

# Exocrine Pancreatic Insufficiency in Chronic Pancreatitis

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## KEYWORDS

Chronic Pancreatitis; Exocrine Pancreatic Insufficiency; Therapy; Diagnosis; Diet.

## INTRODUCTION

Exocrine Pancreatic Insufficiency (EPI) is defined as an inadequate pancreatic enzyme activity, due to insufficient enzyme production, insufficient enzyme activation or early enzyme degradation. Recognition of this entity is highly relevant to avoid malnutrition-related morbidity and mortality. There are many causes of EPI, such as chronic pancreatitis, pancreatic cancer, pancreatectomy, cystic fibrosis, celiac disease, diabetes, gastrointestinal anastomosis or gastrectomy. This paper reviews the epidemiology, pathogenesis, diagnostic and therapy of EPI in chronic pancreatitis.

## MATERIAL AND METHODS

The manuscript was based on extended literature search (Medline/Pubmed) using as key word “ exocrine pancreatic insufficiency”, “ chronic pancreatitis” , “diagnosis”, ”pancreatic enzyme replacement therapy”, ”secretine”, “fecal elastase test” and “breath test”. A total of 767 manuscripts were analyzed from Medline/Pubmed.

# RESULTS

## Epidemiology

Chronic pancreatitis has an incidence of 4 to 22/ 100000 inhabitants and recognizes three phases in its natural history: **Early phase**: approximately the first 5 years of the illness are characterised by acute pancreatitis, pain, hospitalisations and surgical interventions; **Middle phase**: lasting 5–10 years in which acute manifestations are reduced, but stricture of the main biliary duct, chronic pseudocysts and other morphological changes such as duct strictures and pancreatic calcifications become apparent. Pancreatic insufficiencies progressively appear; **Late phase**: from approximately 10 years onwards, acute manifestations become rare and the focus should be put on diabetes mellitus and pancreatic exocrine insufficiency [1].

The EPI in chronic pancreatitis is caused by insufficient enzyme production and it occurs in 35-50% of patients 10 years after the clinical onset and increases thereafter. Its prevalence is 11-20% in low/moderate chronic pancreatitis and 85-94% in severe chronic pancreatitis [1]. In autoimmune pancreatitis, EPI is seen in 80% of the patients and improves under steroids.

## Pathogenesis

The pancreatic secretion contains amylases, lipases, trypsin and bicarbonate. This is stimulated by emptying of the acid content of the stomach, followed by the releasing of the secretin from the duodenal mucosa, which decreases the duodenal pH to an optimal level for activity of the pancreatic enzymes. A second mechanism is the releasing of the Cholecystokinin (CCK) from the duodenal wall following the contact with the nutrients. Subsequently to the CCK release, gallbladder is contracted, acetylcholine is released in the intrapancreatic nerve fibers which stimulates the enzymes secretion.

Chronic pancreatitis represents the main cause of EPI and it occurs when more than 90% of the pancreatic acini are destroyed. Association with ductal obstruction by stricture or stones decreases the outflow of the pancreatic enzymes. As result, besides enzyme supplementation, ductal decompression is indicated. The time point at which maldigestion will occur is not predictable in chronic pancreatitis. The probability of exocrine insufficiency increases with the duration of the disease. After 10 years, more than half of patients with alcohol-associated chronic pancreatitis have exocrine insufficiency; at the end of 20 years almost all of them do EPI [2]. In non-alcohol-related pancreatitis the progression to exocrine pancreatic insufficiency is slower. By contrast, in acute pancreatitis the tissue destruction with EPI may recover over the course of 12 to 24 months [2].

## Diagnostic

The main clinical consequence of EPI is fat maldigestion and malabsorption, resulting in steatorrhea (loose, greasy, voluminous, yellowish, foul-smelling stool with a daily total stool

weight of well over 200 g and the excretion of more than 7 g fat per day in the stool), which are not always evident because patients tend to limit fat ingestion. Fat digestion, however, is largely dependent on pancreatic lipase, but carbohydrate and protein digestion are not evident because they are accomplished by salivary, gastric or intestinal enzymes. These patients have low circulating levels of micronutrients, fat soluble vitamins (A, D, E and K) and lipoproteins, which have been related to a high morbidity and mortality secondary to an increased risk of malnutrition-related complications and cardiovascular events [3].

Other symptoms related to malnutrition may also include anorexia, flatulence, meteorism and weight loss in adults or lack of weight gain in children [4]. Maldigestion is the main cause of weight loss in patients with pancreatic exocrine insufficiency.

However, only relying on symptoms may lead to both the over- and under-diagnosis of EPI. Diarrhea and weight loss may be due to conditions other than EPI, and EPI can also be present in the absence of overt steatorrhea [5].

EPI can be diagnosed by various direct and indirect pancreatic function tests. The principle of direct pancreatic function testing is to collect and measure pancreatic secretions in the duodenal juice and to determine pancreatic secretory capacity under stimulation with secretin as the “gold standard” [6]. Low duodenal level of bicarbonate after secretin stimulation is one of the first signs of CP [7]. This is the most sensitive test for pancreatic function, but it is unpleasant for patients and it is only used in specialized centers that have standardized their own protocol and have individually established normal ranges.

Endoscopic pancreatic function testing which collects the secretine stimulated pancreatic juice through the endoscope test had similar results with the standard secretine test, but it takes about one hour for performing it, so it is rarely performed [8]. The peak of bicarbonate secretion at 60 minutes and the lyplitic activity of the duodenal juice are reduced in chronic pancreatitis.

Secretin-magnetic resonance pancreatography allows quantitative assessment of the exocrine pancreatic function, even in patients with a mild exocrine insufficiency by assessing the duodenal filling [9]. The morphology of the ducts does not correlate always with the EPI. However, the procedure is expensive and diagnostic value is uncertain [10].

The indirect pancreatic function tests are non-invasive and they measure the effects of pancreatic enzymes in the gastrointestinal tract such as undigested food (e.g. fat) or enzymes in blood, urine, or stool (e.g. chymotrypsin and human fecal elastase-1) [6]. These tests are most sensitive when maldigestion is overt. In general, pancreatic function testing requires discontinuation of pancreatic enzyme replacement therapy. The three-days determination of the steatorrhea with a pathological level >7g/day is little used nowadays.

Determination of the levels of human fecal elastase-1 is carried out using an Enzyme-Linked Immunosorbent Assay (ELISA) specific for this human protein [9]. The normal value is >200 mg/g,

values between 100 to 200mg/g are suggestive for moderate EPI and below 100 mg/g are considered for severe EPI[11]. There is no need to stop enzyme therapy for this test because the test results are not influenced by enzyme supplementation. The sensitivity is better (72%) for severe EPI [12] than for mild to moderate form (54%). The specificity is 79% for the diagnosis of mild to moderate EPI [12]. Diagnostic rate is lower in case of diarrhea due to dilutional effect [11] and diabetes [13].

The  $^{13}\text{C}$  -MTGT is more extensively used for the diagnosis of EPI. It is based on the principle that intestinal triglyceride absorption requires prior hydrolysis by pancreatic lipase to produce free fatty acids and mono-acyl-glycerol. These metabolites are absorbed and transported to the liver. Hepatic metabolism subsequently leads to formation of  $^{13}\text{CO}_2$  that is absorbed into the bloodstream, transported to the lung and exhaled. It has been shown that the increase in  $^{13}\text{CO}_2$ -concentration in breath correlates with pancreatic lipase secretion [14]. The cumulative  $^{13}\text{CO}_2$ -exhalation is measured over 5-8 hours, with a normal value under 20% at 5 h. The test sensitivity for EPI is 90% [15]. The patient immobilization is the major drawback of the test. Shortening of the  $^{13}\text{C}$  -MTGT from 6 to 4 hrs of duration [14]. The test results are affected in patients with intestinal malabsorption, liver disease, and/or respiratory disease.

## Efficacy Outcome Measures of the Therapy

The Coefficient Fat Absorption (CFA) by the classical Van de Kamer test is the current standard for evaluating the efficacy of PERT products, although it is not relevant for clinical outcome. Under 72 h controlled high-fat diet 100 g of fat/day or 2g/kg/day and quantitative stool collection,  $\text{CFA} (\%) = 100 \times (\text{fat intake (g/day)} - \text{fat excretion(g/day)}) / \text{fat intake(g/day)}$ . It is considered abnormal if higher than 7% in adults and 15% in children under 6 months [9]. Thus, CFA measures fat absorption serves as a gauge for the lipase activity in pancreatic enzyme supplements.

The Coefficient of Nitrogen Absorption (CNA) would be considered a secondary outcome measure as a measure of protein digestion.  $\text{CFA} (\%) = 100 \times (\text{nitrogen intake (g)} - \text{nitrogen excretion (g)}) / \text{nitrogen intake (g)}$ , where 1 g of protein divided by 6.2 = 1 g of nitrogen.

Breath tests measure the intra-luminal fat digestion by pancreatic lipase using concomitant ingestion of the labeled triglycerides, together with a standard breakfast, followed by the exhalation of labeled  $\text{CO}_2$ . A  $^{13}\text{C}$  -Mixed Triglyceride ( $^{13}\text{C}$  -MTG) breath test has been optimized, standardized, and validated for diagnosing in clinical practice, the effect of enzyme therapy on fat digestion [16]. The  $^{13}\text{C}$  -MTG test was used in a clinical study to demonstrate that the efficacy of pancreatic enzyme supplementation in treating EPI can be optimized by administering enzymes during or directly after meals [17]. The accuracy of the  $^{13}\text{C}$  -MTG test in monitoring the effect of pancreatic enzyme supplementation was confirmed in 29 patients with CP and EPI; the normalization of fat absorption, as assessed by the  $^{13}\text{C}$  -MTG test, was shown to improve nutrition in these patients [15].

Weight gain is useful in long-term follow-up [9]. Weight loss would be an adverse event in a short-term study that employs a placebo, or could be an outcome in a long-term comparator study, and should be closely monitored. Stool frequency (number of bowel movements) and stool characteristics are commonly reported as well [9].

## Treatment

Includes dietary measures, Pancreatic Enzymes Replacement Therapy (PERT) and the treatment of the basic disease (i.e. pancreatic duct decompression).

### PERT Therapy

In a multicenter observational study, PERT improved pain and quality of life for the patients with chronic pancreatitis [17,18]. Improvement of Coefficient Fecal Absorption (CFA) and Coefficient Of Nitrogen Absorption (CNA), together with the stool aspect were noted in several randomized trials [20-23]. The fecal fat excretion compared with placebo is diminished, but this is not normalised completely [24].

The pancreatic enzyme formula must have high lipase activity, protection of the lipase from being destroyed by gastric acid, easiness of mixing with the chyme and leaving the stomach with it, and rapid release of the lipase out of the protective enteric coating into the duodenum [9]. The best particle size for being easily and rapidly released from the stomach through the pylorus is believed to be a diameter of  $\geq 2$  mm, because these particles can exit the stomach at the same time as solid food [25].

Modern preparations contain porcine pancreatic extract encapsulated in microtablets or mini-microspheres with pH-sensitive enteric coating. Because exogenous enzyme should exert their action on the ingested meal, and because gastric emptying of the enzymes should occur in parallel with nutrients to optimize digestion and absorption, pancreatic enzyme preparations should be given (for every meal and snack) during the meal/snack or short time after starting the meal/snack, which gives better recovery than given before the meals [9,17,25].

Doses of 25000-40000 IU lipase/meal proved their usefulness over placebo [20,26] or lower doses [27,28] and they represent starting doses [29,30]. They are adjusted according to EPI severity, fat diet content, adequacy of symptom control and maintenance of the good nutritional status [31] and they can be doubled or tripled [9,25,30].

Severe side effects as inflammatory colonic stenoses have been reported as a side effect of high-dose pancreatin therapy in patients with cystic fibrosis [32], so the maximum dose of 10000IU lipase per kilogram has been proposed [4]. It is not known whether these stenoses were caused by ingredients in the enteric coating or by the high concentration of the digestive enzymes. High doses of 72000 IU lipase/meal were associated with 7.8%-13% complications as abdominal pain, abdominal distention, diarrhea [21,33] or were similar to placebo in other studies [22].

Inadequate patient compliance, the acid intestinal pH present in most patients with EPI and the presence of intestinal bacterial overgrowth are the main factors for treatment failure [25,29].

In a large study comprising 1142 patients from 34 studies single and double blind, the CFA was similar in patients taking IPP and PERT or only PERT [34].

IPP use is appropriate in cases of tablets non-enteric coated. A recent study comprising 34 double blind, open label, parallel group, and crossover, and most randomized studies with 1142 patients, showed no difference in the CFA when IPP were used or not [35]. However, the recent guidelines still indicate IPP when EPI is resistant to the treatment [25,29,30].

## Dietary Management

The diet to follow is not specific, it should be well-balanced, with 35 kcal/kg/day, 1-1.5 g/kg/day of protein and 30% fat, rich in carbohydrates and low in fibers and it is necessary for maintaining the nutritional status [9,36,37]. In order to improve energy and protein intake the diet should be tailored to individual needs and micronutrients should be adequate (vitamin A, D, E and K, calcium, magnesium, zinc, copper, thiamine, vitamin B12 and folic). Patients with EPI should be encouraged to consume small, frequent meals and to abstain from alcohol [25].

Smoking is associated with EPI and more severe features of CP, so smoking cessation should be encouraged in chronic pancreatitis patients [35,37].

Low-fat diets are inferior in terms of total energy and intake of fat-soluble vitamins, so it is not recommended for patients with EPI [25,29]. Moreover, high fat diet is not associated with severity and complications of chronic pancreatitis [38] and normal fat diet is recommended.

Medium-chain triglycerides (coconut oil, palm kernel oil, and camphor tree drupes) are absorbed through the mucosa of the jejunum and ileum without the need for lipase or bile salts. In case of severe steatorrhea, they could be consumed in several (five to seven) small meals, although it doesn't furnish much energy and there is a risk of ketogenesis [39].

The ingestion of fiber-rich foods, including vegetables, inhibits lipase activity by >50%, so reduced fiber intake is beneficial [25,39].

## Influence of Surgical Therapies for Chronic Pancreatitis

In cases of chronic pancreatitis with dilated pancreatic duct, Frey procedure preserved the exocrine function in 30% of the cases [40]. The long-term EPI outcome after a median of > 5 years showed no difference in duoden-preserving procedures (such as Frey or Beger operations) and pancreatoduodenectomy procedures [41]. A promising procedure for preventing EPI in case of total pancreatectomy for chronic pancreatitis is pancreas transplantation [42].

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