Fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes, unique to tropical countries. In earlier reports, patients with FCPD had severe insulin-requiring diabetes, malnutrition and a dismal prognosis. With improvements in nutrition and medical care, the presentation and earlier reports, patients with FCPD had severe insulin-requiring diabetes; these patients were younger [23.7 (8.3) years vs. 28.7 (10.6) years, p = 0.04], and had higher haemoglobin A1c [9.7%].

The clinical spectrum of fibrocalculous pancreatic diabetes in north India

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ABSTRACT

Background. Fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes, unique to tropical countries. In earlier reports, patients with FCPD had severe insulin-requiring diabetes, malnutrition and a dismal prognosis. With improvements in nutrition and medical care, the presentation and prognosis of FCPD may have changed. We report on the clinical profile and prognosis of a cohort of FCPD patients from north India and compare our findings with earlier reports.

Methods. Eighty consecutive FCPD patients who presented to the Diabetes, Gastroenterology and Surgical Gastroenterology services were evaluated for their nutritional status, clinical presentation, β-cell function (fasting C-peptide) and exocrine function (faecal chymotrypsin). All patients diagnosed between 1994 and 2000 (n = 32) were followed prospectively for weight gain and glycaemic control.

Results. Only 55% of FCPD patients had a low body mass index (< 18 kg/m²). At the time of diagnosis of diabetes, only 26 (33%) patients presented with severe insulin-requiring diabetes; these patients were younger [23.7 (8.3) years vs. 28.7 (10.6) years, p = 0.04], and had higher haemoglobin A1c [9.7%].
INTRODUCTION
Fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes, unique to developing countries in tropical regions.1-16 The disease has most commonly been reported from the south Indian state of Kerala,4 but is prevalent throughout India.1 Patients present at an early age with abdominal pain and often develop diabetes before the age of 30 years. The aetiology of FCPD is obscure.1-3 Established risk factors such as alcohol intake, hyperparathyroidism and biliary tract stones are absent. Environmental factors such as protein-calorie malnutrition1-3,6-8,12-15 or the consumption of cassava, a source of cyanogenic glycosides,4,11 are believed to be important in its pathogenesis.

Earlier reports described the disease as occurring among young adults of a poor socioeconomic status.2-15 The patients presented with emaciation, nutritional deficiencies, and severe insulin-dependent (but ketosis-resistant) diabetes.2-10,14,15 The prognosis was described as dismal, with most patients succumbing to the disease within a few years of diagnosis.4 More recently, Yajnik et al. from Pune have described a high mortality rate from infections and acute complications related to diabetes among FCPD patients.10

As a result of improvements in the socioeconomic status and standards of medical care, the clinical presentation and prognosis of patients with FCPD is likely to be different from that previously reported. We report upon the clinical profile and prognosis of FCPD patients who presented to our hospital over a 12-year period and compare our findings with those reported previously.

PATIENTS AND METHODS
Patients
Eighty consecutive FCPD patients, 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 (on abdominal ultrasonography or computerized tomography) and diabetes mellitus.17 Patients with a history of alcohol intake or having obstructive biliary tract disease or hypercalcaemia on investigations were excluded.

All patients belonged to the north Indian state of Uttar Pradesh or adjacent regions. In addition to those with a classical history of abdominal pain and/or steatorrhoea, we screened all patients with onset of diabetes at <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 (severe hyperglycaemia, insulin-dependence since diagnosis, absence of pancreatic calcification on ultrasonography), seen in the Endocrinology Department during the same time period, were used for comparison with FCPD patients. The study was approved by our institutional ethics committee.

Clinical evaluation
Patients were evaluated at the time of presentation for their nutritional status—body mass index (BMI), clinical signs of malnutrition and 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 the urine dipstick test was positive for protein (subsequently confirmed by 24-hour urine protein >0.5 g), or if serum creatinine was >150 μmol/L. Peripheral neuropathy was defined as bilateral absence of ankle jerks and/or objective evidence of sensory loss in the lower extremities. Glycaemic control was assessed by haemoglobin Alc (HbA1c) and β-cell function was evaluated by measuring the fasting C-peptide level. Exocrine pancreatic function was measured by faecal chymotrypsin.

Follow up
All patients diagnosed between 1994 and 2000 (n=32) were followed prospectively for their nutritional status, glycaemic control and ability to return to their previous occupations. Of these, 30 patients had at least one follow up visit during 1999-2000. The mean duration of follow up was 3.2 years (range: 6 months–6 years).

Investigations
Haemoglobin 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). The intra-assay and inter-assay coefficient of variation were 6% and 8.5%, respectively. Faecal chymotrypsin was measured using an enzymatic technique (Boehringer Mannheim, Mannheim, Germany). The intra-assay and inter-assay coefficient of variation for the assay were 3% and 7%, respectively.

Statistics
The results were expressed as mean (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 were analysed 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 per cent of the patients were from a rural background. The patients were evenly distributed throughout the state, with no region having a clustering of cases. There was a preponderance of men (53.2%). Only 20% of the patients belonged to poor socioeconomic strata (monthly family income <Rs 1500). None of the patients gave a history of consuming cassava in their diet.

Clinical features
The mean (SD) age at presentation of diabetes was 27.1(10.1) years (range: 11–60 years); 76% of patients diagnosed were <30
years of age. In comparison, patients with type 1 diabetes had an earlier age at presentation [13.3 (7.1) years, p<0.001, Table I].

The BMI at presentation was 17.9 (3.1) kg/m² (range 10.5-24.5 kg/m²); a low BMI (<18 kg/m²) was found in 55% of FCPD patients. Serum albumin was diminished (<35 g/L) in 26% of patients. None of the patients had parotid gland enlargement, a cyanotic hue or nutritional oedema. Patients with a low BMI had a significantly shorter duration of pain compared to those with normal BMI [8.6 (7.7) years v. 13.7 (10.5) years, p<0.05]. However, they could not be differentiated on the basis of their socioeconomic status, haemoglobin A₁c, C-peptide or faecal chymotrypsin levels.

At the time of diagnosis of diabetes, hyperglycaemia was of variable severity. Twenty-six patients (33%) presented with severe hyperglycaemia and required insulin. Of these, only 2 had ketosis at onset. At the end of the clinical spectrum, 54 (67%) patients were controlled with diet or oral hypoglycaemic agents. Patients requiring diet or oral hypoglycaemic agents at onset could be differentiated from those treated with insulin by a later age at presentation of diabetes, and lower plasma glucose and HbA₁c (Table II). However, fasting serum C-peptide in the two groups did not differ. Nine (12%) patients had no symptoms of hyperglycaemia and were diagnosed after an OGTT. These patients had significantly lower post-meal plasma glucose [233 (27) mg/dl v. 330 (103) mg/dl, p<0.001] and haemoglobin A₁c [5.1 (1.4) v. 8.4 (3.2)%, p<0.001] compared to other FCPD patients. However, other variables did not reach statistical significance.

Of the patients initially on diet/oral hypoglycaemic agents at diagnosis (n=54), 24 patients had a duration of diabetes >5 years when they presented to our hospital. Twenty of these 24 patients (83%) required insulin injections for glycaemic control.

### FCPD patients with a wide range of fasting serum C-peptide (0.03-0.76 nmol/L). Serum C-peptide was higher compared to patients with type 1 diabetes (Table I). Fasting serum C-peptide showed a negative correlation with duration of diabetes (r=-0.48, p=0.001). Faecal chymotrypsin was severely diminished [1.2 (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 levels.

### Microvascular complications

Twelve patients (15%) had diabetic retinopathy (10 with background and 2 with proliferative changes). Nephropathy was present in 15 (19%) patients, while 21 (26%) had peripheral neuropathy. No patient with diabetes for <2 years had any microvascular complications. The prevalence of each of these complications increased if the duration of diabetes was >5 years (retinopathy 33% v. 7%, p=0.01; nephropathy 29% v. 4%, p=0.003; peripheral neuropathy 63% v. 11%, p<0.001).

### Mortality

Current information was available for 50 (63%) patients. Six patients died during the follow up period. Two patients died due to carcinoma of the pancreas, 2 of chronic renal failure secondary to diabetic nephropathy, and 1 each of cirrhosis related to hepatitis B infection and sepsisemia.

### Prospective follow up

Patients (n=32) had significant improvement in their nutritional status [BMI 19.4 (2.9) kg/m² v. 17.0 (3.7) kg/m², p<0.001]; 75% of the patients gained weight. There was also an improvement in glycaemic control [HbA₁c 6.4 (1.6)% v. 8.0 (3.0)%; p<0.001]. Two patients (6%) died—one due to sepsicaemia and one of chronic renal failure. All the remaining patients were able to resume their previous occupations.

### DISCUSSION

The patients in our study differ in many respects from those reported earlier. In previous reports, FCPD occurred predominantly in economically deprived people, who were emaciated and suffered from numerous nutritional deficiencies. In contrast, 80% of our patients belonged to the middle or upper income groups. Similarly, only half of our patients had a low BMI, less than a third had low serum albumin levels, while parotid gland enlargement and nutritional oedema were not encountered. Patients with low BMI had a shorter duration of pain, suggesting that their pancreatitis may be more severe. In contrast to previous reports, the intake of cyanogenic glycosides from cassava was not a risk factor in this cohort. Large epidemiological studies in Africa have earlier failed to find an association between consumption of cassava and FCPD.

In older reports, as well as in some recent studies, most FCPD patients had severe insulin-requiring diabetes at onset. In contrast, in the current study, two-thirds of the patients were initially controlled on diet/oral hypoglycaemic agents. The only clinical characteristics differentiating patients requiring diet/oral medications or insulin were that the latter were younger, and had worse glycaemic control. Fasting C-peptide levels did not differ significantly between these two groups of patients. One reason for

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### Table I. Clinical features of patients with fibrocalculous pancreatic diabetes and type 1 diabetes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1 diabetes</th>
<th>FCPD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.9 (9.0)</td>
<td>31.0 (11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset of diabetes (years)</td>
<td>13.3 (7.1)</td>
<td>27.1 (10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>2.6 (4.3)</td>
<td>4.0 (5.0)</td>
<td>0.054</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>17.1 (4.4)</td>
<td>17.9 (3.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td></td>
<td>38 (7)*</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin A₁c (%)</td>
<td>8.9 (3.2)</td>
<td>8.1 (3.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Fasting C-peptide (nmol/L)</td>
<td>0.17 (0.15)†</td>
<td>0.29 (0.20)*</td>
<td>0.014</td>
</tr>
<tr>
<td>Ketosis</td>
<td></td>
<td>59/84 (70%)</td>
<td>10/80 (12%)</td>
</tr>
</tbody>
</table>

*All values are mean (SD) unless stated. † n=44 FCPD fibrocalculous pancreatic diabetes * n=29 † n=22

### Table II. Comparison between patients with fibrocalculous pancreatic diabetes treated with insulin or diet/oral hypoglycaemics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Diet/oral hypoglycaemics (n=54)</th>
<th>Insulin (n=26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of diabetes (years)</td>
<td>28.7 (10.6)</td>
<td>23.7 (8.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age at onset of pain (years)</td>
<td>19.7 (8.6)</td>
<td>17.0 (8.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>3.8 (4.3)</td>
<td>4.3 (6.3)</td>
<td>0.67</td>
</tr>
<tr>
<td>Gap between onset of pain and diabetes (years)</td>
<td>9.0 (8.9)</td>
<td>7.6 (6.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>18.1 (2.9)</td>
<td>17.4 (3.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Plasma glucose at onset (mmol/L)</td>
<td>15.7 (6.0)</td>
<td>20.3 (5.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Haemoglobin A₁c (%)</td>
<td>7.3 (2.6)</td>
<td>9.7 (3.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fasting serum C-peptide (nmol/L)</td>
<td>0.30 (0.18)*</td>
<td>0.22 (0.14)†</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*All values are mean (SD) * n=29 † n=15
this may be that patients were tested after varying durations of the onset of diabetes. Heterogeneity in clinical presentation has been previously reported in a study on south Indian FCPD patients. In our current study, as well as in an earlier study conducted by us, β-cell function varied widely at presentation. This may be the result of a variable rate of loss of β-cell function, or because patients presented at different stages of pancreatitis. Two recent reports from other regions of India have also described variable C-peptide levels in FCPD patients. In contrast, in the earliest reports, FCPD patients had markedly diminished C-peptide levels. In a study on a large cohort of FCPD patients, the two commonest causes of mortality were diabetic nephropathy and carcinoma pancreas. These data are in contrast to older studies, and to a more recent study by Yajnik and Shelgikar, where a high mortality rate was observed mainly due to infectious diseases, malnutrition and acute diabetes-related complications.

There may be several reasons why the presentation in the present study was different from those reported earlier. Our patients were mainly from the middle income group (rather than more deprived sections), and were likely to have a better nutritional status. They were also likely to have sought medical advice earlier in the course of their illness and have received better medical care compared to that available earlier. In contrast to previous studies, we also included patients presenting to the Gastroenterology and Surgical Gastroenterology services, some of whom were diagnosed by an OGTT and had milder glucose intolerance. Genetic heterogeneity among FCPD patients from different regions is unlikely to be the reason for the observed differences. In two studies from a different part of India (Tamil Nadu), but conducted more than two decades apart, differences in clinical presentation similar to those described by us were noted.

In conclusion, our cohort of FCPD patients differed from those previously described in that they had an improved nutritional status, a varied clinical presentation and course, wide range of β-cell function, and a relatively good prognosis.

REFERENCES

Explanatory models and common mental disorders among patients with unexplained somatic symptoms attending a primary care facility in Tamil Nadu


ABSTRACT

Background. Patients with unexplained somatic symptoms are commonly seen in primary care. We assessed the explanatory models and common mental disorders in patients with unexplained somatic symptoms attending a primary care facility in a rural area of south India.

Methods. One hundred consecutive patients diagnosed to have unexplained somatic symptoms attending a primary care facility were examined. The Tamil version of the Revised Clinical Interview Schedule was used to assess common mental disorders and the Tamil version of the Short Explanatory Model Interview was used to assess their explanatory models.

Results. Ninety-eight patients thought that their problem was serious. Sixty-nine, 41 and 40 claimed that it affected their work, family and social lives, respectively. Forty-two claimed that it affected their health, work, family and social lives, respectively. Sixty-nine, 41 and 40 claimed that it affected their work, family and social lives, respectively.

Conclusion. The majority of patients held strong beliefs regarding the serious nature of their complaints, believed in the serious nature of the problem and feared disability or death. There is a need to elicit specific explanatory models regarding the nature of illness in patients who present with somatic symptoms without organic causes. Understanding the patient's perspectives is a prerequisite for providing the necessary treatment and to dispel fears.

INTRODUCTION

Common mental disorders (CMDs) are among the most frequent causes of morbidity and disability worldwide.1 Several studies have examined the mental health needs of patients attending primary care centres in India (Table I) and have documented that 17%-46% of patients attending these facilities suffer from CMDs.2-9 These patients are frequent users of medical facilities and are a major burden to their families, healthcare services and society.

Patients presenting with physical symptoms without an organic cause (somatizers) usually have CMDs.10-13 Kisely et al.14 measured the physical and psychiatric morbidity among subjects attending primary care in 14 countries. The presence of somatic symptoms, irrespective of aetiology, was associated with social and psychiatric morbidity. Patients who had 5 or more medically unexplained symptoms were significantly younger, had greater psychiatric morbidity, abused alcohol and