ORIGINAL ARTICLE

Prevalence of exocrine pancreatic insufficiency in patients with chronic pancreatitis without follow-up. PANCR-EVOL Study☆

Carlos Marra-Lopez Valenciano [a,b], Federico Bolado Concejo [a], Eva Marín Serrano [c], Judith Millastre Bocos [d], Emma Martínez-Moneo [e], Esperanza Pérez Rodríguez [f], María Francisco González [g], Andrés Del Pozo-García [h], Anaiansi Hernández Martín [i], Elena Labrador Barba [j], María Luisa Orera Peña [j], Enrique de-Madaria [k,*]

[a] Digestive Service, Complejo Hospitalario de Navarra, Pamplona, Spain
[b] Digestive Service, Hospital Universitario Araba, Álava, Spain
[c] Digestive Service, H. La Paz, Madrid, Spain
[d] Digestive Service, H. Universitario Miguel Servet, Zaragoza, Spain
[e] Digestive Service, H. Universitario de Cruces, Vizcaya, Spain
[f] Digestive Service, H. Universitario Reina Sofia, Córdoba, Spain
[g] Digestive Service, Complejo Hospitalario Universitario de Orense, Orense, Spain
[h] Digestive Service, H. 12 de Octubre, Madrid, Spain
[i] Digestive Service, H. San Eloy, Vizcaya, Spain
[j] Medical Department Mylan, Spain
[k] Department of Gastroenterology, H. General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL – Fundación FISABIO), Alicante, Spain

Abstract
Background/objectives: Exocrine pancreatic insufficiency (EPI) is an important complication of chronic pancreatitis (CP). Guidelines recommend to rule out EPI in CP, to detect those patients who would benefit from pancreatic enzyme replacement therapy. The aim of this study was to evaluate the prevalence of EPI in patients with CP without follow-up in the last 2 years and to describe their nutritional status and quality of life (QoL).

Exocrine pancreatic insufficiency; Follow-up

Methods: This was a cross-sectional, multicenter Spanish study. CP patients without follow-up by a gastroenterologist or surgeon in at least 2 years were included. EPI was defined as fecal elastase test <200 mcg/g. For nutritional assessment, laboratory and anthropometric data were obtained. QoL was investigated using the EORTC QLQ-C30 questionnaire.

Results: 64 patients (mean age 58.8 ± 10.3 years, 85.9% men) from 10 centers were included. Median time since diagnosis of CP was 58.7 months [37.7–95.4]. Forty-one patients (64.1%) had EPI. Regarding nutritional status, the following differences were observed (EPI vs. Non-EPI): BMI ($23.9 \pm 3.5\,kg/m^2$ vs. 25.7 ± 2.5, $p = 0.03$); glucose (121 [96–189] mg/dL vs. 98 [90–116], $p = 0.006$); HbA1c 6.6% [6.0–8.4] vs. 5.5 [5.3–6.0], $p = 0.0005$); Vitamin A (0.44 mg/L [0.35–0.57] vs. 0.53 [0.47–0.63], $p = 0.048$) and Vitamin E ($11.2 \pm 5.0\,\mu g/ml$ vs. 14.4 ± 4.3, $p = 0.03$). EPI group showed a worse EORTC QLQ-C30 score on physical (93.3 [66.7–100] vs. 100 [93.3–100], $p = 0.048$) and cognitive function (100 [83.3–100] vs. 100 [100–100], $p = 0.04$).

Conclusions: Prevalence of EPI is high in patients with CP without follow-up. EPI group had higher levels of glucose, lower levels of vitamins A and E and worse QoL.

Prevalencia de insuficiencia pancreática exocrina en pacientes con pancreatitis crónica sin segruimiento. Estudio PANCR-EVOL

Resumen

Antecedentes/objetivos: la insuficiencia pancreática exocrina (IPE) es una importante complicación de la pancreatitis crónica (PC). Las guías recomiendan el seguimiento de la IPE en PC, para identificar a aquellos pacientes que puedan beneficiarse del tratamiento enzimático sustitutivo. El objetivo de este estudio fue evaluar la prevalencia de IPE en pacientes con PC sin seguimiento en los últimos 2 años y describir su estado nutricional y calidad de vida (QoL).

Métodos: estudio trasversal, multicéntrico, español. Se incluyeron pacientes con PC sin seguimiento por un gastroenterólogo/cirujano en los últimos 2años. Se definió IPE como elastasa fecal<200mcg/g. Se recogieron parámetros de laboratorio y datos antropométricos para el análisis nutricional. Para la evaluación de QoL se utilizó el cuestionario EORTC QLQ-C30.

Resultados: se incluyeron prospectivamente 64 pacientes ($58,8 \pm 10,3$ años, media 85,9%) de 10 centros. Tiempo medio desde el diagnóstico de PC: 58,7meses [37,7-95,4]. 41 pacientes (64,1%) tenían IPE. Estado nutricional: se observaron las siguientes diferencias (IPE vs No-IPE): IMC ($23,9 \pm 3,5\,kg/m2$ vs. $25,7 \pm 2,5$, p=0,03); glucosa 121 [96-189] mg/dL vs. 98 [90-116];p =0,006); HbA1c 6,6% [6,0-8,4] vs. 5,5 [5,3-6,0],p=0,0005); Vitamina-A (0,44mg/L [0,35-0,57] vs. 0,53 [0,47-0,63],p=0,048), Vitamina-E ($11,2 \pm 5,0\,\mu g/ml$ vs. $14,4 \pm 4,3$,p=0,03). El grupo de IPE mostró una peor puntuación en el EORTC QLQ-C30 en las funciones física (93,3 [66,7-100] vs. 100 [93,3-100], p=0,048) y cognitiva (100 [83,3-100] vs. 100 [100-100],p=0,04).

Conclusiones: la prevalencia de IPE en pacientes con PC sin seguimiento es elevada. En el grupo de IPE se observaron niveles elevados de glucosa, bajos de vitaminas A y E y peor calidad de vida.

Introduction

Chronic pancreatitis (CP) is a syndrome characterized by inflammation, fibrosis and loss of acinar and pancreatic islet cells.[1] The amount of enzyme-rich fluid secreted by the pancreas is about 10 times the one needed to ensure a normal digestion. Thus, although subtle changes in exocrine function can be detected in patients with early pancreatic disease, overt steatorrhea as a manifestation of exocrine pancreatic insufficiency (EPI) does not occur until approximately 90 percent of glandular function has been lost.[2] According to the recommendations of the Spanish Association of Pancreatology, the term EPI should be only used for the situation in which the alteration of pancreatic function is associated with the inability of the pancreas to perform a normal digestion process.[3]

Thirty percent of subjects with mild CP and 85% with severe CP will develop EPI 10–15 years after the beginning of the disease.[4] Advanced EPI results in maldigestion of fat and protein leading to steatorrhea and weight loss. Vitamins and minerals deficiencies may also appear due to malabsorption. EPI is associated with a worse quality of life in patients with CP.[5]

There is evidence that incidence of CP and CP-related hospitalizations is increasing.[6] Although the follow-up period for PC patients is not stabilised, the Spanish

Association of Pancreatology recommend a clinical and analytical follow-up each six months for the stablished CP patients.[3] Some patients with CP are not followed up adequately and, consequently, the diagnosis of possible complications like EPI could be delayed, limiting our therapeutic action.[7] Early diagnosis of EPI is necessary to prevent symptoms, malnutrition and to minimize the development of possible complications. The aim of the present study is to analyze the exocrine pancreatic function by measuring the fecal elastase (FE-1) concentration in patients with CP that have not been followed up by a gastroenterologist or surgeon for at least two years, and to describe their nutritional status and quality of life (QoL).

Methods

This cross-sectional, multicenter study included 64 patients with CP from 10 centers from Spain. We included patients with CP, that were visit by the gastroenterologist or surgeon some years ago and, who had not been followed up by a gastroenterologist or surgeon, non-necessarily expert in pancreas disease, for at least 2 years. The gastroenterologist participating in the study looked into their hospitals data bases and call these patients to attend to the hospital for review. Chronic pancreatitis was defined as patients that have one of the following criteria: pancreatic calcifications, duct dilation with parenchymal modifications (non-intraductal papillary neoplasia neither CP associated to NMPI), or 5 or more endoscopic criteria for CP.

Patients were included between June 2014 and April 2015. We excluded patients receiving pancreatic enzyme replacement therapy. The main objective of the study was to evaluate the prevalence of EPI among these patients. Secondary objectives included to describe other CP-related complications, assessment of the nutritional status and quality of life (QoL) of these patients.

All patients gave their written informed consent to take part in the study. The study was conducted according to the requirements stated in the Declaration of Helsinki and the current Spanish legislation. The protocol was submitted to the Spanish Agency of Medicines and Medical devices (AEMPS) and approved by the Ethic Committee of all the centers involved. Data were acquired prospectively during the first and subsequent outpatient clinic visits. Confidentiality of personal data was preserved following the guidelines of Spanish Organic law and all personal data were properly anonymized.

CP patients diagnosed before 2012 and without follow-up for at least two years were invited to participate. Data were retrieved from the medical records of each participating center. Those who agreed to participate, signed the informed consent were included and were followed by a gastroenterologist.

Exocrine pancreatic function was analyzed by measuring the FE-1 in a stool sample, considering concentrations below 200 μg/g as indicative of EPI and <100 μg/g consistent with severe EPI.

For the evaluation of the nutritional status, anthropometric (weight, body mass index (BMI)) and laboratory parameters (vitamins A, D, E, K and B12, lipoproteins, triglycerides, magnesium, hemoglobin, gly-cated hemoglobin, retinol binding protein (RBP), albumin and prealbumin), were compared between groups with and without EPI. Collection of laboratory data was done according to usual practice of each participant center and some of these data could not be available.

For the assessment of QoL, the EORTC-QLC-C30 scale was used. Although originally designed for cancer patients, the QLQ-C30 was previously shown to be suitable as an assessment tool for the CP population.[8–11] The questionnaire consists of 30 questions, of which 24 form nine multiquestion scales: one global scale, five functional scales (physical, role, emotional, cognitive, and social) and three symptoms scales (pain, nausea, and fatigue). The six remaining questions aim at reporting six symptoms: dyspnea, insomnia, appetite, constipation, diarrhea, and financial difficulties. The QLQ-C30 produces a complex assessment of the health-related quality of life (HR-QOL). Results are linearly recalculated to a uniform scale of 0–100 points, in which a higher score indicates a more favorable outcome.

Proportion and types of CP-related complications apart from EPI, are described.

Statistical methods

Continuous variables have been analyzed using the following descriptive statistics: sample size, mean, standard deviation (SD), median [Q1–Q3], minimum and maximum. The Shapiro–Wilk test has been used to check if a variable has a normal distribution.

Mean (SD) was used for normal distribution and Median (Q1–Q3) for non-normal distribution.

Categorical variables are presented in contingency tables, calculating absolute and relative frequencies. A category of missing data has been included if needed.

For the comparison between groups of continuous variables, parametric (T-test) or non-parametric tests (Wilcoxon) have been used, depending on the distribution of the analyzed variables in each case.

For the comparison between groups of categorical variables, the Chi-square test or the Fisher test have been used, choosing the most appropriate in each case.

Relative frequencies and descriptive parameters are shown with 2 decimal digits. Descriptive p-values ≥ 0.001 are shown with a four decimal digit precision and p-values <0.001 are shown as <0.001).

All analyses have been performed using the SAS® v9.3 software.

Results

64 patients with CP were finally included in the study. The original diagnosis of CP was made by clinical suspicion and it was confirmed by computerized tomography in most patients (64.8%). Forty-two patients (65.6%) had pancreatic calcifications and 40 (62.5%) biliary duct dilation. The median (Q1–Q3) time since diagnosis of CP was 58.7 [37.7–95.4]). Table 1 shows the baseline characteristics of the study population (64 patients) and the comparison between the EPI and non-EPI group. Forty-one (64.1%) had FE-1 levels <200 μg/g and were diagnosed with EPI, according to the criteria stated in the study protocol. Twenty-nine patients (45.3%) had lev-

Table 1 Baseline characteristics of the study population (N = 64).

	Study population (N = 64)	EPI group(N = 41)	Non-EPI group (N = 23)	p Value
Men	55 (85.9%)	36 (87.8%)	19 (82.6%)	0.7109
Caucasic race	63 (98.4%)	41 (100.0%)	22 (95.7%)	0.3594
Age (years)	58.8 (10.3)	58.6 (9.0)	59.0 (12.4)	0.8799
BMI (kg/m^2)	24.5 (3.3)	23.9 (3.5)	25.7 (2.5)	0.0334
Time since diagnosis of CP (months)	58.7 [37.7,95.4]	62.1 [39.0,104.9]	55.8 [35.4,78.2]	0.7487
Pancreatic calcifications	42 (65.6%)	27 (65.9%)	15 (65.2%)	1.0000
Biliary duct dilation	40 (62.5%)	28(68.3%)	12(52.2%)	0.2142
Bowel movements/day	2.0 [1.0,2.0]	2.0 [1.0,3.0]	1.0 [1.0,2.0]	0.0603
Diabetes	29 (45.3%)	25 (61%)	4 (17.4%)	0.0008
Ethiology of CP				
Alcohol/tobacco[*]	57 (89.1%)	38 (92.7%)	19 (82.6%)	0.2396
Smoking habit				
Smokers	41 (64.1%)	28 (68.3%)	13 (56.5%)	0.6937
No-smokers	23 (35.9%)	13 (31.7)	10 (43.5)	
Cigarettes per day	20 [15,30]	20 [13.5,25]	20 [20,30]	0.3639
Alcohol consumption				
Usual	34 (53.1%)	23 (56.1%)	11 (47.8%)	0.0372
Ex-alcoholic	18 (28.1%)	14 (34.2%)	4 (17.4%)	
Grams of alcohol/day	60 [40,90]	61.5 [40,87]	60 [30,100]	0.9155
Level of education				
1. University	2 (3.5%)	1 (2.70%)	1 (4.8%)	0.2605
2. Secondary	17 (29.3%)	8 (21.6%)	9 (42.9%)	
3. Primary	37 (63.8%)	26 (70.3%)	11 (52.4%)	
4. Analphabets	2 (3.5%)	2 (5.4%)	0 (0.0%)	

Data are presented as *n* (%), mean (SD: standard deviation) or median [Q1, Q3]. BMI: body mass index; CP: chronic pancreatitis.
[*] More than one option could be ticked in the case report form and thus, the main cause of CP could not be established.

els of FE-1 < 100 μg/g and were classified as severe EPI. Five patients had already been diagnosed with EPI when they entered the study. All of them fulfilled the criteria for severe EPI. Median time from the diagnosis of CP was longer in those with severe EPI (68 [36.3–103.3] months vs. 57.3 [45.6–88.4] months) than in the group with mild EPI, though this difference was not statistically significant (p = 0.8286). When we analyzed in patients with EPI the average time from diagnosis of CP according to its etiology (alcohol, tobacco, obstructive, other) we did not find significant differences either. Number of bowel movements was higher in the group with EPI (median 2 [1–3] vs. 1 [1–2]) though this difference did not reach statistical significance (p = 0.0603).

Regarding nutritional status, we found differences (EPI group vs. non EPI group) in BMI (23.9 ± 3.5 kg/m^2 vs. 25.7 ± 2.5, p = 0.0334) and in the following laboratory parameters (Table 2): fasting glucose levels (121 vs. 98 mg/dL, p = 0.0067), glycated hemoglobin (6.6 vs. 5.5%, p = 0.0005), vitamin A (0.44 vs. 0.53 mg/L, p = 0.0480) and vitamin E (11.2 vs. 14.4 μg/ml, p = 0.0259). All these parameters were lowers in the PEI group than in the Non EPI group, although media and median were always into the normal ranges in both groups. When we compared patients with severe EPI with those with mild EPI (Table 3) we observed the following differences: fasting glucose levels (130 mg/dL vs. 101.5 mg/dL, p = 0.0010), HbA1c (7.2% vs. 5.7%, p < 0.0001), LDL cholesterol (100.7 mg/dL vs. 147.9 mg/dL, p = 0.0072), total cholesterol (171 vs. 229 mg/dL, p = 0.0270) and vitamin E (10.1 vs. 13.9 μg/ml, p = 0.0110).

In relation to quality of life, significant differences were detected in functional scores (physical and cognitive functioning) between patients with and without EPI but not in global health status/quality of life, symptoms scales or in single items either (Tables 4 and 5).

Table 6 shows other complications of CP apart from EPI. Most frequent were pseudocysts (21.9%), chronic abdominal pain (12.5%), biliary obstruction (7.8%) and splenic vein thrombosis (6.3%).

Discussion

CP is the most common cause of EPI in adults. Pancreatic function tests have been used over decades for the diagnosis of the disease. Direct tests such as the secretin-pancreozymin test and the endoscopic test are sensitive enough but they are also invasive and cumbersome for routine use in clinical practice. Other tests like the quantification of the coefficient of fat absorption and the ^{13}C-mixed triglyceride breath test[12,13] are complex to perform and not widely available. Fecal elastase-1 test is non-invasive and easily applicable in clinical practice. It is useful for detecting moderate to severe EPI but its sensitivity for the diagnosis of patients with non-advanced CP is limited.[14]

In the present study, we included only patients with CP that had not been followed-up in the last 2 years by a gastroenterologist or a surgeon. These patients are usually managed by general practitioners and may not be included in

Table 2 Laboratory parameters in study population, EPI and non-EPI groups.

	Normal ranges	Study population (*N* = 64)	EPI (*N* = 41)	No EPI (*N* = 23)	*p* (EPI vs. No EPI) value
Glucose (mg/dL)	70–105	110.00 [93.50, 141.00]	121.0 [96.0, 189.0]	98.0 [90.0, 116.0]	0.0067
Magnesium (mg/dL)	1.5–2.4	1.90 [1.8, 2.1]	1.90 [1.8, 2.0]	1.90 [1.9, 2.1]	0.4279
Hemoglobin (g/dL)	Men: 13–18	14.4 (1.6)	14.1 (1.5)	14.9 (1.7)	0.0645
	Women: 12–16				
Albumin (g/dL)	3.5–5.0	4.2 [3.8, 4.4]	4.1 [3.8, 4.4]	4.2 [3.8, 4.4]	0.7137
Prealbumin (mg/dL)	18–45	22.9 (7.8)	21.7 (7.8)	25.3 (7.4)	0.1265
HbA1c (%)	4.7–8.5	6.2 [5.6, 7.7]	6.6 [6.0, 8.4]	5.5 [5.3, 6.0]	0.0005
RBP (mg/dL)	3–6	4.4 [3.2, 5.4]	3.5 [2,0, 5.2]	4.8 [4.3, 5.4]	0.0718
LDL (mg/dL)	≤130	114.9 (40.6)	112.8 (42.9)	119.1 (36.2)	0.6090
HDL (mg/dL)	>40	50 [42.0, 60.0]	48.5 [43.0, 57.0]	52.5 [39.0, 61.0]	0.6006
Apolipoprotein A (mg/dL)	Men: 88–180	135.9 (41.4)	135.9 (43.7)	135.8 (39.0)	0.9986
	Women: 98–210				
Aplipoprotein B (mg/dL)	Men: 55–140	101.00 [78.00, 112.00]	99.0 [78.0, 111.0]	103.5 [77.0, 115.0]	0.7207
	Women: 55–125				
Lipoprotein A (mg/dL)	Men: 110–205	37.0 [1100,56.0]	38.6 [9.3, 56.0]	24.4 [15.7, 85.0]	0.7684
	Women: 125–215				
Cholesterol (mg/dL)	<225	182.5 [159.0, 226.0]	183.0 [156.0, 226.0]	182.0 [161.0, 218,0]	0.8892
Triglycerides (mg/dL)	<250	133.5 [90.0, 179.0]	137.0 [98.0, 172.0]	122.0 [73.0, 181.0]	0.9223
Vitamin A (mg/L)	0.5–2.0	0.5 [0.4, 0.6]	0.4 [0.3, 0.6]	0.5 [0.5, 0.6]	0.0480
Vitamin D (ng/mL)	20–40	18.2 (12.0)	17.2 (12.6)	19.9 (11.1)	0.4490
Vitamin E (mcg/mL)	1.5–63	12.3 (4.9)	11.2 (5,0)	14.4 (4.3)	0.0259
Vitamin K (mcg/L)	0.13–1.19	0.4 (0.3)	0.4 (0.3)	0.4 (0.2)	0.9144
Vitamin B12 (mcg/L)	200–800	384.5 [268.0, 460.0]	423.0 [301.0, 535.0]	325.0 [239.0, 432.0]	0.0740
Prothrombin activity (%)	70–120	98.0 [90.0, 104.0]	99.0 [90.5, 106.5]	98.0 [86.0, 100.0]	0.3607
Fecal elastase-1 (mcg/g)	>200	102.0 [26.6, 306.5]	59.0 [15.0, 100.0]	395.0 [294.0, 500.0]	<0.0001

Figures are expressed as mean (standard deviation) or median [Q1,Q3]. RBP: retinol binding protein. HbA1c: glicated hemoglobin; LDL: low density lipoproteins; HDL: high density lipoproteins.

*Normal ranges according: http://www.msdmanuals.com/es-es/professional/apéndices/valores-normales-de-laboratorio/pruebas-de-sangre-valores-normales#v8508814_es and https://medlineplus.gov/.

Table 3 Laboratory parameters in patients with severe EPI vs. patients with mild EPI.

	Normal ranges[*]	Severe EPI (N = 29)	Mild EPI (N = 12)	Non-EPI (N = 23)	p Value
Glucose (mg/dL)	70–105	130.0 [106.0, 210.0]	101.5 [86.0, 122.5]	98.0 [90.0, 116.0]	0.0010
Magnesium (mg/dL)	1.5–2.4	1.9 [1.7, 2.0]	2.0 [1.9, 2.1]	1.9 [1.9, 2.1]	0.1986
Hemoglobin (g/dL)	Men: 13–18	13.9 (1.6)	14.7 (1.1)	14.9 (1.7)	0.0686
	Women: 12–16				
Albumin (g/dL)	3.5–5.0	4.1 [3.8, 4.4]	4.2 [3.6, 4.5]	4.2 [3.8, 4.4]	0.8447
Prealbumin (mg/dL)	18–45	21.4 (7.7)	22.4 (8.5)	25.3 (7.4)	0.2985
HbA1c (%)	4.7–8.5	7.2 [6.2, 8.6]	5.7 [5.4, 6.3]	5.5 [5.3, 6.0]	<0.0001
RBP (mg/dL)	3–6	3.5 [2.0, 4.4]	4.1 [1.6, 6.0]	4.8 [4.3, 5.4]	0.1545
LDL (mg/dL)	≤130	100.7 (37.6)	147.9 (39.2)	119.1 (36.2)	0.0072
HDL (mg/dL)	>40	47.5 [40.0, 56.5]	53.0 [45.0, 63.0]	52.5 [39.0, 61.0]	0.4867
Apolipoprotein A (mg/dL)	Men: 88–180	134.6 (30.2)	138.8 (68.7)	135.85 (39.0)	0.9763
	Women: 98–210				
Aplipoprotein B (mg/dL)	Men: 55–140	90.1 [73.5, 104.0]	107.0 [94.0, 123.0]	103.5 [77.0, 115.0]	0.1818
	Women: 55–125				
Lipoprotein A (mg/dL)	Men: 110–205	33.5 [9.0, 43.1]	53.6 [30.3, 58.5]	24.4 [15.7, 85.0]	0.6385
	Women: 125–215				
Cholesterol (mg/dL)	<225	171.0 [147.0, 189.0]	229.0 [188.0, 242.5]	182.0 [161.0, 218,0]	0.0270
Triglycerides (mg/dL)	<250	139.0 [106.0, 172.0]	108.5 [85.0, 181.5]	122.0 [73.0, 181.0]	0.8293
Vitamin A (mg/L)	0.5–2.0	0.5 [0.4, 0.6]	0.4 [0.3, 0.5]	0.5 [0.5, 0.6]	0.1163
Vitamin D (ng/mL)	20–40	19.1 (12.6)	11.3 (11.4)	19.9 (11.1)	0.2139
Vitamin E (μg/mL)	1.5–63	10.1 (4.7)	13.9 (4.9)	14.4 (4.3)	0.0110
Vitamin K (μg/L)	0.13–1.19	0.4 (0.3)	0.5 (0.3)	0.4 (0.2)	0.9337
Vitamin B12 (μg/L)	200–800	397.5 [294.0, 446.0]	460.0 [346.0, 607.0]	325.0 [239.0, 432.0]	0.1310
Prothrombin activity (%)	70–120	97.5 [88.5, 103.0]	104.0 [91.6, 108.5]	98.0 [86.0, 100.0]	0.3890
Fecal elastase 1 (μg/g)	>200	15.0 [14.0, 61.0]	125.0 [102.0, 169.0]	395.0 [294.0, 500.0]	<0.0001

Figures are expressed as mean (standard deviation) or median [Q1,Q3]. RBP: retinol binding protein. HbA1c: glicated hemoglobin. LDL: low density lipoproteins; HDL: high density lipoproteins.

[*] Normal ranges according: http://www.msdmanuals.com/es-es/professional/apéndices/valores-normales-de-laboratorio/pruebas-de-sangre-valores-normales#v8508814_es and https://medlineplus.gov/.

Table 4 Results of the functional scales and global health status/Quality of life of the QLQ-C30 quality of life questionnaire: EPI vs. non-EPI groups.

	N	Mean (SD)	Median [Q1, Q3]	p Value
Physical functioning				
EPI	41	81.5 (23.4)	93.3 [66.7, 100.0]	0.0488
Non-EPI	22	93.3 (10.9)	100.0 [93.3, 100.0]	
Role functioning				
EPI	41	79.7 (30.8)	100.0 [66.7, 100.0]	0.0601
Non-EPI	22	93.9 (18.2)	100.0 [100.0, 100.0]	
Emotional functioning				
EPI	41	73.0 (32.4)	83.3 [58.3, 100.0]	0.5008
Non-EPI	22	79.9 (26.9)	91.7 [66.7, 100.0]	
Cognitive functioning				
EPI	41	83.7 (26.2)	100.0 [83.3, 100.0]	0.0356
Non-EPI	22	97.0 (6.6)	100.0 [100.0, 100.0]	
Social functioning				
EPI	41	78.5 (30.6)	100.0 [50.0, 100.0]	0.0757
Non-EPI	22	90.9 (22.8)	100.0 [100.0, 100.0]	
Global health status/QoL				
EPI	41	61.0 (29.0)	66.7 [41.7, 83.3]	0.8905
Non-EPI	22	57.6 (33.8)	66.7 [50.0, 83.3]	

QoL: quality of life; SD: standard deviation.

hospital or gastroenterologist-based surveys. Prevalence of EPI in these patients, with an average time of 5–6 years since diagnosis of CP, was high (64.1%). 70% of patients diagnosed with EPI had levels of FE-1 <100 μg/g (widely considered as severe EPI) what means they were in an advanced stage of the disease. An early diagnosis of EPI allows starting treatment with supplemental enzymes in order to avoid morbidity and mortality linked to patient malnutrition. Randomized studies have demonstrated an improvement in coefficients of fat and nitrogen absorption, fecal appearance and quality of life with this treatment.[15–18]

It has been suggested that, in patients with CP, morphological findings (e.g. pancreatic calcifications, main duct dilation) can be used as an indirect way to diagnose pancreatic exocrine insufficiency.[19] In our study 27 (65.9%) and 28 (68.3%) patients from the EPI group had pancreatic calcifications or pancreatic duct dilation, respectively. Corresponding figures in the non-EPI group were 15 (65.2%) and 12 (52.2%). Thus, 3 out of 10 patients with EPI did not show these changes but they were present in more than 50% of patients without EPI. In addition, about 10% of patients with advanced CP had a preserved exocrine function and may not need enzyme supplementation.[4] This reinforces the necessity of using a pancreatic function test to confirm the presence of EPI.

In a cross-sectional study of patients with alcoholic and idiopathic CP, exocrine dysfunction was present in 63% of patients after 5 years of CP and in 94% of those with disease lasting 10 years or more.[20] Our results are in accordance with the ones of that study, as prevalence of EPI was 64% after an average time of 5–6 years after diagnosis of CP. However, other studies have reported a longer time from the diagnosis of CP to the development of EPI.[21] The main etiology of CP in our study was alcohol and

tobacco consumption. Smoking is currently proposed to be the driving force behind the progression of pancreatitis.[22] In our study 68.3% of patients with EPI were current smokers consuming an average of 20 cigarettes/day and this could have played a role in the development of the exocrine dysfunction. However, in our study we have not observed differences in the smokers' consumers.

The nutritional status of a patient with CP depends, at least in part, on the duration of the disease, its severity and the etiology of CP. The reasons for a compromised nutritional status are mainly low food intake (due to abdominal pain or nausea after eating), maldigestion and malabsorption. The most frequently studied markers of the nutritional status of patients with CP are: liposoluble vitamins (A, D, E and K which correlate well with severity of steatorrhea), serum cholesterol,[23] albumin[24] and serum magnesium levels.[25] Osteopathy (osteoporosis, osteomalacia, osteopenia) may occur in at least 25% of CP patients and it may be related to vitamin D deficiency.[26] Due to inadequate protease secretion by the pancreas, vitamin B12 deficiencies can occur.[27] Zinc deficiency may be seen especially in association with diabetes.[28] Besides, deficiencies in calcium, thiamine and folic acid have been reported. None of these markers can be taken as an isolated parameter for the diagnosis of EPI, but a combination of them could help in its diagnosis.[25]

For the assessment of the patients' nutritional status in our study, anthropometric and laboratory parameters were analyzed. BMI was significantly lower in patients with EPI. This may reflect a worse nutritional status of EPI patients, but we have to bear in mind that both, weight and BMI, do not take body composition into account and may be misinterpreted as a result of fluid changes including ascites and edema.

Table 5 Results of the symptom scales and single ítems of the QLQ-C30 quality of life questionnaire: EPI vs. non-EPI groups.

	N	Mean (SD)	Median [Q1,Q3]	p Value
Symptom scales				
Fatigue				
EPI	41	27.4 (31.6)	11.1 [0.0, 44.4]	0.2694
Non-EPI	22	15.2 (19.3)	11.1 [0.0, 22.2]	
Nausea/vomiting				
EPI	41	7.7 (18.3)	0.0 [0.0, 0.0]	0.5729
Non-EPI	22	6.1 (18.9)	0.0 [0.0, 0.0]	
Pain				
EPI	41	23.6 (32.3)	0.0 [0.0, 33.3]	1.0000
Non-EPI	22	22.0 (30.6)	8.3 [0.0, 33.3]	
Single items				
Dyspnoea				
EPI	41	15.4 (24.8)	0.0 [0.0, 33.3]	0.0945
Non-EPI	22	6.1 (16.7)	0.0 [0.00, 0.0]	
Insomnia				
EPI	41	26.0 (35.4)	0.0 [0.0, 33.3]	0.7586
Non-EPI	22	25.8 (39.7)	0.0 [0.0, 33.3]	
Appetite loss				
EPI	41	24.4 (34.2)	0.0 [0.0, 33.3]	0.5147
Non-EPI	22	19.7 (33.6)	0.0 [0.0, 33.3]	
Constipation				
EPI	41	8.9 (24.7)	0.0 [0.0, 0.0]	0.4354
Non-EPI	22	13.6 (28.5)	0.0 [0.0, 0.0]	
Diarrhoea				
EPI	41	18.7 (34.2)	0.0 [0.0, 33.3]	0.0791
Non-EPI	22	3.0 (9.8)	0.0 [0.0, 0.0]	
Financial difficulties				
EPI	41	21.9 (34.6)	0.0 [0.0, 66.7]	0.1262
Non-EPI	22	9.1 (25.6)	0.0 [0.0, 0.0]	

Table 6 Complications of chronic pancreatitis: EPI vs. non-EPI groups.

	IPE (N = 41)	Non-IPE (N = 23)	Total (N = 64)
Complications of chronic pancreatitis			
Patients without reported complication, N	24	14	38
Patients with reported complication, N	17	9	26
Type of complication[*]			
Pseudocysts, n (%)	12 (29.27)	2 (8.70)	14 (21.88)
Chronic pain, n (%)	4 (9.76)	4 (17.39)	8 (2.50)
Biliary obstruction, n (%)	3 (7.32)	2 (8.70)	5 (7.81)
Splenic vein thrombosis, n (%)	4 (9.76)	0 (0.00)	4 (6.25)
Pancreatic ascites, n (%)	2 (4.88)	0 (0.00)	2 (3.13)
Duodenal obstruction, n (%)	0 (0.00)	2 (8.70)	2 (3.13)
Bacterial overgrowth, n (%)	1 (2.44)	0 (0.00)	1 (1.56)
Mesenteric obstruction, n (%)	1 (2.44)	0 (0.00)	1 (1.56)
Acute cholangitis, n (%)	1 (2.44)	0 (0.00)	1 (1.56)
Groove pancreatitis, n (%)	0 (0.00)	1 (4.35)	1 (1.56)
Pancreatic mass, n (%)	0 (0.00)	1 (4.35)	1 (1.56)
Fluid collections, n (%)	0 (0.00)	1 (4.35)	1 (1.56)

[*] % have been calculated over total population (Total: N = 64; N = 41 in the EPI Group; N = 23 in the non-EPI group).

Regarding laboratory parameters, we only found differences between the EPI and Non-EPI groups in levels of glucose, vitamin A, E and glycated hemoglobin. Significant differences were also present when comparing the severe and mild EPI groups, except for vitamin A. Levels of total cholesterol and LDL cholesterol were also significantly lower, but only in patients with severe EPI compared with those with mild EPI or without EPI. Thus, a decrease in total cholesterol levels could be a marker of advanced stages of EPI. The most frequent vitamin deficiency in patients with CP is vitamin E. It may cause neuromuscular diseases like cerebellar ataxia and amyotrophic myopathy.[29]

There were no significant differences between groups in the levels of magnesium, albumin, hemoglobin, prealbumin or RBP. Mean levels of magnesium in patients without EPI were 1.93 ± 0.21 mg/dL. A study[25] suggested that chronic pancreatitis patients with a magnesium value above 2.05 mg/dL and normal hemoglobin, albumin, prealbumin, retinol binding protein and HbA1C are very unlikely to suffer from PEI and do not require further evaluation of pancreatic exocrine function. Due to the relatively low levels of magnesium in our study population, this rule could not have been applied for the majority of our patients.

Diabetes due to the destruction of islets in patients with CP is termed type 3c diabetes. It is more common than previously believed and might represent at least 8% of all patients with diabetes.[30] It has been suggested that β-cell regeneration is disturbed in pancreatic diseases, which could explain reduced β-cell mass and diabetes in CP. In our study, the prevalence of diabetes was significantly higher in the EPI group (61% vs. 17.4%, $p = 0.0008$). Glucose levels and glycated hemoglobin were significantly higher in patients with EPI compared with those without EPI. We also found a relationship between severity of EPI and levels of glucose and HbA1c, being higher in those with severe EPI. Exocrine pancreatic and diabetes are usually developed in parallel. In contrast, clinical observations lead to the notion that exocrine pancreatic disease is a critical factor for development rather than a sequel to diabetes.[31,32]

CP is a long-term, sometimes progressive and debilitating condition that may have an important impact on QoL. Symptoms like severe abdominal pain and consequences of diabetes mellitus, malabsorption and weight loss could severely affect health-related QoL.[8] In our study, the presence of EPI contributed to aggravate even more the QoL of patients with CP. Cognitive and physical functioning were significantly worse in patients with EPI compared with those without EPI. It has been shown that QoL in patients with EPI improves with pancreatic enzyme supplements.[33,34] Thus, an early diagnosis of EPI in these patients could lead to a better QoL by starting an appropriate treatment.

Regarding other complications of CP, presence of pseucocysts was the most frequent (19.4% of study population). This prevalence is higher than previously described[35] (about 10%) and could be related to a more advanced stage of the disease in our patients. Chronic pain (12.5%), biliary obstruction (7.8%) and splenic vein thrombosis (6.3%) were other frequent reported complications.

Our study have some possible limitations, we used an indirect test (FE-1) to diagnose EPI. It is well known that indirect tests have a lower sensitivity for the diagnosis of early stages of EPI and, because of that, prevalence of EPI in our study population could be underestimated. Though we found some differences in laboratory parameters between both groups, it doesn't necessarily mean that EPI was the cause of those differences, because vitamin deficiencies and cholesterol levels could have been explained by other diseases or treatments.

In conclusion, according to the results of our study, prevalence of EPI is high in a population that is not usually included in epidemiological studies of CP (patients without follow-up by gastroenterologists). Presence of EPI was associated with a poorer quality of life and some nutritional deficiencies. Thus, an adequate follow-up of these patients is warranted.

Conflict of interest statement

E. Labrador Barba and M.L. Orera Peña are employees of Mylan.

Enrique de-Madaria and Carlos Marra-Lopez have received a grant from Mylan and have consulted Mylan in the development and performance of clinical research in pancreatic exocrine insufficiency.

Emma Martinez-Moneo, Esperanza Perez, Andres del Pozo and María Francisco have given lectures sponsored by Mylan partially related with the submitted work.

References

1. Forsmark CE. Management of chronic pancreatitis. Gastroenterology. 2013;144:1282–91.

2. DiMagno EP, Go VLW, Summerskill WHJ. Relations between pancreatic enzyme output and malabsorption in severe pancreatic insufficiency. N Engl J Med. 1973;288:813–5.

3. Martínez J, Abad-González A, Aparicio JR, Aparisi L, Boadas J, Boix E, et al. Club Español Pancreático (CEP). Recommendations of the Spanish pancreatic club on the diagnosis and treatment of chronic pancreatitis: part 1 (diagnosis). Gastroenterol Hepatol. 2013;36:326–39.

4. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early and late onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994;107:1481–7.

5. Czakó L, Takács T, Hegyi P, Prónai L, Tulassay Z, Lakner L, et al. Quality of life assessment after pancreatic enzyme replacement therapy in chronic pancreatitis. Can J Gastroenterol. 2003;17:597–603.

6. Jupp J, Fine D, Johnson CD. The epidemiology and socioeconomic impact of chronic pancreatitis. Best Pract Res Clin Gastroenterol. 2010;24:219–31.

7. Sikkens EC, Cahen DL, Van Eijck C, Kuipers EJ, Bruno MJ. Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. Pancreatology. 2012;12:71–3.

8. Fitzsimmons D, Kahl S, Butturini G, Van Wyk M, Bornman P, Bassi C, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol. 2005;100:918–26.

9. Shah NS, Makin AJ, Sheen AJ, Siriwardena AK. Quality of life assessment in patients with chronic pancreatitis receiving antioxidant therapy. World J Gastroenterol. 2010;16:4066–71.

10. Witzigmann H, Max D, Uhlmann D, Geissler F, Ludwig S, Schwarz R, et al. Quality of life in chronic pancreatitis: a prospective trial comparing classical Whipple procedure and duodenum-preserving pancreatic head resection. J Gastrointest Surg. 2002;6:173–9.

11. Pezzilli R, Morselli-Labate AM, Fantini L, Campana D, Corinaldesi R. Assessment of the quality of life in chronic pancreatitis using Sf-12 and EORTCQlq-C30 questionnaires. Dig Liver Dis. 2007;39:1077–86.

12. Domínguez-Munoz JE. Diagnosis of chronic pancreatitis: Functional testing. Best Pract Res Clin Gastroenterol. 2010;24:233–41.

13. Domínguez-Muñoz JE, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M. ^{13}C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2007;5:484–8.

14. Lankisch PG, Schmidt I, König H, Lehnick D, Knollmann R, Löhr M, et al. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. Gut. 1998;42:551–4.

15. Sikkens EC, Cahen DL, Kuipers EJ, Bruno MJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. Best Pract Res Clin Gastroenterol. 2010;24:337–47.

16. D'Haese JG, Ceyhan GO, Demir IE, Layer P, Uhl W, Löhr M, et al. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. Pancreas. 2014;43:834–41.

17. Ramesh H, Reddy N, Bhatia S, Rajkumar JS, Bapaye A, Kini D, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013;13:133–9.

18. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, et al. Pancrelipase delayedrelease

capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. Am J Gastroenterol. 2010;105:2276–86.

19. Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol. 2011;26: 12–6.

20. Hammer HF. Pancreatic exocrine insufficiency: diagnostic evaluation and replacement therapy with pancreatic enzymes. Dig Dis. 2010;28:339–43.

21. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994;107:1481–7.

22. Rebours V, Vullierme MP, Hentic O, Maire F, Hammel P, Ruszniewski P, et al. Smoking and the course of recurrent acute and chronic alcoholic pancreatitis: a dose-dependent relationship. Pancreas. 2012;41:1219–24.

23. Nakamura T, Takebe K, Yamada N, Arai Y, Tando Y, Terada A, et al. Bile acid malabsorption as a cause of hypocholesterolemia seen in patients with chronic pancreatitis. Int J Pancreatol. 1994;16:165–9.

24. Trolli PA, Conwell DL, Zuccaro G Jr. Pancreatic enzyme therapy and nutritional status of outpatients with chronic pancreatitis. Gastroenterol Nurs. 2001;24:84–7.

25. Lindkvist B, Domínguez-Muñoz JE, Luaces-Regueira M, Castiñeiras-Alvariño M, Nieto-Garcia L, Iglesias-Garcia J. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. Pancreatology. 2012;12:305–10.

26. Dujsikova H, Dite P, Tomandl J, Sevcikova A, Precechtelova M. Occurrence of metabolic osteopathy in patients with chronic pancreatitis. Pancreatology. 2008;8:583–6.

27. Glasbrenner B, Malfertheiner P, Büchler M, Kuhn K, Ditschuneit H. Vitamin B12 and folic acid deficiency in chronic pancreatitis: a relevant disorder? Klin Wochenschr. 1991;69:168–72.

28. Quilliot D, Walters E, Bonte JP, Fruchart JC, Duriez P, Ziegler O. Diabetes mellitus worsens antioxidant status in patients with chronic pancreatitis. Am J Clin Nutr. 2005;81: 1117–25.

29. Kalvaria I, Labadarios D, Shephard GS, Visser L, Marks IN. Biochemical vitamin E deficiency in chronic pancreatitis. Int J Pancreatol. 1986;1:119–28.

30. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes Care. 2008;Suppl. 2:S165–9.

31. Nunes AC, Pontes JM, Rosa A, Gomes L, Carvalheiro M, Freitas D. Screening for pancreatic exocrine insufficiency in patients with diabetes mellitus. Am J Gastroenterol. 2003;98:2672–5.

32. Hardt PD, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, et al., S2453112/S2453113 Study Group. High prevalence of exocrine pancreatic insufficiency in diabetes mellitus: a multicenter study screening fecal elastase 1 concentration in 1021 diabetic patients. Pancreatology. 2003;3:395–402.

33. Trifan A, Balan G, Stanciu C. Pancreatic enzymes replacement therapy in chronic pancreatitis: an update. Rev Med Chir Soc Med Nat Iasi. 2001;105:646–50.

34. D'Haese JG, Ceyhan GO, Demir IE, Layer P, Uhl W, Löhr M, et al. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. Pancreas. 2014;43:834–41.

35. Zerem E, Imamović G, Omerović S. What is the optimal treatment for pancreatic pseudocysts? Scand J Gastroenterol. 2012;47:124–5.