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Pancreatic enzyme treatment in chronic pancreatitis: Quality of management and adherence to guidelines–A cross-sectional observational study

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Abstract

Objectives: Pancreatic exocrine insufficiency (PEI) is a common complication in patients with chronic pancreatitis (CP), leading to increased morbidity and mortality if not treated adequately. Pancreatic enzyme replacement therapy|pancreas enzyme replacement therapy (PERT) is the cornerstone in treatment of patients with PEI. In the present study, we use data from the Scandinavian Baltic Pancreatic Club database to examine adherence of PERT according to United European Gastroenterology evidence-based guidelines treatment of CP.

Patients and methods: Patients with definitive or probable CP according to M-ANNHEIM diagnostic criteria were included. We collected information on exposures, exocrine function, intake of pancreatic enzymes, and markers of nutrition. Fecal elastase <200 μg/g was defined as a marker for PEI. Enzyme replacement therapy of 100,000 lipase units or more was defined as adequate treatment.

Results: We included 1006 patients from 8 centers in five countries. Sixty-four percent of the patients were correctly treated. Twenty-five per cent of PEI patients were not taking enzymes at all, and 20% of PEI patients were undertreated with insufficient PERT doses according to the guidelines. Fourteen percent of patients with sufficient pancreatic function were receiving enzymes despite normal exocrine pancreatic function. There were center differences. Current smoking was associated with lack of treatment and alcohol abuse was associated with under-treatment. There were no associations between "no treatment" or "under-treatment" for underweight or vitamin *D* deficiency.

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Conclusion: In our CP expert centers, the adherence to guidelines for enzyme treatment is insufficient. Both patient factors and center differences have influence on treatment adherence.

KEYWORDS
chronic pancreatitis, pancreatic enzyme replacement therapy, pancreatic exocrine insufficiency, scandinavian baltic pancreatic club, United European Gastroenterology

INTRODUCTION

Chronic pancreatitis (CP) is a multifactorial disease with high impact on morbidity. Pain, nutritional failure, diabetes or consequences from other complications, drug or alcohol abuse are frequent factors reducing quality of life in CP patients.[1–3] Previous studies have demonstrated that exocrine pancreatic insufficiency (PEI) is underdiagnosed, and if found, undertreatment is evident.[4,5] The prevalence of PEI in CP ranges from 30% to 90% in different studies.[6] In a previous publication from the Scandinavian Baltic Pancreatic Club (SBPC) study cohort we found a 68% prevalence of PEI in patients with CP.[7] When PEI is established, the lack of digestive enzymes causes malabsorption of fat, proteins and carbohydrates and increase fecal energy losses.[8] Malabsorption may cause lack of macronutrients, vitamins, and other micronutrients if untreated. In the uttermost consequence it is life-shortening.[9]

Nutritional optimalization and pancreas enzyme replacement therapy (PERT) are cornerstones in treatment of malabsorption and prevention of its consequences.[10] The United European Gastroenterology (UEG) evidence-based guidelines give clear advice on PERT treatment,[11] where 40,000–80,000 European Pharmacopeia (Eur. Pharm) lipase units per main meal and half dose per snack meal is recommended. This advice is based on studies measuring coefficient of fat absorption or coefficient of nitrogen absorption.[12–14] Two studies showed moderate to low adherence to the UEG guidelines in general.[15,16] However, little is known about compliance to these guidelines concerning PERT specifically. In this study we aimed to evaluate PERT treatment in a large, Northern-European CP cohort to (1) assess the quality of adherence to treatment guidelines (2) evaluate risk-factors associated to non-adherence to treatment guidelines and (3) evaluate consequences of non-adherence to the guidelines.

Key summary

Established knowledge on this subject:

- Pancreatic enzyme replacement therapy is the cornerstone in treatment of patients with Pancreatic exocrine insufficiency (PEI).
- Guidelines give recommendations for everyday clinical use of PERT.
- Little is known about clinical implementation of the United European Guidelines.
- Publications about compliance to national or international guidelines in treatment of chronic pancreatitis (CP) and its consequences indicate room for improvement.

Our new findings:

- The presence of factors like smoke and alcohol abuse influence on patient compliance to United European Gastroenterology (UEG) guidelines.
- Lack of adherence to the guidelines have little nutritional consequences.
- Even in expert centers for pancreatic diseases, the adherence to guidelines for enzyme treatment is varying.
- Our findings indicate that differences in applied definitions of PEI may be an explanation to varying guideline adherence.

MATERIAL AND METHODS

Study design

The baseline data collection in this cross-sectional observational study was performed from 1 February 2016, to 1 July 2019, at 12 hospitals in the SBPC database collaboration. Data retrieval was 19 July 2019. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.[17] Permissions for data collection and sharing were obtained from the institutional review board at each participating center. Aalborg University Hospital is coordinating center for the database (200,858-0028, project ID 2018-19). Haukeland University Hospital, Bergen is coordinating the present study (Regional Ethical Committee, Western Norway: 2019/1037). The data are reported according to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement.[18] Written, informed consent was obtained from each patient included in the study.

Subjects

The SBPC database collects data on patients with definite or probable CP according to the M-ANNHEIM diagnostic criteria.[19] We

included centers providing data on fecal elastase (FE) and PERT doses >50%. Four centers did not fulfill these criteria; thus, eight centers were included for this study: Aalborg, Herlev, Hvidovre and Bispebjerg (Denmark), Bergen (Norway), Stockholm (Sweden), Kaunas (Lithuania), Tampere (Finland). Subjects lacking registrations on FE or PERT doses were excluded.

Patient characteristics

At the baseline visit we collected information on sex, age, duration since diagnosis of CP, body mass index (BMI), FE results, hemoglobin, albumin and 25-Hydroxy (OH) vitamin *D* and patient reported PERT doses used per day. We also collected information on current and previous smoking history, alcohol consumption and pain.[20]

Definitions

Pancreatic exocrine insufficiency was defined by FE < 200 μg/g.[21] Sufficient PERT doses were defined as 100,000 lipase units per day or more.[11]

Thus, subjects with PEI and with PERT ≥100,000 lipase units per day and patients without PEI and no PERT treatment were defined as *correctly treated*. Subjects with PEI and no PERT were defined as *not treated*. Subjects with PEI receiving PERT, but with doses of < 100,000 lipase units per day were defined as *undertreated* in accordance with the UEG guidelines. Patients taking enzymes despite FE >200 μg/g were defined as *overtreated*.

Current heavy drinkers were defined as subjects drinking on average five or more standard units of alcohol per day.[22] The presence of pain was classified according to the M-ANNHEIM diagnostic criteria.[19] All categories of intermittent, treated, or continuous pain were defined as *presence of pain*. Underweight was defined as BMI<18.5[23] and severe vitamin *D* deficiency was defined as 25 OH vitamin *D* < 25 ng/ml.[24]

We defined current smoking, current heavy drinking and the presence of pain as possible factors influencing PERT treatment.[16]

Statistical analysis

Continuous variables are presented as means and standard deviations (SD), unless stated otherwise. Evaluation for normality was performed by histograms and Q-Q plots. Comparisons of means were assessed by independent samples *t*-test. Comparisons of binary variables were performed by the chi-square test.

We assessed interactions between factors "current smoking", "current heavy drinking" and pain. There were no significant interactions between current smoking and current heavy drinking. There was a weak interaction between pain and current drinking for the category "no treatment" only. We performed a separate, univariate logistic regression to assess the unadjusted associations between risk factors, covariates to the outcome variables under - or overtreatment. Then we performed a stepwise multivariate logistic regression. In the first step, a backward conditional elimination analysis was performed, excluding the least relevant factor stepwise until only factors with a probability of association ≥90% ($p < 0.10$) were included. In the final multivariate model, we included the remaining factors and the chosen covariates age, gender, and disease duration.

We also performed univariate and multivariate analyses of the groupings "not treated" and "undertreated" and "correctly treated" against outcomes underweight and severe vitamin *D* deficiency using the same model adjusting for all factors from the first analysis as covariates. Final adjustments for the covariate "center" were performed in a separate step in both models. All results were expressed as odds ratio (OR) with 95% Confidence interval (CI). We performed the statistical analyses in SPSS® statistics package version 27 (IBM®, Armonk, NY).

RESULTS

We identified 1488 eligible subjects from 8 centers. We excluded 482 subjects due to lack of reported FE, PERT dose or both, thus 1006 with complete FE/PERT dose pairs could be included for final analysis. We report demographic and clinical patient characteristics in Table 1.

Quality of pancreatic enzyme treatment

Sixty-four percent of the patients were correctly treated according to treatment guidelines. Of the included patients, 64% had PEI. Twenty-five per cent of PEI patients were not taking PERT at all, and 20% of PEI patients were undertreated with insufficient PERT doses according to the guideline. Fourteen per cent of PS patients were receiving enzymes despite normal exocrine pancreatic function. The distribution of enzyme doses according to FE results are displayed in Figure 1.

Factors associated with non-adherence to treatment advice

The univariate and final models are shown in Tables 2 and 3 and the complete multistep regression analysis in supplementary Table S1. In the univariate model, we found that current smoking was associated to no treatment, and current heavy drinking was associated with undertreatment. The presence of pain was negatively associated to correct treatment (OR = 0.72; 95% CI 0.55, 0.94; $p = 0.02$).

We explored the associations in a multivariate model as described above. Here, the independent associations of current smoking (OR = 2.52; 95% CI 1.76–3.61; $p < 0.001$) to no treatment, and current heavy drinking (OR = 2.74; 95% CI 1.50–5.02; $p = 0.001$) to undertreatment, were confirmed.

TABLE 1 Demography

	N	Missing (n)	Mean (STDV)
n = 1006 (PEI 74%)			
Age (years)	1006	0	58 (14)
Gender *n* (% male)	1006	0	65% (*n* = 651)
BMI weight (Kg)/(Height)^2(m)	933	73	23 (4)
Disease duration (years)	984	22	4,3 (6)
Diabetes	927	79	39% (*n* = 389)
HbA1c (mmol/L)	626	380	50 (18)
Current heavy drinkers (>5 drinks/day)	891	115	7% (*n* = 67)
Smoking (pack years)	603	403	32 (20)
Mean cigarettes (day)	920	86	7 (10)
Current smokers	974	32	30% (*n* = 292)
Smokers and heavy drinkers	927	79	5% (*n* = 45)
Fecal elastase (µg/g)	1006	0	144 (168)
Lipase units (Eur. Pharm.)	1006	0	78,761 (83,097)
Subjects treated (PERT)	1006	0	59% (*n* = 594)
Hemoglobin (g/dl)	959	470	12,7 (2,3)
Albumin (g/L)	897	109	38 (6)
D-vitamin (nmol/L)	723	283	65 (38)

Note: Numbers in % present frequencies.

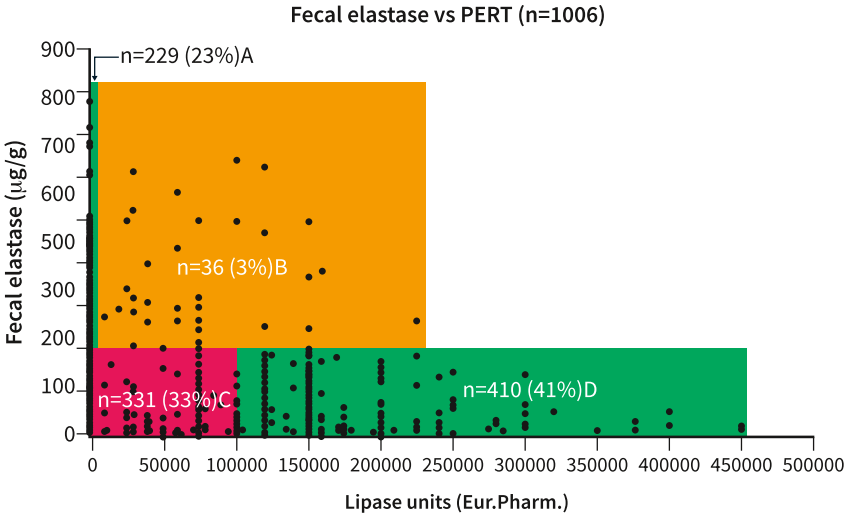

FIGURE 1 Distribution of enzyme doses according to fecal elastase (FE) results. FE <200 µg/g is widely accepted as cut off for Pancreatic exocrine insufficiency (PEI). (a) FE > 200 µ/g, no Pancreatic enzyme replacement therapy|pancreas enzyme replacement therapy (PERT) - correctly not treated. (b) FE > 200 µg/g, PERT - unnecessarily treated? (c) FE < 200 µg/g, PERT <100.000 lipase units - insufficiently treated. (d) FE < 200 µg/g, PERT > 100,000 lipase units - sufficiently treated. Thus 3% of patients with sufficient exocrine pancreatic function got enzymes. Taken into consideration that UEG-guidelines recommend >100,000 lipase units in patients with PEI, 33% were insufficiently treated. FE: fecal elastase. PERT: pancreas enzyme replacement therapy. UEG: United European Gastroenterology guidelines

TABLE 2 Associations between exposures, covariates, and incorrect treatment

	Factor	Univariate			Multivariate regression (final model)		
		OR	95% CI	*p*	OR	95% CI	*p*
Not treated	Current heavy drinking	1.13	0.61, 2.09	0.69			
	Current smoking	2.17	1.55, 3.02	<0.001	2.52	1.76, 3.61	<0.001
	Presence of pain	1.31	0.94, 1.83	0.11			
	Age[a]				1.00	0.99, 1.02	0.71
	Sex (male)				1.01	0.70, 1.47	0.95
	Disease duration[a]				0.95	0.92, 0.99	0.02
Undertreated	Current heavy drinking	2.57	1.44, 4.59	0.001	2.74	1.50, 5.02	0.001
	Current smoking	1.32	0.92, 1.90	0.14			
	Presence of pain	1.27	0.97, 1.68	0.09			
	Age[a]				1.00	0.98,1.01	0.59
	Sex (male)				0.82	0.54, 1.24	0.34
	Disease duration[a]				1.04	1.01, 1.07	0.006
Correctly treated	Current heavy drinking	0,50	0.30, 0.82	0.006			
	Current smoking	0,52	0.40, 0.68	<0.001	0.47	0.35, 0.63	<0.001
	Presence of pain	0,72	0.55, 0.94	0.02	0.75	0.55, 1.01	0.06
	Age[a]				1.00	0.99, 1.01	0.97
	Sex (male)				1.10	0.81, 1.48	0.55
	Disease duration[a]				1.00	0.98, 1.03	0.67
Overtreated	Current heavy drinking	1.16	0.35, 3.89	0.81			
	Current smoking	0.99	0.50, 1.95	0.98			
	Presence of pain	1.96	0.92, 4.17	0.08	2.09	0.96, 4.52	0.06
	Age[a]				1.00	0.97, 1.02	0.69
	Sex (male)				0.95	0.46, 1.98	0.90
	Disease duration[a]				0.97	0.91, 1.04	0.44

Note: Table displaying associations between exposures possibly influencing treatment compliance and groupings of PERT treatment according to recommendations from the UEG guideline for CP. Left columns display unadjusted associations and right columns the final adjusted models including all covariates and exposures with probability of associations <90%. OR: Odds Ratio. CI: Confidence interval.

[a]OR pr. Year. Numbers of patients are shown in Table S1.

The association of pain to overtreatment was weakened to a non-significant trend (OR = 2.09; 95% CI 0.96–4.52; $p = 0.06$). This trend was lost when adjusting for center differences. Longer disease duration was negatively associated to no treatment (OR (per year) = 0.95; 95% CI 0.92–0.99; $p = 0.02$), and positively associated to under treatment (OR = 1.04; 95% CI 1.01–1.07; $p = 0.006$). Neither age nor sex were independently associated to under- or overtreatment.

Center differences in treatment adherence

We demonstrate significant center-wise differences in adherence to the treatment guidelines (Figure 2). Overall treatment adherence ranged from 19% to 87%. The frequency of "not treated" varied from 2% to 39% ($p < 0.001$) and the frequency of undertreatment according to guidelines varied from 5% to 29% ($p < 0.001$). The frequency of overtreatment varied from 0% to 17%. In the multivariate analysis, the cofactor "center" was significantly and independently associated to all treatment classifications. However, adding the covariate "center" did not change the conclusions regarding other described associations.

Consequences of under treatment

We did not find any associations between "no treatment" or "under treatment" and underweight or severe vitamin *D* deficiency. Of the covariates, smoking was associated to both underweight (OR = 2.86; 95% CI 1.76–4.67; $p < 0.001$) and low vitamin *D* (OR = 2.11; 95% CI

TABLE 3 Associations between incorrect treatment and consequences of malabsorption

	Factor	Univariate			Multivariate regression (final model)		
		OR	95% CI	*p*	OR	95% CI	*p*
Underweight	Not treated	0.74	0.42, 1.29	0.29			
	Undertreated	1.63	0.98, 2.71	0.06	1.58	0.88, 2.84	0.12
	Correctly treated	0.92	0.61, 1.40	0,69			
	Current heavy drinking				1.34	0.63, 2.87	0.45
	Current smoking				2.86	1.76, 4.67	<0.001
	Presence of pain				1.59	0.97, 2.60	0.07
	Age[a]				1.00	0.98, 1.02	0.83
	Sex (male)				0.40	0.25, 0.63	<0.001
	Disease duration[a]				1.00	0.96, 1.04	0.96
Severe vitamin *D* deficiency	Not treated	1.12	0.67, 1.87	0.67			
	Undertreated	0.84	0.44, 1.60	0.60			
	Correctly treated	1.11	0.71, 1.72	0.65			
	Current heavy drinking				1.663	0.77, 3.58	0.19
	Current smoking				2.114	1.34, 3.34	0.001
	Presence of pain				1.059	0.67, 1.69	0.81
	Age[a]				0.984	0.97, 1.00	0.049
	Sex				1.815	1.09, 3.02	0.02
	Disease duration[a]				1.023	0.99, 1.06	0.18

Note: Table displaying associations between treatment groupings and underweight or vitamin *D* deficiency. Left columns display unadjusted associations and right columns the final adjusted models including all covariates and groupings with probability of associations <90%. OR: Odds Ratio. CI: Confidence interval.

[a]OR pr. Year. Numbers of patients are shown in Table S1.

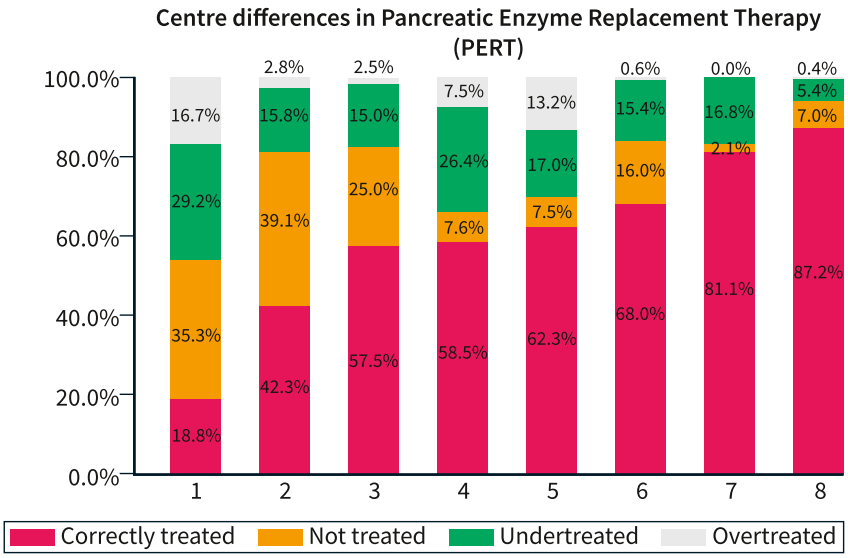

FIGURE 2 Center wise differences in Pancreatic enzyme replacement therapy|pancreas enzyme replacement therapy (PERT). Overtreatment varied from 0% to 17%, undertreatment 5%–30%. Adherence to treatment guidelines varied from 19% to 87%. However, the significant centre wise differences did not change the overall associations. PERT: pancreas enzyme replacement therapy; FE: fecal elastase; Overtreatment: PERT despite of fecal elastase (FE) > 200 µ/g; Undertreatment: Lipase doses <100.000, FE < 200 µg/g; No treatment: Lipase doses 0, FE 100.000 FE

1.34–3.34; $p = 0.001$). Male sex was associated to low vitamin *D* (OR = 1.82; 95% CI 1.09–3.02; $p = 0.02$).

Repeated analyses using fecal elastase as cutoff 100 μg/g

Some centers consider FE < 100 μg/g as a more relevant treatment cutoff. We repeated the analysis using FE < 100 μg/g as cutoff. This improved the center adherence and reduced under treatment in some centers but did not change the conclusions regarding independent associations between risk factors and non-adherence or outcomes from under treatment.

DISCUSSION

Pancreatic exocrine insufficiency represents a typical and severe result of CP. It is notoriously underdiagnosed and undertreated. Since the consequences due to the resulting malnutrition can be severe, such as osteoporosis[25] and cardiovascular events,[26] adequate pancreatic enzyme replacement therapy (PERT) is pivotal and emphasized by the guidelines.[11] In this large cross-sectional study, we found variable adherence to the recommendations of PERT from the UEG guidelines in this large cohort from dedicated specialist centers. One third of patients were not treated according to UEG guidelines with a mixture of non-treatment, insufficient treatment, and treatment without indication. Forty-five percent of patients with PEI were not treated correctly. We found that current smoking was associated to not taking enzymes at all, whereas subjects with alcohol abuse was associated with too low enzyme doses. Surprisingly, we found no clinical or nutritional consequences from undertreatment in the cohort.

A newly published study from the Netherlands on CP demonstrated weak adherence to UEG guidelines.[15] Another study from the US with a large cohort of CP patients and patients with pancreatic cancer emphasizes underdiagnosing PEI and undertreatment.[27] A Swedish single center study about adherence to European Guidelines for treatment and management of PEI in CP patients concludes with "there is room for further improvement".[16] To our knowledge, this is the first multicenter study analyzing the quality of PERT in a large cohort of CP patients and exploring risk factors influencing compliance, and consequences of non-adherence to treatment guidelines.

Factors influencing on treatment adherence

Why are PERT guidelines not followed at highly specialized pancreatology centers? As discussed in the following sentences, incomplete compliance to common guidelines, different interpretations to definitions of diagnostics and therapy, or national differences in provided health care in a challenging patient group, may give some explanations.

The UEG guidelines introduce a graded definition of PEI including both reduced enzyme output, reduced bicarbonate levels and finally consequences of malabsorption in form of a positive ^{13}C mixed triglyceride breath test or increased fecal fat excretion.[11,28] In our database only FE values were available. Many centers start PERT only when consequences of PEI are evident. Following this policy, many patients were defined as undertreated according to our chosen definition based solely on FE.

National differences in health care organization may also have contributed. In countries where PERT is supplied free of charge for the patient, better compliance could be expected.[29] We believe that the differences may represent real variations in approach and guideline adherence between the centers.

Patient compliance is expected to influence the adherence to recommended treatment.[30] We found that smoking and heavy drinking had different, independent associations to treatment adherence. Whereas many current smokers were not taking enzymes at all, heavy drinkers were more likely to be undertreated. A supplementary analysis demonstrated that in the small group of combined smokers and drinkers only 42% were correctly treated. This finding is important and can be explained by both lacking compliance and insufficient follow-up in patients with addiction.[31] Furthermore, patients still smoking despite physician advice, may represent a group less prone to respond to preventive measures. These findings probably indicate the need of increased efforts and follow up for these groups.

When we analyzed the association between other patient factors and treatment adherence, we found no association to age or gender. On the other hand, we found that longer disease duration was negatively associated to "no treatment", but positively associated to undertreatment. This conclusion indicates that neither compliance nor the access to health services in the region is limited by age or sex, but that there may be issues regarding long-term follow-up of patients with CP.

PERT despite no evident exocrine failure in 14% of cases needs some considerations. We found a trend towards an association between presence of pain and overtreatment. Some reports indicate that pain in CP may be reduced by PERT despite of normal pancreatic function.[20,32] PERT is also suggested to have effect in other gastrointestinal diseases inferring abdominal discomfort.[33,34] Additionally, patients with CP, PEI and pain are more likely to be admitted to hospital, including more extensive diagnostic and therapy.[35] This may explain why PERT is prescribed in subjects with challenging pain syndromes or other symptoms like meteorism and loose stools being interpretated as symptoms of steatorrhea.

Normalization of exocrine function after prescription of PERT may result in overtreatment. Both acute, inflammatory episodes, untreated autoimmune pancreatitis and obstruction of the pancreatic duct are explanations of temporary PEI.[36,37] Resolution of inflammation and correction of efferent duct factors may normalize exocrine function in patients still taking their enzymes as prescribed.[38,39]

Both over- and undertreatment could be prevented by regular follow-up of clinical state and laboratory parameters, including FE.[40]

Consequences of under treatment

The presence of PEI is linked to disease progression and severity of CP.[41] We further performed a multivariate analysis to assess the independent implications of under-treatment or lack of treatment on underweight and vitamin *D* deficiency. Surprisingly, the associations of undertreatment to clinical consequences were not evident. The simple conclusion from this finding is to indicate reduced relevance of PERT in PEI. However, the benefit of this treatment has been assessed in a metanalysis, and we believe that other explanations must be sought.[42]

Firstly, the available parameters Vitamin *D* and BMI may not be ideal markers for malnutrition. These parameters may be associated to ongoing exposures, prescribed treatments, or annual cyclic variations, and thus correlate poorly to malnutrition.[43,44] Other parameters like bio-impedance measures for sarcopenia or CT-body composition measures may be better but were not available.[45,46] Vitamin *A*, *E* and *K* are reduced in fat malabsorption and can be used to monitor malnutrition in PEI due to CP.[47] Osteoporosis because of malnutrition in PEI can be monitored by bone density measurements, as recommended in the UEG guidelines.[25] Al these parameters were not available.

Secondly, the treatment recommendation dose is mainly based on expert opinion. The optimal dose recommendation still needs further validation and especially the effect of higher doses of PERT was not tested in this study.

We also suggest that the lack of consequences from under-treatment support the possible interpretation that patients profiting from PERT are selected for treatment. Subjects with evident weight loss or malnutrition will probably receive a more dedicated follow up for such problems, also including a correctly prescribed PERT, and the same subjects will probably have better reasons for good compliance. A study including a measure for malabsorption in the PEI definition may be able to explore this hypothesis better.

Other factors like smoke, alcohol abuse and pain may also contribute strongly to a reduced or unfavorable nutritional supply.[48–50] In our analyses, smoking and gender were the most relevant covariates.

Limitations

Exclusion of centers with poor fulfillment of FE and PERT registrations may have introduced selection bias. Differences in center approach (medical or surgical) may also have created center related variations in patient selections. The included centers are highly specialized centers in pancreatology. Not all conclusions may be applied for the general population of CP patients. However, all centers are general hospitals recruiting from a large catchment area and we believe that the conclusions reflect the general trends in the participating regions.

Biased reporting of risk exposures and differences between prescribed and taken doses of PERT may have disturbed the conclusions. The patients' exposures and treatment doses were collected by the physicians, and we believe that such current reports of exposures and treatment are more accurate than historical data.

We used FE < 200 μg/g as cut-off for PEI. As discussed above, this definition may infer some limitations. Firstly, FE is not a direct parameter for malabsorption.[6] Secondly, malabsorption may be absent until more severe PEI has developed.[51] Finally, there is no complete consensus on the FE cutoff when used as indication for PERT. Some centers consider FE < 100 μg/g as a more relevant treatment cutoff. We repeated the analysis using FE < 100 μg/g as cutoff. This made some alterations in center adherence to the UEG guidelines but did not change the conclusions regarding independent association to non-adherence or consequences from undertreatment. Defining PEI by a pathological direct function test or a test directly assessing malabsorption could overcome the limitations mentioned above but were not available in this multicenter study.

Interactions between patient factors in multivariate analyses may introduce instability to the multivariate regression models. However, preliminary assessment for interactions and the backwards elimination design was used to prevent this effect. All conclusions are based on final models including independent factors only. Finally, the cross-sectional design of the study infers limitation on the ability to conclude on causality. Further studies with prospective, long time follow up of the consequences from insufficient PERT will hopefully be able to better conclude on the associations indicated in this study.

CONCLUSIONS

In conclusion, all over adherence to UEG treatment guidelines was varying. Center related variances, even in expert centers, may be considered worrisome. Such variances may also indicate center differences in the interpretation of the definitions for PEI from the guideline. Our findings underline that focusing on patient follow-up and adherence to UEG guidelines is crucial to improve care for CP patients in all countries contributing to this cohort. Further work improving the clinical appliance of recommendations in the guideline is also highly warranted.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT

The Study protocol and the data that support the findings of this study are available from the corresponding author upon reasonable request.

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