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Subclinical pancreatic exocrine insufficiency is associated with osteopathy in patients with chronic pancreatitis: Implications for management

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ABSTRACT

Background and aims: Patients with chronic pancreatitis (CP) may develop pancreatic exocrine insufficiency (PEI) but data regarding subclinical PEI are scarce. Our objective was to detect subclinical PEI in patients with CP and its functional consequences.
Methods: We prospectively included patients with CP from April 2018–December 2021. Mild PEI and severe PEI were diagnosed if fecal elastase (FE) was 100–200 μg/g and <100 μg/g stool respectively. Vitamin levels and DEXA scan were done to assess functional consequences of PEI. Presence of subclinical PEI in CP (low FE-1 but without steatorrhea) with consequent osteopathy was the primary outcome.
Results: Of 120 patients with CP, subclinical PEI (low FE-1 but no steatorrhea) was present in 84/120(70%) patients: 6/8(75%) in early CP, 41/53(77%) in definite CP and 37/55(67.2%) in advanced CP. Overall, 72.1% patients had osteopathy including 53(62%) among patients with subclinical PEI. There was no difference in osteopathy between subclinical and severe PEI. Patients with severe PEI had lower vitamin A levels as compared to mild PEI and no PEI patients [1.3 ± 0.5 mg/ml vs. 1.7 ± 0.6 mg/ml vs. 1.8 ± 0.5 mg/ml; p = 0.04]. There was no difference in vitamin D levels. Osteopathy was present in 40/56 (71.4%) in advanced, 26/56 (46.4%) in definite and 2/8 (25%) in early CP patients (p = 0.09). On multivariable analysis, patients with advanced CP had the higher risk of osteopathy (odds ratio 7.6, 95% CI 1.9–29.7).
Conclusions: Subclinical PEI was present even in early CP with increased risk of osteopathy and fat-soluble vitamin deficiency.

1. Introduction

Chronic pancreatitis is a chronic inflammatory disease of the pancreas which is characterized by repeated episodes of pancreatic inflammation resulting in parenchymal injury and fibrosis [1]. The world-wide prevalence of CP varies from 36 to 125/100,000 population [2]. Chronic parenchymal injury and resultant fibrosis lead to functional insufficiency. Patients with CP initially develop mild pancreatic exocrine insufficiency (PEI) with decreased enzyme output that is still sufficient to prevent nutrient maldigestion. However, as the disease progresses, patients develop severe exocrine insufficiency with clinical steatorrhea [3]. Thus, clinical steatorrhea is infrequent and occurs late, only when the lipase production falls below 10% of normal levels [4]. However, even though patients with mild PEI do not exhibit overt signs of maldigestion in the form of steatorrhea, subclinical PEI might still lead to maldigestion and micronutrient deficiency particularly of fat soluble vitamins. Testing for PEI is infrequently performed. In a survey of 252 pancreatologists, screening for PEI was performed by 69% and repeated annually only by 21% [5]. In a retrospective study of

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1869 patients with probable or definitive CP, PEI was present in 849 (45.4%) of patients [6].

One of the major consequences of PEI is osteopathy. In the US multicenter PROCEED study, 56% of 282 patients had osteopathy on a dual-energy X-ray absorptiometry (DEXA) scan [7]. In a meta-analysis of 17 studies comprising of 1,659 patients with CP, osteoporosis was seen in 18% and osteopenia in 39% [8]. The data regarding the correlation of the severity of PEI and osteopathy are somewhat contradictory. One study of 50 patients showed PEI as a risk factor for osteopenia [9]. On the other hand, in a study of 211 CP patients of whom 42% had osteopenia, no difference was noted in the fecal elastase levels between those with and those without osteopathy. The significant risk factors for osteoporosis in that study were female sex, age and higher BMI on a multivariable analysis [10]. Although practice guidelines suggest a DEXA scan to screen for osteopathy in patients with CP, it is not generally practiced [11]. In the North American Pancreatitis Study 2 (NAPS2), only 21% (49/239) patients were evaluated by a DEXA scan [12]. The prevalence of subclinical PEI and its effect on osteopathy in different stages of CP are not well known. The primary objective of our study was to detect subclinical PEI in patients with CP and to assess its functional consequences particularly osteopathy.

2. Methods

We carried out an observational cross-sectional study with prospective enrollment of participants at our institute, a tertiary-care academic center. Ethical clearance was obtained from the Institute Ethics Committee (IEC/PG- 290/2018). Participants were included after an informed written consent.

2.1. Inclusion criteria

All consecutive adult (>12 years of age) patients with CP presenting to the Pancreas Clinic between April 2018 till December 2021 were included.

2.2. Exclusion criteria

i. Pregnant patients
ii. Patients with any known liver, intestinal, bone or endocrine disease
iii. Patients on pancreatic enzyme supplementation
iv. Patients refusing to provide consent

2.3. Definitions

The diagnosis of CP was made based as per standard criteria as reported previously [13]. Computed Tomography (CT) scan was the imaging modality of choice. In the presence of a normal or ambiguous CT findings, a magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) and/or an endoscopic ultrasound (EUS) were done to confirm the diagnosis of CP. The etiology of CP was determined as reported previously [14].

Staging of Chronic Pancreatitis: Patients with CP were further classified based on morphology into one of three stages [15]:

- Early CP: Early CP was diagnosed in patients with suspected CP if (i) they had >2 episodes of acute pancreatitis (ii) at least 4 of 9 conventional criteria of CP were present on EUS and (iii) absence of pancreatic calcification or ductal dilatation (Fig. 1a) [16,17].
- Definite CP: Definite CP was diagnosed if calcifications and/or main pancreatic duct dilation with or without ductal contour irregularity were present on cross sectional imaging (Fig. 1b).

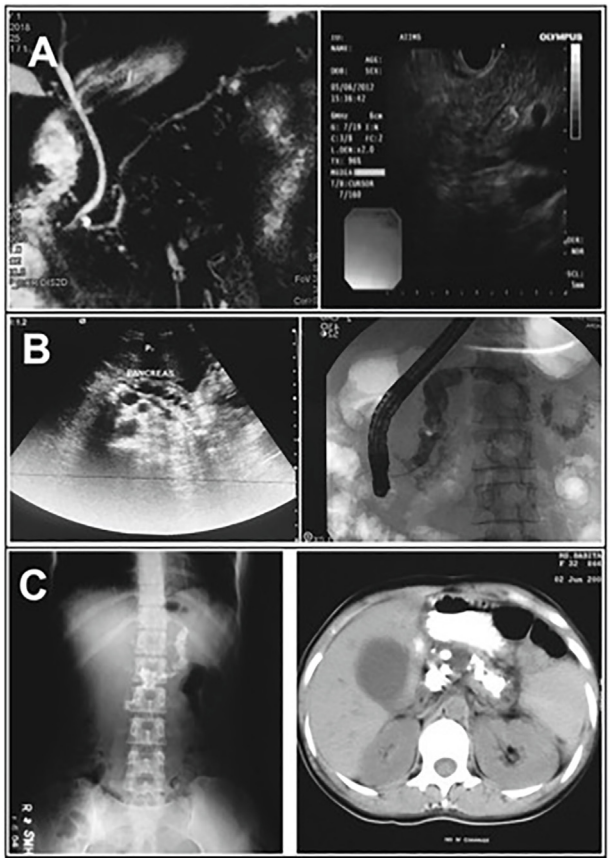

Fig. 1. A) Early CP: EUS showing honey combing, and lobularity. Main pancreatic duct is prominent with hyperechoic foci and strands. B) Established CP showing parenchymal calcification and ductal dilatation with stones C) Advanced end stage CP showing marked parenchymal atrophy with the dilated pancreatic duct filled with large stones.

- Advanced end stage CP: It was diagnosed if the pancreas was atrophic with marked ductal dilation and extensive calcification (Fig. 1c).

2.4. Evaluation of patients

Patients' data were collected as per a study specific proforma for the following variables: age, sex, clinical manifestations, laboratory investigations, radiological imaging and study specific tests. Anthropometry assessment comprised of weight, body mass index (BMI), mid-upper arm circumference (MUAC), and waist-hip ratio.

2.5. Study specific investigations

2.5.1. Assessment of pancreatic exocrine insufficiency

Pancreatic exocrine function (PEI) was assessed by measuring fecal elastase (FE-1) and 24 h fecal fat excretion. FE-1 was measured by ELISA. A FE-1 level of >200 μg/g of stool was considered normal, levels between 100 and 200 μg/g were considered as suggestive of mild PEI, and levels <100 μg/g were taken as suggestive of severe PEI [18]. Fecal fat was measured using the Van de Kamer method following a 72 h period of ingestion of 75 g fat per day [19]. Steatorrhea was diagnosed if the fecal fat excretion was >7 g/day. The methodological details of biochemical tests are given in Appendix 2. Clinical steatorrhea was diagnosed when the patient described the passage of oily or greasy stool with or without increased

frequency of stools [20]. We divided our patients in to two subgroups – overt PEI, defined by the presence of clinical steatorrhea, and subclinical PEI if the FE-1 was <200 μg/gm in the absence of clinical steatorrhea.

Assessment of osteopathy: A dual-energy X-ray absorptiometry (DEXA) bone scan was done. Based on the T-scores of their hip bone mineral density (BMD), patients were diagnosed as either osteopenia or osteoporosis as per the standard criteria [21].

Fat Soluble Vitamins: Blood levels of vitamin A (serum retinol) and vitamin D were measured by dedicated kits. Vitamin D assay was run using a chemiluminescent immunoassay (CLIA) (LIAISON® 25 OH Vitamin D TOTAL Assay, DiaSorin Inc.). Vitamin A assay was run using a triple quadrupole tandem mass spectrometer (4000 Q-Trap, AB Sciex) coupled with high performance liquid chromatography system (HPLC, Agilent Technologies)). Vitamin D deficiency was considered for levels <10 ng/ml, and Vitamin A deficiency was considered for serum retinol levels <20 μg/dl.

2.5.2. Management of patients with CP

All the patients were treated as per a predefined protocol with analgesics on demand, dietary advice, and pancreatic enzyme replacement therapy in the dose of 2 capsules with meals, each containing 8,000 units of lipase and 30,000 USP of proteases (Digestomen-P, Minarini Raunaq Pharma Ltd, India), and antioxidants [22,23]. Additional therapy in the form of endoscopic and/or surgical treatment was provided if the medical treatment failed to relieve the abdominal pain of the patients.

2.5.3. Outcome measures

Primary outcome: Presence of subclinical PEI in CP with its consequences in terms of osteopathy was the primary outcome.

Secondary outcomes:

1. Fat soluble vitamin levels in mild or no PEI, subclinical PEI and severe PEI in CP
2. Osteopathy in mild or no PEI versus severe PEI in CP
3. Correlation between fat soluble vitamin levels and osteopathy with the stage of CP

Sample size: Assuming a prevalence of PEI to be 64% [24], a precision of 10% and a 95% confidence interval, the sample size was calculated to be 89. Assuming a 10% drop out rate, we planned to recruit 100 patients. During the course of the study, some patients did not come for fecal fat estimation so we increased the sample size by 20% and hence the final sample size was 120.

2.6. Statistical analysis

The baseline data were recorded as number (%), mean (SD) or median (range) as appropriate. Intergroup comparison was done using Fischer exact or Chi square test for categorical variables and unpaired Student's t-test for continuous variables with normal distribution and Wilcoxon-Mann-Whitney *U* test for continuous variables without normal distribution. For all univariate analysis, a two-tailed p value of <0.05 was considered statistically significant. A multivariable analysis was done to find out the significant independent risk factors for osteopathy. The independent risk factors included in the univariate analysis were age of the patient, sex, stage of the disease, duration of the disease, etiology of CP, diabetes, and socioeconomic status of the patient. Variables with a p value < 0.10 on univariate analysis were entered in the multivariable analysis. Odds ratios (OR) with 95% confidence intervals (CI) are reported for significant risk factors.

3. Results

A total of 120 patients with chronic pancreatitis were included in the study from April 2018 till December 2021. The baseline characteristics of the study patients are given in Table 1.

The etiology of CP was idiopathic in 103 (85.8%), alcohol in 15 (12.5%) and hereditary in 2 (1.7%) patients. During their course of illness, 101 (84.2%) patients presented with abdominal pain, 45 (37.5%) patients had diabetes and 30 (25%) had clinical steatorrhea. Of the 120 patients, early CP was present in 8 (6.6%) patients, definite CP in 56 (46.7%) patients and advanced end stage CP in 56 (46.7%) patients.

3.1. Prevalence of subclinical PEI and its significance

PEI was present in 114 (95%) of 120 patients: 6 of 8 (75%) patients with early CP, in 53 of 56 (94.6%) patients with definite CP and in 55 of 56 (98.2%) patients with advanced CP. Of the 120 patients, clinical steatorrhea was present in 12/56 (21.4%) patients with definite CP, 18/56 (32.1%) patients with advanced CP but none in early CP. Thus, subclinical PEI (low FE-1 but no steatorrhea) was present in 84 patients: 6/8 (75%) in early CP, 41/53 (77%) in definite CP and 37/55 (67.2%) in advanced CP (see Table 2).

Patients with severe PEI had lower vitamin A levels as compared to those with mild PEI or no PEI [vitamin A level 1.3 ± 0.5 mg/ml in severe, 1.7 ± 0.6 mg/ml in mild and 1.8 ± 0.5 mg/ml in no PEI,

Table 1
Basic demographic data of patients.

Parameter	Value
N	120
Age at enrolment (years)	32.5 ± 11 years
Sex (Male: Female)	80 M: 40 F
Presenting symptoms (n, %)	
Pain	101, 84.2%
Diabetes	45, 37.5%
Clinical Steatorrhea	30, 25%
Asymptomatic	7, 5.8%
Etiology of CP (n, %)	
Alcoholic	15, 12.5%
Idiopathic	103, 85.8%
Hereditary	2, 1.7%
Complications (n, %)	
Pseudocyst	10, 8.3%
Biliary Strictures	3, 2.5%
Others	3, 2.5%
Stage of CP (n, %)	
Early CP (%)	8 (6.7%)
Definite CP (%)	56 (46.7%)
Advanced CP (%)	56 (46.7%)
Baseline Characteristics	
Duration of illness in months (Median; Months)	72 months
Premorbid BMI (kg/m^2)	23.6 ± 13.4
BMI at enrolment (kg/m^2)	20.8 ± 4.0
% Significant weight loss (>5%)	57 (47.5%)
Median value of FE-1 μg/g of stool (n, %)	**15 (5–192)**
FE-1 < 100 μg/g	104, 86.7%
FE-1 100 μg/g – 200 μg/g	10, 8.3%
FE-1 > 200 μg/g	6, 5.0%
Median value of Fecal Fat, N = 65	**8.9 (0.46–46.9) g/day**
Fecal Fat <7 g/day	37, 56.9%
Fecal Fat >7 g/day	28, 43.0%
Subclinical PEI, n (%)*	84, (70.0%)
Mean Vitamin A levels	**1.3 ± 0.5 μg/mL**
Vitamin A deficient #n (%)	2 (1.67%)
Mean Vitamin D levels	**18.3 ± 13.0 ng/mL**
Vitamin D deficient* n (%)	30 (25%)
Osteopathy, n (%)	75, 72.1%

*Vitamin D deficiency if ≤ 10 ng/ml, #Vitamin A deficiency if ≤ 0.2 μg/ml.
*Subclinical PEI = No steatorrhea in the presence of FE-1 levels <200 μg/g.

Table 2
Correlation of PEI (Overt versus subclinical) with nutritional status and bone health (n = 114).

Parameter	Overt PEI	Subclinical PEI[a]	*p-value*
N	30	84	
Age in years Median (IQR)	34 (28–37)	30 (24–38)	*0.42*
Duration of illness in years Median (IQR)	4 (4–14)	5(2–10)	*0.09*
Stage of Disease N (percentage)	0	6 (100)	*0.17*
Early stage	12 (40.0)	41 (48.8)	
Definite stage	18 (60.0)	37 (44.1)	
Advanced stage			
Dilated MPD	27 (90.0)	76 (90.4)	*0.93*
Multiple calcification	28 (93.3)	73 (86.9)	*0.34*
Presence of diabetes N (percentage)	17 (56.7)	27 (32.2)	***0.03***
Serum albumin in g/dl Mean ± SD	4.4 ± 0.7	4.7 ± 0.7	***0.02***
Vit A (μg/mL) (Mean ± SD)	1.2 ± 0.7	1.3 ± 0.5	*0.27*
Vit D levels (ng/mL) (Mean ± SD)	19.6 ± 18.6	17.5 ± 10.1	*0.73*
Osteopenia, N (%)	12 (44.4%)	41 (51.8%)	*0.81*
Osteoporosis, N (%)	6 (22.2%)	12 (14.2%)	
Fecal Elastase levels (μg/g) Median (IQR)	15 (7–22.5)	15.5 (13.5–33.7)	*0.89*
Fecal Fat (g/day) Median (IQR)	19.2 (11.8–24.5)	6.7 (3.9–16.2)	***0.01***

[a] Subclinical PEI = No steatorrhea in the presence of FE-1 levels <200 μg/g.

p = 0.04] but there were no differences in weight loss and vitamin D levels. (Supplementary Table 3).

There was no correlation between the stage of CP with PEI (Supplementary Tables 1 and 2). Fecal fat analysis could be done in 65 patients and revealed median levels of 4.9 g/day in early-stage CP, 11.4 g/day in definite CP and 17.2 g/day in advanced stage CP respectively ($p = 0.09$).

Of the 104 patients in whom a DEXA was done, 75 (72.1%) had osteopathy; 63 (84%) of them had markedly low FE-1 levels (<100 μg/g) while 12 patients (16%) had mild decline or normal FE-1 levels. Among patients with subclinical PEI, osteopathy was present in 53 (63%). There was also no difference in the osteopathy among subclinical PEI (63%) and clinical steatorrhea 18/30 (60%), (p = 0.9). Osteopathy was present in 3 patients with early CP, 29 patients with definite CP and 43 patients with advanced CP [p = 0.007].

3.2. Risk factors for osteopathy and PEI

Multivariable logistic regression for risk of osteopathy (Table 3) revealed that advanced stage of CP was the most significant risk factor for developing osteopathy [OR 7.58, 95% CI: 1.93–29.64] while weight loss, vitamin D or FE-1 levels did not increase the risk.

Multivariable logistic regression for risk factors of severe PEI did not reveal any significant risk factor (Supplementary Table 4).

3.3. Correlation of overt and subclinical PEI with stage of CP, diabetes, nutritional status and bone health

A total of 30 patients had clinical steatorrhea and 84 had subclinical PEI. There was no difference between the two groups with respect to the stage of CP. A higher proportion of patients with overt PEI had diabetes (n = 17/30 (56.7%)) as compared to subclinical PEI (n = 27/84 (32.2%)) (p = 0.03). Serum albumin was lower in patients with overt PEI as compared to those with subclinical PEI [4.4 ± 0.7 gm/dl vs 4.7 ± 0.7 gm/dl, p = 0.01]. There was no difference in levels of Vitamin A and vitamin D between these two groups. There was also no difference in the prevalence of osteopathy between these two groups.

4. Discussion

In the present cross-sectional study with prospective enrollment of patients, we found a very high prevalence of PEI in patients with CP including 70% subclinical PEI. The prevalence of severe PEI (<100 μg/gm stool) was 86.7% in CP. Osteopathy was present in 72.1% patients including 53 (62%) among patients with subclinical PEI. There was no difference in osteopathy between subclinical and severe PEI. Patients with severe PEI had lower vitamin A levels as compared to mild PEI and no PEI patients.

In a recent analysis, Valenciano et al. [24] used FE-1 <200 μg/day as the cut-off for diagnosing PEI, and recorded a prevalence of 64.1%

Table 3
Multivariable regression analysis for risk factors for osteopathy.

Variables	Odd's Ratio	95% Confidence Interval	P value
Stage of Disease (Advanced vs. Early and Definite)	7.58	1.93–29.64	0.04
Weight Loss (5% or more vs less than 5%)	2.18	0.61–7.78	0.23
Vitamin A (<0.78 ng/ml vs. ≥0.78 ng/ml)	1.38	0.13–6.77	0.79
Vitamin D (<10 ng/ml vs. ≥10 ng/ml)	0.99	0.79–1.23	0.92
FE-1 (>100 μg/g vs. ≥100 μg/g)	0.93	0.13–6.78	0.94

for exocrine insufficiency in their patients with CP. Their results may have been influenced by the lower prevalence of pancreatic calcifications (65.6%) and ductal dilation (62.5%), and the shorter duration of illness in their study (4.9 years vs. 6 years in the present study). In a retrospective study of 1869 patients with probable or definitive CP, PEI was present in 849 (45.4%) of patients [6]. However, FE-1 was available in 1083 of 1869 patients in that retrospective study and hence the study could have missed PEI in some patients. In a registry based study from the Netherlands [25], 30.8% of the 987 patients with CP had either clinical steatorrhea or were on pancreatic enzyme replacement therapy (PERT) and 45.7% of patients were categorized as patients with potential PEI for lack of data. The probability of exocrine insufficiency increases with the duration and severity of the disease. In a study, more than half of the patients with alcohol-associated CP had PEI after 10 years and almost all of them developed PEI at the end of 20 years [26]. In the present study, we did not find any correlation between PEI and the stage of CP.

In the present study, we have shown subclinical PEI in 70% which denotes a population of CP having PEI without overt clinical symptoms. This is the group which is often overlooked. Notably, significant proportion of patients in this group also had osteopathy. This highlights the importance of regular screening for PEI in patients with CP. As per a survey, regular screening for exocrine pancreatic insufficiency was performed only by 21% of pancreatologists [5]. The implications of our observations with regard to management are: i) a high PEI prevalence of 95% indicates that clinicians should look out for early/occult signs of pancreatic insufficiency; ii) patients with early CP may also have PEI and should be screened for the same; and iii) patients with CP should be routinely evaluated for osteopathy.

Osteopathy was found in the majority of our patients. There was no association between osteopathy and severity of PEI. The only independent significant risk factor for osteopathy was advanced stage CP. In a US multicentric PROCEED study [7], the prevalence of osteopathy was 56% and 17% had osteoporosis. There was no association between osteopathy and morphology of pancreas or exocrine insufficiency [7]. A recent meta-analysis [27] showed osteopenia in 41.2% and osteoporosis in 20.9% of 20,155 patients with CP across 21 studies. Another meta-analysis, showed a pooled prevalence of osteopathy to be 58% (95% CI: 49–67%) across 17 studies involving 1659 CP patients [8]. The systematic review showed that the risk factors for osteopenia were smoking, alcohol, older age, female sex, low body mass index, lower vitamins D and K [8]. In a study of 211 CP patients of whom 42% had osteopenia, no difference was noted in the fecal elastase levels between those with and those without osteopathy. The significant risk factor for osteoporosis in that study were female sex, age and higher BMI on a multivariable analysis [10]. The possible explanations for end stage CP being the only significant risk factor for osteopathy in the present study could be: i) PEI was highly prevalent across different stages of CP and is unlikely to be the only cause of osteopathy; ii) Patients with advanced CP have recurrent inflammation for a long duration which might have contributed to osteopathy; iii) Diabetes and suboptimal nutrition due to frequent painful episodes could have affected the bone health in them.

Osteopathy in patients with CP is now being recognized as ‘pancreatic osteodystrophy’, an entity comprising of osteopenia, osteoporosis and osteomalacia [28]. The higher prevalence of osteopathy in our study may, in part, have been influenced by hypovitaminosis D in our patient population [29]. In our study, 25% of the patients were found to be deficient in Vitamin D. Osteopathy in CP however, is a complex phenomenon involving an interplay between various factors other than fat malabsorption and consequent nutrient deficiencies. These factors include (but are not limited to) alcohol use and cigarette smoking, alteration of PTH-vitamin D axis, ongoing systemic inflammation, and limited physical activity [9,30–32].

There are certain limitations of our study: a) we could not do fecal fat estimation in all patients because many patients did not consent for that; b) our sample size of patients with early CP was small; and c) we did not study the mechanisms of the development of osteopathy in CP beyond pancreatic exocrine insufficiency and that should be the focus of future research. While fecal elastase test is the most appropriate initial test for evaluation of PEI, a level <100 μg/g of stool provides good evidence of PEI, while levels 100–200 are indeterminate [33]. It has been suggested that instead of T-scores, Z-scores score of −2.0 or lower should be used to diagnose osteopathy in patients younger than 50 years. However, we opted to use T-scores to ensure clinical practice consistency and comparability across literature as the use of T-scores is more widely recognized, especially with regards to actionable interventions including the initiation of osteoporosis drug therapy. Moreover, the use of T-scores provides a uniform assessment across the full spectrum of our study population. Other studies investigating osteopathy in CP such as Hart et al. [7] have also used T-scores to report osteopathy despite have a mean population age of less than 50 years.

In summary, subclinical PEI is common and present even in early stage of CP. With disease progression, there is a risk of osteopathy and deficiency of fat-soluble vitamins. The long-term functional consequences of sub-clinical PEI should be periodically assessed in patients with CP.

Guarantor of the article

Soumya Jagannath, M.D., Pramod Kumar Garg, M.D.

Authors contribution (As per ICJME criteria)

Mehul Gupta: 1. Criteria 1: Substantial Contribution to the conception of the study. 2. Criteria 2: Substantial Contribution to design of the work. 3. Criteria 3: Substantial Contribution to acquisition and analysis of data. 4. Criteria 4: Substantial Contribution to interpretation of data for work. 5. Criteria 5: Substantial Contribution to drafting the manuscript (and/or) revising it critically for important intellectual content. 6. Criteria 6: Read and Approved the final manuscript to be published. 7. Criteria 7: Agree to be held accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Shallu Midha: 1. Criteria 1: Substantial Contribution to the conception of the study. 2. Criteria 2: Substantial Contribution to design of the work. 3. Criteria 3: Substantial Contribution to acquisition and analysis of data. 4. Criteria 4: Substantial Contribution to interpretation of data for work. 5. Criteria 5: Substantial Contribution to drafting the manuscript (and/or) revising it critically for important intellectual content. 6. Criteria 6: Read and Approved the final manuscript to be published. 7. Criteria 7: Agree to be held accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Vikas Sachdeva: 3. Criteria 3: Substantial Contribution to acquisition and analysis of data. 4. Criteria 4: Substantial Contribution to interpretation of data for work. 5. Criteria 5: Substantial Contribution to drafting the manuscript (and/or) revising it critically for important intellectual content. 6. Criteria 6: Read and Approved the final manuscript to be published. 7. Criteria 7: Agree to be held accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Jairam Singh: 3.

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Conflicts of interest

None of the authors declare any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2024.12.017.

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