT.

3.2. Incidence and course of PEI during follow-up

At three months postoperatively, information of 66/72 patients (92%) was available. PEI symptoms and/or abnormal FE-1 levels were present in 58/66 patients (88%). Of these, 46 patients (79%) were treated with PERT, which resulted in resolving of symptoms in 21 patients (Fig. 1). Median PERT dosage was 1800 mg/day (= 150.000 units of lipase) in the undertreated group and 1350 mg/day (= 112.500 units of lipase) in the group that was symptom free after PERT treatment (P = 0.36). FE-1 test results were available in 29/66 patients (44%). Twenty-four patients had severe reduction of pancreatic secretion, three patients had mild-moderate reduction and two patients had normal pancreatic secretion based on FE-1 levels (Fig. 2). Median FE-1 was 15 μg/g (IQR 15–60 μg/g), as compared with 178 μg/g (IQR 25–368 μg/g) preoperatively (P < 0.001) (Supplementary Table 2).

After six months of follow-up, PEI was present in 55/59 patients, with the remaining 4/59 being unknown. Of 55 patients with PEI, 42 patients received PERT, resulting in the resolvement of symptoms in 19 patients (Fig. 1). FE-1 was available in 31 patients: 28 patients had severe reduction of pancreatic secretion and three patients had mild-moderate reduction. No patients were found to have FE-1 levels within the normal range (Fig. 2). Median FE-1 levels did not further change during follow-up (Supplementary Table 2). After twelve and eighteen months, treatment with PERT resulted in relieving symptoms in respectively 19/27 patients and 14/27 patients (Fig. 1).

3.3. Vitamin status

Preoperative vitamin status was available in 59/72 (82%) patients. Vitamin D deficiency was present in 34 patients and vitamin K deficiency occurred in 30 patients, whilst vitamin A or E deficiencies were not present. One patient with vitamin D deficiency received oral vitamin D supplementation. No patients with vitamin K deficiency were supplemented. Median vitamin D levels were 38 nmol/L in patients with abnormal FE-1 and 53 nmol/L in patients without abnormal FE-1 (P = 0.08). Median vitamin K levels were 0.80 nmol/L versus 0.95 nmol/L (P = 0.42) in patients with and without abnormal FE-1, respectively. Median INR was 1.04 versus 0.98 (P = 0.05). Median vitamin A levels were 1.7 μmol/L versus 2.0 μmol/L (P = 0.31) and median vitamin E levels were 38 μmol/L versus 53 μmol/L (P = 0.08) in patients with and without abnormal FE-1, respectively.

At three months of follow-up, 20/34 patients suffered from vitamin D deficiency and 18/33 patients from vitamin K deficiency. One patient had both a vitamin A and vitamin E deficiency (Table 5). Two patients with vitamin D deficiency received supplementation and one patient with vitamin K deficiency received supplementation. After six, twelve and eighteen months, vitamin D deficiency was present in 21/34 patients, 11/23 patients and 8/15 patients, respectively. Vitamin K deficiency was present in 27/34 patients, 13/23 patients and 11/16 patients, respectively (Table 5).

Table 2
Baseline characteristics.

	Cohort A (n = 72) [a]	Cohort B (n = 23) [b]
Age in years, median (IQR)	67 (60–76)	68 (63–73)
Male sex, n (%)	47 (65)	20 (87)
BMI, mean ± SD	27 ± 4.5	26 ± 2.6
ASA score, n (%)		
I	10 (14)	3 (13)
II	42 (58)	15 (65)
III	19 (26)	5 (22)
Type of surgical procedure, n (%)		
Open	56 (78)	22 (96)
Robot-assisted	16 (22)	1 (4)
Type of resection, n (%)		
Whipple	35 (49)	7 (30)
PPPD	37 (51)	16 (70)
Histopathological diagnosis, n (%)		
PDAC	32 (44)	3 (13)
Gallbladder carcinoma	1 (1)	0 (0)
Cholangiocarcinoma	11 (15)	3 (13)
Duodenal adenocarcinoma	8 (11)	1 (4)
Ampullary carcinoma	6 (8)	10 (43)
Ampullary adenoma	5 (7)	1 (4)
IPMN	2 (3)	4 (17)
NET	2 (3)	0 (0)
Other benign	4 (6)	1 (4)
Other malignancy	1 (1)	0 (0)
Pancreatic exocrine secretion inclusion based upon FE-1, n (%)		
Normal pancreatic exocrine secretion (>200 μg/g)	22 (31)	0 (0)
Mild-moderate reduction of pancreatic exocrine secretion (100–200 μg/g)	8 (11)	2 (10)
Severe reduction of pancreatic exocrine secretion (<100 μg/g)	20 (28)	18 (90)
Prevalence of PEI at inclusion, n (%)		
No PEI	26 (36)	0 (0)
Subclinical PEI	11 (15)	4 (19)
Untreated PEI	22 (31)	1 (5)
Undertreated PEI	9 (13)	9 (43)
PEI with resolved symptoms	2 (3)	7 (33)
Unclear	2 (3)	0 (0)

IQR, interquartile range; BMI, Body Mass Index; SD, Standard Deviation; ASA score, American Society of Anaesthesiologists score; PPPD, Pylorus-Preserving Pancreatoduodenectomy; PA, Pathological anatomy; PDAC, Pancreatic Ductal Adenocarcinoma; IPMN, Intraductal papillary mucinous neoplasm; NET, Neuroendocrine Tumour; PEI, Pancreatic Exocrine Insufficiency; FE-1, Faecal Elastase - 1.
[a] Included preoperatively.
[b] Included 24 months following surgery.

3.4. Endocrine pancreatic insufficiency

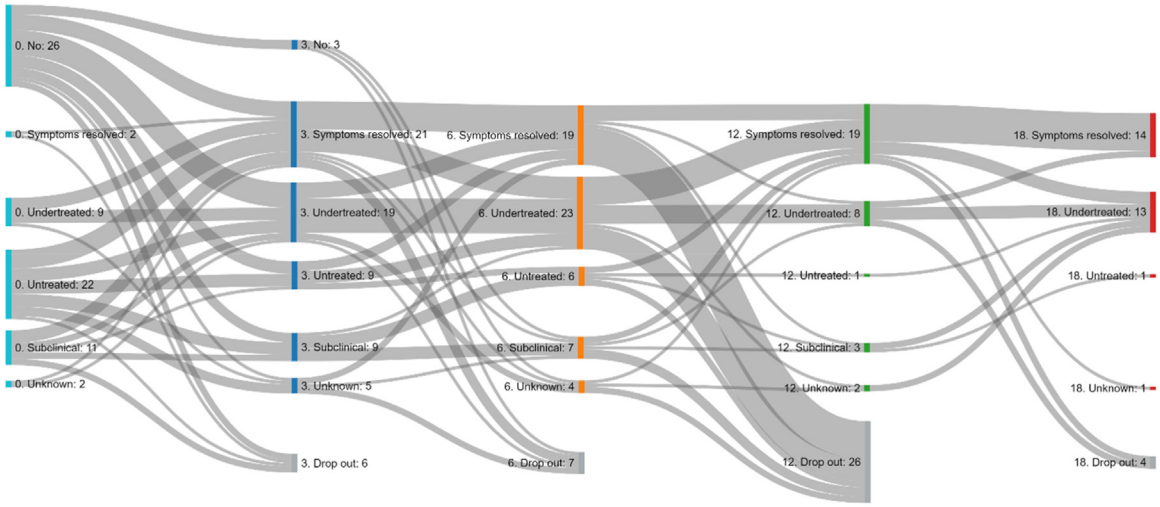
Baseline HbA1c was available for 61/72 patients (85%). Of these, 23 patients experienced endocrine pancreatic insufficiency prior to surgery and nine of them were using oral anti-diabetics and/or insulin. In patients with PEI at baseline, median HbA1c-levels were found to be 42 mmol/mol as compared with 36 mmol/mol in patients without PEI ($P = 0.04$).

4. Discussion

This prospective study found that PEI remains a frequent complication in patients after PD for pancreatic or periampullary (pre)malignancies. Almost all patients had developed PEI three months following surgery and FE-1 testing was abnormal in all but two patients. At six months after surgery, all patients were suffering from PEI, based on symptoms and/or FE-1 testing. In one-to two-thirds of patients with PEI-related symptoms during postoperative follow-up, symptoms persisted despite PERT. Vitamin deficiencies, mainly comprising vitamin D and K, were present in a substantial part of patients, indicating malabsorption. Few of them received vitamin supplements.

The results of this study reflect the widespread incidence of PEI and vitamin deficiencies in patients after PD, and the challenge to resolve PEI-related symptoms with PERT and vitamin supplementation. Treatment of PEI using PERT is proven to increase body weight, with the potential to overcome poor treatment efficacy by increasing the PERT dose [23,24]. In particular for pancreatic cancer patients, a good nutritional status and recovery of body condition after PD is important to increase the eligibility for adjuvant chemotherapy, which is highly associated with improved survival [25]. A study of Mackay et al. showed that a substantial part of patients does not receive chemotherapy after pancreatic cancer resection, due to complications, delayed recovery, and a poor performance state [26]. This emphasizes the need to optimize PERT shortly after resection, focusing on close monitoring for symptoms that indicate un- or undertreated PEI and patient counselling regarding the usage and dosage of PERT.

Nevertheless, as shown in this study, one-to two thirds of patients with PEI had persisting symptoms despite PERT during follow-up after PD, as displayed in the Sankey diagram. A possible explanation for this is that PERT administration was not standardised in the study protocol, but based on the decision of the treating clinician. Current guidelines suggest to use at least 40 000–50 000 units of lipase per meal and 10 000–25 000 units of lipase per snack as starting dose, with the addition of a proton pomp inhibitor if no control of the symptoms is achieved [27–29]. Therefore, patients might have had received inadequate PERT dosages, resulting in the persistence of PEI-related symptoms. In addition, non-compliance to treatment was not adequately evaluated and could have contributed to the persistence of symptoms as well.



Follow-up moment (months)	0.	3.	6.	12.	18.	24.	30.	36.	42.
No PEI	26	3	0	0	0	0	1	1	0
Subclinical PEI	11	9	7	3	0	4	1	1	2
Untreated PEI	22	9	6	1	1	1	0	0	1
Undertreated PEI	9	19	23	8	13	9	5	3	4
PEI with resolved symptoms	2	21	19	19	14	7	7	7	5
Unclear	2	5	4	2	1	0	0	1	1
Drop Out	0	6	7	26	4	0	7	1	0

Fig. 1. Sankey diagram and table of the prevalence and course of PEI during follow-up (n)
Designed with http://www.sankeymatic.com. 0. = preoperative; 3. = 3 months following surgery; 6. = 6 months following surgery; 12. = 12 months following surgery; 18. = 18 months following surgery; 24. = 24 months following surgery; 30. = 30 months following surgery; 36. = 36 months following surgery; 42. = 42 months following surgery. PEI, Pancreatic Exocrine Insufficiency.

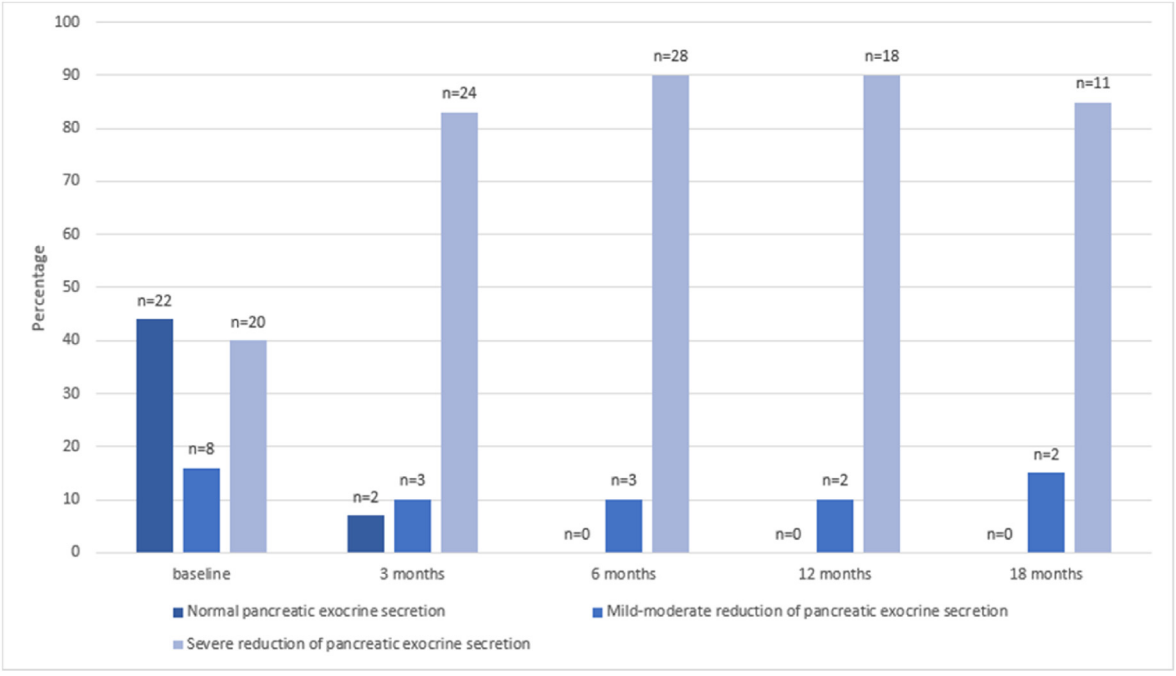


Fig. 2. Pancreatic exocrine secretion as indexed by FE-1 levels (%), numbers above bars reflect actual numbers of patients
Normal pancreatic exocrine secretion = FE-1 > 200 μg/g, Mild-moderate reduction of pancreatic exocrine secretion = FE-1100–200 μg/g, Severe reduction of pancreatic exocrine secretion = FE-1 < 100 μg/g. FE-1, Faecal Elastase – 1.

Table 3
Univariate analyses comparing presence of symptoms, laboratory measurements, and use of supplementation between patients with and without abnormal FE-1 levels.

	Presence of reduced pancreatic exocrine secretion at baseline		
	No (n = 22)	Yes (n = 28)	P-value
Anorexia, n	8	12	0.86
Weight loss, n	12	21	0.22
Nausea, n	8	7	0.58
Vomiting, n	1	5	0.21
Abdominal pain, n	12	16	1.00
Diarrhea, n	3	6	0.71
Malabsorption, n	2	4	0.69
Flatulence, n	7	5	0.42
PERT use, n	1	5	0.21
Vitamin use, n	2	3	1.00
Oral antidiabetics and/or insulin use, n	2	5	0.44
Present steatorrhea, n	4	6	1.00
Former steatorrhea episode, n	5	9	0.83
Weight in kg (median IQR)	76.5 (65.3–85.0)	76.5 (64.8–85.3)	1.00
HbA1c (median IQR)	36 (31–43)	42 (37–51)	0.04
Serum vitamin D (median IQR, nmol/L)	53 (40–66)	38 (24–53)	0.08
Serum vitamin E (median IQR, μmol/L)	35 (31–41)	32 (24–37)	0.08
Serum vitamin A (median IQR, μmol/L)	2.0 (1.7–2.2)	1.7 (1.5–2.2)	0.31
Serum vitamin K (median IQR, nmol/L)	0.95 (0.43–1.50)	0.80 (0.23–1.63)	0.42
INR (median IQR)	0.98 (0.91–1.03)	1.04 (0.96–1.08)	0.05

PERT, Pancreatic Enzyme Replacement Therapy; IQR, interquartile range; INR, International Normalized Ratio.

Table 4
Spearman rank correlation coefficient comparing FE-1 levels to the severity of symptoms[a] at baseline (n = 72) and three months (n = 65) following surgery.

	Baseline		3 months	
	ρ coefficient	P-value	ρ coefficient	P-value
Anorexia	−0.18	0.21	0.28	0.20
Weight loss	−0.18	0.22	0.33	0.12
Vomiting	−0.10	0.50	−0.16	0.45
Nausea	0.04	0.79	0.16	0.47
Abdominal pain	−0.18	0.20	0.38	0.07
Diarrhea	−0.07	0.65	0.26	0.25
Malabsorption	−0.22	0.13	0.08	0.71
Flatulence	0.00	0.98	−0.30	0.17

FE-1, Faecal Elastase − 1; CTC-AE, Common Terminology Criteria for Adverse Events score.
[a] Scored according to the CTA-AE score V4.03.

Some patients whose symptoms had initially resolved after the start of PERT, showed relapses of PEI with re-emerging of symptoms at a later point during follow-up. Therefore, long-term follow-up after PD, preferably using standardised follow-up schemes at centralised expert pancreatic centres including exocrine evaluation by specialised nurses or dieticians, is desired. Patients with persisting symptoms were found to have a higher median PERT dosage than patients with PEI whose symptoms had resolved. This suggests that clinicians increased the PERT dosage in patients with remaining complaints. Although overall treatment remained suboptimal, the high incidence of PEI and persistence of PEI-related symptoms observed in this study has increased the awareness of clinicians regarding this complication and the need to optimize PERT. Possible solutions for patients with persisting symptoms include adding a proton pump inhibitor and opening of capsules to ingest the PERT granules directly [30]. Also, a smartphone application has been developed (MyCyFAPP) to support patients with PEI, by advising on personalised PERT dosage based upon the characteristics of each meal [31]. It is important to note that if symptoms persist despite adequate dosage and counselling, other causes for malabsorption, such as bacterial overgrowth, should be excluded [7]. Additional factors that may contribute to the development of symptoms, independently of the pancreatic exocrine function, are visceral sensitivity, GI motility, microbiome and colonic absorption of water. These factors may also explain why the PEI-related symptoms were not significantly associated with abnormal FE-1 levels.

A specific subgroup for monitoring is patients with PEI based upon mild-moderate reduction of pancreatic secretion. Most of these patients were found to have a diminished secretory capacity without (yet) experiencing symptoms of PEI, thus remaining subclinical. Initiation of PERT despite the absence of symptoms could possibly benefit these patients, to prevent the development of PEI-related symptoms and deficiencies.

After six months of follow-up, none of the patients of whom stool samples were available showed normal FE-1 levels. Moreover, FE-1 levels did not improve during follow-up, which suggests that

Table 5
Presence of vitamin deficiencies and supplementation before and after pancreatoduodenectomy.

	Baseline (n/n_{total})	3 months (n/n_{total})	6 months (n/n_{total})	12 months (n/n_{total})	18 months (n/n_{total})
Vitamin A	0/62	1/34	0/34	0/24	0/16
Suppl.	0/0	0/1	0/0	0/0	0/0
Vitamin D	34/59	20/34	21/34	11/23	8/15
Suppl.	1/34	2/20	6/21	3/11	4/8
Vitamin E	0/62	1/34	0/34	1/24	1/16
Suppl.	0/0	0/1	0/0	0/1	0/1
Vitamin K	30/61	18/33	27/34	13/23	11/16
Suppl.	0/30	1/18	3/27	5/13	3/11

the pancreatic exocrine function remains deteriorated on the long-term. Shin et al. and Sikkens et al. presented similar results, demonstrating that the pancreatic exocrine function, as indexed by FE-1, does not recover to preoperative levels following pancreatectomy [32,33]. Contrastingly, Sato et al. and Tanaka et al. showed that the pancreatic exocrine function of patients with pancreatic and periampullary malignancies first dropped after PD, but recovered to preoperative levels after six to twelve months [34–36]. However, in these studies, a different test was used to assess the pancreatic exocrine function, i.e. the N-benzoyl-L-tyrosyl-p-aminobenzoicacid (BT-PABA) excretion test and few patients were included in the long-term follow-up possibly resulting in survival bias, which could explain the conflicting results. The found discrepancies could also reflect the inaccuracy of clinical tests to reliably objectify the presence and severity PEI during follow-up [11–13,20]. To evaluate the presence and severity of PEI and related symptoms and deficiencies, follow-up visits should therefore be focused on careful assessment of PEI-related symptoms, irrespective of test results.

Vitamin D and K deficiencies occurred in almost half of patients. This is in line with former studies reporting on the incidence of vitamin D deficiencies following PD, whilst studies evaluating vitamin K deficiencies in patients after PD are lacking [37,38]. Lindqvist et al., however, point out that vitamin D deficiency prevalence was similar in healthy controls compared to patients with PEI due to chronic pancreatitis and cystic fibrosis, and therefore possibly not solely caused by PEI [39]. Also, we observed that whilst median vitamin D and K was lower in patients with reduced pancreatic secretion, the difference was insignificant. Perhaps in a larger cohort of patients, a significant difference could be detected. An explanation for the lack of studies evaluating vitamin K in PEI patients could be that in vitamin K is rarely determined in the clinical routine, often INR is used as a substitute. Nevertheless, vitamin deficiencies should be supplemented. Persisting vitamin D deficiency can result in osteopenia or osteoporosis and vitamin K deficiency increases the risk of bleeding [8]. This emphasizes the need for regular assessment of the patients' vitamin status before and after PD, and sufficient supplementation of deficiencies. It might be most pragmatic to start vitamin supplementation for all patients at diagnosis, since vitamin D and K deficiencies are common and treatment of PEI is challenging. Unfortunately, we cannot make any conclusions on the efficacy of treatment in the patients that received vitamin supplementation, as patients would often buy vitamin supplementation themselves and we therefore have no information on dosage.

This prospective study is the first to show the course of PEI and related symptoms and deficiencies, over a period of 3.5 years following PD. This is especially important when considering the increasing number of PDs, due to improved detection of (pre)malignancies and better surgical techniques, resulting in a larger group of patients with longer survival [40]. However, there are several limitations to be acknowledged. First, FE-1 samples were not available for all patients. Nevertheless, in most patients, FE-1 was measured once during follow-up. As median FE-1 levels do not seem to change during follow-up, is it therefore not likely that this would have changed the results. Second, an indirect test (i.e. FE-1) was used to assess PEI. The use of a more specific test, such as 72-h faecal fat excretion, could possibly have provided a more accurate representation of the pancreatic function. Application of this test, however, would be impractical, being more expensive and a greater burden to patients [41]. Also, assessment of the pancreatic function to diagnose and treat PEI should comprise a comprehensive review of the patients' signs and symptoms, rather than solely being based on specific test results. Third, the sample size calculated for cohort A and B was not reached. However, the incidence of PEI in this study is higher than the estimated incidence used to calculate the sample size. Therefore, less inclusions would be needed. Cohort B is still smaller than intended, since patients with a two-year disease-free survival after resection for malignant indications were scarce. Fourth, the drop-out rate during follow-up was substantial. Drop-out occurred mainly in patients with pancreatic and periampullary malignancies experiencing disease recurrence. This was an exclusion criterium to continue study-related follow-up, given that PEI-related symptoms are difficult to distinguish from symptoms of disease recurrence. Inclusion of follow-up data of these patients would result in an overestimation of PEI-related symptoms. Another potential solution would have been to study PEI in a selection of patients with pre-malignancies, such as IPMN, only. This hypothetically would have resulted in a lower drop-out rate. Considering that exclusion of malignant cases would substantially reduce the number of eligible patients, this was not desirable. Nevertheless, for future studies, this could be taken into consideration. Fifth, adjuvant chemotherapy can cause similar symptoms as PEI, therefore being a possible bias for PEI-related symptoms. However, presence of PEI-related symptoms remained similar at six-, twelve- and eighteen months following surgery, when no patients were receiving adjuvant chemotherapy. Sixth, the PEI prevalence in this study might be underestimated, considering that PEI can result in abnormal nutritional parameters despite the absence of symptoms or abnormal FE-1 values [42]. Although the nutritional status was partly evaluated using fat-soluble vitamins, a more extensive nutritional evaluation is expected to provide additional insights and should be considered in further studies [36].

In conclusion, the vast majority of patients undergoing PD for pancreatic or periampullary (pre)malignancies develop PEI after resection, whilst adequate treatment with PERT remains challenging. Vitamin deficiencies, especially vitamin D and K, are common and should be supplemented to improve the nutritional status of patients. Comprehensive assessment of PEI-related symptoms and vitamin deficiencies is important to enhance enzyme- and vitamin supplementation. Long-term follow-up in expert pancreatic centres, preferably by specialised nurses or dieticians, is necessary to optimize care for PEI.

Funding sources

This work was supported by an unrestricted research grant from Mylan Healthcare B.V., a Viatris company and from the University Medical Center Utrecht, Utrecht, the Netherlands.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2022.08.002.

References

[1] Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clin Exp Gastroenterol 2019 Mar 21;12:129–39.
[2] Tseng DS, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer: a systematic review. Pancreas 2016 Mar;45(3):325–30.
[3] Beger HG, Mayer B. Early postoperative and late metabolic morbidity after pancreatic resections: an old and new challenge for surgeons - a review. Am J Surg 2018 Jul;216(1):131–4.
[4] DiMagno EP. Medical treatment of pancreatic insufficiency. Mayo Clin Proc 1979 Jul;54(7):435–42.

[5] Chey WY, Chang TM. Secretin: historical perspective and current status. Pancreas 2014 Mar;43(2):162–82.
[6] Kahl S, Malfertheiner P. Exocrine and endocrine pancreatic insufficiency after pancreatic surgery. Best Pract Res Clin Gastroenterol 2004 Oct;18(5):947–55.
[7] Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Curr Gastroenterol Rep 2007 Apr;9(2):116–22. https://doi.org/10.1007/s11894-007-0005-4. PMID: 17418056.
[8] Gianotti L, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2018 Nov;164(5):1035–48.
[9] Pezzilli R, Caccialanza R, Capurso G, Brunetti O, Milella M, Falconi M. Pancreatic enzyme replacement therapy in pancreatic cancer. Cancers 2020 Jan 22;12(2):275.
[10] Pathanki AM, Attard JA, Bradley E, Powell-Brett S, Dasari BVM, Isaac JR, et al. Pancreatic exocrine insufficiency after pancreaticoduodenectomy: current evidence and management. World J Gastrointest Pathophysiol 2020 Apr 12;11(2):20–31.
[11] Leeds JS, Oppong K, Sanders DS. The role of fecal elastase-1 in detecting exocrine pancreatic disease. Nat Rev Gastroenterol Hepatol 2011 May 31;8(7):405–15.
[12] Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018 Aug;16(8):1220–8. e4.
[13] Vujasinovic M, Valente R, Del Chiaro M, Permert J, Löhr JM. Pancreatic exocrine insufficiency in pancreatic cancer. Nutrients 2017 Feb 23;9(3):183.
[14] Gooden HM, White KJ. Pancreatic cancer and supportive care–pancreatic exocrine insufficiency negatively impacts on quality of life. Support Care Cancer 2013 Jul;21(7):1835–41.
[15] Halloran CM, Cox TF, Chauhan S, Raraty MG, Sutton R, Neoptolemos JP, et al. Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. Pancreatology 2011;11(6):535–45.
[16] Belyaev O, Herzog T, Chromik AM, Meurer K, Uhl W. Early and late post-operative changes in the quality of life after pancreatic surgery. Langenbeck's Arch Surg 2013 Apr;398(4):547–55.
[17] Roberts KJ, Bannister CA, Schrem H. Enzyme replacement improves survival among patients with pancreatic cancer: results of a population based study. Pancreatology 2019 Jan;19(1):114–21.
[18] Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Brink MA, Schaapherder AF, Dejong CH, Spanier BW, Heisterkamp J, van der Harst E, van Eijck CH, Besselink MG, Gooszen HG, van Santvoort HC, Boermeester MA. Dutch pancreatitis study group. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016 May;14(5):738–46.
[19] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. U.S. Department of Health and Human Services. National Institutes of Health, National Cancer Institute; June 14th 2010. Published.
[20] Benini L, Amodio A, Campagnola P, Agugiaro F, Cristofori C, Micciolo R, et al. Fecal elastase-1 is useful in the detection of steatorrhea in patients with pancreatic diseases but not after pancreatic resection. Pancreatology 2013 Jan-Feb;13(1):38–42.
[21] Daniel WW, Metcalfe C. Biostatistics: a foundation for analysis in the health sciences. seventh ed. Wiley; 1999. p. 324–6. Stat Med 2001; 20(2).
[22] Tran TC, van 't Hof G, Kazemier G, Hop WC, Pek C, van Toorenenbergen AW, et al. Pancreatic fibrosis correlates with exocrine pancreatic insufficiency after pancreatoduodenectomy. Dig Surg 2008;25(4):311–8.
[23] Kim H, Yoon YS, Han Y, Kwon W, Kim SW, Han HS, et al. Effects of pancreatic enzyme replacement therapy on body weight and nutritional assessments after pancreatoduodenectomy in a randomized trial. Clin Gastroenterol Hepatol 2020 Apr;18(4):926–34. e4.
[24] de la Iglesia-García D, Huang W, Szatmary P, Baston-Rey I, Gonzalez-Lopez J, Prada-Ramallal G, et al. NIHR Pancreas Biomedical Research Unit Patient Advisory Group. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. Gut 2017 Aug;66(8):1354–5.
[25] Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. Canadian cancer trials group and the unicancer-GI–PRODIGE group. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018 Dec 20;379(25):2395–406.
[26] Mackay TM, Smits FJ, Roos D, Bonsing BA, Bosscha K, Busch OR, et al. Dutch Pancreatic Cancer Group. The risk of not receiving adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma: a nationwide analysis. HPB 2020 Feb;22(2):233–40.
[27] Phillips ME, Hopper AD, Leeds JS, Roberts KJ, McGeeney L, Duggan SN, Kumar R. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. BMJ Open Gastroenterol 2021 Jun;8(1):e000643.
[28] Gianotti L, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2018 Nov;164(5):1035–48.
[29] Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. HaPanEU/UEG Working Group. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). Unit Eur Gastroenterol J 2017 Mar;5(2):153–99.
[30] Pongprasobchai S. Maldigestion from pancreatic exocrine insufficiency. J Gastroenterol Hepatol 2013 Dec;28(Suppl 4):99–102.
[31] Calvo-Lerma J, Martinez-Jimenez CP, Lázaro-Ramos JP, Andrés A, Crespo-Escobar P, Stav E, et al. MyCyFAPP. Innovative approach for self-management and social welfare of children with cystic fibrosis in Europe: development, validation and implementation of an mHealth tool (MyCyFAPP). BMJ Open 2017 Mar 16;7(3):e014931.
[32] Shin YC, Han Y, Kim E, Kwon W, Kim H, Jang JY. Effects of pancreatectomy on nutritional state, pancreatic function, and quality of life over 5 years of follow up. J Hepatobiliary Pancreat Sci 2020 Nov 11. https://doi.org/10.1002/jhbp.861.
[33] Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. Br J Surg 2014 Jan;101(2):109–13.
[34] Sato N, Yamaguchi K, Yokohata K, Shimizu S, Morisaki T, Chijiiwa K, et al. Short-term and long-term pancreatic exocrine and endocrine functions after pancreatectomy. Dig Dis Sci 1998 Dec;43(12):2616–21.
[35] Ohtsuka T, Tanaka M, Miyazaki K. Gastrointestinal function and quality of life after pylorus-preserving pancreatoduodenectomy. J Hepatobiliary Pancreat Surg 2006;13(3):218–24.
[36] Tanaka T, Ichiba Y, Fujii Y, Kodama O, Dohi K. Clinical and experimental study of pancreatic exocrine function after pancreaticoduodenectomy for periampullary carcinoma. Surg Gynecol Obstet 1988 Mar;166(3):200–5.
[37] Armstrong T, Walters E, Varshney S, Johnson CD. Deficiencies of micronutrients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. Pancreatology 2002;2(6):528–34.
[38] Armstrong T, Strommer L, Ruiz-Jasbon F, Shek FW, Harris SF, Permert J, et al. Pancreaticoduodenectomy for peri-ampullary neoplasia leads to specific micronutrient deficiencies. Pancreatology 2007;7(1):37–44.
[39] Lindkvist B, Phillips ME, Domínguez-Muñoz JE. Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: prevalence and diagnostic use. Pancreatology 2015 Nov-Dec;15(6):589–97.
[40] de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, De jong CH, et al. Dutch Pancreatic Cancer Group. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg 2012 Mar;99(3):404–10.
[41] Roeyen G, Berrevoet F, Borbath I, Geboes K, Peeters M, Topal B, et al. Expert opinion on management of pancreatic exocrine insufficiency in pancreatic cancer. ESMO Open 2022 Feb;7(1):100386.
[42] Domínguez-Muñoz JE, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M. 13C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2007 Apr;5(4):484–8.