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Diagnosis of pancreatic exocrine insufficiency in chronic pancreatitis

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1. Introduction

Pancreatic exocrine insufficiency (PEI) is defined as partial or complete loss of digestive enzyme and bicarbonate secretion. In chronic pancreatitis this is caused by a progressive destruction of functioning pancreatic tissue. The overt clinical symptoms of PEI are steatorrhoea, weight loss and abdominal discomfort due to maldigestion. Due to the large reserve capacity of the pancreas symptoms frequently become apparent in only advanced stages. However patients with mild to moderate PEI also have an increased risk of nutritional deficiencies. Several direct and indirect function tests are available for assessment of pancreatic exocrine function, but until today diagnosis of PEI remains difficult because the available tests have either limited availability due to invasiveness and/or high costs or have limited sensitivity and specificity, particularly in patients with mildly impaired pancreatic exocrine function.

Pathophysiology

Progressive inflammatory destruction of pancreatic tissue in chronic pancreatitis leads to reduced synthesis and secretion of pancreatic enzymes in response to food intake. With rare exceptions, clinically overt malabsorption only occurs when enzyme secretion is reduced by more than 90% (6, 7). In alcoholic chronic pancreatitis, this usually takes 10–20 years. Steatorrhea usually occurs earlier and is more severe than malabsorption of other nutrients. This is explained by an earlier decrease in lipase secretion compared with amylase and proteases (8), higher susceptibility of lipase to acidic pH caused by concomitant impairment of bicarbonate secretion, higher susceptibility of lipase to proteolytic destruction during small intestinal transit, additional acidic denaturation of bile acids and marked inhibition of bile acid secretion in states of malabsorption (23). Moreover, only gastric lipase can serve as an extrapancreatic source of lipolytic activity in humans and this enzyme does not compensate for pancreatic lipase deficiency, although it may be elevated in patients with chronic pancreatitis compared to healthy individuals (3). By contrast, more than 80% of carbohydrates can be digested and absorbed in the absence of pancreatic amylase activity (27) and the colonic flora can further metabolize malabsorbed carbohydrates.

Different natural courses suggest that pancreatic exocrine function is preserved longer and consequently exocrine insufficiency may generally be milder in "early onset" idiopathic chronic pancreatitis compared with alcoholic and "late onset" idiopathic chronic pancreatitis (29). However, direct comparisons of pancreatic exocrine function in patients with varying etiologies of chronic pancreatitis have been few, so far (38).

In an unselected group of patients with chronic pancreatitis, mean pancreatic exocrine function is reduced by around 50–80% compared with healthy controls and 80–90% show some degree of PEI (23). In about 65–75% of patients, morphologic alterations and functional impairment

develop in parallel. PEI without morphologic alterations is rare (<5%) yet possible.

In severe PEI with less than 5% of normal enzyme output, about 40% of nutrients from a readily digestible low-calorie meal are malabsorbed and enter the colon (28). Maldigestion can be decreased by oral enzyme supplementation. However, even with clinically established doses of pancreatic lipase, duodenal enzyme delivery remains far below physiologic levels and lipid malabsorption is rarely normalized (22, 36).

Clinical Symptoms of PEI

Typical symptoms of PEI are abdominal discomfort, weight loss, steatorrhoea, malnutrition and signs of vitamin deficiency (1). Steatorrhoea and azotorrhoea, an excessive discharge of nitrogenous substances in the feces, occur when secretion of lipase and trypsin fall below 5-10% of normal levels. Typical features of steatorrhoea are voluminous fatty ("shiny" and "sticky") stools. However, while it is important to evaluate these parameters, stool characteristics are neither sensitive nor specific for detection of steatorrhoea (11, 25).

Steatorrhoea is conventionally diagnosed when daily stool fat excretion exceeds 7 g during ingestion of a diet containing 100 g fat per day (7). Often steatorrhoea is accompanied by diarrhoea. This is partly caused by accelerated gastric emptying and intestinal transit in patients with exocrine insufficiency that can also be reversed by enzyme supplementation (28).

As a consequence of fat malabsorption, fat-soluble vitamins are insufficiently absorbed so that patients may exhibit low vitamin D levels and develop osteopathy, i.e. osteopenia, osteoporosis and osteomalacia. Reduced fecal elastase is observed in significantly more individuals suffering from osteoporotic bone fractures than healthy controls (reduction by 65%). This study excluded patients with overt steatorrhea suggesting that mild to moderate PEI is a risk factor for development of osteoporosis (10, 15, 31, 33). Moreover, there are reports on vitamin A deficiency causing night-blindness, visual impairment and other ocular affections. As a consequence of vitamin E and K deficiency neurologic symptoms or coagulopathy can occur (1).

2. Pancreatic Function Tests

Exocrine function tests are either based on the measurement of secreted enzymes and bicarbonate (direct tests) or they investigate secondary effects which are due to the lack of enzymes (indirect tests) (4, 34, 35).

Direct Tests

Stool Tests

The fecal excretion of pancreatic enzymes correlates with duodenal enzyme secretion (19). However, pancreatic enzymes are inactivated to different degrees during gastrointestinal transit. Chymotrypsin and elastase-1 are more stable enzymes and are therefore suitable for stool testing.

The activity of chymotrypsin in stool can be tested photometrically. To improve the sensitivity of the test, three different stool samples are necessary and this partly explains why chymotrypsin measurements have been largely replaced by measurement of fecal elastase-1 which only requires a single stool sample (compare below). Moreover, since a differentiation between human and substituted chymotrypsin is not possible, the test results are influenced by pancreatin supplementation. Thus, it is important that these enzyme supplements are discontinued at least 5 days before the examination. On the other hand, the chymotrypsin test can also be used to monitor a patient's compliance with enzyme supplementation in refractory cases. The main drawbacks of this test are its low sensitivity and

specificity in patients with mild or moderate PEI (26).

Currently, measurement of fecal elastase-1 concentration in a single stool sample is the preferred and best available pancreatic function test. The concentration of elastase-1 is investigated by an ELISA-test using a specific antibody against the human enzyme, so that pancreatin supplements have no influence on the results and there is no need to discontinue them. Normal stool-concentration of elastase -1 exceeds 200 µg/g stool (depending on the method), and a concentration less than 100 µg/g stool usually means severe PEI. Measurement of fecal elastase-1 is more sensitive and specific than chymotrypsin testing (39). However, as a stand alone test in early chronic pancreatitis the lack of sensitivity (50-93%) and the lack of specificity (62-93%) limit its diagnostic value (39, 40). Moreover, in the differential diagnosis of diarrhea, specificity of the test is rather low since increased stool-water content leads to false positive results (20).

Secretin Test

The secretin (or secretin-pancreozymin) test is an invasive test that requires placement of a duodenal tube. It is regarded as the reference method for evaluation of pancreatic exocrine function. It can also detect mild and moderate PEI but has several disadvantages including invasiveness, high costs, necessity of special equipment and trained personnel (20) and lack of standardization between different centers.

In order to achieve reliable test results, pancreatin preparations have to be discontinued several days in advance. Nicotine, drugs with sedative or anticholinergic effects have to be discontinued at least 24 hours before the secretin-test is performed and the patient has to be fasting for at least 12 hours. The test is contraindicated in patients with acute pancreatitis for the first 8 to 12 weeks after the acute episode.

A commonly applied test protocol requires that the tip of a double-lumen nasoduodenal tube is placed near the ligament of Treitz. One lumen is placed in the gastric antrum for continuous aspiration of gastric secretions which are discarded. Duodenal contents are aspirated via the second lumen of the tube for 30 min under basal conditions followed by a 60 min collection period with intravenous application of secretin. Subsequently, secretion volume, bicarbonate concentration and activity of pancreatic enzymes (trypsin, chymotrypsin, lipase and amylase) need to be determined in duodenal juice samples. Secretin stimulation leads to maximal bicarbonate output but induces only moderate stimulation of pancreatic enzyme secretion. This is why a second stimulation period using a combination of secretin and cholecystokinin (CCK) or the CCK-analog cerulein was usually performed. However, these substances are currently not available in many countries.

To compensate for incomplete aspiration of duodenal contents a dilution marker can be added but this further complicates the procedure.

Moreover, endoscopy based modifications are used by some specialized centers (41, 42). The endoscopic secretin test includes aspiration of duodenal juice through the suction channel of the endoscope at 15, 30, 45 and 60 min after secretin stimulation. A bicarbonate concentration greater than 80 mmol/L in any of the samples is considered as normal. The endoscopic secretin test has demonstrated good sensitivity and specificity compared with conventional, tube based stimulation tests; however, a considerable limitation is that it takes approximately 1 h to perform. Reducing the length to 45 minutes with fluid collections at 30 and 45 minutes provides 94% accuracy compared with the one hour test but further abbreviations appear to lead to inaccurate results, though it is feasible to inject secretin prior to endoscopy so that the duration of intubation can be limited (13, 42). CCK alone or

CCK in combination with secretin has also been used in endoscopic function tests (42).

Lundh Test

The Lundh test (18) also requires intestinal intubation for direct measurement of enzyme output in duodenal juice. However, in contrast to the secretin test, pancreatic exocrine secretion is stimulated by a standardized test meal. This consists of 300 ml of liquid composed of dried milk, vegetable oil and dextrose (67% fat, 5% protein, 15% carbohydrate). Accordingly, release of regulatory mediators from the intestinal mucosa is needed for stimulation of pancreatic secretion and false positive results may occur in intestinal diseases such as celiac sprue or altered gastroduodenal anatomy. Usually only trypsin activity is measured.

Indirect Tests

Fluorecein Dilaurate and NBT PABA Test

The fluorescein dilaurate (pancreolauryl test=PLT) and the NBT-PABA test (N-benzoyl-L-tyrosyl-p-aminobenzoic acid test) are no longer commerciably available in many countries. Briefly, for both tests, the patient ingests a substrate that is metabolized into two or more products by pancreatic enzymes. At least one of the metabolites (fluorescein or PABA) is absorbed from the gut, conjugated, and excreted in urine, where it can be measured. Increased fecal excretion of the unsplit molecule and decreased absorption, blood levels and urinary excretion of the metabolite will occur in patients with PEI. To account for inter-individual variability of intestinal absorption and renal function, the fluorescein dilaurate test includes application of the absorbable metabolite (fluorescein) on a second day and the results of the test are expressed as the ratio of excreted fluorescein on the test and the control day in percent. A ratio of less than 20% is clearly abnormal. A modified serum test eliminates the need for a second test day but does not increase sensitivity and specificity (39).

^{13}C-Breath Tests

Several breath tests using ^{13}C-labeled substrates for measurement of pancreatic function have been developed during the recent years (20). Of these, tests using ^{13}C-labeled lipids are most promising because lipase synthesis and secretion tend to be impaired earlier than those of other pancreatic enzymes in chronic pancreatitis (compare above). The labeled lipids are ingested orally together with a test meal and need to be digested to monoglycerides and free fatty acids by pancreatic lipase prior to absorption. Hepatic metabolism of the absorbed lipids leads to production of $^{13}CO_2$ which is transported to the lung and exhaled. Thus, the ratio of breath $^{13}CO_2/^{12}CO_2$ over time reflects intestinal lipolysis by pancreatic lipase as the rate-limiting step of lipid absorption. Available substrates include 1,3 distearyl-2[^{13}C]-octanoate, called ^{13}C-mixed triglyceride, which has several advantages over other lipid markers and is most commonly used. Other potential lipid markers are uniformly labeled Hiolein® (mixture of long chain triglycerides) and cholesteryl-^{13}C-octanoate (20). Sensitivity and specificity of certain test modifications have been reported to exceed 90% (17). Moreover, a modified version of the ^{13}C-mixed triglyceride breath test has been shown to also detect mild to moderate PEI (21). A major disadvantage of the test is the need for prolonged breath sampling. Retrospective comparison of test results in a large group of patients has shown that an abbreviated version requiring breath sampling for 4 hours still provides a high accuracy but that shorter tests lack specificity (24). Apart from diagnosis of PEI ^{13}C-breath tests can also be used to monitor the effect of enzyme replacement therapy (9).

Fecal Fat Analysis

Quantitative measurement of fecal fat excretion over 72 h during ingestion of a diet containing 100 g fat per day is the reference method for diagnosis of steatorrhea. Under these circumstances, a feal fat excretion of more than 7 g/day fat is abnormal (37). The levels of steatorrhea seen in CP tend to be much higher (often > 20 g/day). Due to its numerous disadvantages including nonspecificity for pancreatic disease, need for prolonged abstinence from pancreatic enzyme preparations and unpleasant sampling, storage and mixing of stool, it is no longer performed for clinical reasons in most centers. Instead, Sudan staining of a random stool sample for fecal fat can be used but is relatively insensitive for fat malabsorption (30).

3. Combined Morphological and Functional Investigations

Secretin-enhanced magnetic resonance cholangiopancreatography (S-MRCP) reveals ductal morphological alterations and simultaneously gives semi-quantitative information on functional changes by evaluation of the degree of duodenal filling (2). However, the number of appropriate studies is limited and sensitivity of this technique for exocrine insufficiency is only about 70%. Thus, normal duodenal filling does not rule out its existence (32). Endoscopic ultrasonography has recently also been combined with secretin-stimulation and, also with this method, fluid filling in the descending part of duodenum was a predictor of pancreatic insufficiency (12).

4. Clinical Role of Pancreatic Function Tests in Chronic Pancreatitis

Most experts agree that diagnosis of CP depends on a combination of clinical, histological, imaging and functional criteria (5, 14, 16, 32). Proof of impaired exocrine function by function testing is particularly important for diagnosis of CP in patients with inconclusive morphological findings. Moreover, staging of disease according to various classifications requires assessment of exocrine function. Function testing is generally recommended in patients with a new diagnosis of chronic pancreatitis to screen for exocrine insufficiency. National guidelines partly recommend repetitive testing at annual intervals in patients with previously normal results (16, 32). When symptoms of exocrine insufficiency persist in spite of adequate enyzme tretament, function tests (^{13}C-breath test, measurement of fecal fat) are to be considered for evaluation of treatment efficacy. From a practical point of view, verification of PEI by a pathological pancreatic function test is a prerequisite for reimbursement of enzyme treatment in some countries.

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