Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: Prevalence and diagnostic use

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ABSTRACT

Pancreatic exocrine insufficiency (PEI) frequently occurs secondary to exocrine pancreatic disease (e.g. chronic pancreatitis, cystic fibrosis, cancer) or pancreatic/gastrointestinal surgery, resulting in the mal-digestion of nutrients and consequently malnutrition. Pancreatic enzyme replacement therapy (PERT) is the cornerstone of PEI management. Despite its clinical relevance, the diagnosis of PEI in clinical practice is challenging, as the current gold standard test is cumbersome, and alternatives have limited availability or accuracy. There is a need for accurate and easily applicable diagnostic modalities. We review the prevalence of clinical symptoms and changes in anthropometric measurements and laboratory nutritional markers indicative of malnutrition in patients with PEI, and the relevance of these findings in diagnosing PEI and monitoring PERT efficacy. Based on limited available evidence, assessment of clinical symptoms, body weight, body mass index and other anthropometric parameters are not sensitive methods for PEI diagnosis, owing to high variability and multiple confounding factors, but appear useful in monitoring PERT efficacy. Limited evidence precludes strong recommendations but suggests that serum levels of vitamin E, magnesium, and plasma proteins, notably retinol binding protein, albumin, and prealbumin, may have diagnostic utility in PEI. Studies show that assessment of changes in these and other nutritional parameters is helpful in monitoring PERT efficacy. Further research is needed to confirm the diagnostic accuracy of these parameters for PEI. Until such data are available, a nutritional evaluation including circulating vitamin E, magnesium, retinol binding protein, albumin, and prealbumin may be used to evaluate the probability of PEI in clinical practice when reliable pancreatic function tests are not available. Copyright © 2015, IAP and EPC. Published by Elsevier India, a division of Reed Elsevier India Pvt. Ltd. All rights reserved.

Introduction

Pancreatic exocrine insufficiency (PEI) is defined as the alteration of pancreatic function leading to malabsorption. Primary PEI results from a reduction of exocrine secretion caused by disease of the exocrine pancreas (e.g. chronic pancreatitis [CP], cystic fibrosis [CF], acute necrotizing pancreatitis, cancer), the endocrine pancreas (e.g. diabetes mellitus) or surgical resection [1]. Secondary PEI may be caused by anatomical changes following other gastrointestinal surgery (e.g. partial/total gastrectomy, gastric bypass, duodenectomy), or other digestive tract disorders (e.g. celiac disease) [1]. The main clinical consequence of PEI is malnutrition, resulting from malabsorption and poor absorption of nutrients, which frequently develops in patients with PEI. Malnutrition-related complications include cardiovascular events, osteoporosis and low-trauma fractures, and infections [2–4]. Untreated PEI was shown to be associated with high mortality after pancreatic surgery and in patients with unresectable pancreatic cancer [5,6]. Finally, malnourished CP patients suffer more pain episodes and require more hospitalizations than those with normal nutritional status [7]. Oral pancreatic enzyme replacement therapy (PERT) is the treatment of choice for PEI, together with nutritional management and specific nutritional supplementation if required.
Despite the clinical relevance of PEI, its diagnosis in clinical practice is challenging. The gold standard is quantification of the coefficient of fat absorption (CFA) [8]; this requires patients to maintain a strict 5-day diet containing 100 g of fat/day and collection of all faeces produced over the last 3 days for faecal fat quantification. CFA values >92–93% are considered normal. However, this test is cumbersome, difficult for patients, unpleasant for laboratory technicians, and available in only very few centres worldwide, making it uneconomical in clinical practice. Furthermore, it is non-specific and the results are influenced by many different methodological issues. The $^{13}$C-labelled mixed triglyceride ($^{13}$C-MTG) breath test is an accurate, reliable, clinically acceptable alternative to CFA quantification, but is not yet approved and has limited availability at present [9]. The faecal elastase-1 (FE-1) test, which quantifies faecal concentration of pancreatic elastase-1, is a widely available, non-invasive method for quantifying pancreatic secretion, and has been used successfully for the diagnosis of moderate to severe CP and PEI in other pancreatic diseases [10–13]. However, its accuracy for PEI diagnosis using appropriate reference methods has been poorly investigated, with conflicting results reported [14–16], and the optimal cut-off value is unknown. Management guidelines suggest trialling PERT, with symptom improvement supporting a diagnosis of PEI [17]. This ‘PERT test’ is often used in clinical practice, although there is currently no direct evidence supporting its use in this way.

Consequently, there is a need for alternative diagnostic modalities for PEI that are accurate and easily applicable in clinical practice. As altered nutritional status is the main consequence of PEI, nutritional evaluation is proposed as an alternative to determine its presence in patients with PEI-associated diseases. Another potential use is to monitor global effects of nutritional support, i.e. PERT, dietary modifications and nutritional supplements. This narrative review examines the prevalence of clinical symptoms and anthropometric measurements for PEI, and evidence for the use of these markers in the diagnosis of PEI and the evaluation of PERT efficacy.

Methods

This paper represents a narrative review. Comprehensive literature searches were conducted in MEDLINE/PubMed prior to drafting using multiple relevant search terms to identify appropriate references (timeframe: past 10 years). Titles and abstracts were screened to identify relevant articles for full review. The bibliography was supplemented with relevant references known to the authors and by older, relevant studies identified during review of these articles. Other than relevance to the topic, no additional systematic process or selection criteria were applied to determine which papers were included.

Clinical symptoms and anthropometric measurements for diagnosis of PEI

Clinical symptoms

Although nutritional status in pancreatic disease is widely studied, most authors define study populations by disease pathology, and the incidence of PEI is not always reported. Consequently, the prevalence of clinical and anthropometric signs of malnutrition in PEI is difficult to determine. Furthermore, there is significant variation in the methods used to quantify clinical symptoms.

There is a lack of consensus in the literature regarding the incidence of diarrhoea in patients with pancreatic disease, with reported frequencies in CP of ~18% (approximately one-third on PERT) [18] and 74% (all on PERT) [19], and 20% in CF (no PERT) [20]. In clinical studies of patients with confirmed PEI, the frequency of clinically overt steatorrhoea varied substantially from 23% to 70% in CP [19,21–24], 46% in pancreatic cancer prior to surgery (33% after surgery) [25], and 15% in CF [20]. In a study of 60 patients with CP, patient-reported steatorrhoea was found to be insufficient as a screening test for PEI, as it was reported by only 18/47 (38%) patients with abnormal steatorrhoea values [26]. Indeed, evidence from small studies suggests very high fat losses in the absence of abdominal symptoms [27], and PEI/malnutrition in the absence of steatorrhoea [28] in some patients. As patient reports of steatorrhoea are subjective, the more objective markers of stool volume/weight and frequency may be better markers of PEI. However, in clinical studies, these parameters do not appear to correlate consistently with CFA values (Table 1).

In clinical studies of patients with confirmed PEI but not taking PERT, the frequency of flatulence (any severity) was also highly variable, ranging from 55% to 100% in those with CP or post-pancreatic surgery [29–31] and from 55% to 90% in CF [32,33], with bloating reported in 15% of patients with CF [20]. Clinical symptoms are likely to correlate poorly with PEI due to the subjective nature of patient reporting [19]. They are also similar to those of many other gastrointestinal (GI) disorders, and are affected by diet, mainly the content of fat and insoluble fibre. Low-

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Table 1: Coefficient of fat absorption compared with stool frequency and volume in patients with PEI (no PERT).

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment group, phase</th>
<th>N</th>
<th>CFA, % (mean ± SD)</th>
<th>Daily stool frequency (mean ± SD)</th>
<th>Stool weight, g (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP [49]</td>
<td>Placebo, run-in phase (Group 1)</td>
<td>12</td>
<td>49.9 ± 8.8*</td>
<td>10.8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Placebo, run-in phase (Group 2)</td>
<td>14</td>
<td>55.9 ± 3.6*</td>
<td>14.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Placebo, double-blind phase (Group 2)</td>
<td>14</td>
<td>68 ± 4.6*</td>
<td>14.6</td>
<td>-</td>
</tr>
<tr>
<td>CP [30]</td>
<td>No PERT, run-in phase (Group 1)</td>
<td>34</td>
<td>66.5 ± 14.1</td>
<td>2.9 ± 1.7</td>
<td>714 ± 284</td>
</tr>
<tr>
<td></td>
<td>No PERT, run-in phase (Group 2)</td>
<td>27</td>
<td>67.0 ± 14.0</td>
<td>2.6 ± 0.9</td>
<td>678 ± 200</td>
</tr>
<tr>
<td>Pancreatic resection [31]</td>
<td>No PERT, run-in phase (Group 1)</td>
<td>24</td>
<td>72.9 ± 11.5</td>
<td>2.5 ± 1.2</td>
<td>565 ± 212</td>
</tr>
<tr>
<td></td>
<td>No PERT, run-in phase (Group 2)</td>
<td>32</td>
<td>56.9 ± 17.6</td>
<td>2.5 ± 1.5</td>
<td>451 ± 210</td>
</tr>
<tr>
<td>CF [32]</td>
<td>Placebo, double-blind phase (Group 2)</td>
<td>26</td>
<td>49.3 ± 23.5</td>
<td>2.3 ± 1.7</td>
<td>487 ± 257</td>
</tr>
<tr>
<td>CF [33]</td>
<td>Placebo, double-blind phase (Group 1)</td>
<td>25</td>
<td>55.5 ± 18.3</td>
<td>2.8 ± 1.5</td>
<td>514 ± 268</td>
</tr>
<tr>
<td>CF [52]</td>
<td>Placebo, double-blind phase (adults)</td>
<td>18</td>
<td>50.9 ± 7.3*</td>
<td>14 per 72 h</td>
<td>-</td>
</tr>
<tr>
<td>CF [51]</td>
<td>Placebo, double-blind phase (paediatric/adolescents)</td>
<td>19</td>
<td>52.2 ± 5.61*</td>
<td>12 per 72 h</td>
<td>-</td>
</tr>
</tbody>
</table>

* Standard error of the mean.

CF: cystic fibrosis; CP: chronic pancreatitis; PERT: pancreatic enzyme replacement therapy.
fat diets can mask PEI by reducing steatorrhoea (but not malabsorption per se) and patients often limit their own fat intake to reduce symptoms, although it is now widely accepted that with adequate PERT, fat restriction is not necessary and contributes to malnutrition. The use of opiate-based pain relievers and other medications influencing bowel function, and the presence of functional bowel disorders, further complicates the situation. These confounding factors, along with wide inter-patient variability and lack of evidence for a clear correlation with degree of fat malabsorption suggest assessment of clinical symptoms has limited utility in diagnosing PEI. The diagnostic use of clinical symptoms has also proven unreliable in other fields, e.g. lactose malabsorption.

**Body weight and body mass index**

The use of body weight and anthropometric data to determine nutritional status is a topic of much debate, predominantly due to the lack of a true gold standard. Percentage weight loss within a 6-month period is considered by many to be the most clinically significant marker of malnutrition [35]. However, there is significant variation in definitions across studies in pancreatic disease (Table 2). Some authors included patients with >10% weight loss in a subgroup defined as ‘well nourished’ [18], whilst others used the same change (>10% loss of pre-illness weight) to define cachexia (wasting) [36]. Furthermore, weight loss does not take into account overall body composition and could be confounded by body fluid changes [37].

A single body mass index (BMI) measurement is of limited use, as no consideration is made of the patients’ pre-morbid state, and it does not account for decreased muscle mass [37]. Studies show a lack of correlation between BMI and broader nutrition assessment tools such as the subjective global assessment [38] and the malnutrition universal screening tool [35], and it is apparent that severely malnourished patients may still present with a BMI within or above the normal range [39]. Several clinical studies in PERT-naive patients with PEI found mean BMI values within the normal range [25,26,40], and in a study of 62 patients with CP (approximately one-third with PEI), ~50% of men were overweight or obese, although the mean BMI was significantly lower in male patients versus controls [41]. In contrast, one study found BMI to be significantly lower in CP patients on PERT with severe steatorrhoea and biochemical nutritional deficiencies versus those without deficiencies [28], and another found a positive correlation between BMI and FE-1 in a cohort study of 101 patients with alcoholic and tropical CP (p = 0.013) [42].

The lack of consistent evidence regarding body weight changes and BMI in relation to PEI suggests that these factors have limited utility in PEI diagnosis.

**Other anthropometric assessments**

There is an absence of interventional studies assessing anthropometric parameters as the primary endpoint. Furthermore, comparable data are scarce in patients with PEI, and difficult to extract for grip strength, triceps skin-fold thickness (TSF) and mid upper arm circumference (MUAC). As there are gender- and age-specific reference ranges, single point data or a range within a cohort is of limited use. There is also considerable inter- and intra-investigator variability with TSF and MUAC measurements. One group found no difference in MUAC but lower TSF in Indian patients with CP versus the general population [38], and a prospective, controlled cohort study of patients with CP (n = 62; approximately one-third with PEI) found significantly lower handgrip strength (men), fat stores (both sexes) and muscle stores (men) versus controls [41]. A study of children aged 8–11 years with PEI due to CF noted suboptimal upper arm fat area Z-scores [43].

Academic research is moving away from traditional anthropometry toward the use of imaging to assess body composition. The acknowledgement that sarcopenia (loss of muscle mass and strength) can occur in the presence of obesity will likely change the focus of many nutritional assessments [44,45]. Data from patients with PEI are currently limited, although one study in CF (97% of patients with PEI) assessing body composition by dual-energy X-ray absorptiometry highlighted a reduction in fat-free mass that did not always correlate with changes in BMI percentile [46]. One group studied changes in body composition using in vivo neutron capture, bioelectrical impedance, skin-fold thickness and circumference after pancreatectoduodenectomy and observed significant drops in all markers in the first 3 months [47]. However, these studies did not sub-group patients by PEI status; therefore the reductions in muscle and fat stores cannot be correlated with PEI.

**Clinical symptoms and anthropometry for monitoring treatment effect of PERT**

Assessment of changes in clinical symptoms appears to be a valid marker of PEI improvement in patients with PEI receiving PERT, based on significant improvements in intervention studies in measures such as stool characteristics, bloating, flatulence and abdominal symptom score [29–33,48–54]. However, a few patients have reported worsening of clinical symptoms, and a study investigating nutritional status in patients with PEI on PERT found that improvement in clinical symptoms did not always signify normal nutritional status [28]. Changes in body weight and BMI also appear to be valid markers of malabsorption improvement in patients receiving PERT, based on clinical study data (Table 3). Data on the use of other anthropometric measures to assess PERT efficacy are limited. One study noted that PERT use starting 1 month after pancreatectoduodenectomy resulted in a return to pre-operative levels in total body protein, potassium and arm muscle area, but not fat mass, at 6 months [47].

**Laboratory nutritional parameters for diagnosis of PEI**

Deficiencies of micro- and macro-nutrients are well-known consequences of malnutrition, and have been identified in
patients with PEI. The prevalence of laboratory nutritional marker abnormalities, including vitamins, minerals, trace elements and plasma proteins, has been investigated in several studies. A limited number have studied the association between nutritional deficiencies and PEI.

**Lipid soluble vitamins**

Lipid soluble vitamins are among the best studied nutritional markers in PEI, and deficiencies in patients with CP and steatorrhea were described several decades ago [55].

**Vitamin A**

Studies investigating the association between vitamin A and PEI are summarized in Table 4. Two CF studies indicated normal retinol levels in the vast majority of cases and that over-substitution of vitamin A to supra-normal, potentially harmful levels may be a more important clinical problem than deficiency [56,57]. Two limited CP studies indicated a high prevalence of vitamin A deficiency in patients with PEI [21,55]. However, the majority of studies in CP populations have concluded that vitamin A deficiency is not a clinically significant problem in PEI [41,58–60]. Recent studies found abnormally low serum levels in only 1/40 patients with CP and no association between low FE-1 and serum levels [58], and no relationship between FE-1 level and vitamin A deficiency [41].

**Vitamin D**

The reported prevalence of vitamin D deficiency in patients with CP is high in most studies, ranging from 33% to 87% regardless of PEI status or PERT use [41,55,58,59]. A trend towards a higher prevalence of deficiency in a study of 40 CP patients with PEI (53%) and notably those with PEI not receiving PERT (78%) was observed versus those without PEI (33%) [58]. Other studies have reported high prevalence of vitamin D insufficiency in CP, with no significant difference between those with and without PEI [41,55,61].

In CF, uptake of vitamin D2 from the intestine has been demonstrated to be impaired despite adequate PERT [62], which may explain why insufficiency is a common finding in CF despite concomitant PERT and/or vitamin D supplementation [63–67] or pancreatic sufficiency [68]. One study observed a higher prevalence of deficiency in PEI (28%) versus non-PEI (3%) patients [67], whereas others found no difference in vitamin D levels according to PEI status [69,70] and a retrospective chart review found that insufficiency/deficiency was equally high in cases with (41%) and without PEI (50%) [71].

A factor that must be considered in this discussion is the high prevalence of vitamin D deficiency in the general population. Two of the above-mentioned studies found no difference in prevalence in CP patients versus healthy controls (58% vs. 62% [41] and 87% vs. 87% [59]). These were studies conducted in Ireland [41] and Northern Germany [59], thus low exposure to sunlight may partially explain low vitamin D levels. Similarly, in a CF study in the United States, insufficiency was shown in 74% subjects in a healthy reference population (vs. 90% subjects with CF on PERT and vitamin D supplementation) [66].

Together, the evidence above suggests no utility for vitamin D deficiency in diagnosing PEI.

**Vitamin E**

Early studies indicated a high prevalence of vitamin E insufficiency, with 67%–83% of patients with PEI or steatorrhea presented with levels below the lower limit of normal [55,60]. Others have demonstrated significantly lower vitamin E levels in CP patients with steatorrhea versus those without [21,23,72]. The correlation between serum vitamin E and fecal fat excretion has been investigated in 2 studies, with 1 indicating no correlation [55] and the other finding a statistically significant correlation [60]. Another study showed no relationship between FE-1 level and vitamin E deficiency [41]. In recent studies, the reported prevalence of vitamin E insufficiency in CP patients has been considerably lower (2%–24%) [41,58,59]. Differences in reference values, patient selection, PERT and vitamin supplementation may have contributed to this discrepancy.

Studies in patients with CF and PEI also show variation in vitamin E levels. Some have reported significantly lower mean concentrations versus healthy controls [73] whereas others reported values within normal ranges in patients on PERT [74] and higher than normal values in 48% of patients on PERT and vitamin supplements [75].

**Vitamin K**

Serum vitamin K levels were investigated in small studies of patients with CP and PEI (no PERT), and deficiency observed in 13%–56% of cases [55,58,60]. However, clinically overt vitamin K deficiency is a rare presentation in patients with CP and PEI. One of these studies reported increased prothrombin time in 2 cases that was normalized by supplementation [55] but the others did not observe any major bleeding problems [58] or prolonged bleeding time [60]. One group found no significant difference in the prevalence of vitamin K deficiency between PEI and non-PEI patients with and without PERT [58].
Vitamin K levels have also been studied in patients with CF and PEI; 1 study reported levels within the normal range [74] but several have reported low vitamin K levels despite concomitant PERT in the majority of cases [67, 76–80] and vitamin K supplementation appears to have been only partially successful [67, 76, 79].

Other vitamins

Studies on serum levels of water-soluble vitamins in patients with PEI are scarce. Vitamin B₁₂ status was investigated in 2 studies, both concluding that deficiency is rare in CP patients with (0% and 6%) and without (0% and 0%) PEI, and there was no overall correlation between the degree of PEI and vitamin B₁₂ values [22, 81]. A low prevalence of folic acid insufficiency was also reported in both studies, and levels did not correlate with PEI [22, 81].

Plasma proteins

Total and individual plasma proteins are frequently used as markers for malnutrition in general. Abnormally low total plasma protein levels appear to be an infrequent marker for malnutrition in general. Abnormally low total plasma protein levels in patients with PEI were reported in 2 studies [77, 78].

Minerals and trace elements

Zinc

Results on zinc levels have been divergent in studies comparing patients with and without PEI. A correlation between PEI and serum zinc concentration was suggested by observations that low FE-1 was associated with low serum zinc concentration in CP [40] and low serum zinc after pancreatoduodenectomy [85], and that high faecal fat levels were associated with low serum zinc after pancreatoduodenectomy [85]. Such surgery would also directly affect absorption owing to removal of the duodenum, an intestinal}

<table>
<thead>
<tr>
<th>Population</th>
<th>Study design</th>
<th>Prevalence of deficiency</th>
<th>Comparison of PEI versus non-PEI patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF and PEI [56]</td>
<td>Prospective study of children and young adults (N = 78) 58% on Vitamin A supplements</td>
<td>Serum retinol concentration: 0% below LLN(^a) 42% within reference range(^a)</td>
<td>–</td>
</tr>
<tr>
<td>CF and PEI [57]</td>
<td>Cross-sectional study of children (N = 73); 90% receiving vitamin supplements</td>
<td>Serum retinol concentration: 1 patient &lt; 5th percentile(^a) 47% &gt; 95th percentile(^a)</td>
<td>–</td>
</tr>
<tr>
<td>CF [69]</td>
<td>Audit of newly diagnosed infants with CF (newborn screening), 71% with PEI</td>
<td>60%</td>
<td>Mean ± SD vitamin A, µmol/L With PEI: 0.58 ± 0.19 Without PEI: 0.75 ± 0.19 Difference –0.16 (95% CI –0.29, –0.04), p = 0.01</td>
</tr>
<tr>
<td>CF [67]</td>
<td>Retrospective analysis of children aged ≤ 18 years (N = 530), 87% with PEI</td>
<td>Low levels in 15% (80/526)(^b)</td>
<td>Proportion of patients deficient With PEI: 10% Without PEI: 0%</td>
</tr>
<tr>
<td>CP [41]</td>
<td>Prospective, controlled cohort study (N = 62)</td>
<td>14.5% deficient (&lt;1.6 µmol/L) 19% with excess (&gt;3.7 µmol/L)</td>
<td>No relationship between FE-1 levels and Vitamin A deficiency</td>
</tr>
<tr>
<td>CP and PEI [58]</td>
<td>Prospective study (N = 40)</td>
<td>0/12 without PEI 1/9 with PEI</td>
<td>Low FE-1 not associated with lower vitamin A serum levels</td>
</tr>
<tr>
<td>PEI due to pancreatic cancer or CF [59]</td>
<td>Prospective study, all receiving PERT (N = 140)</td>
<td>0% with PEI on PERT</td>
<td>–</td>
</tr>
<tr>
<td>CP [60]</td>
<td>Prospective, CP with steatorrhoea (no PERT) (N = 12)</td>
<td>CP: 38 ± 0.4 µg/dL Controls: 49 ± 10 µg/dL</td>
<td>–</td>
</tr>
<tr>
<td>CP [55]</td>
<td>Case series, PEI and steatorrhoea receiving PERT (N = 15)</td>
<td>≤ 50% CP patients had low serum levels 7/15 below LLN 3/15 deficient</td>
<td>No statistical correlation between serum levels and faecal fat excretion</td>
</tr>
<tr>
<td>CP [21]</td>
<td>Prospective, patients with (n = 13) and without steatorrhoea (n = 18)</td>
<td>38% of patients with steatorrhoea 0% of patients without steatorrhoea</td>
<td>–</td>
</tr>
</tbody>
</table>

LLN: lower limit of normal.
\(^a\) Of the National Health and Nutrition Examination Survey.
\(^b\) Reference range 0.8–2.5 mmol/L.
absorption site for zinc [86]. However, other studies report no difference in serum zinc levels when comparing healthy controls and patients with CP [72] or CF [87,88], and no difference in serum zinc was found when comparing CP patients with [72] and without PEI (PERT-naïve) [81], and CF patients with and without PEI [88]. One study reported significantly higher serum zinc concentration and urinary excretion in patients with CP and advanced PEI versus those without evidence of PEI [89].

Zinc absorption was demonstrated to be lower in 8 patients with CP and PEI versus healthy controls [90]. Decreased secretion of binding proteins that are important for zinc absorption in the pancreatic juice may explain compromised absorption of zinc in patients with PEI [91]. It can be speculated that decreased zinc absorption in PEI can be compensated by homeostatic regulatory mechanisms in the majority of cases. Furthermore, zinc can be easily substituted to normal or even supra-normal levels; a study of patients with CF on PERT and zinc supplements found levels within or above the normal range in all patients [43].

**Magnesium**

In patients with idiopathic steatorrhoea, serum magnesium was negatively correlated with degree of steatorrhoea and could be improved with a low-fat diet [92]. This may be due to the formation of insoluble complexes between magnesium and fatty acids, and suggested that serum magnesium may be a pseudo-marker for steatorrhoea [81,93]. Less than 1% of the total body magnesium is found in the blood, and serum magnesium may therefore be a poor marker for the total body reserve. In a study investigating the prevalence of magnesium deficiency using an intravenous magnesium loading test, 10/13 patients with CP (majority with PEI) demonstrated signs of magnesium deficiency but only 1 had clear hypomagnesaemia [24]. In a CF study, serum magnesium levels were found to be within normal ranges, although most patients were receiving PERT and the recommended dietary allowance of Mg from diet and supplements [65].

Only 1 study has investigated the correlation between serum magnesium and PEI in patients with CP [81], and demonstrated a linear correlation between serum magnesium concentration and degree of fat malabsorption. Serum magnesium was significantly lower in PERT-naïve CP patients with PEI versus those without PEI (mean ± SD 1.87 ± 0.19 mg/dL vs. 2.09 ± 0.18 mg/dL, respectively; p < 0.001). Furthermore, magnesium <2.05 mg/dL detected PEI with a sensitivity of 0.88 (95% CI 0.66–0.97) and a specificity of 0.66 (0.48–0.80). Adjusting for alcohol consumption, a potential confounder given the previously known association between low serum magnesium and alcoholism [93], did not influence the association between PEI and serum magnesium in this study [81].

**Calcium**

Studies on the association between serum calcium levels and PEI are scarce. Small studies comparing patients with CP (PEI status not specified) and controls showed no difference [94] and significantly lower levels of calcium uncorrected for albumin (majority with PEI) [24]. Patients with CP and PEI on PERT included in a randomized clinical trial showed calcium levels within the normal range at baseline [48]. A study of patients with CF (78% on PERT) indicated calcium levels within the normal range [65]. Only one study has compared calcium levels according to PEI status, and observed no difference in levels between CP patients with and without PEI [61].

**Iron**

Studies have explored the association between PEI and serum markers such as iron, transferrin and ferritin. Two studies could not find evidence for a higher prevalence of iron deficiency in CP patients with PEI versus those without [28,81], and in a clinical trial assessing PERT in patients with PEI due to CP (who had received previous PERT), mean transferrin levels were within the normal range at baseline [82]. A small study of patients with CF found 74% of subjects with iron deficiency; however, the degree of deficiency was associated with the severity of suppurative lung manifestations and unrelated to PERT use [95].

**Selenium**

One study reported significantly lower selenium levels in 35 CP patients (40% with confirmed PEI) versus 14 healthy controls, but no difference between CP patients with and without steatorrhoea [72]. In another study, significantly lower levels of selenium versus healthy controls were found in patients with CP and PEI but there was no difference between CP patients without PEI and healthy controls [96].

**Lipids**

An older study demonstrated lower total blood lipid levels in CP patients with steatorrhoea compared to those without [23]. In a more recent study of PERT-naïve patients with CP, mean triglyceride levels were unexpectedly significantly higher in patients with PEI versus those without; there was also a non-significant tendency towards lower total cholesterol in PEI patients [81]. In patients with CP, PEI and ongoing PERT included in randomized clinical trials, mean total cholesterol, HDL, LDL and triglyceride levels were reported to be within normal ranges [48,82]. In a study of CF patients (majority on PERT), mean total cholesterol and triglyceride concentrations were within the normal range [65].

**Nutritional parameters for monitoring treatment effect of PERT**

One research group explored the concept of using nutritional markers in the monitoring of PERT in a study of 30 patients with newly diagnosed steatorrhoea due to alcohol-related CP [9]. PERT doses were titrated with the aim of preventing diarrhoea and weight loss. After 1 year of treatment, nutritional evaluation demonstrated that two-thirds of patients still had abnormally low RBP and an abnormal 13C-MTG breath test on current PERT dose. Optimization of PERT resulted in normalization of breath test results in parallel with significant improvement in nutritional parameters (prealbumin, RBP) and body weight, providing proof of concept that nutritional parameters can be used as markers for the effect of PERT in PEI.

The concept of using nutritional parameters to monitor treatment effect in PEI has been adopted in recent clinical trials. In open-label clinical intervention studies in patients with PEI due to CP or pancreatic surgery, significant improvements in total cholesterol, HDL, LDL, RBP, transferrin and vitamin E were observed, over a 1-year treatment period [82] and small but non-clinically meaningful increases in mean levels of RBP, albumin and prealbumin were observed in a similar study after 6 months of PERT [48]. Changes in other nutritional parameters such as triglycerides were not seen. In clinical intervention studies in patients with CF and PEI, I showed improvements in total serum cholesterol, HDL and serum vitamins A and E after ~30–44 days on PERT [51], whereas another found no clinically significant changes in albumin, prealbumin, fasting triglycerides, cholesterol or fat-soluble vitamins over 1 year of PERT [74]. However, it has to be taken into account that the patients participating in these trials were not required to be PERT-naïve and had received PERT prior to study entry. It is highly likely that PERT treatment was more intensive during the study period, which may
explain why some nutritional parameters improved despite prior PERT use in some patients.

The limited evidence suggests that laboratory nutritional parameters such as RBP, and possibly albumin and prealbumin, may be suitable markers for monitoring efficacy of PERT in patients with PEI, although baseline nutritional status and prior PERT use should be taken into account.

Conclusions

PEI is frequent secondary to pancreatic diseases such as CP, CF, and pancreatic cancer, pancreatic resection, and some extra-pancreatic conditions such as GI surgery [1]. Diagnosis of PEI is, however, challenging. Tests directly evaluating maldigestion are cumbersome and non-specific (e.g. CFA) or have limited availability (e.g. 13C-MTG breath test) [9,28]. The FE-1 test is widely used, but the optimal cut-off point for PEI is unknown and its diagnostic accuracy is rather low [14–16].

Based on the limited available evidence, assessment of symptoms, body weight, BMI and other anthropometric parameters are non-sensitive for PEI diagnosis, as summarized in Table 5. Nutritional deficiency is the most relevant consequence of PEI and normalization of nutritional status is the main goal of PERT. Thus, use of a detailed nutritional evaluation for the diagnosis of PEI and for monitoring PERT efficacy is an attractive approach in clinical practice. However, evidence supporting the use of nutritional parameters for these purposes is currently very sparse, and limited by the lack of consideration of PEI status or the use of suboptimal diagnostic tests (e.g. FE-1, presence of steatorrhoea). Despite these limitations, the presence of nutritional deficiencies can be used to estimate the probability of PEI in patients with an associated disease or condition in a clinical situation when reliable tests of pancreatic function are not available, and if other potential causes of malnutrition (e.g. dietary limitations) can be excluded [81].

Among the vitamins assessed, vitamin E appears the best marker of PEI, since several studies have indicated an association between levels and PEI [21,23,60,72,73]. Despite most patients with CP and PEI having vitamin D deficiency [41,55,58,59], it is not a useful marker of PEI due to the high prevalence of this deficiency in the general population, at least in northern countries [41,59]. Nevertheless, it appears to be an important clinical problem in patients with CP given the high frequency of bone metabolism disorders [4]. The clinical relevance of deficiencies in other fat-soluble vitamins and water-soluble vitamins, and their utility in diagnosing PEI, is less evident. It should also be taken into account that serum levels of lipid soluble vitamins are poor markers of total body stores. Plasma proteins may also be useful for the diagnosis of PEI, with evidence suggesting that lower RBP is a marker for PEI, at least in patients with CP [21,81]. Based on the findings of one study, low serum magnesium also appears to be an accurate marker to predict PEI [81]. In that study, which assessed nutritional markers in patients with CP, serum magnesium <2.05 mg/dL had the highest odds ratio for PEI of all the markers tested, with haemoglobin, albumin, prealbumin, and RBP levels below the lower limit of normal, and HbA1C above the upper limit of normal also showing an association with PEI [81]. Based on their findings, the authors suggested that a normal nutritional status (magnesium >2.05 mg/dL, normal haemoglobin, albumin, prealbumin, RBP and HbA1C) may exclude PEI in these patients [81].

Although no strong recommendations can be made based on the limited available evidence, nutritional evaluation may help in some cases. Given that only a small proportion of patients with PEI may have a deficiency in a particular parameter, any nutritional evaluation for PEI should comprise multiple nutritional markers, and include at least circulating levels of fat soluble vitamins (preferably vitamin E), prealbumin, RBP, zinc and magnesium [81]. However, further evidence is required to determine the optimal panel of markers for nutritional evaluation, and the utility, reliability and accuracy of these nutritional parameters in diagnosing PEI. Additional blood parameters as well as anthropometric measurements are usually required for complete nutritional evaluation but are of limited value for PEI diagnosis. It is important to point out that all nutritional deficiencies discussed in this review are unspecific for PEI, and other causes (i.e. chronic liver disease, inflammation, poor nutritional intake) have to be considered in the individual patient. Albeit not evidence-based, PERT is sometimes administered during a test period in patients with a clinical suspicion of PEI in order to confirm or reject the diagnosis. If this “PERT test” is applied, it is important that PERT is administered at an adequate dose (e.g. a minimum of 50,000 lipase units with meals, 25,000 units with snacks), and we suggest that evaluation of nutritional markers before and after initiation of therapy is included as an additional parameter to evaluate treatment effect. However, this recommendation is not based on direct evidence and warrants further investigation/validation. A large, prospective, ideally multicentre study is needed, with proper classification of patients by disease (e.g. CP) and an appropriate reference test for PEI (e.g. CFA or 13C-MTG breath test), to evaluate the diagnostic sensitivity and specificity of different nutritional and anthropometric parameters for PEI and their utility in monitoring PERT efficacy. Until such data are available and based on the limited reported evidence, we suggest that evaluation of nutritional

Table 5 Evidence and limitations for clinical symptoms, body weight and anthropometry in diagnosing and monitoring PEI.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prevalence</th>
<th>Limitations</th>
<th>Diagnostic utility</th>
<th>Utility in monitoring response to PERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms</td>
<td>Highly variable</td>
<td>Inconsistent reporting methods, subjective nature, impact of concomitant medications, diet, presence of functional GI disorders</td>
<td>Low — insufficient evidence to make a recommendation</td>
<td>Level 1 evidence for improvement in symptoms in patients treated with PERT (Grade Ib)</td>
</tr>
<tr>
<td>Weight loss or BMI</td>
<td>Variable</td>
<td>Variation in definition of weight loss, do not encompass body composition, single measurement of limited use, may be normal even in malnourished patients, other factors inhibiting oral intake (e.g. pain, gastric outflow obstruction, anorexia)</td>
<td>High level of suspicion of PEI in the presence of pancreatic pathology and theoretically adequate oral intake (Grade IV)</td>
<td>Level 1 evidence for weight gain and BMI increase in patients treated with PERT (Grade Ib)</td>
</tr>
<tr>
<td>Anthropometry</td>
<td>Not quantifiable (data lacking)</td>
<td>Inter- and intra-investigator variability, differences by gender and age, other factors inhibiting oral intake (such as pain, gastric outflow obstruction or anorexia)</td>
<td>High level of suspicion of PEI in the presence of pancreatic pathology and theoretically adequate oral intake (Grade IV)</td>
<td>Level 3 evidence for improvement in body composition markers in patients treated with PERT (Grade III)</td>
</tr>
</tbody>
</table>
markers can be used to estimate the probability of PEI, and to monitor the efficacy of PERT, in clinical situations where reliable pancreatic function tests are not practical or available.

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