

Comparison of Exocrine Pancreatic Function by Two Tubeless Tests in Fibrocalculous Pancreatic Diabetes (FCPD) and Insulin Dependent Diabetes Mellitus (IDDM)

V. Mohan

ABSTRACT

Two tubeless tests of exocrine pancreatic function, the NBT-PABA test and faecal chymotrypsin (FCT) assay were compared. Thirteen patients with Fibrocalculous Pancreatic Diabetes (FCPD), 12 patients with Insulin Dependent Diabetes Mellitus (IDDM) and 13 control subjects were studied. Using a PABA excretion value < 43%, 100% of FCPD patients and 58.3% of IDDM patients had abnormal exocrine pancreatic function. Using an FCT value < 5.9 units/gram, 92.3% of FCPD patients and 25% of IDDM patients had exocrine pancreatic insufficiency. Thus both PABA and FCT tests were found to be useful in differentiating the two diabetic groups from controls but were poor discriminators of FCPD and IDDM forms of diabetes. Comparing the two tests, the FCT test has a slightly lower sensitivity, but is simpler and considerably cheaper than PABA test and hence suitable for routine clinical use.

INTRODUCTION

Fibrocalculous Pancreatic diabetes (FCPD) is a form of diabetes secondary to tropical, chronic, calcific pancreatitis [1]. FCPD is unique in that its distribution, is confined to tropical countries and Southern India has the highest known prevalence of the disease [2]. We have earlier reported on the clinical and biochemical features of FCPD particularly on pancreatic endocrine function studies in this disorder [3,4]. This paper reports on exocrine pancreatic function in FCPD and compares two simple non-invasive tests namely the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (NBT-PABA or bentrimide) test and the faecal chymotrypsin test (FCT).

Materials and Methods

The Following groups were studied:

1. Controls (n = 13)

Healthy non-diabetic subjects mostly drawn from the staff of the diabetes center. None of the subjects had any systemic illness and there was no family history suggestive of diabetes or pancreatitis. None of the subjects had a history of pain in the abdomen, chronic diarrhoea, flatulence or symptoms suggestive of steatorrhoea.

2. Insulin Dependent Diabetes Mellitus (IDDM) (n = 12)

Young diabetes with abrupt onset of symptoms who were prone to ketosis in the basal state or who had established ketoacidosis in the past required insulin continuously from the time of diagnosis. None gave a history of abdominal pain, chronic diarrhoea, flatulence or of passing oily or greasy stools. All had normal abdominal X-rays and ultrasonograms.

3. Fibrocalculous Pancreatic Diabetes (FCPD) (n = 13)

All patients gave histories of recurrent abdominal pain from childhood, were young, lean and had evidence of diabetes according to WHO study group criteria [1]. Most patients with FCPD had frequent episodes of diarrhoea and flatulence. Six of the thirteen patients gave typical history of passing greasy and sometimes frank oily stools especially when fatty foods were consumed. All patients had evidence of pancreatic calculi on X-ray of abdomen and the presence of pancreatic calculi and other features of chronic pancreatitis were confirmed on ultrasonography. All were treated with insulin for control of diabetes but none of the patients had evidence of ketonuria at any time.

Study subjects in all three groups were non-alcoholics and were drawn from similar socio-economic background. All had normal hepatic and renal function tests.

Blood samples were drawn after a 12 hour fast for plasma glucose (Glucose oxidase, Boehringer Mannheim), glycosylated hemoglobin [5] and C-peptide measurements [6]. Faeces were collected in the special tubes provided with the kit for FCT test by Boehringer Mannheim, West Germany. The sample was pressed into a hollow cavity in the base of the cap of the tube and leveled off the surface, with a spatula. The tube was firmly pressed onto the base cap and 10 ml of the solvent was added and the tube was tightly closed. The sample was homogenized by vortexing and the mixing was facilitated by the spiral metal present in the tube. The supernatant was used for the photometric assay using the procedure of Kasper and Neumann [7]. The substrate used was Succ-Ala-Ala-Pro-Phe-4-nitro anilide. The measurement was carried out at 37°C using the kinetic procedure.

From M. V. Diabetes Specialities Centre, 44, Royapettah High Road, Madras – 600 014, India.

The PABA test was carried out as follows: The bladder was completely emptied while the subject was still fasting. One gram Bentriomide (approximately equal to 333 mg PABA) was given orally with a breakfast consisting of one cup of tea without sugar (approximately 200ml) and one slice of bread with 10 gm butter. Drinking of 0.5 liter water was allowed during the course of the next hour. Careful collection of urine for a six hour period following the ingestion of tablets was done. After measuring the volume of urine, a 10 ml portion was used for the PABA assay. Total aromatic amines were determined by the method of Bratton and Marshall as modified by Smith et al. The results were expressed as percent recovery of PABA in the urine.

All values are expressed as Mean \pm SD. One way analysis of variance (ANOVA) and correlation coefficients were used as tests of statistical significance.

Results

The clinical details of the study groups are shown in Table 1. The sex distribution was similar in all 3

Table 1
Clinical Details of Study Groups

	Controls (n=13)	IDDM (n=12)	FCPD (n=13)
Sex ratio (M : F)	10 : 3	10 : 2	11 : 2
Age (years)	27 \pm 5	24 \pm 7 ^{a,b}	28 \pm 8
Duration of Diabetes (years)	--	2.3 \pm 2.4	3.6 \pm 3.0
BMI (kg/m ²)	20.3 \pm 2.0	16.8 \pm 2. ^{3b,c}	19.4 \pm 3.3
FPG(mg/dl)	89 \pm 10	215 \pm 120	156 \pm 59
HbA1(%)	7.0 \pm 0.3	12.3 \pm 3.0	10.9 \pm 2.1
Fasting C-peptide (pmol/ml)	0.58 \pm 0.23	0.09 \pm 0.07 ^c	0.17 \pm 0.08 ^d
FCT (units/gm)	19.9 \pm 7.0	11.6 \pm 8.1 ^c	3.4 \pm 3.2 ^{d,e}
PABA (%)	59.7 \pm 8.4	38.5 \pm 15.2 ^c	8.4 \pm 9.7 ^{d,f}

a P = 0.02, IDDM vs. Controls d P < 0.001 FCPD vs. Controls

b P = 0.03, IDDM vs. FCPD e P = 0.02 FCPD vs. IDDM

c P < 0.001, IDDM vs. Controls f P < 0.001 FCPD vs. IDDM

FPG – Fasting Plasma Glucose

FCT – Faecal chymotrypsin

BMI – Body Mass Index

IDDM – Insulin Dependent Diabetes Mellitus

FCPD – Fibrocalculous Pancreatic Diabetes

HbA1 – Glycosylated Hemoglobin

Values are Mean \pm SD

groups. The ages of the FCPD and control groups were similar but the IDDM's were younger (p = 0.02 and p = 0.03 vs. controls and FCPD respectively).

The duration of diabetes in the two diabetic groups was similar. The body mass index (BMI) of the FCPD and control groups were similar but the IDDM patients had lower BMI (p < 0.001 vs. controls; p = 0.03 vs. FCPD). The fasting plasma glucose, glycosylated hemoglobin and fasting C-peptide concentrations were not significantly different between the two diabetic groups.

Faecal chymotrypsin (FCT) levels were grossly diminished in the FCPD groups (p < 0.001 vs. controls). In IDDM patients also the FCT levels were significantly lower compared to control values (p < 0.001). However, the mean levels in IDDM were higher than those seen in FCPD (p = 0.02).

The mean PABA levels were markedly diminished in FCPD patients compared to controls (p < 0.001). In IDDM patients, the mean PABA levels were lower than control subjects (p < 0.001), but significantly higher than the levels in FCPD patients (p < 0.001).

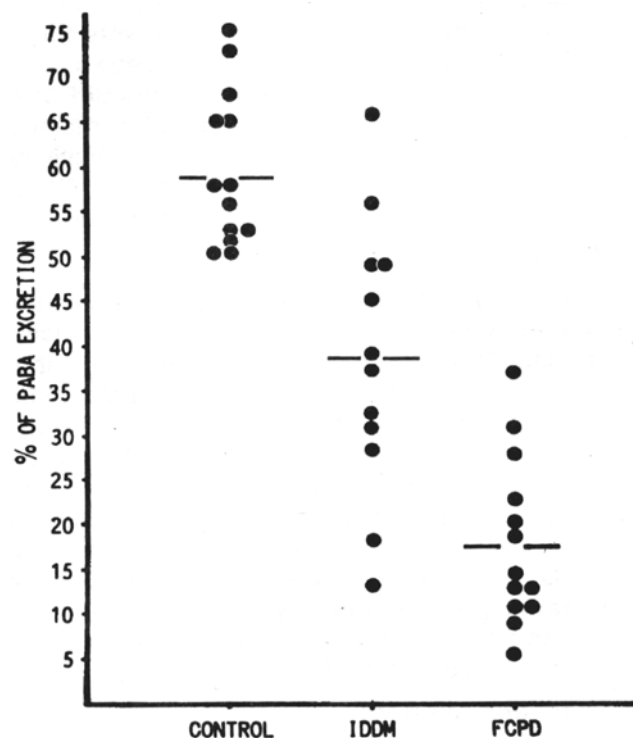


Fig 1 : Distribution of percent PABA excretion in controls, IDDM and FCPD patients
IDDM – Insulin Dependent Diabetes Mellitus.
FCPD – Fibrocalculous Pancreatic Diabetes.

Figure 1 shows a scatter diagram of the PABA levels in the three study groups. Using a PABA excretion value below 43%, (Mean - 2 S.D. of control value) as the cut off point for diagnosis of exocrine pancreatic insufficiency, all FCPD patients (100%) and 7 IDDM patients (58.3%) had values in this range. Using a

FCT value < 5.9 (Mean – 2 S.D. of control value) as the cut off point for diagnosis of exocrine pancreatic insufficiency, 12/13 of the FCPD patients (92.3%) and 3/12 IDDM patients (25%) had values in this range.

There was no correlation between the PABA and the FCT levels in any of the groups studied. There was also no correlation between the C-Peptide levels with either PABA or FCT levels in any of the study groups.

Discussion

This study reports on exocrine pancreatic function as assessed by two tubeless tests, namely the NBT-PABA test and the faecal chymotrypsin test (FCT) in tropical forms of diabetes. Earlier studies have shown variable impairment of exocrine pancreatic function in FCPD (9-11). Using the Lundh Meal Test, Punnose et al [12] found that 93% of the calcific and 27% of the non-calcific cases had low tryptic activities. Yajnik et al [13] using serum immunoreactive trypsin (IRT) levels to assess exocrine pancreatic function, found that 93% of FCPD patients had subnormal IRT levels.

The aim of the present study was to compare two non-invasive tests for assessment of exocrine pancreatic dysfunction in FCPD. Tests like Endoscopic Retrograde Cholangio Pancreatography (ERCP) or Secretin-Pancreozymin test are invasive tests and hence unsuitable for large scale use. Ultrasonography and CT scan are simpler but are expensive and have a high false positive and false negative rates [14].

We intentionally selected FCPD patients with pancreatic calculi for the following reasons. Firstly, pancreatic calculi are a hallmark of chronic pancreatitis. Secondly, in FCPD the frequency of pancreatic calculi is very high (70% - 90%) compared to other forms of chronic pancreatitis seen in temperate zones [2]. The aim of the study was to see whether either of these tests could be used as a biochemical screening test which would at least pick up the calcific cases.

We found that the sensitivity of the PABA test is higher than FCT. Thus 100% of our FCPD patients had abnormal PABA tests compared to 92.3% of patients who had abnormal FCT tests. According to the literature, the sensitivity of the NBT-PABA test in chronic pancreatitis varies from as low as 50% to 100% [15, 16]. The wide differences are undoubtedly due to differences in the severity of the exocrine

pancreatic involvement. In cases with mild to moderate severity, the PABA sensitivity is low, whereas in those with advanced stages of chronic pancreatitis (CP) the sensitivity is over 90% [16]. In another study, Ammann [17] found that the sensitivity of the FCT was in fact higher than the PABA test. The 100% sensitivity noted in our study could be because patients with calculi and diabetes, both late features of chronic pancreatitis, were selected.

One of the problems with the PABA test is that several substances are known to interfere with it and produce false results. Drugs such as sulphonamides, sulphonylureas, diuretics, paracetamol, chloramphenicol, anti-tuberculous drugs and food stuffs such as prunes and certain berries that contain hippurate precursors could interfere with the PABA test. These substances should therefore be withheld at least 3 days prior to the test. Another disadvantage with the PABA test is that it is much more expensive (about 60 U.S. dollars per test) compared to 6 U.S. dollars per test for the FCT and hence the cost-benefit ratio favors the FCT in poor developing countries.

In an earlier study, we found that 23.5% of IDDM patients had low FCT levels [18]. In this study also we found that 25% of IDDM patients had low FCT levels. In contrast 58.3% of IDDM patients had abnormal PABA tests. The fact that two tests of exocrine pancreatic function were abnormal in a significant number of IDDM patients shows that there could be some degree of involvement of exocrine pancreatic function in these individuals. This is in agreement with earlier reports in IDDM patients using other tests of exocrine pancreatic function [19-2]. Lankisch et al [19] using the Secretin-Pancreozymin test found that 23/43 IDDM patients (43%) had abnormal exocrine pancreatic function. Moles et al [20] found that 19.7% of their IDDM patients had low trypsin like immunoreactivity (TLI) and 25% had low serum pancreatic isoamylase (PIA). Dandona et al [21] found that 61.3% of their IDDM patients had low serum immunoreactive trypsin concentrations and 48% had low PIA activities.

In summary, while both PABA test and FCT are useful tests for differentiating diabetic patients from controls, they are poor tests too differentiate FCPD from IDDM. The PABA test had a slightly higher sensitivity but the cost is a major limitation. Despite its slightly lower sensitivity, the FCT is simpler and cheaper. However, in view of the poor differentiation from IDDM, those with positive tests would then need to go on to have other tests like abdominal x-rays or invasive tests of pancreatic exocrine function to confirm the diagnosis of chronic pancreatitis.

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