Natural Course and Treatment of Pancreatic Exocrine Insufficiency in a Nationwide Cohort of Chronic Pancreatitis

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Objectives: Pancreatic exocrine insufficiency (PEI) is a common complication of chronic pancreatitis. However, little is known about the natural course of PEI and the effect of pancreatic enzyme replacement therapy on symptoms. The aim of this study was to evaluate the natural course and treatment of PEI in a nationwide cohort of patients with chronic pancreatitis.

Methods: Patients with chronic pancreatitis were selected from the multicenter Dutch Chronic Pancreatitis Registry. Patients were classified in 3 groups: definite PEI, potential PEI, and no PEI. Definite PEI and no PEI were compared regarding the course of disease, symptoms, treatment, and quality of life.

Results: Nine hundred eighty-seven patients were included from 29 centers, of which 304 patients (31%) had definite PEI; 451 (46%), potentially PEI; and 232 (24%), no PEI. Patients with definite PEI had significantly more malabsorption symptoms, a lower body mass index, and aberrant defecation. Lowered quality of life was not independently associated with PEI. Of the PEI patients using pancreatic enzyme replacement therapy, 47% still reported steatorrhea.

Conclusions: Pancreatic exocrine insufficiency is associated with malabsorption symptoms and a lower body mass index. Some form of pancreatic enzyme replacement therapy is reasonably effective in alleviating malabsorption symptoms, but improvement of treatment is needed.

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Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas, which causes destruction and fibrosis of functional pancreatic tissue and obstruction of the pancreatic duct, which leads to exocrine and endocrine function loss of the pancreas.

Pancreatic exocrine insufficiency (PEI) is reported in 21% to 94% of patients with CP, and its incidence increases with disease duration.[1–3] It is associated with steatorrhea, weight loss, and abdominal discomfort. Because of malabsorption and maldigestion, a deficit of fat-soluble vitamins is present in up to 65% of patients with CP, resulting in clinical manifestations as osteoporosis, fractures, immune deficiency, and infections.[4–6]

No malabsorption-related symptom can definitely prove the presence of PEI, but in patients with these symptoms, the diagnosis of PEI can be made when the clinical presentation is combined with exocrine pancreatic function tests.[7] Current criterion standard for fat malabsorption is the coefficient of fat absorption test. This test, however, is very invasive as the patient has to maintain a strict diet for 5 days and has to collect the total amount of feces for 3 days. Therefore, the fecal elastase test (FE-1) is widely accepted as a noninvasive pancreatic function test in clinical practice, despite a lower accuracy.[8]

Pancreatic enzyme replacement therapy is the mainstay of treatment in patients with PEI due to CP and reduces maldigestion and malabsorption.[7,8] Although pancreatic enzyme replacement therapy is effective to reduce fecal fat excretion, the benefit for clinical and nutritional outcomes remains equivocal.[9,10] Recent literature showed that 70% of the CP patients with PEI have steatorrhea-related complaints despite pancreatic enzyme replacement therapy, suggesting undertreatment of PEI.[11]

Although PEI is common in CP and enzyme replacement therapy has been extensively studied, little is known about the natural course of exocrine insufficiency, the effect on well-being, and the effect of treatment in clinical practice. Therefore, the aims of this study were to evaluate the natural course of exocrine insufficiency in CP patients with respect to course of disease, symptoms, and quality of life and to evaluate the effect of pancreatic enzyme replacement therapy.

MATERIALS AND METHODS

We performed a cross-sectional analysis of data that were collected prospectively as part of the Dutch Chronic Pancreatitis Registry (CARE).[12] This study is written according the

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[13]

CARE Database

The Dutch Chronic Pancreatitis Registry is a nationwide observational cohort study, coordinated by the Dutch Pancreatitis Study Group, in 29 participating hospitals. In CARE, patients with CP or recurrent acute pancreatitis (RAP) are included between 2011 and 2017. Data are being collected prospectively since 2011 by screening medical records and by at least yearly repeated sending of validated questionnaires. All included patients had already an RAP or CP diagnosis before inclusion. Therefore, data from before 2011, for example, the diagnosis date of CP, were collected retrospectively by screening of medical records.[12]

Safety

This study was executed according the principles of the Declaration of Helsinki and the human research laws in the Netherlands. The Dutch Chronic Pancreatitis Registry has been reviewed by the medical ethical committee of the University Medical Center Utrecht and received an exempt status due to its descriptive nature (ID: AvG/rc/10/05699; March 17, 2010). All patients gave written informed consent for participation and permission to use their medical records for this study.

Patient Selection

Patients who had definite CP according the M-ANNHEIM criteria were included.[14] We classified PEI in patients with CP in 3 groups: definite PEI, potential PEI, and no PEI. For the diagnosis of PEI, we used exocrine pancreatic function tests, steatorrhea complaints, and usage of pancreatic enzyme replacement therapy. Threshold of exocrine function test for diagnosis of exocrine insufficiency was less than 200 μg/g for the fecal elastase-1 test, for the coefficient of fat absorption test greater than 5% fat or greater than 7 g/24 h, and greater than 10% for the acid steatocrit test.[15–17]

Definite PEI was defined as either (1) an abnormal exocrine function test plus either steatorrhea or the use of pancreatic enzyme replacement or (2) no exocrine function test but steatorrhea with a positive response on pancreatic enzyme replacement therapy. Patients were considered having no PEI when having no steatorrhea and no pancreatic enzyme replacement therapy, without a documented abnormal exocrine function test or with a documented normal exocrine function test. All other patients were considered as having potential PEI. In this group, patients had (1) steatorrhea or pancreatic enzyme replacement therapy without an exocrine function test, (2) an abnormal exocrine function test but no steatorrhea or pancreatic enzyme replacement therapy, or (3) steatorrhea or pancreatic enzyme replacement therapy but with a normal exocrine function test.

Data

Data were collected at inclusion in the registry by using a questionnaire consisting of questions on demographics, intoxication (ie, alcohol, smoking), symptoms, defecation characteristics, and medication usage. In addition, the validated Izbicki pain questionnaire and validated Short-Form 36 (SF-36) for quality of life were collected.[18,19] Medical records were reviewed for data regarding pancreatic function, imaging, hospitalization, and treatment.

We compared patients with definite PEI and no PEI for symptoms, course of disease, treatment, and quality of life at inclusion in the registry. Patients with potential PEI were only presented in patient characteristics and in the regression analysis for quality of life, but not included in the comparison analysis because the diagnosis of PEI was arguable in these patients. Additionally, in patients with definite PEI, we examined the correlation between usage of pancreatic enzyme replacement therapy on one end, and patient-reported symptoms and dosage of enzymes on the other end. Thereby, we compared pain and quality of life in patients with and without steatorrhea despite pancreatic enzyme replacement therapy.

Statistical Analysis

Parametric data are expressed as mean with standard deviation (SD), whereas nonparametric data are expressed as median with interquartile range (IQR). Statistical comparison was performed using χ^2 test or Fisher exact test for categorical data and the Student *t* test or Mann-Whitney *U* test for continuous data. $P < 0.05$ was considered to represent a significant statistical difference. Missing values were not imputed.

Additionally, multivariate linear regression analyses were performed to assess the independent predictors, including PEI and pancreatic enzyme replacement therapy, of physical and mental quality of life. Variables were excluded through backward selection until only statistically significant variables were selected in the final model.

RESULTS

Patient Characteristics

Patient characteristics per group are listed in Table 1. From the 1360 patients prospectively included between 2011 and 2017 in CARE, a total of 987 patients had CP according the M-ANNHEIM criteria; the remaining patients had RAP and were excluded from the present study. Three hundred four of 987 patients (30.8%) had definite PEI; 451 (45.7%), potential PEI; and 232 (23.5%), no PEI. The flowchart of patient selection and group definition is depicted in Figure 1. Of the 987 included patients, mean age (SD) was 58 (11.5) years, and 67% were men. Four hundred eighty-seven patients (49%) underwent exocrine function testing, and 344 of them had an abnormal pancreatic function. Alcohol was the most common etiology (51%) followed by idiopathic etiology (26%). One-third of the patients were active alcohol users (33%), and a majority consisted of current smokers (60%).

Course of Disease

Median disease duration of CP was 83 months (IQR, 41–158 months) at inclusion in the registry. Disease duration was significantly longer in patients with PEI, with a median difference between definite PEI and no PEI of 26 months ($P < 0.001$). Mean age at diagnosis was significantly lower in patients with definite PEI compared with patients without PEI (50 [SD, 13] years vs 53 [SD, 12] years; $P = 0.01$). Figure 2 visualizes the relation between the percentage of patients with PEI and the duration of CP in a 1 − survival plot. According this figure, the percentage of PEI is steadily increasing from 20% after 5 years of CP to 70% after 20 years of CP. Diabetes mellitus was present in 50% of patients with PEI compared with 18% in patients without PEI ($P < 0.001$). Previous surgery was associated with the presence of PEI, whereas previous endoscopy was not associated ($P < 0.001$ and $P = 0.709$, respectively) (Table 1).

Symptoms and Treatment of PEI

Pancreatic exocrine insufficiency was inversely associated with body mass index (BMI); significantly more PEI patients were classified as underweight compared with CP patients without PEI

TABLE 1. Patients Characteristics

	All CP (n = 987, 100%)	PEI (n = 304, 30.8%)	No PEI (n = 232, 23.5%)	Potential PEI (n = 451, 45.7%)	*P* (PEI vs No PEI)
Age, mean (SD), y	58 (11.5)	58 (11.0)	58 (11.7)	58 (11.7)	0.923
Duration of CP, median (IQR), mo	83 (41–158)	97 (50–181)	64 (34–114)	94 (47–175)	<0.001
Duration symptoms CP, median (IQR), y	91 (47–170)	119 (58–200)	71 (39–130)	85 (41–159)	<0.001
Sex, male, n (%)	659/987 (66.8)	203/304 (66.8)	155/232 (66.8)	301/451 (66.7)	0.993
BMI, median (IQR), kg/m^2	23.4 (21.0–26.1)	22.8 (20.2–25.0)	23.8 (21.5–26.9)	23.5 (21.0–26.6)	<0.001
Etiology CP, n (%)					0.796
Alcohol	435/854 (50.9)	138/270 (51.1)	101/203 (49.8)	196/381 (51.4)	
Idiopathic	219/854 (25.7)	70/270 (25.9)	50/203 (24.6)	99/381 (26.0)	
Other	200/854 (23.4)	62/270 (23.0)	52/203 (25.6)	86/381 (22.6)	
Smoking, n (%)					0.407
Never	117/981 (11.9)	35/304 (11.5)	25/231 (10.8)	57/446 (12.8)	
Past	273/981 (27.8)	80/304 (26.3)	73/231 (31.6)	120/446 (26.9)	
Current	591/981 (60.2)	189/304 (62.2)	133/231 (57.6)	269/446 (60.3)	
Pack-years, median (IQR), y	27.0 (10.0–40.0)	27.0 (8.9–40.0)	24.4 (8.4–37.5)	28.5 (10.3–41.0)	
Alcohol, n (%)					0.784
Never	122/981 (12.4)	31/304 (10.2)	27/232 (11.6)	64/445 (14.4)	
Past	534/981 (54.4)	172/304 (56.6)	125/232 (53.9)	237/445 (53.3)	
Current	325/981 (33.1)	101/304 (33.2)	80/232 (34.5)	144/445 (32.4)	
Alcohol, units/d, median (IQR)	5 (1–10)	5 (2–10)	5 (2–10)	4 (1–8)	
Diabetes mellitus, n (%)	371/987 (37.6)	152/304 (50.0)	43/232 (18.5)	176/451 (39.0)	<0.001
Previous endoscopy, n (%)	262/987 (26.5)	86/304 (28.3)	60/232 (25.9)	116/451 (25.7)	0.709
Previous surgery, n (%)	304/987 (30.8)	115/304 (37.8)	52/232 (22.4)	137/451 (30.4)	<0.001

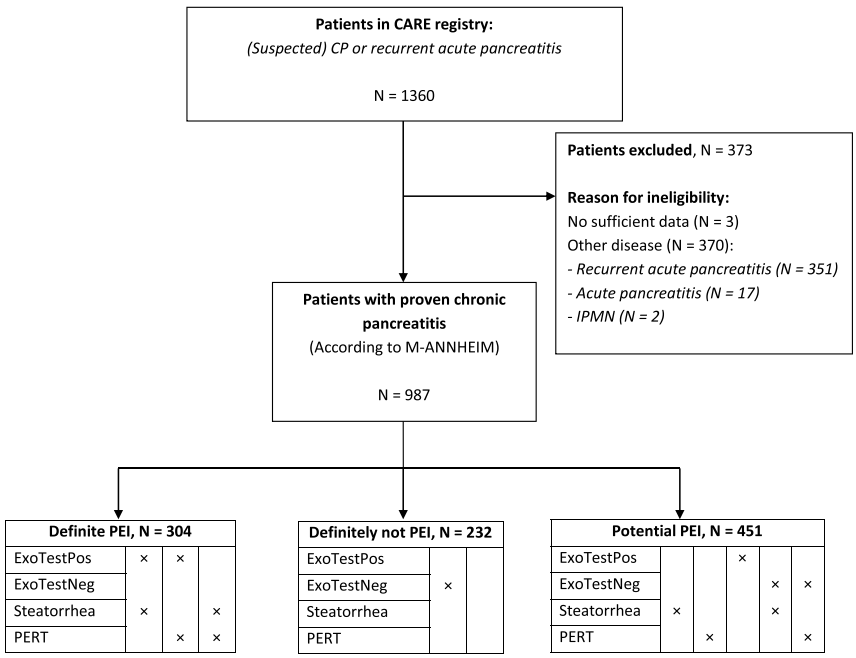

FIGURE 1. Flowchart of patient enrollment and group selection. Definite PEI: positive exocrine function test plus either steatorrhea or the use of pancreatic enzyme replacement (columns 1 and 2) or no exocrine function test but steatorrhea with a positive response on pancreatic enzyme replacement therapy (column 3). Definitely no PEI: having no steatorrhea and no pancreatic enzyme replacement therapy, with a documented abnormal exocrine function test (column 1) or without a documented normal exocrine function test (column 2). Potential PEI: steatorrhea or pancreatic enzyme replacement therapy without an exocrine function test (columns 1 and 2), an abnormal exocrine function test but no steatorrhea or pancreatic enzyme replacement therapy (column 3), or steatorrhea or pancreatic enzyme replacement therapy but with a normal exocrine function test (columns 4 and 5). ExoTestPos, exocrine pancreatic function test positive; ExoTestNeg, exocrine pancreatic function test negative; IPMN, intraductal papillary mucinous neoplasm; PERT, pancreatic enzyme replacement therapy.

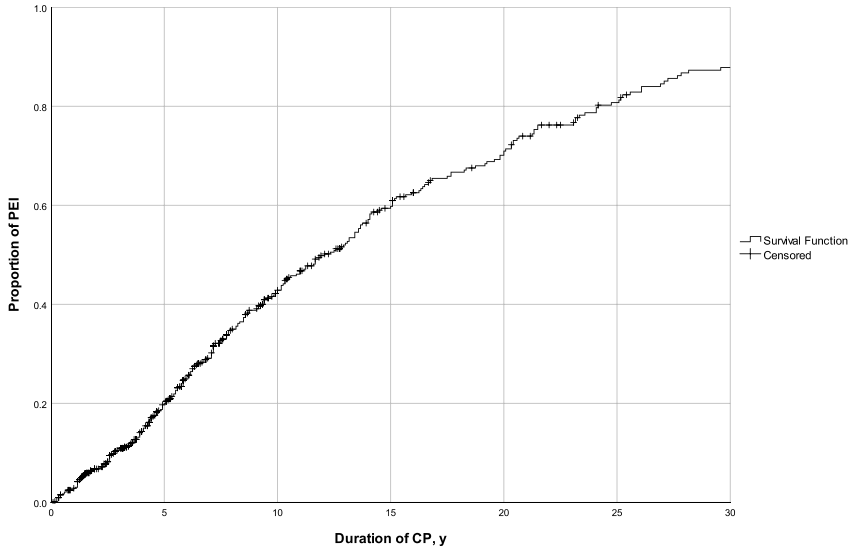

FIGURE 2. Percentage of PEI after the onset of chronic pancreatitis. Correlation between duration CP and percentage PEI shown in a 1 – survival plot.

(12% vs 3%, $P < 0.001$). Both PEI and no PEI groups had a high percentage of unintended weight loss of 38% and 34%, respectively. Malabsorption-related symptoms such as nausea after a meal, pain after a meal, and steatorrhea were significantly associated with PEI, but were also present in some proportion of CP patients without PEI. Defecation frequency was higher and of looser consistency in patients with definite PEI. The Izbicki pain score at present cross-sectional analysis was higher in the definite PEI group with a mean score of 45 points (SD, 30) compared with 35 (SD, 27) in the no PEI group ($P < 0.001$).

Eighty-eight percent of patients with definite PEI were treated with pancreatic enzyme replacement therapy with a median dosage of 100,000 units of lipase a day (IQR, 75,000–175,000); 56% of patients with PEI used a proton pump inhibitor (PPI). Only 31% of all patients with PEI were referred to a dietitian. Detailed information about symptoms and treatment of PEI is listed in Table 2.

Quality of Life

Overall, patients had a mean score of 41.9 (SD, 11.3) for the physical component and 46.0 (SD, 12.1) for the mental component on the quality-of-life SF-36 questionnaire compared with the standard mean score of 50 (SD, 10) of the reference Dutch population. The physical component was significantly lower in patients with PEI compared with patients without PEI (40.5 vs 44.0, $P < 0.001$; Table 2). However, in the multivariate analysis, PEI was not associated with a lower quality of life. Predictors of a lower physical quality of life were younger age, female sex, smoking, and a higher Izbicki pain score. Predictors for a lower mental quality of life were younger age, alcoholic etiology of CP, and a higher Izbicki pain score (Supplemental Table 1, http://links.lww.com/MPA/A767). When excluding the Izbicki pain score in the multivariate regression analysis, PEI was significantly associated with a lower physical quality of life, suggesting that patients with PEI have more complaints and therefore a lower quality of life (Supplemental Table 2, http://links.lww.com/MPA/A767).

Pancreatic Enzyme Replacement Therapy in Definite PEI Patients

Symptoms for PEI patients with and without pancreatic enzyme replacement therapy are listed in Table 3. Pancreatic enzymes were used by the vast majority of patients with definite PEI (88%). Nevertheless, 47% of patients receiving pancreatic enzyme replacement still reported steatorrhea. Furthermore, unintended weight loss, postprandial nausea, and pain directly after meal still were present in a considerable proportion of those patients (36%, 26%, and 42%, respectively). The relation between malabsorption-related complaints and dosage of pancreatic enzyme replacement therapy is presented in Supplemental Figure 1, http://links.lww.com/MPA/A767. No correlation was seen between the malabsorption-related complaints (steatorrhea, weight loss, postprandial nausea, postprandial pain, appetite) and dosage.

In patients without pancreatic enzyme replacement therapy, prevalence of symptoms of unintentional weight loss, steatorrhea, or nausea after meal was higher than in patients with pancreatic enzyme replacement therapy. Stool was often loose in nonusers (75%) compared with users of pancreatic enzyme replacement therapy (54%, $P = 0.038$). Pain scores and quality of life were comparable between pancreatic enzyme replacement therapy users and nonusers. Also, in the multivariate regression analysis, pancreatic enzyme replacement therapy was not associated with quality of life (Supplemental Table 3, http://links.lww.com/MPA/A767).

In patients with pancreatic enzyme replacement therapy and without steatorrhea (adequate treatment), the Izbicki pain score was lower compared with patients with steatorrhea despite pancreatic enzyme replacement therapy (nonadequate treatment) (−13.3 points, $P = 0.002$). Thereby, quality of life was significantly higher in patients without steatorrhea. Mean units of lipase per day were the same between both groups (Table 4).

DISCUSSION

In this representative Dutch multicenter CP registry, approximately 1 in 3 patients had definite PEI after a median CP duration of 6.9 years. Prevalence of PEI steadily increased with disease

TABLE 2. Symptoms and Treatment

	All CP (n = 987, 100%)	PEI (n = 304, 30.8%)	No PEI (n = 232, 23.5%)	*P* (PEI vs No PEI)
BMI classification (WHO), kg/m^2, n (%)				<0.001
Underweight (<18.5)	75/983 (7.6)	35/302 (11.6)	7/232 (3.0)	
Normal range (18.5–24.9)	582/983 (59.2)	191/302 (63.2)	138/232 (59.5)	
Overweight (25.0–29.9)	253/983 (25.7)	64/302 (21.2)	64/232 (27.6)	
Obese (>30)	73/983 (7.4)	12/302 (4.0)	23/232 (9.9)	
Unintended weight loss, n (%)	350/975 (35.9)	116/302 (38.2)	79/230 (34.3)	0.335
Nausea after meal, n (%)	153/680 (22.5)	70/242 (28.9)	33/204 (16.2)	0.001
Pain after meal, n (%)	242/680 (35.6)	106/242 (43.8)	54/204 (26.5)	<0.001
No appetite, n (%)	143/679 (21.1)	55/242 (22.7)	36/204 (17.6)	0.185
Steatorrhea, n (%)	207/681 (30.4)	135/244 (55.3)	0/232 (0.0)	<0.001
Defecation frequency, median (IQR), times a day	2 (1–2)	2 (1–3)	1 (1–2)	<0.001
Defecation consistency, n (%)				<0.001
Liquid	46/637 (7.2)	17/225 (7.6)	12/195 (6.2)	
Loose	219/637 (34.4)	113/225 (50.2)	34/195 (17.4)	
Normal	357/637 (56.0)	90/225 (40.0)	146/195 (74.9)	
Hard	15/637 (2.4)	5/225 (2.2)	3/195 (1.5)	
Defecation color, n (%)				<0.001
Black	21/651 (3.2)	9/234 (3.8)	2/194 (1.0)	
Brown	549/651 (84.3)	175/234 (74.8)	185/194 (95.4)	
White	81/651 (12.4)	50/234 (21.4)	7/194 (3.6)	
Izbicki pain score, mean (SD), 0–100	40.8 (28.5)	45.1 (30.0)	34.6 (26.6)	<0.001
Quality of life (SF-36), mean (SD)				
Physical component	41.9 (11.3)	40.5 (11.0)	44.0 (11.2)	<0.001
Mental component	46.0 (12.1)	45.5 (12.4)	46.8 (11.4)	0.220
Medical treatment				
PERT, n (%)	471/987 (47.7)	266/304 (87.5)	0/232 (0.0)	<0.001
Dosage PERT, median (IQR)	100,000 (75,000–150,000)	100,000 (75,000–175,000)	0 (0–0)	
PPI, n (%)	463/987 (46.9)	171/304 (56.3)	85/232 (36.6)	<0.001
Dietitian referral, n (%)	245/979 (25.0)	93/303 (30.7)	33/230 (14.3)	<0.001

PERT indicates pancreatic enzyme replacement therapy; WHO, World Health Organization.

duration to more than 80% after 30 years. Patients with PEI had significantly more malabsorption-related symptoms, a lower BMI, and more frequent defecation and of loose consistency despite pancreatic enzyme replacement therapy in the vast majority of these patients. Patients with PEI had a lower physical quality of life, but PEI was not one of the predictors of a lower quality of life. Potentially, PEI patients have a more advanced stage of disease with more complaints, including pain, and therefore a lower quality of life. Pancreatic enzyme replacement therapy in patients with definite PEI was associated with a reduction of malabsorption complaints and defecation problems. Surprisingly, 47% of patients who used pancreatic enzyme replacement therapy still had malabsorption-associated complaints, and no correlation between dosage and malabsorption complaints was seen. However, the median dosage of 100,000 units a day was quite low compared with current clinical guidelines.[8] These patients had more pain and a lower quality of life compared with patients with adequate pancreatic enzyme replacement therapy.

Previous publications report that 63% and 71% to 87% of patients with CP had PEI 5 years after diagnosis of CP.[1,3] Our percentage of 31% PEI is much lower, which is most likely due to the differences in establishing the diagnosis of CP and PEI. In the present study, criteria for diagnosis of PEI were much stricter compared with the criteria of Dumasy et al[1] and Ammann et al,[3] as we diagnosed PEI only when a patient had malabsorption complaints and additionally an abnormal pancreatic function test or positive effect on pancreatic enzyme replacement therapy. The increase of PEI with disease duration that was present in our cohort has also been demonstrated by Dumasy et al.[1] In that study, PEI increased from 63% within 5 years after diagnosis to 95% after 10 years of CP diagnosis.[1] In our study, the percentage was much lower, also most likely due to our strict PEI diagnosis criteria (20% after 5 years to 43% after 10 years of CP diagnosis).

Patients with CP demonstrate an overall reduction in quality of life for both physical and mental components, which is similar to the quality of life of patients with other chronic diseases.[20]

In our study, PEI in CP was not associated with a more impaired quality of life. Although pancreatic enzyme replacement therapy improved malabsorption-related symptoms such as steatorrhea and nausea, it was vice versa not associated with a higher quality of life. A recent systematic review on efficacy of pancreatic enzyme replacement therapy has shown that pancreatic enzyme replacement therapy improves gastrointestinal symptoms and quality of life.[10] Also another cohort showed that pancreatic enzyme replacement therapy was associated with symptom relief and improvement in quality of life.[21] We are not certain why the use of pancreatic enzymes was not associated with an increased quality of life. However, a logical explanation may be that

TABLE 3. Symptoms in Patients With PEI

	All PEI (n = 304, 100%)	PERT (n = 266, 87.5%)	No PERT (n = 38, 12.5%)	*P* (PERT vs No PERT)
BMI, median (IQR), kg/m^2	22.8 (20.2–25.0)	23.5 (20.4–25.1)	22.6 (20.2–25.0)	0.604
Unintended weight loss, n (%)	116/302 (38.2)	95/264 (36.0)	21/38 (55.3)	0.022
Nausea after meal, n (%)	70/242 (28.9)	54/205 (26.3)	16/37 (43.2)	0.037
Pain after meal, n (%)	106/242 (43.8)	86/205 (42.0)	20/37 (54.1)	0.172
No appetite, n (%)	55/242 (22.7)	47/205 (22.9)	8/37 (21.6)	0.862
Steatorrhea, n (%)	135/244 (55.3)	97/206 (47.1)	38/38 (100)	<0.001
Defecation frequency, median (IQR), times a day	2 (1–3)	2 (1–2.5)	2 (1–3)	0.193
Defecation consistency, n (%)				0.038
Liquid	17/225 (7.6)	12/192 (6.3)	5/33 (15.2)	
Loose	113/225 (50.2)	92/192 (47.9)	21/33 (63.6)	
Normal	90/225 (40.0)	83/192 (43.2)	7/33 (21.2)	
Hard	5/225 (2.2)	5/192 (2.6)	0/33 (0.0)	
Defecation color, n (%)				0.767
Black	9/234 (3.8)	8/199 (4.0)	1/35 (2.9)	
Brown	175/234 (74.8)	150/199 (75.4)	25/35 (71.4)	
White	50/234 (21.4)	41/199 (20.6)	9/35 (25.7)	
Izbicki pain score, mean (IQR), 0–100	45.1 (30.0)	44.0 (29.8)	53.2 (30.5)	0.094
Quality of life (SF-36), mean (SD)				
Physical component	40.5 (11.0)	40.6 (11.0)	39.9 (11.6)	0.711
Mental component	45.5 (12.4)	45.6 (12.5)	44.9 (11.3)	0.729

PERT indicates pancreatic enzyme replacement therapy.

symptoms such as pain had a much higher impact on quality of life, exemplified by the fact that a higher Izbicki pain score was strongly associated with a lower quality of life. We deliberately used the SF-36 questionnaire to measure quality of life, being a general questionnaire that has been validated for many diseases and used extensively for CP as well.[22,23] This allows for reliable comparison between our cohort and previous cohorts. Thereby, no real specific quality-of-life questionnaire exists, except the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 with Pancreatic Cancer 28 module, which is a much longer questionnaire and is used much less frequently.[24] Moreover, it has actually been adapted from the PAN-26 which was developed for pancreatic cancer, with the addition of 2 questions about alcohol use.

Notably, almost half of patients with pancreatic enzyme replacement therapy still reported steatorrhea. The high percentage of steatorrhea in pancreatic enzyme replacement therapy users was also mentioned by Sikkens et al.[11] In their survey about PEI in patients with CP, 70% of the patients reported steatorrhea-related complaints despite pancreatic enzyme replacement therapy.[11] This could possibly be related to insufficient dosing of pancreatic enzymes, but in our cohort, no relation was seen between dosage of pancreatic enzyme replacement therapy and malabsorption-related complaints (Supplemental Fig. 1, http://links.lww.com/MPA/A767). Perhaps, steatorrhea despite prescribed treatment dosage is caused by a low compliance of the patient or an inadequate administration of enzymes. Although it is stated in the United European Gastroenterology Guidelines for CP that dietitian referral and administration of PPI are advised to improve complaints of PEI, only 30% of the patients were referred to a dietitian, and 56% had a PPI as comedication with their pancreatic enzyme replacement therapy.[8] Thus, in current clinical practice, patients with PEI are probably not optimally educated about diet and enzyme use and not treated according to the guidelines. The efficacy

TABLE 4. Outcomes of Adequate PERT Treatment

	All PERT* (n = 206, 100%)	PERT With Steatorrhea (n = 97, 47%)	PERT Without Steatorrhea (n = 109, 53%)	*P* (Steatorrhea vs No Steatorrhea)
PERT dosage, median (IQR)	100,000 (75,000–175,000)	106,250 (75,000–175,000)	106,250 (75,000–159,375)	0.904
Izbicki pain score, mean (SD), 0–100	44.0 (29.8)	50.9 (28.7)	37.6 (29.6)	0.002
SF-36: physical component summary, mean (SD)	40.6 (11.0)	38.7 (10.9)	43.5 (10.0)	0.001
SF-36: mental component summary, mean (SD)	45.6 (12.5)	43.1 (13.1)	48.2 (11.2)	0.003

*Steatorrhea data were missing in 60 patients.

PERT indicates pancreatic enzyme replacement therapy.

of pancreatic enzyme replacement therapy in clinical practice has to be frequently monitored for each patient individually and tailored to complaints, the diet, and remnant pancreatic function. Thereby a patient has to be educated about diet and enzyme administration to aid in compliance on treatment and to reduce steatorrhea complaints.

To avoid contamination between the groups of patients with definite PEI and without PEI, we aimed to define strict criteria to divide these groups, resulting in a relatively large group of patients with no proven PEI, which was considered as having potential PEI. However, this selection may have introduced selection bias by allocating patients with mild PEI in the potential PEI group. Hence, this study may have overestimated the differences between patients with definite PEI and without PEI, because the PEI group potentially missed the mild PEI patients. A second limitation of this study is the cross-sectional analysis. This makes it impossible to determine cause and effect. For example, malabsorption-related symptoms are the reason to start pancreatic enzyme replacement therapy but are also the outcome to measure effect of pancreatic enzyme replacement therapy. Therefore, determining the association between malabsorption-related symptoms and pancreatic enzyme replacement therapy dosage is difficult. All patients are included prospectively, but they had already a diagnosis of RAP of CP at inclusion. Therefore, we had to collect data retrospectively from before inclusion, which may have introduced recall bias. However, this was a small amount of the data and was only collected by screening medical records. Therefore, the influence of recall bias in this study is very limited.

Further research should focus on the diagnosis of PEI by developing an accurate tool, or a combination of tools, to evaluate PEI. Also, more research is needed on how to improve the efficacy of pancreatic enzyme replacement therapy because a high percentage of patients using these medications still suffer from malabsorption-related symptoms. Our study suggests that just increasing the dosage without appropriate dietary counseling and use of necessary adjuvant therapy (eg, PPI) does not lead to fewer malabsorption-related symptoms.

Physicians should frequently measure symptoms and test pancreatic function to diagnose PEI in the CP population and offer patients optimal treatment using an adequate dosage of pancreatic enzymes and counseling. To achieve optimal result of treatment in PEI patients, comedication, dietary referral, and frequent counseling to evaluate the effect of therapy are needed.

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