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RESEARCH ARTICLE

Pancreatic Enzyme Replacement Therapy After Pancreatoduodenectomy: Are Patients Treated Adequately? A Systematic Review Correlated with a Prospective Cohort

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ABSTRACT

Background: Treatment with pancreatic enzymes is necessary to improve nutrient digestion and to prevent malabsorption in patients with exocrine pancreatic insufficiency (EPI) after pancreatoduodenectomy. Aim of this study was to identify the optimal dosage of pancreatic enzymes in patients with EPI after pancreatoduodenectomy based on studies available and to evaluate if patients in our cohort are treated adequately.

Methods: A systematic review of literature was performed to identify all randomized controlled trials reporting on the effect of treatment with pancreatic enzymes on nutritional parameters after pancreatoduodenectomy. Alongside a prospective observational study was performed, where the administered dosage of pancreatic enzymes was evaluated by a questionnaire in patients after pancreatoduodenectomy with EPI (defined as fat absorption < 85 %), and was compared to their dietary fat intake. Endpoints of this study were (1) the percentage of patients that received an adequate dosage based on the results of the systematic literature study, (2) the ratio between reported dose lipase (PhEur units) and fat intake (g), and reported dose of protease (PhEur units) and protein intake (g).

Results: The systematic review revealed three randomized controlled trials, their results indicate that an effective dosage of pancreatic enzymes to treat EPI following pancreatoduodenectomy should consists of at least 40000 PhEur units lipase per main meal. Twenty-nine patients with EPI after pancreatoduodenectomy were included in the prospective study. The recommended dosage (minimum 40000 PhEur units of lipase) was administered in 52% of the patients. The lowest ratio of the PhEur units of lipase per gram dietary fat intake was observed during dinner (2521 ±1770 units/gram fat) and the highest ratio was observed during breakfast (4441 ± 6936 units/gram fat).

Conclusion: According to the cut-off of minimal 40000 PhEur units of lipase per main meal, only half of the patients are using the minimum dosage of pancreatic enzymes. The variability between the ratios of the reported dose of lipase (PhEur units) and fat intake (g) fat intake per main meals is large and prescribing pancreatic enzymes adjusted to fat intake (as ratio's) seems more appropriate.

Keywords: Pancreatoduonectomy, exocrine pancreatic insufficiency, pancreatic enzymes, nutritional intake

Introduction

Exocrine pancreatic insufficiency (EPI) following pancreatoduodenectomy occurs in 24-100 % of patients [1]. A deficiency or absence of pancreatic digestive enzymes, including lipase, amylase and protease, leads to maldigestion of nutrients and consequently to malnutrition[2,3]. The risk of developing EPI following surgery depends on the type and extent of pancreatic resection, and technique of reconstruction. In patients with preoperative dilatation of the main pancreatic duct, a hard pancreatic structure, and adjuvant chemotherapy the risk of EPI post-surgery is even higher [4-7]. In clinical practice the key problem of EPI is the impaired digestion of fat, since lipase is the only enzyme to hydrolyze dietary fat into glycerol and fatty acids, which results in fat malabsorption [3,8]. This will consequently lead to malnutrition, gastro-intestinal complaints, such as flatulence, steatorrhea, bowel habit alterations, and deficiencies in fat-soluble vitamins. On the long-term EPI may negatively affect a patients' quality of life [9,10]. Untreated orundertreated EPI after pancreatic surgery can ultimately lead to decreased long-term survival [10-13]. Therefore, it is important to treat patients with EPI after pancreatoduodenectomy adequately [8,14-17].

Prescribing an adequate dose of pancreatic enzymes is mandatory to obtain an optimal fat digestion and prevent malnutrition and gastrointestinal complaints [5,18-20]. In clinical practice, this can be challenging because dosage of pancreatic enzymes depends on the remaining function of the pancreas, a patient's diet, and the postsurgical anatomy. Previous studies reporting on the usage of pancreatic enzymes show that a substantial number of patients after pancreatic surgery are under dosed and report complaints of steatorrhea and weight loss despite treatment with pancreatic enzymes [21-23]. Therefore, this study aimed to 1) systematically review the present literature to determine the optimal dosage of pancreatic enzymes in patients with EPI after pancreatoduodenectomy and 2) to evaluate the actual administered dosage of pancreatic enzymes by patients with EPI after pancreatoduodenectomy and its relation with their fat and protein intake per meal.

Methods

The here presented study consists of two parts. First a systematic literature search was conducted to define the optimal dosage of pancreatic enzyme therapy after pancreatoduodenectomy, based on the available literature. The second part of this study investigated, in a prospective cohort, the actual administered dosage of pancreatic enzymes compared to the dietary fat and protein intake during main meals used by patients with EPI after pancreatoduodenectomy.

Systematic literature review

The database of PubMed was searched systematically from inception until 2nd June 2023 by a medical information specialist to identify all literature reporting on the treatment with pancreatic enzymes in patients with EPI after pancreatoduodenectomy to determine the optimal dosage of lipase. Search terms that were used included: ''pancreas resection'', ''pancreatic function'' / ''insufficiency'' and ''pancreas enzymes''. The full search strategy can be found in Appendix 1.

All randomized controlled trials reporting on the effect of pancreatic enzymes in patients after pancreatic surgery were included. Outcome measures of interest were effect of pancreatic enzymes on fat and protein absorption, nutritional parameters, such as Body Mass Index (BMI) or weight, and gastrointestinal complaints. Only studies in English were accepted. Study selection was performed independently by two investigators (CB and LB) based on title and abstract. Full text was screened in studies with the predetermined inclusion criteria based on title and abstract. A third reviewer was available to assess and discuss articles if necessary. Reference lists of the included studies were screened to identify studies that were missed in the initial search. The following data were collected from the included articles: Study design, JADAD score, number of patients that were included in the study, patient characteristics, type and indication for resection, the way to diagnose EPI, dosage of pancreatic enzymes and the effect of pancreatic enzymes on the outcome measurements.

Study design prospective cohort

The actual given treatment dose of pancreatic enzymes in a prospective cohort of patients were correlated with the outcomes to the results found in our systematic review. The included patients in this cohort participated in a prospective observational cross sectional cohort study, the OPPERT-trial [International Clinical Trials Registry Platform, ID NL8038] that investigated several diagnostic tests to determine the presence of EPI after pancreatoduodenectomy. The Medical Ethics Review Committee of Amsterdam UMC approved the study protocol and written informed consent was obtained from all patients.

The OPPERT-trial included 50 patients after pancreatoduodenectomy (Whipple, pylorus preserving pancreatoduodenectomy, pylorus resecting pancreatoduodenectomy) in stable postoperative situation (2 - 12 months after surgery) who were operated between 2014-2020 for benign, pre-malign and malign diseases in the periampullary region. A stable postoperative situation entailed: adequate recovery from surgery and complications (if applicable), with no signs of recurrence of disease. A minimal dietary fat intake of 60 g/day was required to participate in this study. Patients who used tube feeding or parenteral feeding or patients who suffered from pre-existent diseases with a high risk of malabsorption or maldigestion (i.e. patients preoperatively diagnosed with chronic pancreatitis (i.e. according to the M-ANNHEIM classification) or with extensive small bowel resection) were excluded. Patients with acute pancreatitis were not excluded since a substantial part of the patients with pancreatic lesions, especially periampullary cancer, have had episodes of acute pancreatitis prior to surgical resection.

The presence of EPI was assessed by fecal elastase-1 (levels below 200 µg/g feces) and coefficient of fat absorption (percentage of fat absorption (CFA) < 85 %) [24,25]. Three-day stool collections without use of pancreatic enzymes were performed to quantify the daily fecal fat excretion (g/day). Combined with a 96-hours (weighted) nutritional diary according to former described procedures, to determine the daily fat intake (g/day), the CFA was calculated by the following formula: CFA (%) = 100 x (fat intake (g/day) – fat excretion (g/day) / fat intake (g/day)) [24]. The local hospital protocol for treating EPI after pancreatoduodenectomy contains a starting dose of 1 capsule (25000 PhEur units of lipase) at breakfast, 1 capsule at lunch and 2 capsules at dinner. Dosing is then adjusted based on patient's experience, weight, and complaints of steatorrhea. In the majority of patients a specialist dietician is consulted to guide patients in their treatment with pancreatic enzymes. To assess the treatment of EPI patients received a questionnaire containing questions about the current use of pancreatic enzymes per meal. The full questionnaire can be found in Appendix 2.

End points

Primary endpoint of this study was the percentage of patients in our cohort that received an adequate dosage of pancreatic enzymes based on the results of the systematic review of the literature. Secondary endpoint was to determine the relation between dosage of lipase per main meal and dietary fat intake. Therefore, the ratio between reported dose lipase (PhEur units) and fat intake (g) and reported dose of protease (PhEur units) and protein intake (g) was determined. These ratios were calculated with the following formula: PhEur units of lipase / gram fat intake and PhEur units of protease / gram protein intake.

Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for Social Science (SPSS®) software tool (version 25.0). Descriptive statistics were used. Continuous variables were presented as mean (± standard deviation) or median (interquartile range [IQR]) depending on the distribution of data. Dichotomous data were presented as frequency numbers with percentages.

Results

Systematic literature review

Of the 4028 studies that were originally screened on title and abstract, 48 articles were selected. After applying in- and exclusion criteria to the full text, three randomized controlled trials were identified that investigated the effect of a certain dosage of pancreatic enzyme replacement therapy after pancreatoduodenectomy. The flow chart of study selection is showed in figure 1.

The complete study characteristics are summarized in Appendix 3. Two studies examined the effect of pancreatic enzymes on fat absorption and nitrogen absorption [8,26] and one study examined the effect of pancreatic enzymes on body weight, bowel habits, nutritional status, and quality of life [9]. Whitcomb et al. (N=54) [8] found that fat and nitrogen maldigestion after total or partial pancreatectomy is treated effectively with a dosage of 72000 PhEur units of lipase per main meal and 36000 PhEur units of lipase per snack. Patients followed a diet with a minimum of 80 grams of fat. The fat absorption coefficient (CFA) improved significantly in the group who received pancreatic enzymes (CFA 32.1 ± 18.5 %) compared to the group who received placebo medication (CFA 8.8 ± 12.5 %) ($P < 0.0001$). Also, the nitrogen absorption coefficient (CNA) was higher in patients who used pancreatic enzymes (CNA 97.7 ± 82.3 %) compared to placebo medication (CNA 24.4 ± 101.0 %) ($P = 0.0013$). Stool characteristics, flatulence and stool consistency also improved significantly in patients with pancreatic enzymes compared to placebo medication.

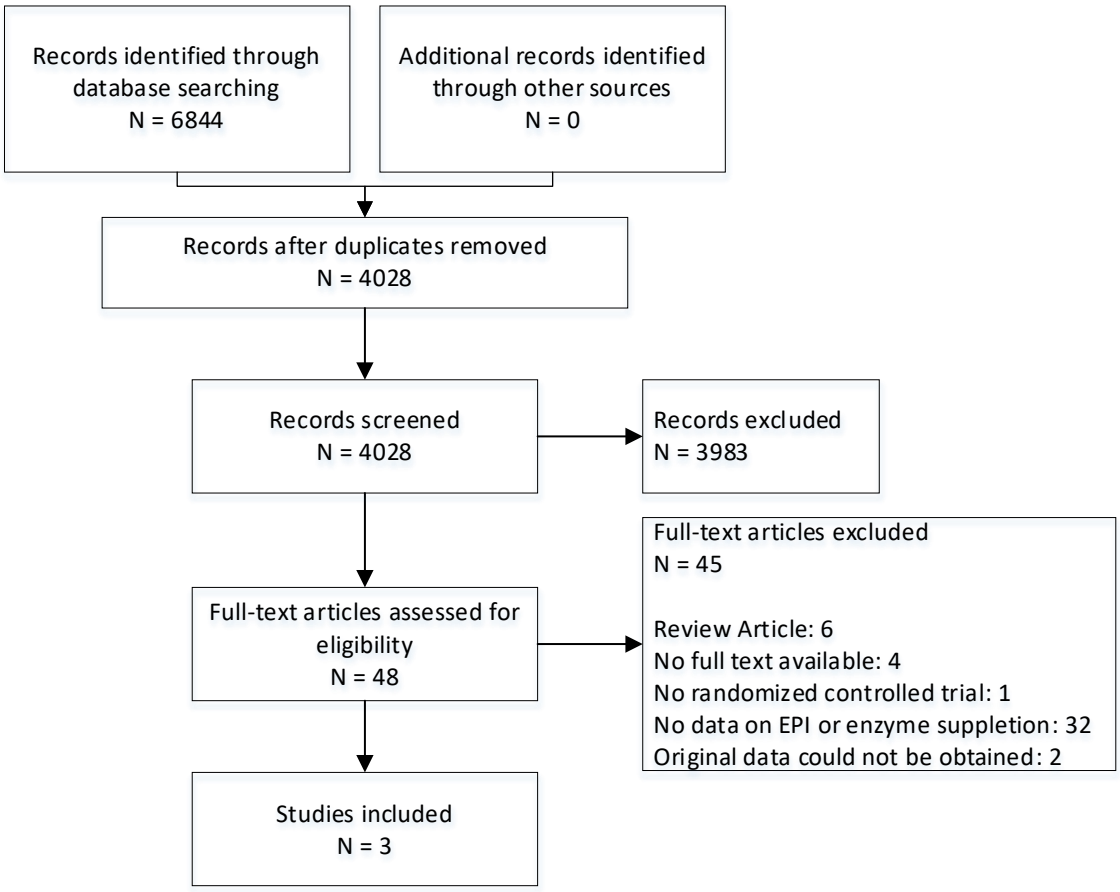


Figure 1. Flowchart of study selection

In the study from Seiler et al. (N = 58)[27] patients were included for a 1-week double blind randomized controlled trial with a 1-year open label extension. Pancreatic enzymes dosed in 75000 PhEur units of lipase for main meals and 50000 PhEur units of lipase for snacks, were compared to placebo medication. Patients were on a diet including 80-100 grams of fat during the study. After the double-blind period (7 days) the CFA increased in the group with pancreatic enzymes and decreased in the placebo group, resulting in a significant treatment difference (25.6 %, P < 0.001). Furthermore, they reported a treatment difference favoring pancreatic enzymes in protein absorption of 29.2 % (P < 0.001) and fecal fat loss of 30.2 gram/day (P < 0.001). Body weight at baseline was 68.2 (± 15.8) kg and at the end of the open-labeled period with usage of pancreatic enzymes (52 weeks) 70.5 (± 16.3) kg (P < 0.05). For BMI this was respectively 23.6 (± 5.2) kg/m^2 and 24.5 (± 5.4) kg/m^2 (P < 0.05).
Kim et al. (N = 164) 9 also compared treatment with pancreatic enzymes with placebo medication. Patients used 40000 PhEur units of lipase per main meal. This study found that patients in the pancreatic enzyme group gained a mean of 1.09 kg in bodyweight and patient in the placebo group lost a mean of 2.28 kg at three months after surgery (difference between groups, 3.37 kg; P < 0.001).

In conclusion, despite the different dosages of lipase used in these studies, all studies showed a positive effect of pancreatic enzyme therapy on fat absorption, nitrogen absorption, bodyweight, BMI, bowel habits and quality of life. Based on these studies, an effective dosage of pancreatic enzymes to treat EPI after pancreatoduodenectomy is at least 40000 PhEur units of lipase per main meal, with a range of 40000-75000.

Characteristics of prospective study cohort
Of the 50 patients included in the OPPERT-trial, 30 patients (60 %) were diagnosed with EPI requiring pancreatic enzyme replacement therapy. One patient was excluded due to incomplete information about the actual administered dosage of pancreatic enzymes. Hence, a total of 29 patients were included in the current analysis. About half of the patients were male (55 %) and mean age was 68 (± 9) years. Patients were included after a median of eight months [IQR 6–23] postoperatively. Most patients had undergone a classic Whipple

procedure (52 %), followed by pylorus preserving pancreatoduodenectomy (41 %) and pylorus ring resecting pancreatoduodenectomy (7 %). The most common final histopathological diagnosis was pancreatic ductal adenocarcinoma (69 %).

Table 1. Characteristics of prospective study cohort

N	29
Sex, male n (%)	16 (55)
Age at surgery (year), mean (SD)	68 (9)
Preoperative Body Mass Index (kg/m²), mean (SD)	24.9 (3.5)
Body Mass Index at study inclusion (kg/m²), mean (SD)	23.9 (3.3)
Time after surgery (months), median [IQR]	8 [6-23]
Actual alcohol use, yes, n (%)	16 (55)
Units of alcohol per week, mean (SD)	5 (5)
Medical history of diabetes mellitus, n (%)	8 (28)
ASA classification	
I – Normal healthy patient, n (%)	1 (3)
II – Mild systemic disease, n (%)	25 (86)
III – Severe systemic disease, n (%)	2 (7)
Missing	1 (3)
Neoadjuvant therapy	
Chemoradiotherapy, n (%)	0 (0)
Chemotherapy, n (%)	6 (21)
None, n (%)	23 (79)
Type of surgery	
Pancreatoduodenectomy (standard Whipple), n (%)	15 (52)
Pylorus preserving pancreatoduodenectomy, n (%)	12 (41)
Pylorus ring resecting pancreatoduodenectomy, n (%)	2 (7)
Final histopathological diagnosis	
Adenocarcinoma, n (%)	20 (69)
Neuroendocrine tumor, n (%)	2 (7)
Intraductal papillary mucinous neoplasm, n (%)	3 (10)
Other, n (%)	4 (14)
Origin	
Pancreas, n (%)	17 (59)
Distal bile duct, n (%)	7 (24)
Duodenum, n (%)	4 (14)
Other (stomach), n (%)	1 (3)
Adjuvant therapy	
Yes, n (%)	6 (21)
None, n (%)	23 (79)

Exocrine pancreatic insufficiency

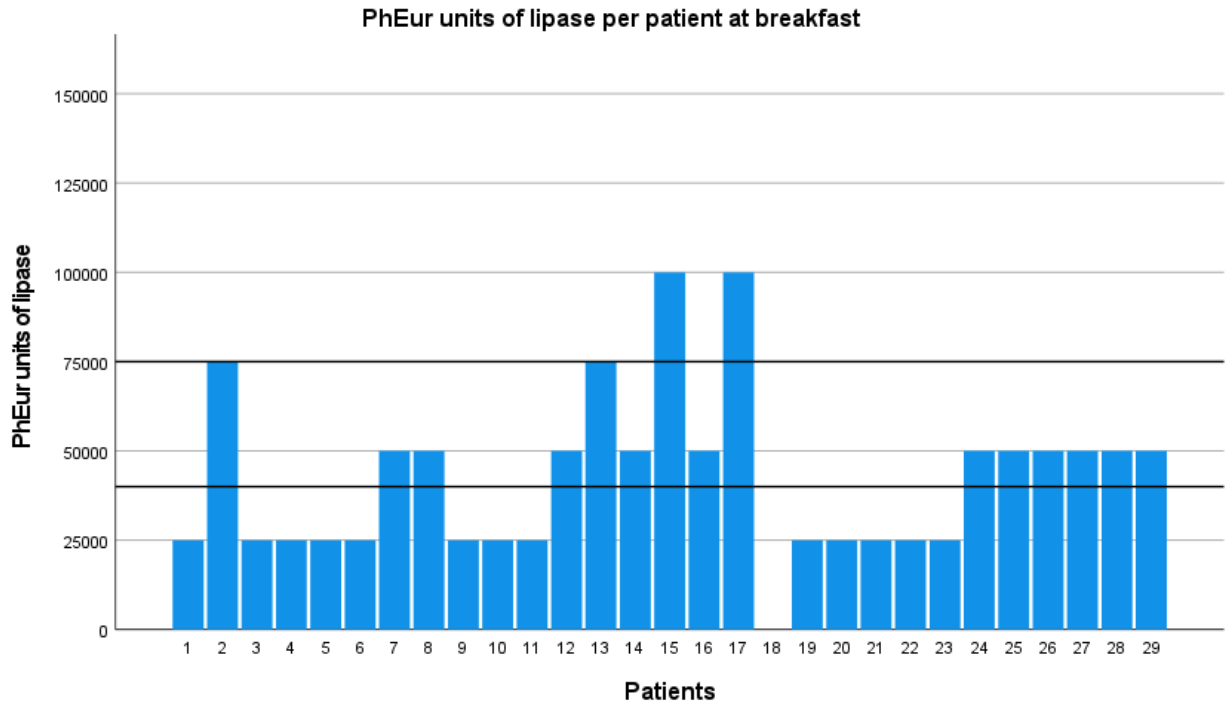
Table 2 shows details about EPI. The median CFA in the study population was 52 % [IQR 26–76]. In 90 % of patients pancreatic enzymes were started in accordance with postoperative protocol. Other patients started on pancreatic enzymes because of complaints of EPI (4 %) or after diagnosis of EPI by a diagnostic test (4 %). All patients in this study used

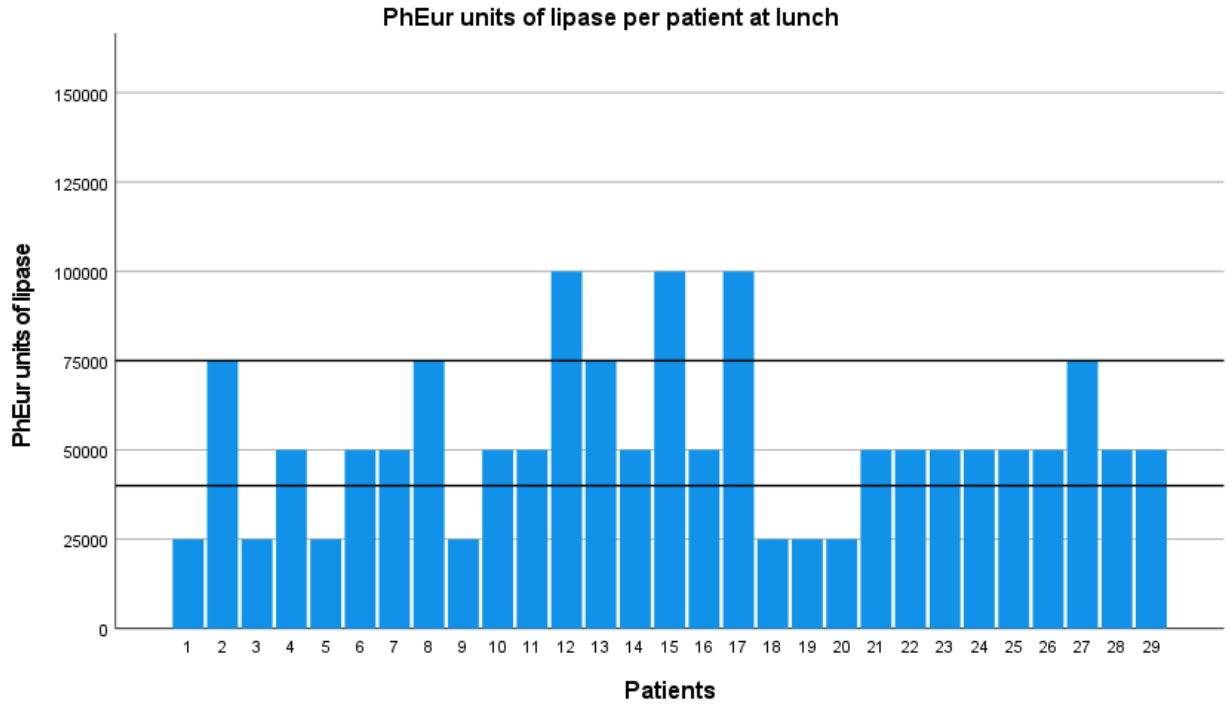
capsules containing 25000 PhEur units of lipase. Figure 2 shows patients' intake of PhEur units of lipase per meal. Based on three meals per day 15 patients (52 %) used a dosage of at least 40000 PhEur units of lipase per main meal in all three meals, indicating an adequate dosage based on our literature study, five patients (17 %) in two meals per day, six patients (21 %) in one meal per day and three patients (10 %) were dosed below 40000 PhEur units in all meals. When assessing all meals separately, a dosage of at least 40000 PhEur units of lipase was administered in 61 out of 87 meals (70 %).

When comparing different prescription assessment routes: there were nine patients (31 %) who assessed and adjusted their dosage with the help of a dietician, in this group six patients (67 %) achieved the minimum dosage of 40000 PhEur units of lipase in all meals. Another group of nine patients (31 %) where prescribed a fixed dosage per meal, the minimum dosage was obtained in only three patients (33 %). Lastly, one group of six patients (21 %) adjusted dosage based on their fat intake and in this group the minimum dosage of 40000 PhEur units of lipase was obtained in only two patients (33 %).

Table 2. Exocrine pancreatic insufficiency

Fecal elastase-1 (µg/g), median [IQR]	15 [15-42]
Coefficient of fat absorption %, median [IQR]	52 [26-76]
Dietary intake of fat (g/day), median [IQR]	102 [76-112]
Fecal loss of fat (g/day), median [IQR]	43 [21-78]
Dosage of pancreatic enzymes ≥ 40.000 PhEur units of lipase	
Breakfast, yes (%)	15 (52)
Lunch, yes (%)	22 (76)
Dinner, yes (%)	24 (83)
Determination of optimal dosage	
Based on amount of fat (gram) in meal, n (%)	6 (21)
In consultation with dietician, n (%)	9 (31)
Fixed dose, n (%)	9 (31)
Combination of the above, n (%)	3 (10)
Missing	2 (7)
Proton pump inhibitor	
Yes, n (%)	25 (86)
No, n (%)	4 (14)


PhEur units of lipase per patient at breakfast
PhEur units of lipase
150000
125000
100000
75000
50000
25000
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Patients


PhEur units of lipase per patient at lunch
PhEur units of lipase
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Patients

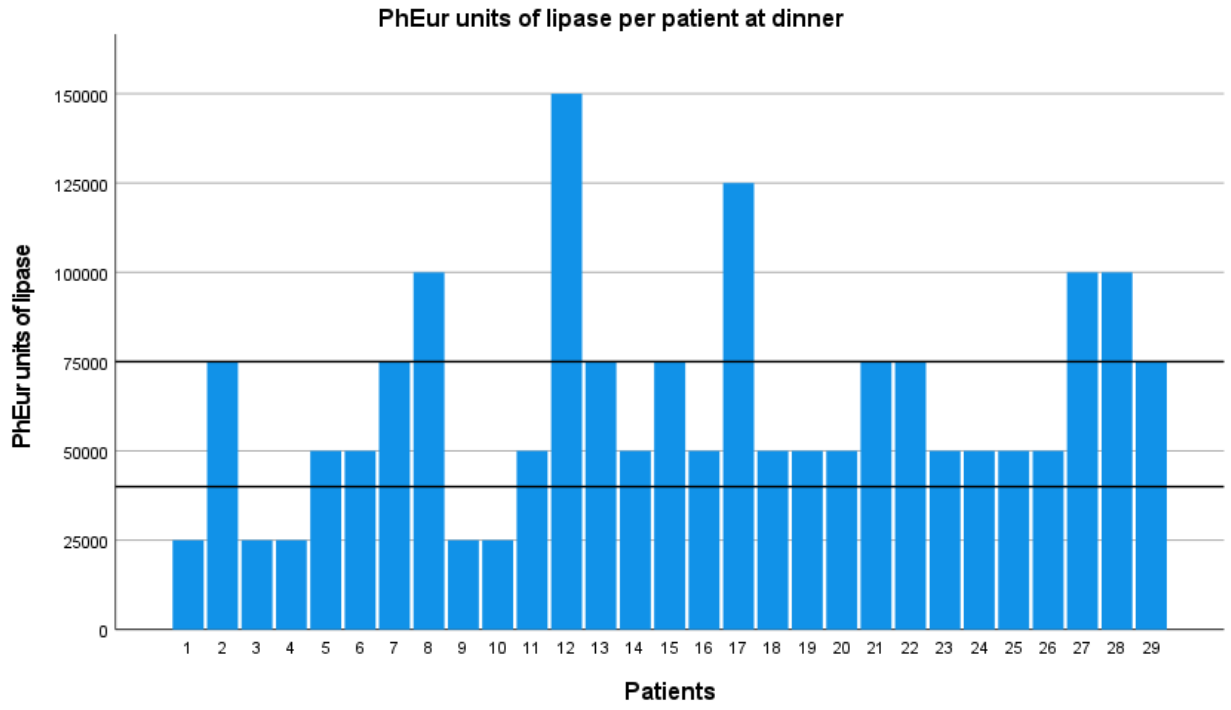

Figure 2. Units of lipase (PhEur) per main meal (breakfast, lunch and dinner)

Treatment with pancreatic enzymes in relation to dietary intake

Details about patients' lipase administration and dietary intake of macronutrients, including fat and protein, are presented in Table 3. The highest amount of lipase was taken during dinner (62931 ± 30341 PhEur units), corresponding the highest fat intake (30 ± 11 gram). However, during dinner patients had the lowest ratio of lipase per gram dietary fat intake (2521 ± 1770 PhEur units of lipase/gram fat) compared to lunch and breakfast. During breakfast, patients took the lowest amount of lipase (42241 ± 23245 PhEur units), however patients also had a lower intake of dietary fat (20 ± 13 gram) which results in the highest ratio (4441 ± 6936 PhEur units of lipase/gram fat) compared to lunch (respectively 52586 ± 22505 PhEur units of lipase, 23 ± 13 gram fat, 2964 ± 2129 PhEur units of lipase/gram fat) and dinner.

Table 3. Dietary intake of macronutrients in relation to dosage of pancreatic enzymes

	Breakfast	**Lunch**	**Dinner**
Fat digestion			
PhEur units of lipase, mean (SD)	42241 (23245)	52586 (22505)	62931 (30341)
Dietary intake of fat (g/day), mean (SD)	20 (13)	23 (13)	30 (11)
Ratio PhEur units of lipase/gram dietary fat intake, mean (SD)	4441 (6936)	2964 (2129)	2521 (1770)
Protein digestion			
PhEur units of protease, mean (SD)	1724 (1032)	2138 (990)	2560 (1322)
Dietary intake of protein (g/day), mean (SD)	18 (8)	23 (9)	36 (11)
Ratio PhEur units of protease/gram dietary protein intake, mean (SD)	132 (114)	115 (91)	77 (40)

Discussion

This study shows that, based on available literature, a minimum of 40000 PhEur units of lipase per main meal appears to be an effective dosage to treat EPI after pancreatoduodenectomy. It also shows that in a prospective cohort of patients with EPI after pancreatoduodenectomy, only half of the patients (52%) reaches the minimum dose per main

meal. Besides, due to variation in dietary intake of fat per main meal, dosing based on dietary intake, instead to a fixed amount per meal, seems indicated.

The incidence of pancreatic cancer has increased in the last decade and due to multimodal treatments, and consequently improved overall survival, it is expected that more patients will suffer from the burden of EPI after surgery in the upcoming years [28]. Optimizing treatment of EPI to improve, and maintain, patients nutritional status is needed. Patients are often prescribed a fixed dose of pancreatic enzymes. Nutritional intake, however, varies daily and dosing pancreatic enzymes based on the dietary intake of fat and protein to achieve a higher efficacy seems more appropriate. In our study patients had the lowest fat intake at breakfast and lunch and as a result used relatively more units of lipase per gram of fat intake during these meals, as compared to dinner. Indicating that dosage of pancreatic enzymes should be more flexible than a fixed dose. This was also demonstrated by a study that compared the efficacy of a fixed dosage of pancreatic enzymes and compared it to self-dosing in patients with chronic pancreatitis [29]. In patients who applied self-dosing according to their fat intake more capsules of pancreatic enzymes were used (5 ± 1.3 to 11.4 ± 2.4; P<0.001), daily frequency of bowel movements decreased, and abdominal pain improved significantly. Self-dosing, however, did not have any significant effect on nutritional variables as body weight [29].

Besides the variation in fat intake, there is also a large variation in severity of EPI. In our cohort of patients, the CFA ranged from 2 to 84 %. In patients with severe fat malabsorption, it might be necessary to use higher dosages of pancreatic enzymes to achieve an adequate digestion of fat. Quantitative fecal fat analysis comprises information about the severity of malabsorption of fat, and therefore the remaining pancreatic function, and it allows follow-up of the digestive capacity of the gastrointestinal tract and need for pancreatic enzymes in a quantitative manner [24]. In addition, measurement of CFA is useful to evaluate the effect of therapy.

By dosing pancreatic enzymes based on fat intake it is assumed that all ingested fat needs to be absorbed in the small intestine. In healthy subjects the pancreas produces a maximum of 3000-6000 lipase per minute postprandial and more than 90 % of the ingested fat is digested and absorbed in the intestines [24,30,31]. Enzyme substitution therapy should be able to mimic this pattern in case of pancreatic exocrine insufficiency. There are, however, no pancreatic enzyme preparations that are able to deliver active lipase in these high doses in the duodenum after meals. Previous studies have shown that normalization of fat digestion and absorption can be established with lower amounts of lipase delivered to the duodenum. This can be explained by the effect of gastric lipase and the residual exocrine pancreatic function [31-33]. Dimagno et al. showed that steatorrhea was only observed in patients with chronic pancreatitis where the lipase output was less than 10 % of the normal, indicating that the pancreas has a high residual capacity [32]. Whether this also applies to patients after pancreatoduodenectomy remains unclear, because not only pancreatic enzyme secretion, but also the changes in gastrointestinal anatomy after surgery contribute to an impaired digestion and absorption of nutrients. The anatomical alterations lead to an inadequate mixing of chyme and enzymes, bacterial overgrowth can influence patients' digestion, and an inadequate secretion of bicarbonate can lower the intestinal pH and inactivate pancreatic enzymes. Addition of acid suppression to inhibit gastric acid secretion to improve efficacy of pancreatic enzymes could therefore be helpful in patients with insufficient response to pancreatic enzymes. In our cohort in the majority of patients used gastric acid suppression postoperatively.

Another important factor in treatment of EPI, is patients' compliance. A recent study showed that up to 37 % of the prescriptions for pancreatic enzymes were never used [34]. Education of healthcare professionals and proper guidance of patients may improve these outcomes. The management of pancreatic enzymes adjusted on dietary fat and protein intake can be better facilitated by counseling from a specialized dietician [21].

Strength of this study is that the included patients all had a proven fat malabsorption based on gold standard methods after pancreatoduodenectomy, and the cohort therefore describes only patientswith a strict indication for treatment with pancreatic enzymes. This is in contrast with previous studies that investigated the dosage of pancreatic enzymes in patients after pancreatic surgery, most patients were diagnosed with EPI only based on clinical symptoms resulting in an increased risk of under- or over diagnoses [21,35-37]. Consequently, due to this strict patient selection, our study population is relatively small. Besides the relatively small study population, all patients were treated in a tertiary referral center for pancreatic surgery, where

treating physicians and dieticians are likely to be more experienced in diagnosing and treating EPI. Previous studies have shown that in high volume pancreatic cancer centers pancreatic enzymes are prescribed more frequently, and probably more adequately, compared to low volume centers [38].

The variation in individual dose response and the lack of practice guidelines studies to determine the adequate dose of pancreatic enzymes makes it difficult to treat individual patients adequately. Our systematic literature review identified only three RCTs that indicated that a minimum dosage of 40000 PhEur units of lipase per meal is sufficient to treat EPI [8,9,26]. It should be noted that the purpose of these studies was not to investigate the optimum dosage of pancreatic enzymes in these patient groups, but compared a fixed dose to placebo treatment. No data is available on different (e.g. lower or higher) dosages of pancreatic enzymes in the treatment of EPI. Despite the limited data that is available a reasonable guideline of minimum 40000 PhEur units of lipase per main meal can help and guide patients and physicians when initiating treatment with pancreatic enzymes. Future studies should aim to find better tools to diagnose EPI and assess the response to pancreatic enzyme replacement therapy. Furthermore, innovative training tools should be developed to help patients with EPI and physicians assess and adapt pancreatic enzymes dosages when needed.

Conclusion

In conclusion, from available literature a minimal of 40000 PhEur units of lipase per main meal seems sufficient to treat EPI in patients after pancreatoduodenectomy. According to this cut-off, only half of the patients after pancreatoduodenectomy in our cohort are using an adequate dosage of pancreatic enzymes in their main meals. Although a start dose of 40000 PhEur units of lipase per main meal may be used to initiate treatment. But prescribing dosage of enzymes per main meal based on actual fat intake (ratio) seems more appropriate given the large variability between the dietary fat intake per main meal.

Conflicts of Interest Statement: The authors have no conflicts of interest to declare.

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SUPPLEMENTARY MATERIAL

Appendix 1. The full search strategy

Search strategy for PubMed (2 June 2023)

Search	Query	Results
#3	**(#1 AND #2) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])**	2,397
#2	**"Pancreatic Extracts"[Mesh] OR "pancreatic enzym*"[tiab] OR "pancreas enzym*"[tiab] OR "pert"[tiab] OR "pancreatic extract*"[tiab] OR "panteric*"[tiab] OR "panzytrat*"[tiab] OR "pancreatin*"[tiab] OR "cotazym*"[tiab] OR "creon*"[tiab] OR "encron*"[tiab] OR "ilozym*"[tiab] OR "ku zyme"[tiab] OR "lipram*"[tiab] OR "pancrease*"[tiab] OR "pancrecarb*"[tiab] OR "pancron*"[tiab] OR "panokase*"[tiab] OR "pertzye*"[tiab] OR "protilase*"[tiab] OR "ultrase*"[tiab] OR "viokase*"[tiab] OR "zymase*"[tiab] OR "cotazym*"[tiab] OR "pancrelipase*"[tiab] OR "eurobiol"[tiab] OR "extractum pancreati*"[tiab] OR "pancreas lyophilisate*"[tiab] OR "pancreas lyophilizate*"[tiab] OR "pancreas powder*"[tiab] OR "pancreatic extract*"[tiab] OR "accelerase*"[tiab] OR "alipase*"[tiab] OR "catazyme*"[tiab] OR "entolase*"[tiab] OR "enzepi*"[tiab] OR "enzipan*"[tiab] OR "festal"[tiab] OR "festale"[tiab] OR "ilozyme*"[tiab] OR "krebsilasi*"[tiab] OR "kreon*"[tiab] OR "kutrase*"[tiab] OR "lipancreatin*"[tiab] OR "panase*"[tiab] OR "pancreaze*"[tiab] OR "pangestyme*"[tiab] OR "pankrease*"[tiab] OR "plaretase*"[tiab] OR "prolipase*"[tiab] OR "promylin*"[tiab] OR "protilase*"[tiab] OR "robile"[tiab] OR "ultrase*"[tiab] OR "ultresa*"[tiab] OR "viokace*"[tiab] OR "vitazyme*"[tiab] OR "zenpep*"[tiab]**	26,500
#1	**"Pancreatectomy"[Mesh] OR "Pancreaticoduodenectomy"[Mesh] OR "Pancreas/surgery"[Mesh] OR "Pancreatic Diseases/surgery"[Mesh] OR "Pancreatic Neoplasms"[Mesh] OR "pancreatoduodenectom*"[tiab] OR "duodenopancreatectom*"[tiab] OR "pancreatectom*"[tiab] OR "pancreatom*"[tiab] OR (("pancrea*"[tiab] OR "whipple*"[tiab] OR "peri ampull*"[tiab] OR "periampull*"[tiab]) AND ("surgery" [Subheading] OR "Surgical Procedures, Operative"[Mesh] OR "surger*"[tiab] OR "surgical*"[tiab] OR "operation*"[tiab] OR "operative*"[tiab] OR "perioperati*"[tiab] OR "extracti*"[tiab] OR "excisi*"[tiab] OR "resect*"[tiab])) OR "insulinoma*"[tiab] OR "gastrinoma*"[tiab] OR "glucagonoma*"[tiab] OR "somatostatinoma*"[tiab] OR "vipoma*"[tiab] OR (("pancrea*"[tiab] OR "islet cell*"[tiab] OR "island cell*"[tiab] OR "gastrin producing"[tiab]) AND ("Neoplasms"[Mesh] OR carcinoma*[tiab] OR neoplas*[tiab] OR tumour*[tiab] OR adenoma*[tiab] OR adenocarcinoma*[tiab] OR tumor*[tiab] OR cancer*[tiab] OR oncolog*[tiab] OR malignan*[tiab] OR carcinogen*[tiab] OR oncogen*[tiab] OR anticarcinogen*[tiab]))**	218,636

Search strategy for Embase.com (2 June 2023)

Search	Query	Results
#5	#4 NOT ('conference abstract'/it OR 'conference review'/it)	2,519
#4	#3 NOT ([animals]/lim NOT [humans]/lim)	4,106
#3	#1 AND #2	4,953
#2	'pancreas extract'/exp OR 'pancreatic enzym*':ti,ab,kw OR 'pancreas enzym*':ti,ab,kw OR 'pert':ti,ab,kw OR 'panteric*':ti,ab,kw OR 'panzytrat*':ti,ab,kw OR 'pancreatin*':ti,ab,kw OR 'creon*':ti,ab,kw OR 'encron*':ti,ab,kw OR 'ilozym*':ti,ab,kw OR 'ku zyme':ti,ab,kw OR 'lipram*':ti,ab,kw OR 'pancrease*':ti,ab,kw OR 'pancrecarb*':ti,ab,kw OR 'pancron*':ti,ab,kw OR 'panokase*':ti,ab,kw OR 'pertzye*':ti,ab,kw OR 'viokase*':ti,ab,kw OR 'zymase*':ti,ab,kw OR 'cotazym*':ti,ab,kw OR 'pancrelipase*':ti,ab,kw OR 'eurobiol':ti,ab,kw OR 'extractum pancreati*':ti,ab,kw OR 'pancreas lyophilisate*':ti,ab,kw OR 'pancreas lyophilizate*':ti,ab,kw OR 'pancreas powder*':ti,ab,kw OR 'pancreatic extract*':ti,ab,kw OR 'accelerase*':ti,ab,kw OR 'alipase*':ti,ab,kw OR 'catazyme*':ti,ab,kw OR 'entolase*':ti,ab,kw OR 'enzepi*':ti,ab,kw OR 'enzipan*':ti,ab,kw OR 'festal':ti,ab,kw OR 'festale':ti,ab,kw OR 'ilozyme*':ti,ab,kw OR 'krebsilasi*':ti,ab,kw OR 'kreon*':ti,ab,kw OR 'kutrase*':ti,ab,kw OR 'lipancreatin*':ti,ab,kw OR 'panase*':ti,ab,kw OR 'pancreaze*':ti,ab,kw OR 'pangestyme*':ti,ab,kw OR 'pankrease*':ti,ab,kw OR 'plaretase*':ti,ab,kw OR 'prolipase*':ti,ab,kw OR 'promylin*':ti,ab,kw OR 'protilase*':ti,ab,kw OR	31,638

	'robile':ti,ab,kw OR 'ultrase*':ti,ab,kw OR 'ultresa*':ti,ab,kw OR 'viokace*':ti,ab,kw OR 'vitazyme*':ti,ab,kw OR 'zenpep*':ti,ab,kw	
#1	'pancreas surgery'/exp OR 'pancreas tumor'/exp OR 'pancreatoduodenectom*':ti,ab,kw OR 'duodenopancreatectom*':ti,ab,kw OR 'pancreatectom*':ti,ab,kw OR 'pancreatom*':ti,ab,kw OR (('pancrea*':ti,ab,kw OR 'whipple*':ti,ab,kw OR 'peri ampull*':ti,ab,kw OR 'periampull*':ti,ab,kw) AND ('surgery'/exp OR 'surgeon'/exp OR surger*:ti,ab,kw OR surgical*:ti,ab,kw OR surgeon*:ti,ab,kw OR operation*:ti,ab,kw OR operative*:ti,ab,kw OR perioperative*:ti,ab,kw OR extracti*:ti,ab,kw OR excisi*:ti,ab,kw OR resect*:ti,ab,kw)) OR 'insulinoma*':ti,ab,kw OR 'gastrinoma*':ti,ab,kw OR 'glucagonoma*':ti,ab,kw OR 'somatostatinoma*':ti,ab,kw OR 'vipoma*':ti,ab,kw OR (('pancrea*':ti,ab,kw OR 'islet cell*':ti,ab,kw OR 'island cell*':ti,ab,kw OR 'gastrin producing':ti,ab,kw) AND ('neoplasm'/exp OR 'carcinoma*':ti,ab,kw OR 'neoplas*':ti,ab,kw OR 'tumour*':ti,ab,kw OR 'adenoma*':ti,ab,kw OR 'adenocarcinoma*':ti,ab,kw OR 'tumor*':ti,ab,kw OR 'cancer*':ti,ab,kw OR 'oncolog*':ti,ab,kw OR 'malignan*':ti,ab,kw OR 'carcinogen*':ti,ab,kw OR 'oncogen*':ti,ab,kw OR 'anticarcinogen*':ti,ab,kw))	364,694

Search strategy for Clarivate Analytics/Web of Science Core Collection (2 June 2023)

3	**#2 AND #1**	1,928
2	**TS=("pancreatic enzym*" OR "pancreas enzym*" OR "pert" OR "pancreatic extract*" OR "panteric*" OR "panzytrat*" OR "pancreatin*" OR "cotazym*" OR "creon*" OR "encron*" OR "ilozym*" OR "ku zyme" OR "lipram*" OR "pancrease*" OR "pancrecarb*" OR "pancron*" OR "panokase*" OR "pertzye*" OR "protilase*" OR "ultrase*" OR "viokase*" OR "zymase*" OR "cotazym*" OR "pancrelipase*" OR "eurobiol" OR "extractum pancreati*" OR "pancreas lyophilisate*" OR "pancreas lyophilizate*" OR "pancreas powder*" OR "pancreatic extract*" OR "accelerase*" OR "alipase*" OR "catazyme*" OR "entolase*" OR "enzepi*" OR "enzipan*" OR "festal" OR "festale" OR "ilozyme*" OR "krebsilasi*" OR "kreon*" OR "kutrase*" OR "lipancreatin*" OR "panase*" OR "pancreaze*" OR "pangestyme*" OR "pankrease*" OR "plaretase*" OR "prolipase*" OR "promylin*" OR "protilase*" OR "robile" OR "ultrase*" OR "ultresa*" OR "viokace*" OR "vitazyme*" OR "zenpep*")**	35,346
1	**TS=("pancreatoduodenectom*" OR "duodenopancreatectom*" OR "pancreatectom*" OR "pancreatom*" OR (("pancrea*" OR "whipple*" OR "peri ampull*" OR "periampull*") AND ("surger*" OR "surgical*" OR "surgeon*" OR "operation*" OR "operative*" OR "perioperative*" OR "extracti*" OR "excisi*" OR "resect*")) OR "insulinoma*" OR "gastrinoma*" OR "glucagonoma*" OR "somatostatinoma*" OR "vipoma*" OR (("pancrea*" OR "islet cell*" OR "island cell*" OR "gastrin producing") AND ("carcinoma*" OR "neoplas*" OR "tumour*" OR "adenoma*" OR "adenocarcinoma*" OR "tumor*" OR "cancer*" OR "oncolog*" OR "malignan*" OR "carcinogen*" OR "oncogen*" OR "anticarcinogen*")))**	203,690

Appendix 2. Questionnaires

Study-specific questionnaire about exocrine pancreatic insufficiency

1. During the past month, which of the following complaints did you have for 3 or more days a week? (*multiple answers possible*)

□ Bowel rumblings
□ Bowel cramps
□ Excessive flatulence
□ Greasy stools (abnormal color / sticky / grease floats on it / floats)
□ Very smelly stools
□ Unintentional weight loss while eating as usual
□ None

2. Do you suffer from abdominal pain during the day?

□ Not at all
□ A little
□ Quite a bit
□ Very much

3. Do you use antacids, such as omeprazole, pantoprazole or esomeprazole, (almost) daily?

□ Yes
□ No

4. How often do you have stool?

□ Less than once a week
□ 1-3 times a week
□ 4-7 times a week
□ 2-3 times a day
□ 4 or more times a day

5. What is the aspect of your stool?

□ Separate hard lumps
□ One hard sausage-like lump
□ Smooth, soft sausage
□ Soft blobs with clear-cut edges
□ Mushy consistency with ragged edges
□ Liquid consistency (diarrhea) with no solid pieces

6. For what reason did you contacted a dietician during the past three months? (*multiple answers possible*)

□ Weight loss
□ Diabetes mellitus
□ Suspicion on impaired digestive function of the pancreas
□ Another reason, namely: _____
□ I have not been in contact with a dietician during the past three months

7. What does your diet look like?

□ I am on a high protein diet
□ I am on an energy-enriched diet

□ I am on a low-fat diet
□ I am on another kind of diet, namely: _____
□ I am not on a specific diet

8. Have you made any adjustments to your diet?
□ No
□ Yes, namely: _____

The following questions are about the use of pancreatic enzymes. If you do not use pancreatic enzyme supplementation the questionnaire ends here.

9. Which brand of pancreatic enzymes do you use?
□ Pancreaze
□ Creon
□ Panzytrat
□ Pancreatin
□ Other, namely: _____

10. What is your **daily** dosage of pancreatic enzymes?
Pay attention: this question is divided into capsules or granules.
If you use **capsules**:

	Number of capsules	Capsule dosage in mg or units of lipase
Breakfast		
Lunch		
Snacks		
Dinner		

If you use granules:
Number of spoons per day: ☐

Color of the spoon:
□ Green
□ Orange
□ Transparent

11. How do you take the capsules?
□ I swallow the whole capsule
□ I open the capsule and take the granules

12. When did you (approximately) start enzyme supplementation?
□ Less than 3 months ago
□ 3 – 6 months ago
□ 7 – 12 months ago
□ 1 – 2 years ago
□ More than 2 years ago

13. At what moment during your meal do you normally take the pancreatic enzymes? *(multiple answers possible)*

Breakfast	□ Before	□ During	□ After	□ No enzymes
Lunch	□ Before	□ During	□ After	□ No enzymes
Snacks	□ Before	□ During	□ After	□ No enzymes
Dinner	□ Before	□ During	□ After	□ No enzymes

14. How do you determine the dosage of capsules or enzymes? *(multiple answers possible)*
□ Based on the amount of fat per meal
□ I discussed the dosage of capsules or enzymes with the dietician
□ I use a standard dosage (for example 2 capsules with dinner and 1 with small meals)

15. How many days of the week do you really take the pancreatic enzymes?
□ Once a week
□ 2 – 4 times a week
□ 5 – 6 times a week
□ Every day

16. Which of the following statements applies to you since you started pancreatic enzyme supplementation?
□ I have no more complaints
□ I have less complaints
□ I still have complaints
□ I have more complaints

17. Do you experience any side effects from the pancreatic enzyme supplementation, such as abdominal pain, obstipation, or rash?
□ I have no side effects
□ I have side effects

Appendix 3. Study characteristics

Author	Study design	JADAD score	Total number of patients	Male (female)	Age (mean, SD)	Patient population	Diagnosis of EPI	Dosage of pancreatic enzymes intervention group	Primary outcome measure	Effect of treatment
Kim et al. (2020)	Double blinded RCT	4	164	90 (74)	Intervention group: 62.5 (8.1) Placebo group: 62.6 (8.7)	Pancreatic surgery	Fecal elastase <200 µg/g.	1 capsule per main meal (3 times/day, 40000 IU lipase).	Change in body weight.	Improvement in weight (intervention group +1,09 kg, placebo group -2.28 kg, p<0.001).
Seiler et al. (2013)	Double blinded RCT	5	58	35 (23)	Intervention group: 57.6 (10.2) Placebo group: 59.3 (8.7)	Pancreatic surgery	Coefficient of fat absorption (CFA) <80%.	Main meals: 75.000 IU lipase. Snacks: 50.000 IU lipase.	Change in CFA and CNA.	Improvement in CFA (intervention group +21.4%, placebo group -4.2%, p<0.001). Improvement in CNA (intervention group +18.9%, placebo group -10.3%, p<0.001).
Whitcomb et al. (2010)	Double blinded RCT	5	54	39 (15)	Intervention group: 52.0 (9.6) Placebo group: 50.5 (7.7)	Pancreatic surgery and chronic pancreatitis	Abnormal-secretin test, fecal elastase <100 µg/g, 72-hour fecal fat test >15 g/day or total pancreatectomy.	Main meals: 72.000 IU lipase. Snacks: 36.000 IU lipase.	Change in CFA.	Improvement in CFA absorption (intervention group +31.1%, placebo group +8.8%, p<0.0001).

RCT; randomized controlled trial, IU; international units, CFA; coefficient of fat absorption, CNA; coefficient of nitrogen absorption.