Chapter 12

Exocrine pancreatic function in fibrocalculous pancreatic diabetes

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Summary

In fibrocalculous pancreatic diabetes (FCPD), manifestations of pancreatic exocrine deficiency are variable and clinical presentation with steatorrhoea is uncommon. However objective tests of pancreatic exocrine functions are generally abnormal in FCPD, which represents a late stage of the disease. Though considered to be the gold standard, direct pancreatic function tests such as secretin-pancreozymin (CCK) test and Lundh meal test are time consuming, invasive, expensive and hence beyond the reach of non-specialized centers. Stool fat estimation is cumbersome and difficult to set up and perform routinely. Most of the centers now perform simple tests such as faecal chymotrypsin. Fecal elastase is being more commonly used in many centers. Though this is very specific, it is sensitive only in advanced stages of the disease. With the wide availability of imaging of the pancreas by ultrasound, computerized tomography, endoscopic retrograde pancreatography and magnetic resonance pancreatography, early and noncalcific stages of the disease can be diagnosed with reasonable certainty. In these situations exocrine pancreatic function tests are not an absolute necessity for the diagnosis of chronic pancreatitis and are mainly used for assessing the extent of exocrine pancreatic dysfunction. The need of the hour is for more sensitive, simple and less expensive exocrine pancreatic function tests, which could also be used for screening purposes.

Introduction

Fibrocalculous pancreatic diabetes (FCPD) is characterized by diabetes presenting at a young age secondary to chronic calcific nonalcoholic pancreatitis. This is more common in tropics and is synonymous with tropical calcific pancreatitis (TCP). Exocrine pancreatic deficiency is common. Clinical manifestation of steatorrhoea may be seldom noticed (<20%), though objective tests for exocrine function often show abnormal results. This is thought to be due to the low fat intake by the patients.[1] A variety of tests are available to assess exocrine function in chronic pancreatitis but their published use in tropical calcific pancreatitis is limited. The role of exocrine pancreatic function tests (PFT) in diagnosis of chronic pancreatitis has diminished considerably due to advances in imagining modalities such as ultrasound scan, computerized

tomography, and endoscopic retrograde pancreatography and magnetic resonance pancreatography. Pancreatic function tests are very valuable in cases of chronic pancreatitis particularly when imaging modalities are inconclusive; unfortunately only invasive tests are sensitive in mild cases. They are also valuable to determine if pancreatic insufficiency is contributing to malabsorption, to determine the adequacy of pancreatic enzyme replacement therapy and to assess the extent of insufficiency before undertaking pancreatic resection as a part of surgical management.

Pancreatic exocrine function tests may be direct tests or indirect tests. In the direct tests the parameters of pancreatic secretion are measured in duodenal or pure pancreatic juice after stimulation of the pancreas. The secretin- pancreozymin (CCK) test is considered as the gold standard with false positive of 8% and false negative of 6%. Lundh meal test is simple and physiological. A variety of indirect tests are available which include stool tests like faecal fat estimation, faecal chymotrypsin, faecal elastase, faecal immunoreactive lipase, serum tests of pancreatic enzymes particularly is amylase and immunoreactive trypsin; NBT -P ABA (N-Benzoyl -2- Tyrosil- P- amino benzoic acid) and pancreolauryl tests. Other tests include breath analysis test, dual labeled Schilling test and plasma amino acids estimation after stimulation with secretin and pancreozymin. The results of indirect PFT depend on the severity of exocrine pancreatic insufficiency. In cases of mild exocrine pancreatic insufficiency all indirect PFT may yield falsely normal results.

The data on exocrine pancreatic functions in TCP is limited mainly because the previously available tests of PFT were laborious and expensive. Since their introduction simple and less expensive tubeless tests of pancreatic function are more widely used.

Direct tests

Lundh meal test is simple and valuable in assessing exocrine deficiency in tropical pancreatitis. In a series reported by Punnose et al the mean tryptic activity was less than 2 iu/ml in 93% of the calcific group and 27% in the non-calcific group with a cut off level of 12.4 iu/ml in the controls. Calcification seemed to correlate with a gross reduction of tryptic

activity though this did not strictly correlate with the degree of steatorrhoea. Ninety percent of TCP patients had subnormal duodenal tryptic activity.[2] Reduction of tryptic activity in one hundred percent of patients with chronic pancreatitis was reported from Chandigarh. [3]

Secretin-pancreozymin (CCK) test, using a special double lumen tube with a pyloric balloon, was done by Balakrishnan and Sarles in TCP patients and south Indian controls (adults and children). The duodenal aspirate was analyzed for volume, pH, bicarbonate, calcium, lipase, phospholipase, trypsin, chymotrypsin and lactoferrin. They compared their findings with those from alcoholic chronic pancreatitis patients from Marseille, France and French controls. The analysis showed high calcium content in Indian patients and controls, with marked reduction of phospholipase values in Indian patients. The volume and bicarbonate levels were markedly reduced while the lactoferrin values in the duodenal aspirate were elevated in Indian patients. [1] In one earlier report by Chirayath using the secretin- pancreozymin (CCK) stimulation test the volume, HC03, amylase and lipase of duodenal contents were studied; volume was reduced in 40%, HC03 reduced in 50% of cases, amylase in 10% and lipase in 80% of cases. [4] Secretin-pancreozymin (CCK) test done by Tripathy et al in a small group of FCPD patients showed that pancreatic enzyme output was grossly diminished, trypsin more affected than amylase. [5] In another study by Sarles and Augustine pure non-activated pancreatic juice was collected at endoscopy in 10 Indian TCP patients, 12 normal South Indian and 23 normal French controls. The pancreatic juice of TCP was characterized by decreased volume, normal bicarbonate, increased protein and calcium concentration with normal citrate concentration. During cerulein stimulation there was no significant difference in protein concentration between TCP patients and Indian controls. The changes were very similar to those observed in French patients with chronic alcoholic pancreatitis.[6]

Indirect tests

Serum levels of enzymes

Estimation of serum level of amylase and lipase are not found to be useful in TCP and even in acute exacerbation the values are usually not elevated. [7] However lipase levels were reported to be significantly lower

than controls in some studies. [8] Evocative serum enzyme studies (after stimulation with secretin- pancreozymin) did not show any rise in amylase or lipase levels. [4] Serum immunoreactive trypsin (IR T) levels were assayed for exocrine pancreatic function in FCPD by Yajnik et al and 93 percent of patients had low IRT levels. [9] IRT and C peptide levels were clinically correlated. [10] In another study the same group observed that, in TCP subjects with normal glucose tolerance and impaired glucose tolerance, the IRT levels were subnormal in a few cases while in FCPD these were severely reduced in more than two third of the patients. Elevated levels of IRT seen in early stages of the disease may suggest active pancreatitis. However a third of their IDDM and some of their NIDDM patients also showed subnormal IRT levels. They suggested IRT level as a simple marker for exocrine pancreatic function. Serum pancreatic iso-amylase [PIA] levels in FCPD patients were significantly lower than controls. [11] Although PIA is highly specific, it is not sensitive enough to be used as a screening test for exocrine pancreatic deficiency; however it could be used to determine the etiology of steatorrhea.[12]

Is there an entity called "Subclinical pancreatopathy of tropics"? In their landmark paper, Balakrishnan and Sarles made the interesting observation that even many of their south Indian controls had subnormal secretion of pancreatic enzymes and very high calcium levels in their pancreatic juice, compared to French controls, and put forth the interesting concept of an entity of "Subclinical Pancreatopathy of the Tropics".[1] They also found a high carbohydrate, low potein and very low fat intake in the diet of their south Indian patients and controls, and proposed the hypothesis that the imbalanced dietary intake might be a possible cause for the pancreatic functional alterations in their "normal" controls.[1] Subsequently, in another study, subnormal values of IR T have been shown in controls from tropics.[17]

Faecal tests

Stool fat estimation: In the past, 24 hrs stool fat estimation by Van de Kamer method was the most commonly done test to assess exocrine pancreatic function but seldom used now. Only a minority of TCP patients complain of clinical steatorrhoea, as their fat intake is low. Analysis of

the diet of TCP patients studied by Balakrishnan et al showed mean daily fat consumption of 27g only .On a high fat diet (100 g butter) steatorrhoea was noted in 76% (24hr stool fat averaged I8.43gm). [7]

Faecal chymotrypsin (FCT): Faecal chymotrypsin in FCPD studied by Mohan et al showed abnormal values in 87.5% of patients. [8] FCT is considered abnormal if the test value is less than 6 ulgm. FCT estimation is simple and can be done in small institutions with minimal equipment The disadvantage is that as with other tubeless pancreatic function tests FCT is not sensitive in early disease. In FCPD, which represents advanced disease, FCT values are almost invariably abnormal. Since FCT is less expensive and easier to perform, this test is the preferred exocrine pancreatic function test in FCPD. There are several reports using faecal chymotrypsin as a screening test for evaluating exocrine pancreatic function in TCP patients. [8,11,19] FCT was screened in three groups of diabetic patients with FCPD and type 1 and type 2 diabetes and found that exocrine pancreatic insufficiency as shown by low faecal chymotrypsin levels (defined as, 5.8 units/g of faecal mass) was present in 87.5% of patients with FCPD, 23.5% with type 1 diabetes, and 4.5% with type 2 diabetes.[8]FCT was studied in three groups of TCP patients having variable glycemic status (normal glucose tolerance, Impaired GTT, and DM). Mean FCT levels in all 3 subgroups were very low, 87-96% reduction in exocrine pancreatic dysfunction. [20]

Low sensitivity is the only drawback with faecal chymotrypsin, as it may not detect many mild cases of chronic pancreatitis, although its specificity is quite high. In a study faecal chymotrypsin was compared with another tubeless test, N-benzoyl L–tyrosyl–para-aminobenzoic acid (BT-PABA) test. [18] Although the faecal chymotrypsin test has a slightly lower sensitivity, it is simpler and considerably cheaper than the PABA test. However the BT-PABA/p-amino salicylic acid is a more efficient test to diagnose TCP as it has a very high sensitivity and specificity. [15] Among malnutrition related diabetes of north Indian patients FCT levels were significantly lower in subjects with FCPD (median 0.4 U/g, range 0-8.9 U/g), in comparison with those with PDPD (4.7 U/g, 0.6-40.5 U/g; $P < 0.001$). Of the FCPD patients, 13 of 20 (65%) had severe exocrine pancreatic deficiency (FCT < 1 U/g) vs. 3 of 19 (15.8%) PDPD subjects ($P < 0.01$). [21] However another study from Delhi on a smaller number of

patients found the exocrine function using stool fat estimation were comparable among these two groups. [22] Newer faecal tests such as immunoreactive lipase and faecal elastase are promising simpler tests but have low sensitivity in mild disease and utility in FCPD has to be further evaluated.[13,14]

Miscellaneous tests

NBT- PABA / PAS test showed sensitivity of 75% and specificity of 81 % in tropical pancreatitis. PABA / PAS excretion index (PEI) showed a sensitivity of 75% and specificity of 92%, using a cut off value of 0.75. [15] The usefulness of this test as a screening test in field surveys of tropical pancreatitis has to be substantiated by further studies. In a comparative study of NBT PABA test and FCT, one hundred percent of FCPD patients had abnormal NBT PABA test while 92.3% had abnormal FCT.[16]

Yajnik et al in a comparative study of IRT, FCT, and PIA suggested a possible sequence of events in TCP. FCT levels come down progressively in TCP while IRT levels may be elevated or normal in the early stages due to disease activity. In advanced stages of TCP both tests are severely affected. Trypsin secretion seems to be affected earlier than amylase as evidenced by preservation of PIA levels till late stages of the disease. Similarly FCT level was reduced even while serum amylase and lipase levels were normal.[11]

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