

Chapter 16

**Fibrocalculous pancreatic diabetes  
as currently seen in  
Lucknow, Uttar Pradesh**

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## Summary

*Eighty consecutive FCPD subjects were evaluated for their nutritional status, clinical presentation, b-cell (fasting C-peptide) and exocrine function (fecal chymotrypsin). All patients diagnosed between 1994-2000 (n=32) were followed prospectively for weight gain and glycemic control. Only 20% of patients were of lower socio-economic status, while 55% had a low body mass index (<18 kg/m<sup>2</sup>). At onset of diabetes, only 26 (33%) presented with severe insulin-requiring diabetes. Subjects had a wide range of fasting serum C-peptide (0.03-0.76 nmol/l); C-peptide was negatively associated with duration of diabetes (r = -0.48, p=0.001). Fecal chymotrypsin was severely decreased (1.2±3.2 u/g, normal >8.4 u/g), but did not correlate with C-peptide. Of the 50 patients on whom current data was available, 6 (12%) had died. On prospective follow-up (mean 2.3 years), there was a significant improvement in body mass index (19.4±2.9 kg/m<sup>2</sup> vs. 17.0±3.7 kg/m<sup>2</sup>, p<0.001) and hemoglobin A1c (6.4±1.6% vs. 8.0±3.0%, p<0.001). FCPD patients in this study differed from those described in earlier reports in many respects, including improved nutritional status, a wider range of clinical presentation and b-cell function, and a more favorable prognosis.*

## Introduction

In the Indian sub-continent, fibro-calculous pancreatic diabetes (FCPD) was originally described from Kerala and subsequently other south Indian states. More recently, it has been described from all parts of the country. The disease as we see it has evolved considerably from earlier clinical presentations where subjects presented an early age, had marked emaciation, severe hyperglycemia and a very poor prognosis ((1, 6-8, 10, 14, 15). More recent studies have shown a later age of onset, much better nutritional status, wide range of glucose tolerance and an improved prognosis. The cause for this changed spectrum of the disease is not clear. Is it a result of changes in nutrition, improved health facilities and economic status of the population? Or is it attributable to the fact that genetic and/or environmental factors, which predispose to the illness, are different?

In the current presentation, the clinical features of (mainly middle class) patients with FCPD presenting to a tertiary care center in Lucknow, Uttar Pradesh are delineated and a brief comparison is made with previous studies from different parts of India over past few decades. Earlier reports described the disease as occurring among young adults of a poor socio-economic status.

## **Patients and methods**

### **Patients**

Eighty consecutive patients of FCPD who presented to our hospital (Endocrinology, Gastroenterology or Surgical Gastroenterology services) from 1989 to 2000 were included in the study. Of these, 5 patients were related and belonged to 2 families. FCPD was diagnosed on the basis of abdominal pain, pancreatic ductal calcification and diabetes mellitus (WHO criteria, 1985) (17). Subjects with a history of alcohol intake or having obstructive biliary tract disease or hypercalcemia on investigations were excluded.

All the patients belonged to the north Indian state of Uttar Pradesh or adjacent regions. In addition to patients with a classical history of abdominal pain and/or steatorrhea, we screened all patients with onset of diabetes <30 years by ultrasonographic examination of the pancreas. Also, all patients diagnosed to have tropical calcific pancreatitis without prior evidence of diabetes underwent an oral glucose tolerance test (OGTT).

Clinical features of 97 patients with type 1 diabetes, seen in the Endocrinology department during the same time period, were used for comparison with FCPD subjects.

### **Clinical evaluation**

Patients were evaluated at the time of presentation for their nutritional status (body mass index (BMI), clinical signs of malnutrition, serum albumin). Evaluation for microvascular complications was performed annually. Fundus examination was performed by direct ophthalmoscopy by a trained ophthalmologist. Retinopathy was classified as background

(non-proliferative) or proliferative. Nephropathy was diagnosed if urine dipstick test was positive for protein (subsequently confirmed by 24 hour urine protein >0.5 gm), or if serum creatinine was  $\geq 150$  mmol/l. Peripheral neuropathy was defined as bilateral absence of ankle jerks and/or objective evidence of sensory loss in the lower extremities. Glycemic control was assessed by hemoglobin A1c (HbA1c), and b-cell function by measuring fasting C-peptide. Exocrine pancreatic function was estimated by faecal chymotrypsin.

### **Follow up**

All patients diagnosed between 1994 and 2000 (n=32) were followed prospectively for their nutritional status, glycemic control and ability to return to their previous occupation. The mean duration of follow-up was 3.2 years (range 1 month – 6 years).

### **Investigations**

Hemoglobin A1c was measured by ion-exchange chromatography (Biorad, Hercules, California). The normal range was 4-6%. Fasting C-peptide was measured by radioimmunoassay (Diagnostic Systems Laboratory, Webster, Texas). Faecal chymotrypsin was measured using an enzymatic technique (Boehringer Mannheim, Mannheim, Germany).

### **Statistics**

The results were expressed as mean  $\pm$  SD. Continuous variables were compared by the Student's t-test and categorical variables by the chi-square test or Fisher's exact test. Follow-up data was analyzed by the paired t-test. Correlation between variables was computed using Pearson's correlation coefficient. A two tailed p value <0.05 was considered to be significant.

### **Results**

#### **Demographic Data**

Thirty percent of the patients were of rural background. The patients

were evenly distributed throughout the state, with no region having a clustering of cases. There was a male preponderance (53:27). Only 20% of the patients belonged to poor socio-economic strata (monthly family income <1,500 rupees). None of the patients gave a history of consuming cassava in their diet.

### Clinical features

Abdominal pain was present in 68 (85%) cases. The onset of pain was always prior to the detection of diabetes. The mean age at onset of diabetes was  $27.1 \pm 10.1$  years (range 11-60 years), with 76% of subjects having an onset <30 years. In comparison, patients with type 1 diabetes had an earlier age at the onset of diabetes ( $13.3 \pm 7.1$  years,  $p < 0.001$ , Table 1)

**Table 1: A comparison between clinical features of patients with FCPD and type 1 diabetes**

	Type 1 Diabetes	FCPD	P Value
Age (years)	$15.9 \pm 9.0$	$31.0 \pm 11.1$	<0.001
Onset of diabetes (years)	$13.3 \pm 7.1$	$27.1 \pm 10.1$	<0.001
Duration of diabetes (years)	$2.6 \pm 4.3$	$4.0 \pm 5.0$	0.054
BMI ( $\text{kg}/\text{m}^2$ )	$17.1 \pm 4.4$	$17.9 \pm 3.1$	0.17
Serum albumin (g/l)	-	$38 \pm 7$ (n=57)	-
HbA1c (%) (normal range 4%-6%)	$8.9 \pm 3.2$	$8.1 \pm 3.1$	0.23
Fasting serum C-peptide (nmol/l)	$0.17 \pm 0.15$ (n=22)	$0.29 \pm 0.20$ (n=44)	0.014
Ketosis	59/84 (70%)	10/80 (12%)	<0.001

*Note: Values are as Mean  $\pm$  SD. FCPD: fibrocalculous pancreatic diabetes; BMI: body mass index; HbA1c: hemoglobin A1c*

The mean BMI at presentation was  $17.9 \pm 3.1$   $\text{kg}/\text{m}^2$  (range 10.5-24.5  $\text{kg}/\text{m}^2$ ). A low BMI (< 18  $\text{kg}/\text{m}^2$ ) was found in 55% of FCPD patients, while serum albumin was diminished (<35 g/l) in 26% of patients. None of the patients had parotid gland enlargement, a cyanotic hue or

nutritional edema. Subjects with low BMI had a significantly shorter duration of pain compared to those with normal BMI ( $8.6 \pm 7.7$  years vs.  $13.7 \pm 10.5$  years,  $p < 0.05$ ); however, they could not be differentiated on the basis of their socio-economic status, hemoglobin A1c, C-peptide or fecal chymotrypsin levels.

At the time of diagnosis of diabetes, hyperglycemia was of variable severity. Fifty four (67%) patients were controlled with diet or oral hypoglycemic agents, including 9 (12%) patients who were asymptomatic and diagnosed after an OGTT. At the other end of the clinical spectrum, 26 (33%) patients presented with severe insulin-requiring diabetes, though only 2 patients had ketosis at onset. Of the 54 patients on diet/oral hypoglycemic agents at diagnosis, 24 subjects had a duration of diabetes  $> 5$  years when they presented to our hospital. Twenty of these 24 patients (83%) required insulin injections for glycemic control. Patients requiring diet/oral hypoglycemic agents at onset could be differentiated from subjects treated with insulin by an later age at onset of diabetes, and lower plasma glucose and HbA1c (Table 2). However fasting serum C-peptide in the two groups did not differ.

**Table 2: Comparison between FCPD patients treated with insulin versus diet/oral agents**

	Diet/OHA	Insulin	P value
N	54	26	
Age at onset of diabetes (years)	$28.7 \pm 10.6$	$23.7 \pm 8.3$	0.04
Age of onset of pain (years)	$19.7 \pm 8.6$	$17.0 \pm 8.8$	0.23
Duration of diabetes (years)	$3.8 \pm 4.3$	$4.3 \pm 6.3$	0.67
Gap between pain and diabetes (years)	$9.0 \pm 8.9$	$7.6 \pm 6.3$	0.48
BMI ( $\text{kg}/\text{m}^2$ )	$18.1 \pm 2.9$	$17.4 \pm 3.6$	0.38
Plasma glucose at onset (mmol/l)	$15.7 \pm 6.0$	$20.3 \pm 5.6$	0.01
HbA1c (%)	$7.3 \pm 2.6$	$9.7 \pm 3.8$	0.005
Fasting serum C-peptide (nmol/l)	$0.30 \pm 0.18$ (n=29)	$0.22 \pm 0.14$ (n=15)	0.12

*Note: Values are as Mean  $\pm$  SD. FCPD: fibrocalculous pancreatic diabetes; HbA1c: hemoglobin A1c, BMI: body mass index.*

## **Family history**

A history of type 2 diabetes was present in first-degree relatives in 36% of patients. Eight (10%) patients had family history of tropical calcific pancreatitis.

## **β-cell and exocrine function**

FCPD patients presented with a wide range of fasting serum C-peptide (0.03-0.76 nmol/l). C-peptide levels were higher compared to subjects with type 1 diabetes (Table 1). Fasting C-peptide showed a positive correlation with BMI ( $r=0.42$ ,  $p=0.004$ ), and a negative correlation with duration of diabetes ( $r=-0.48$ ,  $p=0.001$ ). Fecal chymotrypsin was severely diminished ( $1.2\pm 3.2$  U/g of stool, normal  $>8.4$  U/g;  $n=62$ ). Chymotrypsin levels were not related to duration of pancreatitis or to fasting C-peptide.

## **Complications**

Twelve patients (15%) had diabetic retinopathy (10 with background and 2 with proliferative changes). Nephropathy was present in 15 (19%) subjects, while 21 (26%) had peripheral neuropathy. No patient with duration of diabetes  $< 2$  years had any microvascular complications.

## **Mortality**

Of the 50 (63%) patients on whom current information was available, 6 (12%) had died. Two patients died due to carcinoma of pancreas, 2 of chronic renal failure secondary to diabetic nephropathy, 1 of cirrhosis related to hepatitis B infection and 1 of septicemia.

## **Prospective follow up**

Subjects ( $n=30$ ) had significant improvement in their nutritional status (BMI  $19.4\pm 2.9$  kg/m<sup>2</sup> vs.  $17.0\pm 3.7$  kg/m<sup>2</sup>,  $p<0.001$ ); 75% of the patients gained in weight. There was also an improvement in glycemic control (HbA1c  $6.4\%\pm 1.6\%$  vs.  $8.0\%\pm 3.0\%$ ,  $p<0.001$ ). Two patients (6%) died (one due to septicemia and one of chronic renal failure). All patients who were living were able to resume their previous occupation.

## Discussion

The patients we have described differ in many respects from the older descriptions of FCPD (1-9, 11-15). In previous reports, the disease occurred predominantly in economically deprived subjects, who were emaciated and suffered from numerous nutritional deficiencies (3-9, 11-15). In contrast, 80% of our patients belonged to a middle or upper income group. Similarly, only a half of our patients had a low BMI, only a third had low serum albumin levels, while parotid gland enlargement and nutritional edema were not encountered. These facts strengthen the hypothesis that protein calorie malnutrition does not play a primary role in the susceptibility to FCPD (1-3, 18). Subjects with low BMI had a shorter duration of pain, suggesting that their pancreatitis may be more severe. As in many previous studies (1, 8, 10, 15, 16, 19, 20), intake of cyanogenic glycosides from cassava was not a risk factor in this cohort. There was a high prevalence of chronic pancreatitis in family members, suggesting that genetic factors may be important in its etiology (21).

In contrast to older reports, where most patients at onset had severe insulin-requiring diabetes (1-12, 15), two-thirds of the patients in the current study were initially controlled on diet/oral hypoglycemic agents. Heterogeneity of clinical presentation has also been reported in two recent studies from different regions of India (22, 23). The only clinical characteristics differentiating patients requiring diet/oral hypoglycemic agents or insulin were that the latter were younger, and had worse glycemic control. In contrast to previous reports (22), fasting C-peptide levels did not differ significantly between these two groups of patients.

It has been previously reported that FCPD subjects have markedly diminished C-peptide levels (3, 24, 25). In contrast, in the current study, as well as in other recent studies conducted by others (22, 23, 26), and by our group (27), b-cell function varied widely at presentation. This may reflect the fact that patients now present earlier in the course of their illness. We found that b-cell function was negatively associated with increasing duration of diabetes. This is the likely reason why a large proportion of FCPD patients on diet/oral medications required insulin after 5 years. In their conversion to a state of insulin-dependence over a short time period, these FCPD patients clinically resemble subjects

with slowly progressive type 1 diabetes (28).

In contrast to b-cell function, exocrine function was markedly diminished in all FCPD subjects by the time of presentation. As we have shown previously (16, 27), there was no correlation between fecal chymotrypsin levels and C-peptide levels. While chronic inflammatory changes in the exocrine pancreas may lead to  $\beta$ -cell damage and diabetes, other factors, such as islet cell regeneration (29), may influence the further rate of decline of  $\beta$ -cell function. Our data are in contrast to an earlier study by Yajnik et al (23), which reported that b-cell dysfunction and exocrine function are directly correlated.

It was earlier believed that being a secondary diabetes, microvascular complications might be uncommon in FCPD (5, 8). However, we detected a high prevalence of such complications in this relatively young population. This confirms data from more recent studies from other parts of India (10, 22, 30). Unlike in type 2 diabetes, none of the patients with duration of diabetes <2 years had any microvascular complications. This may reflect the relatively abrupt onset of symptoms of diabetes in FCPD patients.

Patients with FCPD, in addition to having to manage diabetes, also have the burden of complications related to pancreatitis, including recurrent abdominal pain and steatorrhoea. Enzyme supplements are expensive and most of our patients could not afford these on a regular basis. Despite these difficulties, the prospective arm of our study showed that FCPD patients did well on follow-up. Despite having severely diminished fecal chymotrypsin levels, they exhibited a sustained, significant improvement in weight. They also had improvement in their glycemic control with therapy and were able to resume their prior occupations.

In our entire cohort, 6 (12%) patients died, but this figure is likely to be an underestimate since we could not obtain follow-up information on 30 (37%) patients. In our prospective study, only 2 of 30 (6%) patients died. Renal failure and carcinoma of the pancreas were the two most common causes of mortality. This data is similar to a recent study on a large cohort of FCPD patients in which, due to a longer life expectancy

after diagnosis, the two commonest causes of mortality were diabetic nephropathy and pancreatic carcinoma. (31). These data are in contrast to older studies (4), and to more recent study by Yajnik et al (10), where a high mortality rate has been noticed mainly due to infectious diseases, malnutrition and acute diabetes-related complications.

Why is the presentation in the current study different from those reported earlier? Our patients were mainly from the middle-class (rather than from more deprived sections), and are likely to have sought medical advice earlier in the course of their illness. They are likely to have received better medical care compared to that available earlier. Two studies from the same region in south India, conducted more than two decades apart, have reported changes in clinical presentation similar to what we observed (8, 22). This suggests that that genetic heterogeneity is unlikely to be the reason for the observed differences. This conclusion is supported by reports that the genetic predisposition to FCPD appear to be similar in different regions of the subcontinent (32-34)

Our cohort of FCPD patients differed from those described in earliest reports in that they had an improved nutritional status, a varied clinical presentation and course, wide range of beta-cell function, and a relatively good prognosis.

## References

1. Barman KK, Premalatha G, Mohan V: Tropical chronic pancreatitis. *Postgrad Med J* 79: 606-615, 2003
2. Rao RH: Diabetes in the undernourished: coincidence or consequence? *Endocrine Rev* 9: 67-87, 1988
3. Abu-Bakare A, Taylor R, Gill GV, Alberti KGMM: Tropical or malnutrition-related diabetes: a real syndrome? *Lancet* i: 1135-1138, 1986
4. Geevarghese PJ: Pancreatic diabetes. Popular Prakashan, Bombay, 1968
5. Geevarghese PJ, Pillai VK, Joseph MP, Pitchumoni CS: The diagnosis of pancreatogenous diabetes mellitus. *J Assoc Physicians India* 10: 173-180, 1973
6. Shaper AG: Chronic pancreatic disease and protein malnutrition. *Lancet* i: 1223-1224, 1960
7. Zuidema PJ: Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. *Trop Geogr Med* 11: 70-74, 1959
8. Viswanathan M: Pancreatic diabetes in India: an overview. In *Secondary diabetes: The spectrum of the diabetic syndromes*. Podolsky S, Viswanathan M, Eds. New York, Raven Press, 1980, p. 105-116
9. Chandraprasert S, Samranvej P, Arthanchinta S, Isarena S: Diabetes mellitus and tropical form of chronic calcific pancreatitis in Thailand. *Aust N Z J Med* 6: 316-320, 1976
10. Yajnik CS, Shelgikar KM: Fibrocalculous pancreatic diabetes in Pune, India. Clinical features and follow-up for 7 years. *Diabetes Care* 16: 916-921, 1993
11. Nagartnem N, Gunawardene KRW. Aetiological factors in pancreatic calcification in Ceylon. *Digestion* 5: 9-16, 1972
12. Kinnear TWA: Patterns of diabetes in a Nigerian teaching hospital. *W Afr Med J* 40: 228-233, 1963
13. McMillan DE, Geevarghese PJ: Dietary cyanide and tropical malnutrition diabetes. *Diabetes Care* 2: 202-208, 1979
14. Vannasaeng S, Nitiyanant W, Vichayanrat A: Case control study on risk factors associated with fibrocalculous pancreatic diabetes. *Diabetic Med* 5: 835-839, 1988
15. Tripathy BB, Samal KC: Chronic calcific pancreatitis with diabetes in the young in Orissa. In: *Chronic pancreatitis in India: proceedings of a workshop on chronic pancreatitis*. Balakrishnan V, Thankappan KR, Eds. Trivandrum, Kerala, St Joseph's Press p. 87-96, 1987
16. Bhatia E, Baijal SS, Kumar R, Choudhuri G: Exocrine pancreatic and b-cell function in malnutrition related diabetes among North Indians. *Diabetes Care* 18: 1174-1178, 1995

17. World Health Organization. Diabetes Mellitus: report of a WHO study group. World Health Organ Tech Rep Ser 727, 1985
18. Hoet JJ, Tripathy BB: Malnutrition and diabetes in the tropics. *Diabetes Care* 19:1014-1017, 1996
19. Swai ABM, Mclarty DG, Mtinangi BL Tatala S, Kitange HM, Mlinge N, Rosling H, Howett WP, Brubaker GR, Alberti KGMM. Diabetes is not caused by cassava toxicity. A study in a Tanzanian community. *Diabetes Care* 15: 1378-1385, 1992
20. Teuscher T, Baillod P, Rosman JB, Teuscher A: Absence of diabetes in a rural West African population with a high carbohydrate/cassava diet. *Lancet* i: 765-768, 1987
21. Mohan V, Chari ST, Hitman GA, Suresh S, Madanagopalan N, Ramachandran A, Viswanathan M: Familial aggregation in tropical fibrocalculous pancreatic diabetes. *Pancreas* 4: 690-693, 1989
22. Mohan V, Mohan R, Susheela L, Snehalatha C, Bharani G, Mahajan VK, Ramachandran A, Viswanathan M, Kohner EM: Tropical pancreatic diabetes in south India: heterogeneity in clinical and biochemical profile. *Diabetologia* 28: 229-232, 1985
23. Yajnik CS, Shelgikar KM, Sahasrabudhe RA, Naik SS, Pai VR, Alberti KGMM, Hockadat TD, Kattrak A, Dandona P: The spectrum of pancreatic exocrine and endocrine (beta cell) function in tropical calcific pancreatitis. *Diabetologia* 33: 417-421, 1990
24. Vannasaeng S, Nitiyanat W, Vichayanrat A, Ploybutr S, Harthong S: C-peptide secretion in calcific tropical pancreatic diabetes. *Metabolism* 35:814-817, 1986
25. Yajnik CS, Shelgikar KM, Naik SS, Kanitkar SV, Orskov H, Alberti KGMM, Hockaday TDR: The ketosis-resistance in fibro-calculous-pancreatic-diabetes. Clinical observations and endocrine-metabolic measurements during oral glucose tolerance test. *Diabetes Res Clin Pract* 15,2,149-56, 1992.
26. Yajnik CS, Kanitkar SV, Shelgikar KM, Naik SS, Alberti KGMM, Hockaday TDR: Pancreatic C-peptide response to oral glucose in fibrocalculous pancreatic diabetes. Improvement after treatment. *Diabetes Care* 13:525-527, 1990
27. Mehrotra RN, Bhatia E, Chouduri G: b-cell function and insulin sensitivity in tropical calcific pancreatitis from North India. *Metabolism* 46:441-444, 1997
28. Leslie RDG, Pozzilli P. Type 1 diabetes masquerading as type 2 diabetes. *Diabetes Care* 17, 1214-1219, 1994
29. Govindrajan M, Mohan V, Deepa R, Ashok S, Pitchomoni CS: Histopathology and immunohistochemistry of pancreatic islets in fibrocalculous pancreatic diabetes. *Diabetes Res Clin Pract* 51, 29-38, 2001
30. Geevarghese PJ, Abraham A: Diagnosis, course and complications. In *Calcific pancreatitis and diabetes in the tropics*. Geevarghese PJ, Abraham A, Eds. Trivandrum, St Joseph's Press, p 99-107, 1995

31. Mohan V, Premalatha G, Padma A, Chari ST, Pitchumoni CS: Fibrocalculous pancreatic diabetes. Long-term survival analysis. *Diabetes Care* 19: 1274-1278, 1996.
32. Bhatia E, Choudhuri G, Sikora SS, Landt O, Kage A, Becker M, Witt H. Tropical calcific pancreatitis: strong association with SPINK1 trypsin inhibitor mutations. *Gastroenterology* 123: 1020-1-25, 2002
33. Schneider A, Suman A, Rossi L, Beglinger C, Parvin S et al. SPINK1/PST1 mutations are associated with tropical pancreatitis and type 2 diabetes in Bangladesh. *Gastroenterology* 123: 1026-1030, 2002
34. Chandak GR, Idris MM, Reddy DN, Mani KR, Bhaskar S, Rao GV, Singh L. Absence of PRSS1 mutations and association of SPINK1 trypsin inhibitor mutations in hereditary and non-hereditary chronic pancreatitis. *Gut* 53:723-728, 2004

