ORIGINAL ARTICLE

Clinical Profile and Management of Pancreatic Exocrine Insufficiency in Patients with Chronic Pancreatitis in India

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Abstract

Objectives: Pancreatic exocrine insufficiency (PEI), a major complication in chronic pancreatitis (CP), is not wellinvestigated in India. We report the epidemiology and management practices of PEI with underlying CP in real-world setting.

Methods: This cross-sectional study conducted across 8 tertiary centers, analyzed data from records pertaining to disease profile and progression from CP to PEI. Diagnostics, management, nutritional status, and quality of life (QoL) were also assessed.

Results: Of the 278 patients, majority were males (74.5%). The mean age was 40.0 (±13.12) years and that at PEI diagnosis was 34.9 (±13.04) years. The median duration from CP diagnosis to PEI was 3 (0, 16) years. Tropical chronic pancreatitis (TCP) was the most common etiology (43.9%), followed by idiopathic chronic pancreatitis (ICP) (41.4%), obstructive (34.2%) and alcoholic (19.8%). Diabetes was the most frequently reported (81, 29.1%) comorbidity. Of 86.3% and 24.5% of patients with history of abdominal pain and steatorrhea, respectively, 56.1% and 9% had ongoing pain, and steatorrhea. Weight loss and bloating were reported in 64.4% and 37.8% of patients, respectively. Most patients were well nourished (88.5%) and had good QoL (scores ≥83) (90.3%), except for patients with alcoholic and hereditary pancreatitis. As pharmacotherapy, 91.7% of patients were prescribed pancreatic enzyme replacement therapy (PERT) (mean duration, 52.4 months); 98.4% of them were on pancreatin, thrice a day regimen (78.5%) (median daily dose: 75,000; range: 10,000 to 350,000) units.

Conclusion: The results show TCP, ICP as the major etiologies of CP followed by obstructive chronic pancreatitis &ACP, which may predispose patients to early-onset PEI. PERT is routinely prescribed for managing PEI in India.

Introduction

Chronic pancreatitis (CP) is characterized by a progressive, nonhealing inflammation of the pancreas causing fibrosis of the pancreatic parenchyma leading to exocrine and endocrine pancreatic insufficiency.[1] Pancreatic exocrine insufficiency (PEI) is a major complication observed in patients with CP.[2] PEI results from a progressive loss of acinar cells leading to the insufficient secretion of enzymes, primarily lipase. Patients with PEI present with fat malabsorption, and subsequent steatorrhea with loose, greasy, foul-smelling stools.[3] PEI is a feature in 35 to 50% of patients, 10 to 15 years after the clinical onset of CP, and generally increases thereafter.[4] Li et al (2016) reported a cumulative prevalence of 21.87% and 41.14% of steatorrhea after 10 and 20 years of diagnosis of CP, respectively.[5] The reported prevalence of PEI in CP patients varies largely among studies conducted in India. A study in North India involved 155 CP patients, of which 7.3% were diagnosed with PEI.[6] By contrast, in a study (comparing the etiological factors in CP patients over a 14-year period) in South India, PEI was observed in 38.9% of patients.[7] Both studies reported idiopathic chronic pancreatitis (ICP) as the predominant etiology. Regunath et al (2011) compared tropical and alcoholic CP patients and reported severe PEI in 77.8% of CP patients.[8] The PEI onset time varies according to CP etiology.[9] However, evidence delineating the PEI onset time with different CP etiologies in India is lacking.

Patients with untreated PEI develop deficiencies of micronutrients such as lipid-soluble vitamins, calcium, and phosphorus, resulting in complications like osteoporosis,[10] and have a poor quality of life (QoL).[11] PEI predisposes mortality as well in CP patients.[12] Hence, an early diagnosis and management of PEI is of high clinical importance. The diagnosis of PEI is based on methods evaluating digestion, such as fecal fat quantification and the ^{13}C-mixed triglycerides test, symptoms, signs of malnutrition in blood tests, fecal elastase 1 (FE1) levels, and signs of morphologically severe CP on imaging. However, laboratory-based diagnosis may be cumbersome in routine clinical practice.[2] Thus, exploring the diagnostic practices regarding PEI in India is essential.

Pancreatic enzyme replacement therapy (PERT) is indicated to correct PEI and malnutrition in CP. International and Indian studies[13,14] have reported that Pancreatin (pancrelipase) has a positive benefit-risk ratio in treating PEI in patients with underlying CP. According to a 2008 World Health Organization report, pancreatic enzyme use in developing countries like India is inadequate because of economic constraints and lack of support from health programs.[15] Multiple factors such as poor awareness of PEI, low and late diagnosis of PEI, subtherapeutic dosing with PERT, and poor compliance are some of the challenges in the effective and timely management of PEI patients in the Indian setting. Improper

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PERT use may exacerbate disease complications, thereby increasing healthcare expenditure and overall economic burden on patients.

There are limited data available from Indian patients from a real-world scenario with CP who eventually develop PEI regarding demographic and clinical profile, natural history, diagnostic and management practices. Here, we present findings from a multicenter cross-sectional study conducted to investigate these factors in PEI patients with an underlying etiology of CP attending tertiary care centers in India. To understand the natural history of PEI in CP patients, we analyzed retrospective data collected from patients' medical records pertaining to the duration of PEI diagnosis from CP diagnosis, age at PEI onset, and PEI classification based on CP etiology. We also investigated the practices being followed for diagnosing PEI, the management of PEI including nutritional assessment, and the impact of PEI on QoL in our clinical settings.

Methods

Study design

This crosssectional study was conducted across 8 Indian tertiary care centers; one center each from Andhra Pradesh, Chandigarh, Delhi, Gujarat, Maharashtra, and Rajasthan and 2 centers from Kerala between February 2016 and January 2017. After obtaining approval from the Institutional Review Boards /Institutional Ethics Committees, the study was conducted in compliance with the protocol and all relevant regulatory guidelines.

Adult (18 to 75 years of age) male patients or non-pregnant, nonbreastfeeding female patients, clinically diagnosed with PEI based on investigator's judgment because of underlying CP for at least 5 years, and under routine clinical care at gastroenterology and gastro surgery outpatient departments were enrolled. All patients provided a written informed consent for voluntary participation.

Patients with acute pancreatitis, gastrointestinal surgery (e.g., Whipple's procedure, gastric surgery, bariatric surgery, and pancreatic surgery), pancreatic carcinoma, or extrapancreatic disorders such as irritable bowel syndrome, celiac disease, Crohn's disease, primary biliary cirrhosis, primary sclerosing cholangitis, or Zollinger-Ellison syndrome were excluded.

Demographic data (age, gender, education, and socioeconomic status), possible risk factors for CP (smoking and alcohol drinking), a history of previous pancreatic disease, significant medical history, etiology, symptoms and clinical signs (fever, pain, steatorrhea, weight loss, abdominal distension, diarrhea, hair fall, vomiting, nausea, lethargy, etc.), diagnostic work-up (laboratory parameters and imaging techniques), treatment, and complications were collected on the case report forms.

Detailed treatment history included PERT prescriptions (formulation, dosing regimen, and treatment duration) and other co-therapies advised.

Dietary history included a 24hour dietary recall and the frequency of food items consumed per day. A nutritionist analyzed the patients' daily intake of carbohydrates, fats, proteins, vitamins, and minerals.

Nutritional status was assessed using the modified subjective global assessment (SGA) scale and patients were categorized as A=well nourished; B=moderately malnourished; and C=severely malnourished depending on the scores.[16] The QoL was measured using the gastrointestinal QoL Index (GIQLI) scale, a 36item questionnaire comprising 5 subscales (scales for symptom, physical function, social function, emotional function, and burden of medical treatment). A GIQLI score of ≥83 is the QoL score observed in an average healthy individual.[17]

Statistical analysis

Data were analyzed using SAS® version 9.2 (SAS Institute Inc., USA). Statistical tests were performed at 5% level of significance. Mean and standard deviation (SD), and median and range were calculated for continuous variables (age, age at onset of CP and PEI, GIQLI overall score and subscale scores, and PERT dosing strengths). The median time (in months) to PEI development since CP diagnosis along with its 95% confidence interval (CI) was calculated using the Kaplan-Meier method. Categorical variables (such as different modified SGA categories, GIQLI scores of ≥83 and <83, socioeconomic class categories, PERT formulations) were summarized in terms of counts and proportions of patients in each category.

Results

Demographic characteristics

A total of 278 patients diagnosed with PEI due to underlying CP were enrolled. The mean (±SD) age of the patients was 40.0 (±13.12) years; most were males (207, 74.5%). The mean (±SD) age of the patients at PEI diagnosis was 34.9 (±13.04) years. Most patients were graduates (100, 36%) and belonged to the uppermiddle socioeconomic class (95, 34.2%). Approximately three-fourths of the enrolled patients were nonalcoholics (208, 74.8%) and nonsmokers (212, 76.3%) at enrolment. Table 1 summarizes the demographic and clinical characteristics of enrolled patients.

Onset, Etiology, and Comorbidities

The median (range) duration for PEI development after CP diagnosis was 3 (0, 16) years (36.0 months [95% CI: 24.0, 36.0] per the Kaplan-Meier method). Patients had CP since mean (±SD) duration of 8.0 (±4.33) years. Tropical chronic pancreatitis (TCP) was the most common etiology (122, 43.9%), followed by ICP (115, 41.4%) and obstructive etiologies (95, 34.2%). Other etiologies of CP were alcoholic chronic pancreatitis (ACP) (55, 19.8%), hereditary (6, 2.2%), autoimmune (3, 1.1%), and nutritional (1, 0.4%). Figure 1 shows the mean age at the onset and duration of PEI since CP diagnosis with respect to different etiologies.

A total of 150 (54.0%) patients had a history of at least 1 additional medical condition. Diabetes was the most frequent (81/278 [29.1%]) comorbidity. Endocrine, metabolic, and nutritional disorders (such as diabetes, dyslipidemia, hypoglycemia, hypothyroidism, and hyperthyroidism) were the most common medical conditions observed in 110/150 (73.4%) patients. Hepatobiliary disorders were observed in 33 (22%) patients, of which 23 (69.7%) had hepatic steatosis. Seventeen (11.33%) patients had hypertension. Fifty-five (36.7%) patients had undergone previous surgical and medical procedures, of which 39 (70.9%) had pancreatic stent placement (Table 2).

Table 1: Demographic and clinical characteristics of the patients

Characteristic	All Patients (N=278)
Age (years)	
Mean (±SD)	40.0 (±13.12)
Age at diagnosis of CP (years)	
Mean (±SD)	31.9 (±12.92)
Median (min, max)	31.5 (5, 66)
Duration since CP diagnosis (years)	
Mean (±SD)	8.0 (±4.33)
Median (min, max)	6 (1, 30)
Age at diagnosis of PEI (years)	
Mean (±SD)	34.9 (±13.04)
Median (min, max)	34 (10, 68)
Duration of PEI diagnosis since onset of CP (years)	
Mean (±SD)	3.1 (±2.86)
Median (min, max)	3 (0, 16)
Sex	
Men	207 (74.5%)
Women	71 (25.5%)
Education, n (%)	
Professional or honors	8 (2.9)
Postgraduate and above	26 (9.4)
Graduate	100 (36)
High school	84 (30.2)
Secondary school	48 (17.3)
Primary school	6 (2.2)
Illiterate	6 (2.2)
Socioeconomic status, n (%)[a]	
Lower socioeconomic class (Score <5)	4 (1.4)
Upper-lower socioeconomic class (Score 510)	81 (29.1)
Lower-middle socioeconomic class (Score 1115)	62 (22.3)
Upper-middle socioeconomic class (Score 1625)	95 (34.2)
Upper socioeconomic class (Score 2629)	36 (12.9)
Current consumption of alcohol, n (%)	
Yes	70 (25.2)
Mean (±SD) years of alcohol abuse (n=70)	15.3(±7.63)
Cessation of alcohol after CP diagnosis (n=70)	51 (18.3)
Smoking habit, n (%)	
Never smoked	212 (76.3%)
Former smoker	41 (14.7%)
Current smoker	25 (9.0%)
Mean (±SD) pack years of smoking (n=25)	9.4 (±8.57)

CP: chronic pancreatitis; Min: minimum; max: maximum; N: total number of patients enrolled in the study; n: number of patients in a given category; PEI: pancreatic exocrine insufficiency; SD: standard deviation [a]Per Kuppuswamy scale

Clinical presentation

Symptoms of PEI Secondary to Underlying CP

A total of 240 (86.3%) patients had a history of abdominal pain; 213 (76.6%) patients had episodes of abdominal pain within 6 months before enrolment and 156 (56.1%) had ongoing abdominal pain at enrolment. Sixtyeight (24.5%) patients had a history of steatorrhea, and 25 (9%) patients had it at enrolment. Patients also had a history of other cardinal symptoms such as weight loss (179, 64.4%), bloating (105, 37.8%), diarrhea (21, 7.6%), hair fall (103, 37.1%), lethargy (46, 16.5%), and joint pain (39, 14.0%) (Figure 2). A small proportion of the patients (2.9%3.6%) had peripheral edema, oral ulcers, and skin manifestations.

Table 2: Summary of medical history

Preferred term/System organ class (N=150)	Patients having at least 1 medical history n (%)
Endocrine, metabolism, and nutrition disorders	110 (73.4)
Surgical and medical procedures	55 (36.7)
Hepatobiliary disorders	33 (22)
Vascular disorders	17 (11.3)
Gastrointestinal disorders	8 (5.3)
Renal and urinary disorders	6 (4.0)
Cardiac disorders	5 (3.33)
Infections and infestations	3 (2)
Reproductive system disorders	2 (1.33)
Respiratory, thoracic, and mediastinal disorders	2 (1.33)
Skin and subcutaneous tissue disorders	1 (0.6)
Congenital, familial and genetic disorders	1 (0.6)
Blood and lymphatic system disorders	1 (0.6)
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	1 (0.6)

N: number of patients in a given category; n: total number of patients having at least one medical history

Nutritional Assessment, Diet, and QoL

The patients had a mean (±SD) body mass index (BMI) of 21.5 (±3.66) kg/m^2, mean (±SD) mid-upper arm circumference of 26.8 (±3.58) cm, and mean (±SD) triceps skin fold of 10.3 (±2.36) mm (data not shown).

Per the modified SGA scale rating, 246 (88.5%) patients were well nourished, 24 (8.6%) were moderately nourished, and 8 (2.9%) were severely malnourished. Patients consumed a median diet of 1807.0 (range: 824, 3070) kcal per day according to 24hour diet recall; carbohydrates were the major food component (280.3 g, 62% of total diet). Most patients consumed a diet moderate or low in fiber, vitamins, and mineral content (Figure 3) per the analysis by the study nutritionist.

The study population had an overall mean (±SD) GIQLI score of 109.1 (±20.23). A total of 251 (90.3%) patients had GIQLI scores ≥83. Mean (±SD) GIQLI scores for all CP etiologies, except for hereditary pancreatitis, were ≥83, which is the score seen in an average healthy person with a good QoL. More than 20% of ACP patients (12/55, 21.8%) had GIQLI scores <83. Patients with hereditary pancreatitis had the lowest mean (±SD) GIQLI score of 64.3 (±37.6).

Laboratory investigations for PEI

Patients' medical records were reviewed for the assessment of diagnostic practices in PEI patients. The diagnostic work-up for PEI included estimations of FE1 levels and primarily quantitative nutritional assessments. These estimations were available for only a small subset of patients. FE1 and vitamin D (25 hydroxycholecalciferol) levels were below the lower limit of normal in 93.3% (14/15) and 76.9% (40/52) of patients, respectively.

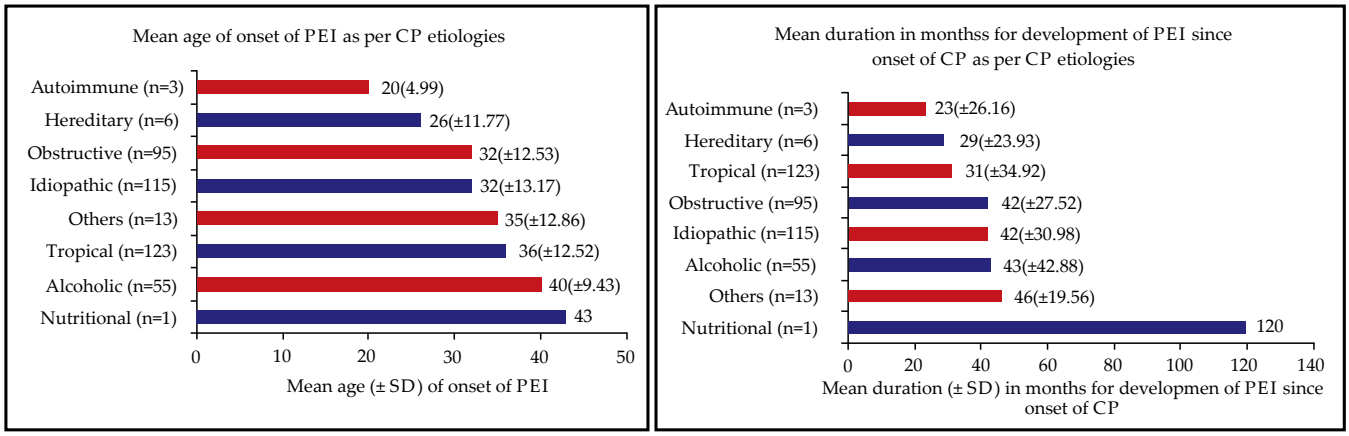
Of 81 patients with diabetes mellitus, glycosylated hemoglobin (HbA1c) levels (n=70) and postprandial blood glucose (PPG) levels (n=75) were elevated in 52.9% and 58.7% of patients, respectively. Serum lipase (n=105) and amylase (n=107) levels were within normal limits for 41 (39%) and 65 (60.7%) of patients, respectively (Table 3).

Management of PEI

PERT was the major component of PEI pharmacotherapy; other concomitant medications included gastric acid-lowering agents, nutritional supplements, and analgesics.

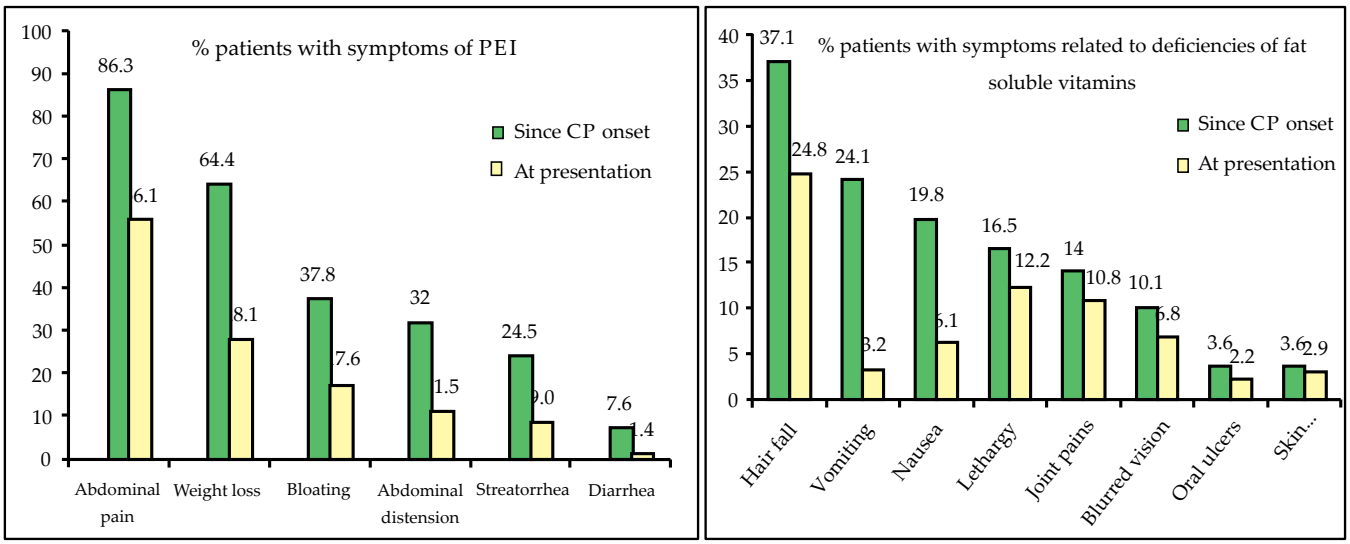
PERT: Dosage Regimen

Of the 278 enrolled patients, 255 (91.7%) were prescribed PERT; the remaining 23, who were recently diagnosed, were not initiated on PERT at the time of study enrolment. Patients were on PERT for a mean (±SD) duration of 52.4 (±51.64) months. Pancreatin, a combination of amylase, lipase, and protease, was the most frequently prescribed PERT (251/255, 98.4%), with a median (range) daily dose of 75,000 (10,000 to 350,000) units. Thrice



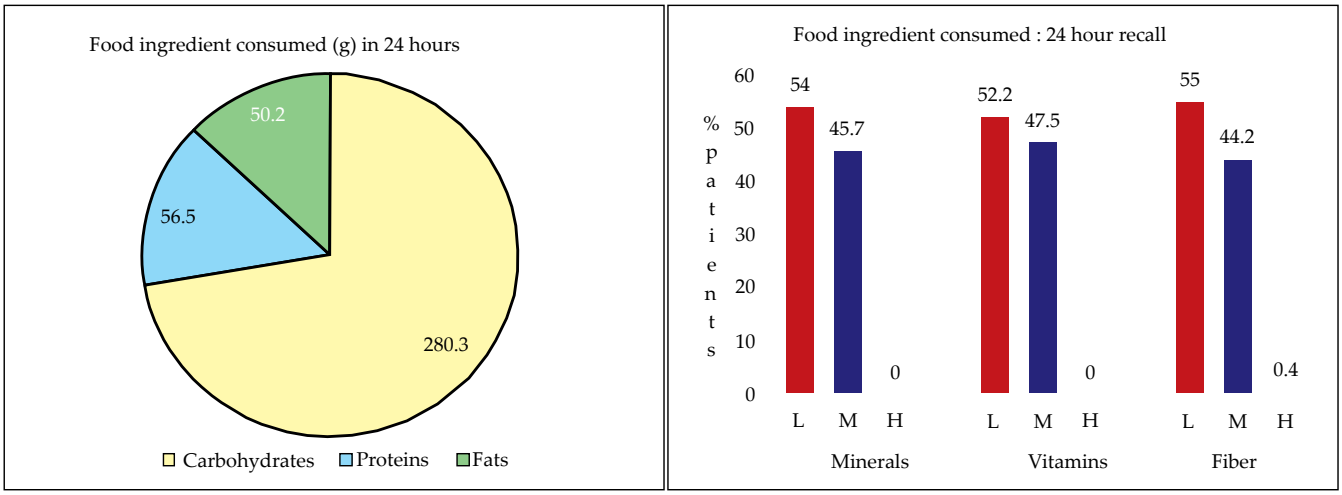
CP : chronic pancreatitis; n: number in the subcategory; PEI: pancreatic exocrine insufficiency; SD: standard deviation

Fig. 1: Mean age at onset of and duration of PEI since diagnosis of chronic pancreatitis



CP : Chronic pancreatitis; PEI : pancreatic exocrine insuficiency

Fig. 2: Symptoms of pancreatic exocrine insufficiency



H: high; L: low; M: moderate

Fig. 3: Food ingredients in the diet

Table 3: Summary of laboratory estimation

Parameter	Number of patients (N)	Mean (±SD)	Normal n (%)	Out of normal range n (%)	
				Low	High
Serum amylase (U/L)	107	184.6 (453.16)	65 (60.7)	6 (5.6)	36 (33.6)
Serum lipase (U/L)	105	242.0 (392.26)	41 (39.0)	14 (13.3)	50 (47.6)
Postprandial blood glucose (mg/dL)	75	197.4 (101.77)	30 (40)	1 (1.3)	44 (58.7)
Glycosylated Hb (HbA1c)	70	7.6 (2.09)	20 (28.6)	13 (18.6)	37 (52.9)
25 hydroxycholecalciferol (ng/mL)	52	19.1 (9.12)	10 (19.2)	40 (76.9)	2 (3.8)
Serum albumin (mg/dL)	40	3.9 (0.59)	32 (80.0)	8 (20.0)	0
Vitamin B12 (ng/mL)	36	418.6 (240.75)	29 (80.6)	6 (16.7)	1 (2.8)
Serum prealbumin (mg/dL)	32	24.7 (6.92)	25 (78.1)	6 (18.7)	1 (3.1)
Fecal elastase-1 (µg elastase/g)	15	105.3 (72.20)	1 (6.7)	7 (46.7%)	7 (46.7%)
Serum retinol-binding protein (mg/dL)	2	7.4 (0.28)	1 (50.0)	0	1 (50.0)
Serum transferrin (mg/dL)	31	260.7 (58.96)	24 (77.4)	6 (19.4)	1 (3.2)

Hb: hemoglobin; N: number in main category; n: number in subcategory *Percentage out of N

Table 4: Summary of dosing pattern of pancreatic enzyme replacement therapy

Dosing Pattern	Overall (N=278)		
	Pancreatin Formulation 1 (n=251)	Pancreatin with Dimeticone Formulation 2 (n=9)	Pancreatin with Sodium Tauroglycocholate Formulation 3 (n=1)
Daily dose prescribed (Units)			
Mean (SD)	65,053.3 (±31,812.25)	46,850.0 (±17,612.57)	40,000 (±20,000)
Median (Min, Max)	75,000 (10,000, 350,000)	50,000 (19,500, 75,000)	40,000 (20,000, 60,000)
Frequency, n (%)			
Once a day	46 (18.3)	0 (0)	0 (0)
Twice a day	41 (16.3)	2 (22.2)	0 (0)
Thrice a day	197 (78.5)	8 (88.9)	1 (100)
Other	1 (0.4)	0 (0)	0 (0)
Dosing Pattern, n (%)			
Breakfast	230 (91.6)	8 (88.9)	1 (100)
Lunch	217 (86.5)	9 (100)	1 (100)
Dinner	217 (86.5)	9 (100)	1 (100)
Snacks	2 (0.8)	0 (0)	0 (0)
Timing, n (%)			
Before food	41 (16.3)	0 (0)	0 (0)
During food	199 (79.3)	9 (100)	1 (100)
After food	11 (4.4)	0 (0)	0 (0)
PERT Formulation, n (%)			
Enteric-coated tablets	137 (54.6)	9 (100)	1 (100)
Enteric-coated granules	19 (7.6)	0 (0)	0 (0)
Enteric-coated minimicrospheres	114 (45.4)	0 (0)	0 (0)

Min: minimum; max: maximum; n: number in the subcategory; N: number of patients enrolled; PERT: pancreatic enzyme replacement therapy; SD: standard deviation

a day was the most preferred dosing frequency for administering pancreatin alone (197/251, 78.5% patients) or in combination (pancreatin with dimeticone: 8/9, 88.9% and pancreatin with sodium tauroglycocholate: 1/1, 100%). Almost all formulations were advised to be taken with food at the time of breakfast, lunch, and dinner in most patients (approximately 80%) which is according to the label of PERT administration One hundred thirty-seven (54.6%) patients received enteric-coated pancreatin tablets and others received enteric-coated capsules containing minimicrospheres (114/251, 45.4%). Other combinations of PERT were given in the form of enteric-coated tablets only (Table 4).

Table 5 presents a summary of the duration of PERT doses with respect to CP etiologies. The longest duration of PERT was 130 months for a patient having pancreatitis of nutritional origin. This was followed by 109.2 (±70.23) months for 6 patients with PEI due to CP of hereditary etiology.

Patients with TCP were prescribed a lower median daily dose of pancreatin (60,000 [range 10,000 to 350,000] units), whereas patients with ACP, ICP, and hereditary CP received a higher median daily dose of 75,000 units of pancreatin. Per SGA score, well-nourished patients received a median (range) daily dose of 60,000 (10,000 to 350,000) units; moderately and severely malnourished patients received higher doses of 75,000 (30,000 to 150,000) units and 75,000 (50,000 to 120,000) units, respectively (data not shown).

Other Co-therapies

Seventeen (6.1%) patients underwent surgical and medical procedures (pancreaticojejunostomy: 16, 94.1%; lithotripsy: 1, 5.9%). Sixty-nine (24.8%) patients were referred for endotherapy.

Concomitant Medications

Two hundred one (72.3%) patients were treated with drugs for acidrelated disorders, of which 131 (65.2%) and 44 (21.9%) received pantoprazole and rabeprazole, respectively. Vitamin supplements were prescribed to 167 (60.1%) patients, of which 76 (45.5%) received ascorbic acid, retinol, selenium, and tocopheryl.

Analgesics were prescribed to 121 (43.5%) patients, of which 89 (73.6%) were given tramadol. Other concomitant medications prescribed included antibacterial and anti-inflammatory drugs (Figure 4).

Discussion

This clinicoepidemiological study describes the clinical course, diagnostic work-up, and management practices being followed for PEI in routine clinical practice. Most participants were in their 30s and 40s (mean [±SD] age: 40.0 [±13.12] years) and were being followed up for a median (range) duration of 6 (1, 30) years after CP diagnosis. This representation demonstrates that our patients were comparatively younger at the time of CP diagnosis (mean [±SD] age, 31.9±12.92 years) than those in other similar epidemiological studies. A CP etiology study in the United States of America reported 50% of patients were between 35 and 65 years of age at CP diagnosis.[18] The mean age at CP onset was 38 years in China.[5] In a PanIndia study involving 1033 CP patients, most patients were in their early 30s at CP onset.[19]

Our study shows male preponderance (74.5%), which has been

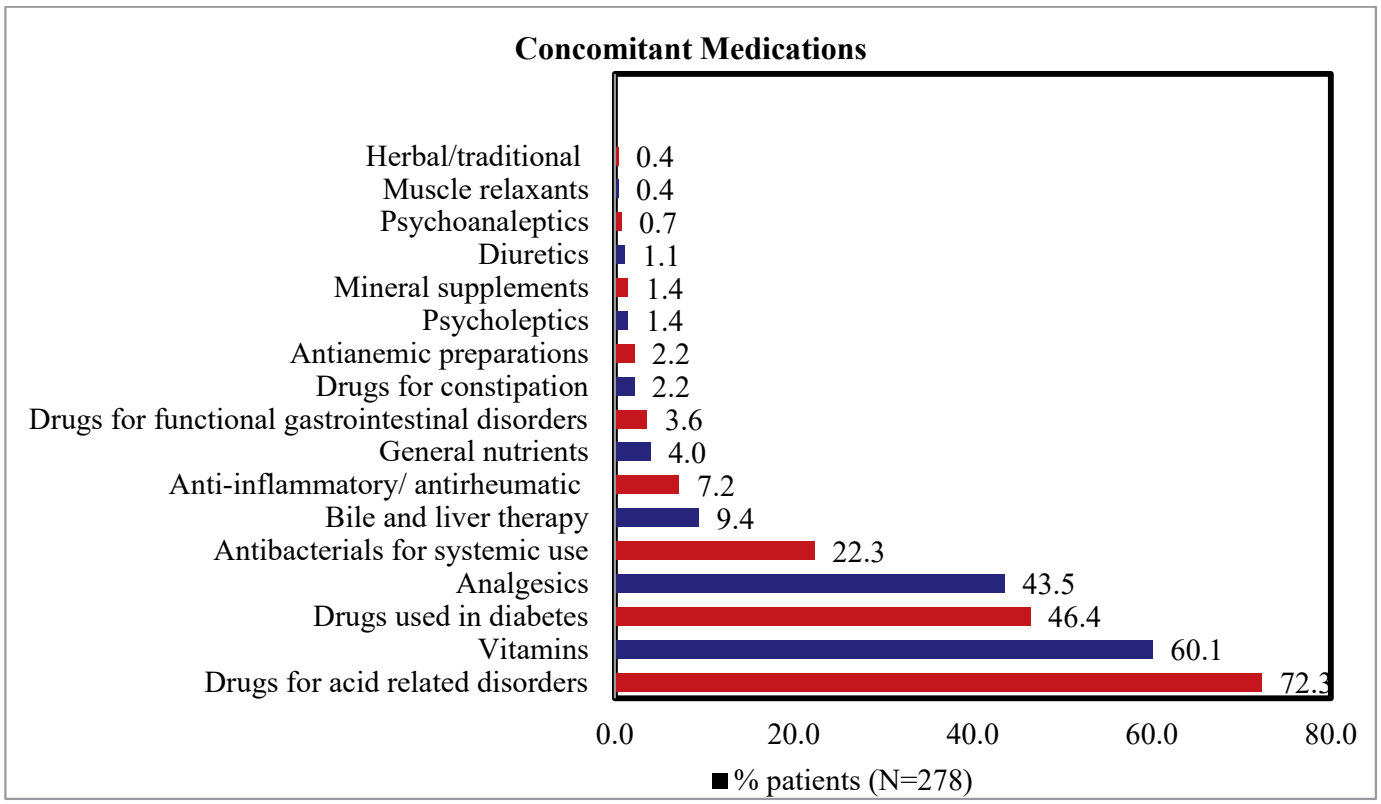
observed in other studies describing the clinical profile of CP.[20,21] Nearly half of the patients (48.3%) were graduates, postgraduates, and professionals. More than half of the study population (56.5%) represented the middle socioeconomic class (upper-middle: 34.2% and lower-middle: 22.3%). A small proportion of our patients reported alcohol consumption and smoking habits. BMI, anthropometric parameters, and modified SGA scores observed in our study indicate normal nutritional status in most patients. Balakrishnan et al (2008) described patient characteristics similar to those observed in this study possibly because of similarities in the recruitment sites (tertiary care hospitals).[19]

Lower rate of alcoholism and smoking in our study explains the finding of TCP and ICP being the most frequent etiologies of CP. In most AsiaPacific countries, alcoholic pancreatitis accounts for approximately 60%-70% of all cases of CP. However, in certain tropical countries, such as India, most patients with CP suffer from nonalcoholic idiopathic pancreatitis; some of these cases are labeled as TCP.[22] By contrast, Udayakumar and Jayanthi report a decline in classical TCP cases and a rapid increase in ICP cases because of the interaction of many factors, with clinical presentation overlapping both TCP and ACP.[23] This observation corroborates our study finding. In a Chinese study assessing risk factors for steatorrhea, ICP was the most prevalent etiology of CP,[5] which again is in agreement with our study finding. ICP was also the most

Table 5: Summary of pancreatic enzyme replacement therapy doses with respect to etiologies of chronic pancreatitis

Etiology (N=278)	Duration of PERT (Months) mean (±SD)	Daily dose (units) median (range)		
		Pancreatin formulation 1 (n=251)	Pancreatin with dimeticone formulation 2 (n=9)	Pancreatin with sodium tauroglycocholate formulation 3 (n=1)
Tropical (n=122)	73.8 (±58.90)	60,000 (10,000, 350,000)	60,000 (30,000, 60,000)	40,000 (20,000, 60,000)
Idiopathic (n=115)	38.5 (±38.71)	75,000 (10,000, 120,000)		
Obstructive (n=95)	37.9 (±38.01)	75000 (10,000, 120,000)		
Alcoholic (n=55)	48.9 (±47.86)	75,000 (10,000, 150,000)	60,000 (19,500, 75,000)	
Others (n=13)	8.8 (±7.08)	55,000 (3000, 55,000)		
Hereditary (n=6)	109.2 (±70.23)	75,000 (60,000, 120,000)	60,000 (60,000, 60,000)	
Autoimmune (n=3)	66.3 (±56.61)	67,500 (30,000, 75,000)		
Nutritional (n=1)	130.0	10,000 (10,000, 10,000)		

n: number in the subcategory; N: number of patients enrolled; PERT: pancreatic enzyme replacement therapy; SD: standard deviation



%: percentage; CP: chronic pancreatitis; PEI: pancreatic exocrine insufficiency; SD: standard deviation

Fig. 4: Summary of concomitant medications

prevalent etiology of CP reported by Balakrishnan et al, followed by ACP.[19] A trend analysis on CP etiology reported an increasing prevalence of ACP than of ICP in 2007-2013 in southern India, but ICP was more prevalent before 2006.[7] However, in northern India, ICP is more prevalent than ACP[6] as observed in our study. Our patients were mainly recruited from the northwestern and southern regions. The results confirm the predominance of non-alcoholic etiologies, mainly ICP and TCP, in India, as reported by most other Indian studies. PEI is the major complication of CP, which manifests with steatorrhea. Because of the large reserve capacity for enzyme secretion by the exocrine pancreas, overt steatorrhea does not occur until approximately 90% of glandular function has been lost.[24] Valenciano et al (2017) reported that the median time to PEI onset from CP diagnosis was longer in patients with severe PEI than in patients with mild PEI (68 [36.3103.3] months vs. 57.3 [45.688.4] months).[20] In our study, patients developed PEI in a shorter time period (3 years) after CP onset at a comparatively younger age (34.9±13.04 years), which is alarming.

There are mixed reports on the prevalence of different CP etiologies in PEI patients. An Indian study reported increased prevalence of late-onset PEI as compared with early-onset ICP.[7] In another Indian study, the prevalence of exocrine insufficiency was similar in patients having ACP and TCP.[8] However, no data are available on the onset of PEI in patients with different etiologies. Thus, we explored the duration of PEI development in different etiologies and found that the mean duration was lower in patients with hereditary CP (29±23.93 months) and TCP (31±34.92 months) than in patients with ACP (43±42.88 months) and ICP (42±30.98 months). The mean age at PEI onset for ACP (40±9.43 years) was higher than that for ICP (32±13.17 years). Because most of our patients were younger at enrolment, we probably may not have recruited PEI patients with ACP as they generally develop PEI at a later stage. These findings indicate a gap in the present evidence base for which long-term follow-up studies are required to investigate the association between CP etiologies and PEI development. This will help to monitor CP patients with a specific etiology more rigorously until the onset of PEI.

Most of our patients (86.3%) had a history of abdominal pain and more than half (56.1%) complained of pain at enrolment. Weight loss and bloating were other predominant symptoms. Nearly onefourth of the patients had a history of steatorrhea, which reduced to 9% (25 patients) at enrolment. Symptoms related to nutrient deficiencies were prevalent in about onefourth of the patients. The most common symptoms of PEI-associated maldigestion reported in previous studies are abdominal pain, steatorrhea, malnutrition, and weight loss.[21] Similar clinical presentations in this study cohort reiterate the importance of routinely assessing these symptoms while managing patients with CP and/or PEI.

This study shows limited use of formal laboratory assessments including diagnostics in PEI patients. Very few patients were evaluated objectively for malnutrition by estimating serum retinolbinding protein and prealbumin. Similar pattern was found for other assessments, including FE-1, amylase, lipase levels, calcium, albumin, and transferrin estimations. In other similar studies, FE-1 was used to diagnose PEI [20, 7]; however, these were not real-world studies. The patients with available results had deficient levels of vitamin D and FE-1, illustrating the need to include these assessments in the standard of care. Currently, the early diagnosis of PEI is difficult because of lack of sensitive blood, imaging, and functional biomarkers.

Pathophysiologically, diabetes mellitus can predispose to PEI and, conversely, longstanding PEI may be associated with diabetes.[25] Approximately onethird of our patients had diabetes mellitus and most had increased HbA1c and PPG levels; Valenciano et al (2017) have reported similar findings in patients with severe PEI.[20] Therefore, better diabetic control is required for overall management of PEI patients.

PEI with steatorrhea either proven or implied, and/or weight loss, is an indication for the trial of PERT.[26] Several studies have demonstrated that PERT improved fat absorption coefficient, serum nutritional parameters, gastrointestinal symptoms, and QoL and reduced maldigestion-related symptoms.[12,14,27,28] PERT is indicated to correct PEI and malnutrition in CP. It remains the mainstay therapy in patients with proven or implied steatorrhea.[26] The objective of PERT is to deliver sufficient enzyme activity into the duodenal lumen simultaneously with the meal to restore normal digestion, which aids absorption. An adequate dose of 25,000 to 50,000 units of lipase per meal is recommended to be consumed with or immediately following meals.[26] Most patients (255, 91.7%) in our study were receiving PERT for a mean (±SD) duration of 52.4 (±51.64) months. Almost all patients received pancreatin, instructed to be taken with meals (breakfast, lunch, and dinner); thrice a day was the most preferred frequency with a median daily dose of 75,000 (10,000 to 350,000) units, which was per the guideline recommendations. Wellnourished patients were receiving a lower daily dose. Well-nourished status (88.5%) with a mean BMI and anthropometric parameters within the normal range and the consumption of a low-fiber diet (55%) indicate that patients were receiving nutrition counseling.

Most of our patients were prescribed antisecretory drugs such as pantoprazole and rabeprazole for acid-related disorders. Deficiencies of fat-soluble vitamins are very common in PEI patients[10] and vitamin supplementation should be given if necessary.[26] In this study, 167 (60.1%) patients received vitamin supplementation.

Our study represents a large cohort of PEI patients (almost 92%) receiving PERT, with only 9% complaining of steatorrhea. It appears that physicians do not recommend laboratory assessment as part of clinical management, and that they are proactively treating PEI with PERT. Another striking finding is that probably PERT is being initiated before the onset of overt steatorrhea, based on symptoms of nutritional deficiencies. The low rate of steatorrhea, in spite of mean fat consumption (50.2g) being above Indian recommended dietary allowance (adult male: 25-40g/day and adult female: 20-30 g/day)[29] in our patients probably indicates that initiating PERT at an asymptomatic stage might delay overt symptoms of PEI. Normal QoL and wellnourished nutritional status in most of our patients, with a lower symptom burden

at enrolment, suggest the benefit of early initiation of PERT for effectively controlling PEI. However, a prospective study is required to confirm this assumption.

Limitations

We included only tertiary care hospitals from urban areas of southern and northwestern regions, so the results cannot be generalized to the entire PEI patient population in India. The prevalence of steatorrhea reported in our study was subjective and not based on laboratory assessments such as fecal fat estimations. However, the findings provide an estimate and insight of clinical practice for diagnosis and management of PEI patients in the real-world settings. Because of the crosssectional design, the effectiveness and safety of PERT could not be studied systematically and correlated with symptomatic and QoL improvement in a prospective manner.

Conclusion

The study demonstrates TCP, ICP, and ACP to be the major etiologies, which may predispose patients to early-onset PEI. PERT is routinely prescribed for managing PEI. Comprehensive assessment of nutrition, digestion, and absorption is essential as part of the standard of care of PEI to enable better disease management, which may improve the long-term patient outcomes before the complications of PEI set in.

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