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Utility of Fecal Elastase-1 to diagnose severe exocrine insufficiency in chronic pancreatitis: Real world experience

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ABSTRACT

Introduction: Quantitative fecal fat estimation is the gold standard test to diagnose steatorrhea (fecal fat >7 g/day) in chronic pancreatitis (CP), but cumbersome and inconvenient. So, fecal elastase-1 (FE) is proposed as a good alternative but the data on the diagnostic utility of FE to diagnose steatorrhea is variable.

Methods: This retrospective study included adult CP patients evaluated with both 24-h fecal-fat and FE tests within a 3-month period. The objective was to evaluate the diagnostic performance of FE to diagnose steatorrhea and to evaluate the FE progression over 9-month period.

Results: Among the 147 included patients, the frequency of steatorrhea (fecal fat >7 g/day) was 34%. The sensitivity, specificity, and negative likelihood ratio (LR) of FE was 90%, 28.9% and 0.35 at cut-off of <100 μg/g stool to diagnose steatorrhea; and 96%, 11.3% and 0.35 at cut-off of <200 μg/g stool, respectively. The optimal cut-off of FE was <20 on receiver operating characteristic curve (sensitivity 66%; specificity 69%; positive LR 2.14). There was no statistically significant variation in FE levels over 9 months interval among a hundred patients.

Conclusion: Compared to FE ≥ 200 μg/g stool, FE ≥ 100 can used to exclude steatorrhea (better specificity and negative LR). FE < 20 alone cannot replace fecal fat estimation to confirm steatorrhea but to be interpreted with clinical features. Repeat FE testing for exocrine insufficiency progression can be done at least a year later.

1. Introduction

Pancreatic exocrine insufficiency (PEI) can occur due to chronic pancreatitis (CP), cystic fibrosis, pancreatic surgery, pancreatic necrosis after acute pancreatitis, pancreatic duct obstruction etc. Chronic pancreatitis remains a common cause of PEI. PEI in CP is associated with weight loss, malnutrition, and poor quality of life [1]. In CP, PEI is said to be mild if one or more enzymes output has been reduced with normal bicarbonate concentration, moderate when both bicarbonate concentration and enzyme output reduced and severe if reduction in bicarbonate and enzyme output results in steatorrhea [2]. The role of pancreatic enzymes replacement therapy (PERT) in cases with steatorrhea is well established and in mild to moderate PEI (fecal fat estimation <7 g/day), the indication for PERT is unclear [3].

The gold standard test for evaluating pancreatic exocrine function is direct secretin-stimulated pancreatic function test, which has limited utility due to its invasiveness, patient discomfort and limited availability. Among the noninvasive indirect pancreatic function tests for PEI, 72-h fecal fat estimation is the gold standard and 24-h fecal fat estimation is an alternative standard test employed for the diagnosis of steatorrhea [4]. It detects severe PEI and has limited diagnostic value in mild to moderate PEI. It is a test for assessing overall fat absorption and cannot differentiate between the various causes of steatorrhea. 72-hour or 24-h fecal fat estimation is time consuming, affected by PERT, inconvenient to the laboratory personnel and to the patients in terms of stool collection and high fat intake before testing.

Another noninvasive indirect pancreatic function test of widespread use is fecal pancreatic elastase-1 (FE). This enzyme passes

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through gut with little degradation and stable at room temperature for up-to one week. The advantages with FE are requirement of single random stool sample, cost-effective and unaffected by oral pancreatic enzyme supplementation as the test detects only the human form of FE [1,2]. In view of the disadvantages with fecal fat estimation and the ease of FE testing, guidelines recommend FE for evaluating PEI [5].Very few studies had compared FE with the 72-h or 24-h fecal fat estimation in chronic pancreatitis (Supplementary Table 1) [6,27–29]. In CP, the pooled sensitivity and specificity of FE compared to secretin stimulation test are 73% (56–85%) and 89% (79–95%), respectively with lower sensitivities for mild and moderate PEI [4,6,7]. In a recent systematic review, the pooled sensitivity and specificity of FE were 96% (79–99%) and 88% (59–97%), respectively compared to quantitative fecal fat estimation. This systemic review included 345 patients with PEI, of which majority were cystic fibrosis and post pancreatic surgery patients while the number of CP cases were 80 only [4].And FE was not found to useful in post pancreatic resection cases to identify steatorrhea. Hence this systematic review results can differ in a cohort with non-operated CP patients alone [8]. (Supplementary Table 1)

PEI usually progresses slowly over the years and the prevalence of severe exocrine insufficiency (steatorrhea) steadily increases from 13 to 20% after 5years of diagnosis of CP to 25–40% after 10 years of CP [9,10]. However the method and frequency of monitoring the progression of PEI to diagnose severe PEI (steatorrhea) is not clear. Although United European Gastroenterology guideline recommend annual testing for PEI progression, there is very limited data to support the recommendation [5].

Hence, this retrospective study was performed to evaluate the diagnostic performance of FE compared to 24-h fecal fat estimation to diagnose steatorrhea in chronic pancreatitis and to assess the progression of exocrine function over 9-month period by evaluating the change in FE levels.

2. Methodology

This was a retrospective study conducted in the department of gastroenterology at a tertiary care academic institute of North India. We reviewed all the adult patients (≥18 years) diagnosed with chronic pancreatitis from January 2013 to January 2020, whose both 24-h fecal fat estimation and pancreatic fecal elastase-1 (FE) estimation were done within a time frame of 3 months and were included. During this study period, fecal elastase levels were done every 3 months in 100 patients enrolled in an RCT, which showed that antioxidants had no effect on fecal elastase levels in CP [11]. Among these 100 patients, pancreatic enzymes were initiated if fecal fat >7 g/day (FE levels are not affected by pancreatic enzyme supplementation). The following patients were excluded from the study: exocrine evaluation done while on pancreatic enzyme therapy, age <18 years, pregnancy, history of prior pancreatic or other gastrointestinal surgery, other associated co-morbidities like malignancy, chronic infections like HIV or TB, and those have incomplete information for inclusion. The study protocol was in accordance with the 1964 Helsinki declaration and its later amendments.

Chronic pancreatitis was diagnosed based on appropriate clinical presentation including typical pancreatic pain, diabetes, or clinical steatorrhea along with radiological imaging features like pancreatic atrophy, ductal stricture, parenchymal or ductal calcifications and/or ductal dilatation etc. [9] Alcoholic CP was diagnosed if a patient was consuming ≥60 g alcohol per day for at least 2 years [12]. A diagnosis of idiopathic CP was made when no identifiable cause could be assigned as etiology despite detailed etiological workup including serum calcium, parathyroid hormone levels, serum triglyceride levels and imaging as appropriate. Clinical steatorrhea was said to be present if patient gave history of oily or greasy stools. Steatorrhea was diagnosed if 24-h fecal fat measured by Van de Kamer method was >7 g and diabetes as per standard definition [9]. A commercially available enzyme-linked immunosorbent assay (ELISA) was used for the measurement of FE-1 (based on monoclonal antibody; ScheBo Biotech AG) on well-formed stool according to the manufacturer's instructions. The lower detection limit of FE was 15 μg/g stool. In this study, all FE values ≤ 15 was taken as 15 for data analysis.

Patients were managed for abdominal pain, diabetes, and steatorrhea as per the standard management discussed elsewhere. Patients with pain not responding to medical management and with ductal calculi with favorable anatomy for endoscopic management were managed with endoscopic retrograde cholangiopancreatography (ERCP) and main pancreatic duct (MPD) drainage with or without extracorporeal shock-wave lithotripsy (ESWL). Complications of chronic pancreatitis like pseudocyst or pseudoaneurysms or biliary strictures were managed through a multidisciplinary approach involving gastroenterology, surgery, and radiology teams [13].

3. Objectives

1. To evaluate the diagnostic performance of fecal elastase compared to 24-h fecal fat estimation to diagnose steatorrhea (fecal fat >7 g/day) in chronic pancreatitis
2. To evaluate the test-retest reliability of fecal elastase test by repeat testing of FE levels in same individual at 3 months
3. To assess the progression of exocrine function over a 9-month period by fecal elastase testing

4. Statistical analysis

Baseline data of included patients was expressed as number (percentage) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables with normal or skewed distribution, respectively. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios were estimated for fecal elasase-1 test at various cut-offs to diagnose steatorrhea. Correlation between fecal elastase levels and 24-h fecal fat was studied using estimation of Pearson's product-moment correlation coefficient (r), with r^2 to represent the amount of variance explained. Significant correlations between the two were represented using scatterplots with regression line. The diagnostic performance of fecal elastase in comparison to 24-h fecal fat as gold standard was represented using receiver-operator characteristics (ROC) curve, and performance characteristics at different cut-off points for fecal elastase were calculated. Test-retest reliability of FE test was checked by evaluating the correlation between FE levels done at baseline and repeated at 3 months interval. Linear Mixed Effects Models were constructed using presence of elevated fecal fat and time as fixed effects and patient ID as random effect for assessment of change in fecal elastase levels across different strata of fecal fat (with steatorrhea and no steatorrhea groups). Results were represented using profile plots. The data was entered using Microsoft Excel 2011 and was analysed using R studio. In addition to the base packages in R, tidyverse, plot ROC, Optimal Cut points, lme4 and readxl packages were used.

5. Results

Baseline data: A total of 790 patients record of CP were screened for inclusion. Among these, two hundred and fifty-two patients of CP had both 24-h fecal fat estimation and fecal

elastase estimation within a timeframe of 3 months and others were could not undergo these tests within 3 months period due to logistics and personal reasons. Of these, 105 patients were on PERT during quantitative fecal fat testing, and these were excluded. Rest of 147 patients who were not on PERT while testing for exocrine insufficiency were included. The mean age of the study population was 32.5 ± 10.8 years, and the etiologies of CP were idiopathic (76.2%) and alcohol (23.8%). The median duration of illness as 3 years (IQR:1.25–5) and the prevalence of diabetes and steatorrhea (24-h fecal fat >7 g) were 36.7% and 34%, respectively. Although 34% had steatorrhea on testing, only 8.2% had history of oily or greasy stools. The percentage of patients with normal fecal elastase levels (≥200 μg/g stool) was 8.8.% (Table 1).

Diagnostic performance of FE: Fecal elastase levels correlated well with 24-h fecal fat estimation (Spearman's rho −0.38, $p < 0.001$) (Fig. 1). The optimal cut-off for the diagnosis of steatorrhea by ROC for FE was <20 μg/g stool, and the area under the curve was 0.70 (0.61–0.80) (Fig. 2). To detect steatorrhea, FE < 20 μg/g stool showed sensitivity of 66%, specificity of 69%, positive predictive value (PPV) of 52.4%, negative predictive value (NPV) of 80%, positive likelihood ratio of 2.14 and negative likelihood ratio of 0.49. The sensitivity, specificity, positive and negative predictive value of FE was 90%, 28.9%, 39.5% and 84.8% at cut-off of <100 μg/g stool and 96%, 11.3%, 35.8% and 84.6% at cut-off of <200 μg/g stool, respectively (Table 2).

Test-retest reliability of FE test: One hundred patients underwent FE testing every 3 months over a period of 9 months. Among these patients, the correlation between the FE levels done at baseline and at 3 months was 0.83. The median change in FE levels over 3 months was 0 μg/g (−5.99 to 5.87) in patients with steatorrhea and 1.5 μg/g (−19 to 30) in patients without steatorrhea.

Progression of exocrine insufficiency over 9-month period: There was no statistically significant difference in FE levels over 9 months interval among both the groups of patients with steatorrhea ($p = 0.57$) and without steatorrhea ($p = 0.83$) (Fig. 3).

Table 1
Baseline demographic variables of the study cohort in patients with chronic pancreatitis (N = 147).

Variables	N = 147
Males	108 (73.5%)
Age (years)	32.5 ± 10.8
Etiology	
Idiopathic	112 (76.2%)
Alcoholic	35 (23.8%)
Active alcohol consumption	6 (4.1%)
History of smoking	21 (14.3%)
Median duration of disease (years)	3 (1–5)
Pancreatic pain	122 (83%)
Diabetes mellitus	54 (36.7%)
History of greasy/oily stool	12 (8.2%)
Steatorrhea (24-h fecal fat >7 g/day)	50 (34.0%)
Fecal elstase-1 estimation (μg/g stool)	
<20	63 (42.9%)
20–99	51 (34.7%)
100-199	20 (13.6%)
≥200	13 (8.8%)
BMI (kg/m^2)	20.2 ± 4.1
Imaging features	
Pancreatic calcifications	126 (85.7%)
Main pancreatic duct dilatation	128 (87.1%)
Active proton pump inhibitor use	49 (33.3%)

Abbreviation- BMI: Body mass index.

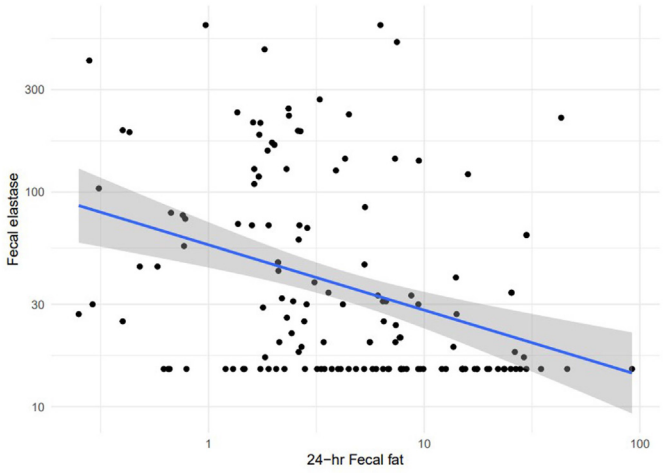

Fig. 1. Correlation between 24-h fecal fat and fecal elastase1 levels in chronic pancreatitis patients ($p < 0.001$).

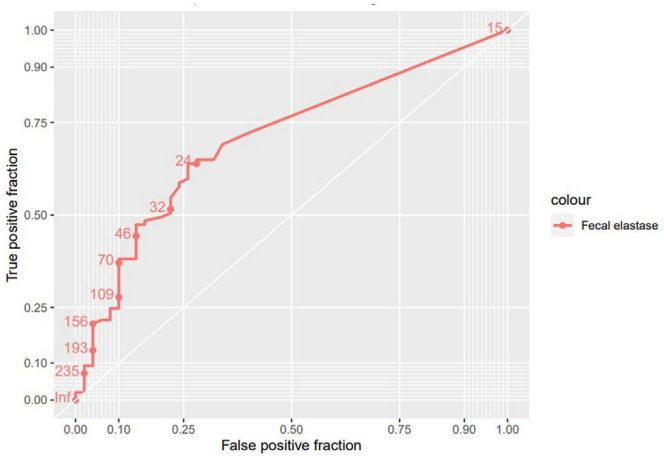

Fig. 2. Area under receiver operating characteristic (ROC) curve for fecal elastase-1 test to diagnose steatorrhea (Fecal fat > 7 g/day) in chronic pancreatitis.

6. Discussion

This retrospective study in patients with chronic pancreatitis showed that the commonly used FE cut-off of 200 μg/g stool has excellent sensitivity to diagnose steatorrhea but poor specificity. Using the ROC curve, the optimal cut-off of FE was <20 μg/g stool for the diagnosis of steatorrhea but the FE < 20 has specificity of 69% and positive likelihood ratio of 2.14. The correlation between two FE tests repeated in same individual over short period of 3 months is 0.83. There was no statistically significant progression of exocrine function (by FE levels) over 9 months interval.

7. Diagnostic performance of FE

Compared to FE < 200, FE < 100 μg/g stool has similar negative predictive value of 85% and sensitivity of 90% to diagnose steatorrhea with comparatively better specificity and negative likelihood ratio (0.35). Although a systematic review showed the pooled sensitivity and specificity of FE to diagnose steatorrhea as 96% (79–99%) and 88% (59–97) respectively, it included only 80 cases of

Table 2
Diagnostic performance of fecal elastase-1 measurement compared to 24-h fecal fat estimation in chronic pancreatitis at various fecal elastase-1 cut-off levels (N = 147).

Fecal elastase-1 Cut-off value (μg/g stool)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
<20	66.0% (51.2%–78.8%)	69.1% (58.9%–78.1%)	52.4% (43.5%–61.1%)	79.8% (72.4%–85.6%)	2.14 (1.49–3.06)	0.49 (0.33–0.74)
<100	90.0% (78.2%–96.7%)	28.9% (20.1%–38.9%)	39.47% (35.8%–43.28%)	84.8% (69.7%–93.2%)	1.27 (1.08–1.48)	0.35 (0.14–0.84)
<200	96.0% (86.3%–99.5%)	11.3% (5.8%–19.4%)	35.8% (33.8%–37.9%)	84.6% (55.9%–96.0%)	1.08 (0.99–1.19)	0.35 (0.08–1.54)

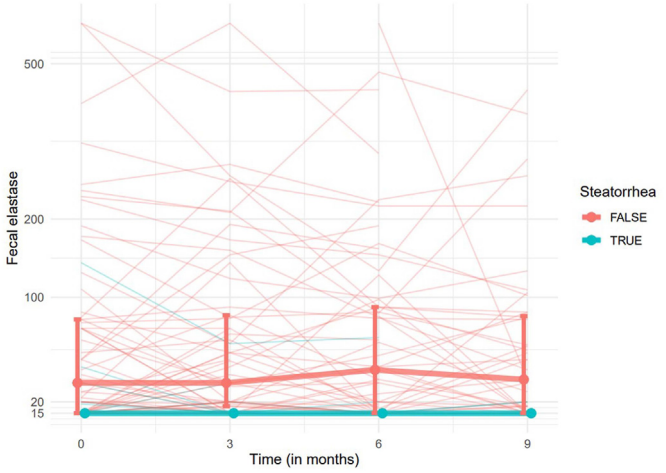

Fig. 3. Follow up of fecal elastase (FE) levels in 100 patients (assessed every 3 months) with steatorrhea (True, represented by turquoise color, n = 25) and without steatorrhea (False, represented by red/teal color lines, n = 75) over 9 months interval. Each line represents progression of FE over the time.

CP out of 345 total patients and majority of patients were of cystic fibrosis and post-surgical cases [4]. Previous studies in CP patients alone (Supplementary Table 1) showed that FE < 200 cut-off had good sensitivity but varied specificity ranging from 10 to 83% [6,27–29]. So, we propose FE ≥ 100 μg/g stool for excluding steatorrhea (severe exocrine insufficiency). The optimal cut-off for the diagnosis of steatorrhea by ROC for FE was <20 μg/g stool and this cut-off showed specificity of 69%, positive likelihood ratio of 2.14 and positive predictive value of 52.4% only. Hence, FE testing alone cannot replace fecal fat estimation to confirm steatorrhea and must be interpreted along with clinical features.

Test-retest reliability of FE test: One of the important characteristics of a good diagnostic test is its test-retest reliability over repeated measurement. Loser et al. and Gullo et al. evaluated daily variation in FE in very small number of CP patients (<10 patients in each study) and observed that FE values showed low day to day variation of 10–15% [14,15]. As the pancreatic exocrine insufficiency does not progress over a short 3-month interval, FE values repeated at 3 months should not change from baseline [16]. Our study with a larger sample compared to previous studies showed little variation confirming the test-retest reliability of FE test. Hence a single analysis of stool for FE would be sufficient and may be repeated only in cases with borderline FE values with high clinical suspicion of steatorrhea.

Progression of exocrine insufficiency and frequency of FE testing: We assessed the exocrine insufficiency progression by testing FE levels and observed that FE levels were static among the patients with steatorrhea and without steatorrhea over 9 months (Fig. 3). Similarly, Naruse et al. noted that FE levels don't change significantly over a year [16]. So, a repeat FE need not be performed in less than a year in patients with CP for monitoring exocrine function. This provides evidence to the annual FE testing recommendation of the United European Gastroenterology guidelines for the evaluation of exocrine insufficiency progression in CP [5].

An algorithm to diagnosis steatorrhea in CP in real world setting: In view of practical difficulties with 72 h or 24-h fecal fat estimation, it will be useful and convenient if we can utilize FE-1 along with additional clinical features to diagnose steatorrhea in CP. Earlier few algorithms had been proposed to diagnose steatorrhea/severe exocrine insufficiency with minimal use of fecal fat testing [17,18].We also propose an algorithm to diagnose steatorrhea in CP with FE-1 testing and minimal use of fecal fat testing especially in resource limited setting (Fig. 4).

Patients with evidence of CP on imaging are evaluated for PEI by fecal elastase test on undiluted formed stool. If FE > 100 μg/g stool, steatorrhea can be ruled out (negative predictive value 85% and negative likelihood ratio 0.35). If patient has clinical features of exocrine insufficiency like low BMI (<18.5 kg/m^2) or significant weight loss, he or she will be evaluated for other causes like recurrent pain, poor glycemic control, inadequate dietary intake, local complications (pseudocyst, gastric outlet obstruction, malignancy etc.), active alcohol consumption or smoking [9,19,20]. If there is clinical steatorrhea or alternate causes of low BMI/weight loss ruled out, assess for possible associated causes of malabsorption like small intestinal bacterial overgrowth (SIBO), celiac disease, or giardiasis and if present, treat accordingly and assess for response [3]. In setting with limited resources, patient can be empirically treated for SIBO as it is commonly associated with CP and can cause symptoms [21]. If patient improves, he can be followed with annual FE testing. If there is no improvement in above mentioned symptoms, fecal fat estimation is advised to confirm steatorrhea as cause of the symptoms. In patients with FE ≥ 20 and asymptomatic can be followed up and FE can be repeated at least a year later. In patients with clinical feature of PEI and FE between 20 and 100, fecal fat estimation is advised along with assessment for alternate causes on case-to-case basis. If FE < 20 (specificity 69%; positive likelihood ratio of 2.14) and asymptomatic, fecal fat estimation is advised to decide on PERT. In asymptomatic cases with fecal fat between 7 and 15 g/day, pancreatic enzyme replacement therapy (PERT) can be decided on case-to-case basis [3]. If there is clinical feature of PEI and FE < 20, these patients can be started on PERT and alternate cause of symptoms can be evaluated on case-to-case basis.

Some authors had proposed testing for serum fat soluble vitamin levels vitamin A and vitamin E to stage pancreatic exocrine insufficiency [17,18].We did not include the serum fat soluble vitamins A and E estimation in the diagnosis of steatorrhea (severe PEI) for the following reasons. Earlier studies with limited sample size showed a high prevalence of vitamin A deficiency in CP patients with steatorrhea and the recent studies showed that vitamin A deficiency is less common and not associated with steatorrhea [22–25].Hence we did not propose serum vitamin A testing. The

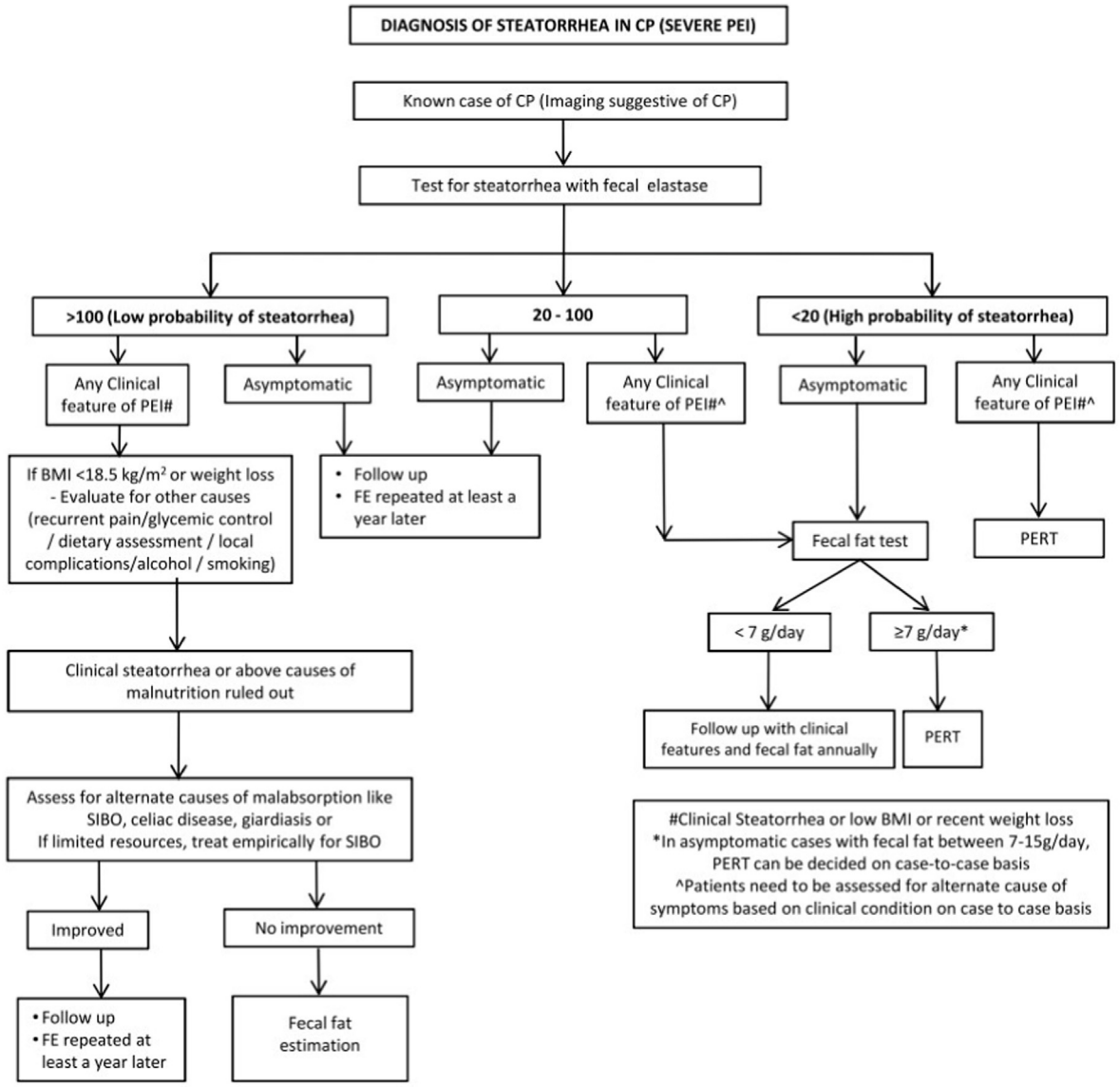

Fig. 4. Algorithm for the diagnosis and management of steatorrhea (Fecal fat > 7 g/day) with fecal elastase (FE) testing and clinical features in chronic pancreatitis (CP) in real world setting.
Abbreviations: CP: chronic pancreatitis, PEI: Pancreatic Exocrine Insufficiency, BMI: Body Mass Index, SIBO: Small Intestinal Bacterial Overgrowth, PERT: Pancreatic Enzyme Replacement Therapy.

overall prevalence of vitamin E deficiency in CP patients was considerably lower in recent studies than in previous studies [22,23]. Studies based on fecal fat estimation observed association between lower vitamin E levels and steatorrhea while studies based on fecal elastase showed no association [22–24,26]. Among the fat-soluble vitamins, vitamin E alone has some evidence as a marker of steatorrhea [25].Ad-hoc analysis of previously published data from our group did not show any association between fat-soluble vitamin deficiency and steatorrhea [11]. (Supplementary Table 2) Clinical features of malnutrition like low body mass index are strongly associated with steatorrhea (although less sensitive) and can supplement FE test to improve its diagnostic accuracy to detect steatorrhea [9,10].In view of additional cost, limited availability of its testing and limited evidence, vitamin E testing may be avoided in resource limited setting. Instead, we screen the patients for any fat-soluble vitamin deficiency clinically (history and examination) during nutritional screening irrespective of fecal elastase levels. If there is suspicion of deficiency, the same can be confirmed by laboratory testing.

This study has the largest sample size till date to evaluate the diagnostic performance of FE in detection of severe pancreatic insufficiency (steatorrhea) in CP patients without surgery. And this study also evaluated the progression of exocrine insufficiency with FE test. This was a retrospective study from a referral institute and hence some selection bias and referral bias exist although all the data was prospectively collected. We did not evaluate for other causes of steatorrhea like small intestinal bacterial overgrowth in these patients. The percentage of patients with steatorrhea (fecal fat >7 g/day) and FE > 100 is less than 5% in our study, and it indicates possibly low proportion of patients with other causes of steatorrhea. Finally, FE testing for a 9-month period to evaluate for exocrine insufficiency progression could not be done in all included patients.

8. Conclusion

Compared to FE < 200, FE < 100 μg/g stool has similar sensitivity of 90% to diagnose steatorrhea with comparatively better specificity and negative likelihood ratio (0.35). So, FE ≥ 100 μg/g stool can used to exclude steatorrhea. The optimal cut-off by ROC, FE < 20 μg/g stool, showed specificity of 69% and positive likelihood ratio of 2.14. Hence, FE testing alone cannot replace fecal fat estimation to confirm steatorrhea but can be used as a surrogate marker along with clinical features. FE has good test-retest reliability and repeat FE testing for progression of exocrine insufficiency can be done at least a year later.

Guarantor of the article

Deepak Gunjan MD DM and Anoop Saraya MD DM.

Author contributions

1. Srikanth Gopi: study concept and design, acquisition of data, interpretation of data and drafting of the manuscript
2. Namrata Singh: analysis and interpretation of data, drafting of the manuscript, acquisition of data
3. JatinYegurla: acquisition of data and drafting of the manuscript
4. Mohammad Tabish: acquisition of data and drafting of the manuscript
5. Samagra Agarwal: analysis and interpretation of data, statistical analysis, drafting of the manuscript, acquisition of data
6. Sumaira Qamar: acquisition of data, drafting of the manuscript
7. Deepak Gunjan: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content and study supervision
8. Anoop Saraya: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content and study supervision

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2023.01.002.

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