

## Staging chronic pancreatitis with exocrine function tests: are we better?

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**Key words:** chronic pancreatitis, exocrine pancreatic insufficiency, fecal elastase-1, pancreatic function tests, steatorrhea

**Core tip:** Classification of chronic pancreatitis is useful for planning adequate diagnosis and management of the disease, particularly in the early detection and prevention of related-complications. Recognition of pancreatic exocrine insufficiency is useful for graduating severity of chronic pancreatitis in modern classification systems, and fecal elastase determination appears the better method in term of simplicity and sensitivity to stage exocrine function of the pancreas. However, sensitivity of elastase-1 is low in early stage of chronic pancreatitis, and new diagnostic tools or combination of different procedures are needed to better stage pancreatic function.

### INTRODUCTION

Chronic pancreatitis (CP) is the most commonly known cause of pancreatic exocrine insufficiency (PEI) [1]. Every patient with a new diagnosis of CP should be screened for PEI and in order to detect maldigestion prior to the occurrence of overt clinical symptoms, the presence of PEI should be evaluated annually in patients with CP. PEI can lead to poor quality of life, steatorrhea, abdominal pain and malabsorption, and early diagnosis of PEI is important to prevent malnutrition-related complications. Many tests are nowadays available for the diagnosis of PEI, but each one has some diagnostic limitations. As a consequence, PEI is still underdiagnosed and undertreated. In addition to its clinical relevance, PEI represents an helpful method for staging CP in different classification systems. The M-ANNHEIM classification is a new system for staging and grading the severity of CP [2]. The M-ANNHEIM classification system is based on the categorization determined by etiological factors, clinical stage and severity of CP. This system constitutes a simple, objective, accurate and non-invasive method for clinicians which combines the influence and interaction of several risk factors on the course of the disease. These multiple (M) risk factors included the subsets of alcohol consumption (A), nicotine consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and various rare miscellaneous and metabolic (M) factors [2]. The M-ANNHEIM staging of CP is divided into an asymptomatic phase (stage 0) and a symptomatic phase (stages I, II, III, IV) of the disease [2]. The latter phase represents the period of clinically evident chronic inflammation of the pancreas. The evaluation of the symptomatic phases of CP is based on pain and on the presence and degree of PEI [2]. An accurate evaluation of PEI is therefore necessary to validate the diagnosis and allow the proper treatment of the disease. In fact, a correct diagnosis of PEI suggests the pancreatic enzyme replacement therapy (PERT) and it is essential to monitor the efficacy of treatment in order to avoid complications of CP. Only few studies in the literature have compared the different diagnostic power of the tests available to evaluate PEI, and only few data are available for determining their role in the present staging system of CP.

### STUDY ANALYSIS

In the recent issue of the World Journal of Gastroenterology, Kamath et al [3] reported a prospective analysis comparing two tests for PEI to use in M-ANNHEIM staging for pancreatitis. In this study, 116 patients with CP were included. PEI was analyzed by faecal elastase-1 (FE-1) value and fecal fat excretion by the acid steatocrit method. Based on the results of the two tests, the patients were separately categorized as per M-ANNHEIM stages. Among the 116 patients with CP, the presence of PEI was evident in 61 (52.5%) and 79 (68.1%) by the acid steatocrit method and FE-1, respectively. A statistically significant difference was seen

between the M-ANNHEIM stages as classified separately by acid steatocrit and the FE-1. The Authors concluded that FE-1 estimation permits better staging of pancreatitis by the M-ANNHEIM classification, since it diagnosed a higher number of patients with exocrine pancreatic insufficiency. They recommend the use of FE-1 test for staging CP by the M-ANNHEIM classification. The study of Kamath et al [3] is interesting because it deals with the assessment of PEI, which still remains a diagnostic challenge in patients affected by CP.

The ideal test for the diagnosis of PEI should be accurate, non-invasive, widely available and easy to perform. In our Center, in twenty years of experience, we observed 325 patients with a diagnosis of CP, and among them 253 received surgery [4, 5]. In this period, different tests were used to diagnose PEI (fecal fat excretion, p-aminobenzoic acid test, coefficient of fat absorption, fecal chymotrypsin) [4, 5, 6], and in more recent years they have been replaced by FE-1 test. Nowadays, two different groups of tests (direct and indirect tests) are available for the diagnosis of PEI [1] (Table 1). Among direct tests, the most sensitive method is derived from the aspiration of the pancreatic secretions during secretin-cholecystokinin/erulein administration [7]. However, this test is invasive and it is available only in few specialized centers [7]. Among indirect test, the coefficient of fat absorption (CFA), the fecal-elastase-1 determination and the acid steatocrit test are the most frequently used [7]. FDA have approved treatments for PEI based on randomized controlled trials that used CFA to define PEI [8]. The CFA is also useful to monitor pancreatic enzyme replacement therapy (PERT). The CFA requires patients to maintain a strict diet containing 100 g of fat per day over five days, and to collect the total amount of stools excreted over the last three days [9]. A CFA < 93% is considered pathological [9]. However, this test is not easy to perform, it is difficult to control the amount of fat consumed, especially in alcoholic patients, and collection of faeces is unpleasant and cumbersome for patients. Fecal Elastase-1 (FE-1) is an indirect assessment of the pancreatic secretion. This test is easy to perform, widely available and only requires a small stool sample for analysis [10]. However, FE-1 test is not able to exclude mild to moderate PEI, and there is no consensus concerning the ideal cut-off for PEI in patients with CP: figures of < 15, 50, 100 and 200 mg/g have been proposed, and a threshold of 200 mg/g has been used most frequently in accordance with the intended use label of the test [11]. The acid steatocrit method is a quantitative measurement of fat expressed as a proportion of an entire centrifugated homogenized stool sample; it correlates well with the 72 h quantitative faecal fat estimation [12]. However, the acid steatocrit method has some disadvantages which include a lack of standardization of the test and the possible effect of dietary fat intake during the sample collection [12].

Other tests are currently available. The 13 C-Mixed Triglyceride Breath test (TGBT) is a valid alternative to the CFA, both for the diagnosis of PEI and for evaluating the efficacy of PERT in clinical practice [13]. Modifications of the test may allow the detection of mild to moderate PEI [13]. However, the test also has limitations in terms of specificity (false positive results in non-pancreatic fat malabsorption), it is not easily available since it is commercialized only in few European countries. Pancreatic secretion volume can be evaluated semiquantitatively by secretin enhanced-MRCP (s-MRCP) [14]. Pancreatic secretion evaluated by this technique correlates with FE-1 test results; however, its sensitivity for PEI is as low as 69% [14]. In addition, there is very limited evidence supporting this technique for the diagnosis of PEI in clinical practice.

In conclusion, many tests are available for the diagnosis and evaluation of PEI in CP, but every test has some limits and pitfalls. In particular, a diagnostic, non-invasive method to differentiate mild and moderate PEI is still required. Further studies are needed to identify the ideal method in the diagnostic setting of PEI.

## **PERSPECTIVE**

Accurate staging of pancreatitis is crucial to study both the natural history of the disease and the effect of treatment. In the study by Kalmath et al [3], acid steatocrit and FE1 were compared, while other standard tests like CFA or the 13 C-Mixed Triglyceride Breath test were not considered. It would be interesting in future studies to investigate the comparative usefulness of

these tests comprehensively. Moreover, it is reasonable to believe that the additional use of biomarkers could improve the staging systems and this aspect should be explored in future studies. Recently, it has been reported that serum monocyte chemoattractant protein-1 levels were lower in patients with CP and PEI as compared to patients with CP without PEI [15]. A panel of 6 serum miRNA has been recently suggested as potential useful investigation for diagnosis of CP, especially for the early diagnosis of CP [16]. Future studies concerning the association of tests, such as pancreatic function tests, biomarkers or radiological-endoscopic imaging, could be helpful for the early detection of CP.

**Table 1 Advantages and pitfalls of function tests for pancreatic exocrine insufficiency**

Test	Advantages	Pitfalls
Aspiration of pancreatic contents (during secretin-cholecystokinin/erulein administration)	High sensitivity	Invasive; only available in specialized centers
CFA	Gold standard; useful in monitoring PERT	Need of a strict diet; unpleasant and long sample collection; no simultaneous PERT
FE-1	Easy test; widely available; no need to stop PERT	Low sensitivity in mild PEI; not clear cut-off
Acid steatocrit	Good correlation with CFA	Lack of standardization; Influenced by dietary fat intake
<sup>13</sup> C-mixed Triglyceride Breath Test	Good sensitivity in detecting mild to moderate PEI; useful in monitoring PERT	Only available in specialized center; false positive results in non pancreatic fat malabsorption

CFA: Coefficient of fat absorption; PERT: Pancreatic enzyme supplementation therapy; FE-1: Fecal elastase-1; PEI: Pancreatic exocrine insufficiency.

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Chronic pancreatitis (CP) is an inflammatory disease of the pancreas evolving in progressive fibrotic disruption of the gland with exocrine and endocrine pancreatic insufficiency. Although imaging features of CP are well known, their correlation with exocrine pancreatic function tests are not obvious, particularly in the early stage of the disease. There are many clinical classification of CP, all suggested for better distinguish and manage different forms based on etiological and clinical factors, and severity of the disease. Recently, a new classification of CP has been suggested: the M-ANNHEIM multiple risk factor classification that includes etiology, stage classification and degree of clinical severity. However, more accurate determination of clinical severity of CP requires a correct determination of exocrine function of the pancreas and fecal fat excretion. Recently, Kamath et al. (2017) demonstrated that the evaluation of exocrine pancreatic function by acid steatocrit and fecal elastase-1 (EF-1) was helpful, but EF-1 was able to detect exocrine pancreatic insufficiency in more patients, upgrading some patients in higher stage of disease according to M-ANNHEIM classification. So, EF-1 is a more accurate test to determine exocrine pancreatic insufficiency and to stage chronic pancreatitis in the M-ANNHEIM classification. On the contrary, EF-1 determination shows low sensitivity in detecting exocrine pancreatic insufficiency in early stage of the disease.