Original Article

Prevalence of End-Organ Damage, Beta Cell Reserve, and Exocrine Pancreas Defect in Fibrocalculous Pancreatic Diabetes: An Eastern India Perspective

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Abstract

Background: Data on prevalence and burden of end-organ damage in fibrocalculous pancreatic diabetes (FCPD) from eastern India is scant. This study investigated the burden of end-organ damage and exocrine pancreatic defect in FCPD patients in Eastern India. **Materials and Methods:** Consecutive FCPD patients underwent evaluation of glycemic control, C-peptide, fecal elastase, body fat percent, tests for cardiac autonomic neuropathy (CAN), neuropathy, nephropathy, and retinopathy which were compared with data from type-1 diabetes (T1DM) and type-2 diabetes (T2DM). **Results:** Data from 101 FCPD, 41 T1DM, 40 T2DM, and 40 controls were analyzed. Body fat percent was lowest in FCPD and T1DM. Similarly, fasting and stimulated C-peptide was significantly lowest in T1DM, followed by FCPD. Significant elevations in stimulated C-peptide were observed in FCPD. Fecal elastase was lowest in FCPD. Exocrine pancreas defect in FCPD, T1DM, and T2DM was 100%, 53.66%, 27.5%, respectively. HbA1c was worst in FCPD. About 40% of FCPD patients had CAN while 13.33% had borderline CAN. Isolated parasympathetic dysfunction was the commonest (66.67%) among them. FCPD patients with CAN had lower fecal elastase, higher HbA1c, microalbuminuria, steatorrhea, neuropathy, retinopathy, and nephropathy, compared to those without CAN. On binary logistic regression, diabetes duration was a significant predictor of end-organ damage in FCPD. Fecal elastase and body fat percent were independent predictors for insulin therapy in FCPD. **Conclusion:** CAN is common in FCPD while exocrine pancreas defect is most severe in FCPD followed by T1DM and T2DM. Fecal elastase has an important prognostic role for insulinization in FCPD. Role of pancreatic enzyme replacement on glycemic control in diabetes with exocrine pancreas defect needs investigation.

Keywords: End-organ damage, exocrine defect, fibrocalculous pancreatic diabetes

Introduction

Tropical calcific pancreatitis with diabetes, better known as fibrocalculous pancreatic diabetes (FCPD) is a rare variant of diabetes, predominantly limited to the tropics and characterized by pancreatic intraductal calcifications with typically ketosis-resistant lean diabetes; associated with progressive and irreversible destruction of the pancreatic parenchyma.[1,2] Etiopathogenesis is multifactorial and not yet well determined, with malnutrition, cassava intake, micronutrient deficiencies, serine protease inhibitor kazal type 1 (SPINK-1) gene variations being implicated.[1-3] In contrast to the initial belief that, end-organ damage (microvascular and macrovascular complications) are uncommon in FCPD; recent reports have suggested the increased occurrence of such complications in FCPD.[3] However, the data on the burden of end-organ damage in FCPD remains scant, especially for eastern India. This study aimed to determine the burden of end-organ damage and severity of the pancreatic exocrine defect in a cohort of FCPD patients from eastern India.

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Methods

This was a cross-sectional observational study carried out from January 2014–December 2016. Consecutive patients diagnosed with FCPD, attending the diabetes clinic of the Department of Endocrinology and Metabolism at Institute of Postgraduate Medical Education and Research, Kolkata were considered for the study. FCPD was diagnosed as per the criteria proposed by Mohan *et al*. viz.

1. Occurrence in a "tropical" country/region,
2. Diabetes by the WHO study group criteria, and
3. Evidence of chronic pancreatitis with pancreatic calculi visualized on X-ray or at least three of the following [Figures 1-3]:
   a) abnormal pancreatic morphology by sonography;
   b) chronic abdominal pain since childhood;
   c) steatorrhea;
   d) abnormal pancreatic function tests; along with the absence of other causes of chronic pancreatitis (alcoholism, hepatobiliary disease, and primary hyperparathyroidism).[4]

The study protocol was discussed, and only those who gave informed written consent were included in the study. Consecutive ambulatory patients of T1DM and T2DM, without any severe comorbid states (chronic liver disease, malignancy, infections, tuberculosis), disease who gave informed written consent were included in the study as diabetes controls. Normoglycemic nondiabetic hospital staff, who gave consent, were recruited as healthy controls. The Institutional Ethics Committee approved the study.

All included patients underwent a detailed clinical evaluation which included duration of diabetes, current medications, history of steatorrhea, microvascular complications, and macrovascular complications. Height (up to ± 0.1 cm) was measured in all the individuals using a Charder HM200PW wall-mounted stadiometer [calibrated using a 36" calibration rod (Perspective Enterprise, Portage, Michigan, USA)], and body weight (up to ± 100 g) measured using an electronic calibrated scale (Tanita, Japan, Model-HA521, Lot number-860525). Waist circumference was measured at the level of the umbilicus with a flexible and inextensible measuring tape. Total body fat was measured by the bioelectrical impedance between two feet by Omron, body fat monitor BF-60 (Omron Corporation, Kyoto, Japan). Increased body fat percentage was defined as >20% in males and >30% in females.[2]

Digital fundus photography was performed to assess diabetic retinopathy which was diagnosed using the early treatment of diabetic retinopathy study (EDTRS) criteria.[5] Vibration perception threshold was measured using a bioesthesiometer and neuropathy was graded as nil (VPT <15 mV), mild (15–25 mV), moderate (25–42 mV), and severe (>42 mV). Among the macrovascular complications of T2DM, only coronary artery disease (CAD) was screened for the study cohort. Clinical and/or electrocardiogram (ECG) evidence of CAD was used for CAD screening in this study.[6]

CAN was evaluated using an automated CAN System Analyzer (CANS 504), a computer-based analyzer which analyzes both sympathetic nervous system (SNS) and parasympathetic nervous system (PNS).[7] It uses an ECG (R–R interval) and an advanced automatic non-invasive blood pressure module to conduct a series of tests, elaborated elsewhere.[7] PNS evaluation included heart rate response to deep breathing expressed as expiration (E): inspiration (I) ratio; heart rate response to Valsalva maneuver expressed as Valsalva ratio; and heart rate response to standing expressed as 30:15 ratio. SNS evaluation included blood pressure response to standing assessment and blood pressure response to sustained handgrip. The criteria proposed by Ewing *et al*. were used to define normal, borderline, and abnormal values.[8] The normal and abnormal values for interpretation of the tests evaluating autonomic function have been elaborated in Table 1. The patient was defined to have PNS abnormality if ≥1 of the three tests were found to be abnormal/borderline while the patient was defined to have SNS abnormality if one of the two tests were found to be abnormal/borderline. Patients were defined as having combined PNS and SNS abnormality if any tests of PNS, as well as, SNS were abnormal or borderline.

Blood samples 5 mL each were collected in plain and EDTA vacutainer (Becton Dickinson) in overnight fasting state. Serum was separated from blood collected in plain vacutainer and processed immediately for routine biochemical analysis. Clinical chemistry autoanalyzer based on dry chemistry microslide technology (VITROS 350 chemistry system, Johnson and Johnson, USA) was used for evaluation of glucose, C-peptide, HbA1c, lipids, and renal function. One hour post standardized breakfast, blood sample was collected for evaluation of stimulated C-peptide levels. Serum C-peptide was estimated using solid-phase, enzyme-labeled chemiluminescent immunometric assay (Immulite 1000, Siemens, Gwynedd, UK). The intra-assay CV was 3.8% and inter-assay CV was 3.9%. Fresh stool samples were used for measuring the fecal elastase. The stool samples were collected and transported at room temperature (<35°C). Fecal elastase was measured by ELISA method (BIOSERV diagnostics,

Table 1: Normal and abnormal values in tests of cardiac autonomic function

Test	Normal	Borderline	Abnormal
Parasympathetic Functions			
Resting heart rate	<100 BPM	-	>100 BPM
Deep breathing (E–I Difference)	>14 BPM	11–14 BPM	<11 BPM
Standing (30:15 RR ratio)	>1.03	1.01–1.03	<1.01
Valsalva ratio	>1.20	1.10–1.20	<1.10
Sympathetic Functions			
Systolic blood pressure fall on standing	<11 mm Hg	11–29 mm Hg	>29 mm Hg
Hand Grip Test*	>15 mm Hg	11–15 mm Hg	<11 mm Hg

BPM: Beats per minute; E: Expiration; I: Inspiration; *Diastolic blood pressure changes with a sustained handgrip for 3 min

Germany). The diagnostic specificity of the assay was 95%, diagnostic sensitivity for severe chronic pancreatitis was 94%, and mild chronic pancreatitis was 63%. Intra-assay variation coefficients were: 5.2% (4.1–6.9%) for the decision limit 100 μg elastase/g stool and 4.3% (2.8–6.8%) for the decision limit 200 μg elastase/g stool. Inter-assay variation coefficients were 7.7% (6.5–9.1%) for the decision limit 100 μg elastase/g stool and 7.9% (7.1–8.9%) for the decision limit 200 μg elastase/g stool. Severe exocrine pancreatic insufficiency was defined as <100 μg elastase/g feces, moderate exocrine pancreatic insufficiency as 100–200 μg elastase/g feces and >200 μg elastase/g feces was considered as normal pancreatic exocrine function.[9,10]

Statistical analysis

Normality of the distribution of variables was checked using the Kolmogrov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation. All non-normally distributed variables were expressed as median [25–75th percentile]. Chi-square tests were used for categorical variables. A P value <0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS) version 20 (Chicago, IL, USA) was used for data analysis.

Results

Around 101 patients with FCPD, 41 patients with type-1 diabetes (T1DM), 40 patients with type-2 diabetes (T2DM), and 40 healthy controls, who gave informed written consent, were evaluated in this study. The clinical, biochemical, and end-organ damage profile of patients with FCPD, T1DM, T2DM, and healthy controls have been elaborated in Table 1. Steatorrhea was documented in 76 out of 101 FCPD patients. In patients with FCPD, the site for stone location in the pancreas was most commonly found throughout the pancreas (n = 59), followed by the head of the pancreas (n = 24), head and body (n = 16), and only in the body of the pancreas (n = 2) [Figure 2]. The average size of the largest stone in patients with FCPD was 8.95 ± 4.63 mm. Two patients of FCPD were diagnosed with pancreatic cancer.

BMI and waist circumference were significantly different among patients with FCPD, T1DM, T2DM, and healthy controls with the lowest being in patients with T1DM and FCPD [Table 2]. Percent body fat was lowest in patients with FCPD, followed by T1DM, and highest in patients with T2DM (higher than healthy controls) [Table 2]. Fasting and meal stimulated C-peptide levels were significantly different among the groups with the lowest being in patients with T1DM, followed by FCPD, and highest being in patients with T2DM. Significant elevations in postmeal C-peptide levels were seen in patients with FCPD and T2DM as compared to T1DM.

Fecal elastase was lowest in patients with FCPD (almost nondetectable), followed by patients in T1DM, T2DM, and highest in healthy controls [Table 2]. Based on fecal elastase levels, all the patients with FCPD had severe exocrine pancreas insufficiency [Table 2]. In T1DM, only 46.34% of patients had normal exocrine pancreas function [Table 2] while 31.7% and 21.95% of patients had moderate and severe exocrine pancreatic function defect [Table 2]. In T2DM patients, 72.5% had normal exocrine pancreas function, whereas 22.5% patients had moderate exocrine pancreas function defect [Table 2].

Glycemic control (HbA1c) was poor in all our study cohort patients, with the worst being in patients with FCPD, followed by T1DM and T2DM. Serum total cholesterol was significantly lowest in patients with FCPD. Other lipid parameters were comparable among the study groups. Spot urine ACR was significantly lowest in patients with FCPD [Table 2].

The details of Cardiac Autonomic Neuropathy (CAN) evaluation were available in 90 out of 101 patients with FCPD. Eight patients did not turn up for CAN evaluation and three patients refused to consent. The details of CAN in patients with FCPD have been elaborated in Table 3. Among the tests for PNS, 14% of patients had resting tachycardia. The 30:15 R–R ratio on standing was abnormal in 30% of those tested and borderline in 75 patients. None of the patients had an abnormal E: I or Valsalva ratio. Among the tests for SNS, a borderline drop in standing blood pressure was detected in 14% of patients. About 21 (23.33%) and 6 (6.67%) patients had abnormal and borderline sustained handgrip test, respectively. Since none of the patients were able to sustain handgrip for the stipulated 3 min, this parameter was not considered in the analysis and only postural drop in blood pressure was taken for the evaluation for abnormality of SNS. Considering all these tests together, 36 patients (40%) had overtly abnormal tests of CAN and 12 patients (13.33%) had borderline abnormalities in the tests of CAN. Isolated PNS dysfunction was the commonest type of CAN observed in 24 patients (66.67% of all CAN). Six patients had isolated SNS dysfunction (16.67%) and 6 patients (16.67%) had combined dysfunction of SNS and PNS.

FCPD patients with CAN had significantly lower fecal elastase levels, higher spot urine albumin creatinine ratio (ACR), and total cholesterol as compared to those without CAN [Table 4]. HbA1c was higher in FCPD patients with CAN, which approached statistical significance (P = 0.08) [Table 4]. The occurrence of steatorrhea, peripheral neuropathy, retinopathy, and nephropathy was significantly higher in FCPD patients with CAN, as compared to those without CAN [Table 4].

On binary logistic regression analysis, the duration of diabetes was a significant predictor of end-organ damage (microvascular and/or microvascular) in patients with FCPD [Table 4]. Fecal elastase, followed by percent body fat was the strongest and statistically significant independent predictor for the need of insulin for glycemic control in patients with FCPD [Table 5]. All the patients in the FCPD group (n = 91) had exocrine pancreatic insufficiency, in contrast to 33 patients (40.74%) in the non-FCPD diabetes control group (n = 81). This evaluation achieved more than 95% power, keeping type-I error (alpha) at 5%.

Table 2: Clinical and biochemical profile of patients with fibrocalculous pancreatic diabetes as compared to those with type-1, type-2 diabetes, and healthy controls

Parameter	FCPD (*n*=101)	Type-1 DM (*n*=41)	Type-2 DM (*n*=40)	Healthy Controls (*n*=40)	*P*
Age (years)	34.71±10.34	12.08±4.67	40.05±10.09	36.85±12.24	**<0.001**
Male: Female	44:57	14:27	18:22	19:21	0.632
Duration of diabetes (years)[a]	4.6 [1.25–8.0]	4 [3.0–6.0]	4 [2.0–5.0]	-	**<0.001**
BMI (kg/m^2)	18.62±3.17	18.53±2.96	24.19±5.12	24.31±2.60	**<0.001**
Waist Circumference (cm)	72.20±8.42	71.32±6.43	94.18±12.98	87.63±5.78	**<0.001**
Fasting C-peptide (ng/ml)	0.80±0.48	0.49±0.17	1.49±0.53	-	**<0.001**
1hour post meal C-peptide (ng/ml)	1.53±0.99	0.65±0.21	3.90±1.94	-	**<0.001**
Fecal Elastase (µg elastase/g stool)[a]	8 [5–19]	183 [97–314]	257 [122–460]	403 [276–500]	**<0.001**
Severity of pancreatic insufficiency					
Normal	0	19 (46.34%)	29 (72.5%)	38 (95%)	**<0.001**
Moderate	0	13 (31.70%)	9 (22.5%)	2 (5%)	**<0.001**
Severe	101 (100%)	9 (21.95%)	2 (5%)	0	**<0.001**
HbA1c (%)	9.58±2.21	8.95±1.64	8.53±1.94	4.89±0.64	**<0.001**
Ketosis	3 (2.97%)	18 (43.9%)	0	-	**<0.001**
Peripheral Neuropathy	27 (26.7%)	1 (2.43%)	12 (30%)	-	**<0.001**
Retinopathy	7 (6.93%)	1 (2.43%)	8 (20%)	-	**<0.001**
Medications					
Insulin	82	41	2	-	-
Metformin	26	0	40	-	-
Sulfonylureas	19	0	35	-	-
Pioglitazone	2	0	24	-	-
Other OADs	0	0	25	-	-
Percent Body Fat (%)	16.69±9.16	18.12±8.98	29.84±5.98	26.14±6.29	**<0.001**
Total Cholesterol (mg/dl)	153.92±36.26	155.12±21.31	164.5±38.82	178.62±35.96	**0.049**
LDL-C (mg/dl)	90.95±27.12	91.92±22.54	99.77±34.34	105.76±23.60	0.168
HDL-C (mg/dl)	46.36±13.72	47.11±18.54	41.89±8.31	50.63±10.03	0.437
Triglycerides (mg/dl)	132.21±63.54	137.17±32.18	151.93±48.32	113.3±20.41	0.114
Creatinine (mg/dl)	0.91±0.18	0.91±0.14	0.89±0.15	0.88±0.54	0.869
Spot urine ACR (mg/gm)[a]	23 [10.7–59.0]	52 [34–69]	55 [31–60]	-	**<0.001**

ACR: Albumin creatinine ratio; BMI: Body mass index; CAN: Cardiac autonomic neuropathy; DM: Diabetes; LDL: Low density lipoprotein; HDL: High density lipoprotein; HbA1c: Glycated hemoglobin; GFR: Glomerular filtration rate; All continuous variables expressed as mean (standard deviation); [a]all non-normally distributed variable expressed as median [inter quartile range]; all discreet variables have been expressed as absolute numbers (percentage);[a]not normally distributed, Kruskal-Wallis 1-way ANOVA used for analysis; normality checked using Kolmogorov-Smirnov test; $P<0.05$ considered statistically significant; [#]*P*-value calculated using Chi-square test; Retinopathy was diagnosed using EDTRS criteria; presence of nephropathy was defined as glomerular filtration rate (CKD-EPI) <60 ml/min and/or presence of microalbuminuria/overt proteinuria; presence of peripheral neuropathy was defined as defect in 10 gm Semmes-Weinstein monofilament test and/or impaired vibration perception threshold test with/without symptoms of neuropathy. Bold: $P<0.05$ suggests statistical significance

Discussion

India is witnessing an exponential increase in the burden of T2DM.[11] T2DM onset is nearly 2 decades earlier in India and Indians have one of the highest global rates of prediabetes progression to T2DM, highlighting a more aggressive disease phenotype.[12] The secular trends of FCPD in India are in sharp contrast to what we are witnessing with T2DM.[13] In an evaluation of long-term data from a center in south India, the prevalence of FCPD was documented to decrease from 1.6% during 1991–1995 to 0.2% during 2006–2010.[13] Our study looked at the prevalence of FCPD and the associated complications of diabetes in this Eastern Indian cohort.

In our cohort of 101 FCPD patients, a majority of the patients (58.41%) has diffuse disease involving the entire pancreas. FCPD patients were as lean as T1DM patients. In fact, the body fat percent was lowest in FCPD patients, even lower than T1DM. The C-peptide reserve (basal and stimulated) in FCPD patients was significantly higher in patients with FCPD as compared to T1DM, but much lower than patients with T2DM. Fecal elastase assessment has been accepted to be a reliable measure of exocrine pancreas function and considered to be a gold standard test for screening for exocrine pancreatic insufficiency in different disease states.[9,10,14] Fecal elastase level was lowest and almost negligible in patients with FCPD. Fecal elastase levels were highest in normal controls, followed by T2DM and T1DM in decreasing order. In terms of assessment for the severity of exocrine pancreas function defect based on fecal elastase levels, our study showed that the burden of exocrine pancreas defect in FCPD, T1DM,

T2DM, and in healthy controls was 100%, 53.66%, 27.5%, and 5% respectively. Hence, our study highlights that, there is a significant burden of exocrine pancreas function defect not only in FCPD but also in T1DM and T2DM. Exocrine pancreatic insufficiency (low fecal elastase) has been documented previously in T2DM.[15,16] Fecal elastase was documented to have a direct correlation with beta-cell reserve (C-peptide) and an inverse correlation with T2DM duration.[15] In a study from Chile, South America, in a cohort of 67 T2DM patients with a mean age of 60 years one-third of T2DM patients were documented to have fecal elastase deficiency.[16] Similarly, in a cohort of 323 T1DM and 697 T2DM patients from Germany, fecal elastase was normal (>200 microg/g) in 59.3% patients.[17] Moderate (100–200microg/g) and severe exocrine pancreatic insufficiency (<100 microg/g) was observed in 17.8% and 22.9% patients, respectively.[17] Lack of trophic insulin action causing acinar atrophy,[18] autonomic neuropathy leading to impaired entero-pancreatic reflexes,[19] angiopathy leading to pancreatic fibrosis,[20] and chronic inflammation causing simultaneous damage to the exocrine and endocrine portions of the parenchyma[21] are some of the theories put forward to explain pancreatic exocrine insufficiency in diabetes. Whether enzyme replacement therapy could have an impact on glucose metabolism remains speculative and warrants further research.

Our study highlighted that, glycemic control in FCPD patients was worst among the different types of diabetes. FCPD patients with a good beta-cell reserve can be effectively managed with oral antidiabetes (OAD) medication. However, FCPD patients with poor beta-cell reserve need insulin for optimal glycemic

Table 3: Profile of abnormalities in tests of cardiac autonomic function in patients with fibrocalculous pancreatic diabetes (*n*=90)

Characteristics	Normal N (%)	Borderline N (%)	Abnormal N (%)
Parasympathetic Function			
Resting Heart rate	78 (86.67)	-	12 (13.33)
Deep breathing (E:I ratio)	90 (100.00)	-	-
30:15 RR ratio on standing	57 (63.33)	6 (6.67)	27 (30.00)
Valsalva ratio	90 (100.00)	-	-
Sympathetic Function			
Systolic BP fall on standing	78 (86.67)	12 (13.33)	-
Diastolic BP change with handgrip*	63 (70.00)	6 (6.67)	21 (23.33)

*None of the patients were able to sustain handgrip for the stipulated 3 min. Hence, this parameter was not considered in the final analysis; BP: Blood pressure; N: Number of patients

Table 4: Clinical and biochemical profile of patients of fibrocalculous pancreatic diabetes with cardiac autonomic neuropathy (CAN) as compared to those without CAN

Parameter	FCPD with CAN (*n*=36)	FCPD without CAN (*n*=54)	*P*
Age (years)	35.51±9.61	33.8±10.9	0.581
Male:Female	16:20	23:31	0.862
Duration of diabetes (years)	6 [3–9]	3 [1–11.75]	0.127
BMI (kg/m^2)	18.93±3.65	17.92±2.72	0.138
Waist Circumference (cm)	71.61±9.24	72.33±8.19	0.753
Fasting C-peptide (ng/ml)	0.76±0.36	0.86±0.58	0.435
1hour post meal C-peptide (ng/ml)	1.44±0.88	1.57±0.98	0.583
Fecal Elastase (µg elastase/g stool)[a]	7.5 [3.5–13.75]	10 [5–20]	**0.048**
HbA1c (%)	10.12±2.33	9.28±2.12	0.081
Ketosis	2	1	0.351
Steatorrhea	33	35	**0.003**
Peripheral Neuropathy	21	3	**0.002**
Retinopathy	5	0	0.157
Nephropathy	27	14	**<0.001**
Percent Body Fat (%)	16.77±9.87	15.84±8.93	0.643
Total Cholesterol (mg/dl)	165.3±42.43	147±31.4	**0.024**
LDL-C (mg/dl)	93.11±33.2	88.6±19.5	0.430
HDL-C (mg/dl)	50.3±17.8	43.5±9.2	**0.022**
Triglycerides (mg/dl)	135.6±17.9	133.6±63.66	0.884
Creatinine (mg/dl)	0.93±0.17	0.90±0.17	0.437
Spot urine ACR (mg/gm)[a]	58.9 [17.7-73]	19 [8.98-32.0]	**0.001**

ACR: Albumin creatinine ratio; BMI: Body mass index; CAN: Cardiac autonomic neuropathy; DM: Diabetes; LDL: Low density lipoprotein; FCPD: Fibrocalculous pancreatic diabetes; HDL: High density lipoprotein; HbA1c: Glycated hemoglobin; GFR: Glomerular filtration rate; All continuous variables expressed as mean (standard deviation); [a]all non-normally distributed variable expressed as median [inter quartile range]; all discreet variables have been expressed as absolute numbers (percentage); normality checked using Kolmogorov-Smirnov test; $P<0.05$ considered statistically significant; [#]*P*–value calculated using Chi-square test; Retinopathy was diagnosed using EDTRS criteria; presence of nephropathy was defined as glomerular filtration rate (CKD-EPI) <60 ml/min and/or presence of microalbuminuria/overt proteinuria; presence of peripheral neuropathy was defined as defect in 10 gm Semmes-Weinstein monofilament test and/or impaired vibration perception threshold test with/without symptoms of neuropathy. Numbers in bold indicate values of statistical significance

control. Our clinical experience in treating these patients showed that they were very insulin sensitive and hence prone to repeated episodes of hypoglycemia. Challenges with diagnosis, lack of knowledge of optimal beta-cell reserve resulting in lack of best treatment regimen for managing FCPD (OAD and/or insulin) and fear of hypoglycemia may contribute to poor glycemic control. Our study highlighted that fecal elastase and body fat percent can be a good predictor for the need for insulin use for optimal glycemic control in FCPD [Table 6].

Although it was initially thought that FCPD being a secondary form of diabetes, diabetes-related complications were uncommon; later reports defied this opinion.[22] As the longevity of these patients increased due to better pain and diabetes management, diabetes-related micro and macro-vascular complications have been reported. There was a high incidence of peripheral neuropathy as tested by the vibration perception threshold in our study. Around

Table 5: Binary logistic regression analysis showing factors that independently predict the occurrence of end-organ damage (micovascular and/or macrovascular complications) in patients with fibrocalculous pancreatic diabetes

Variable	β	Exp(B) [95% Confidence Interval]	*P*
Age	-0.236	0.790 [0.585–1.065]	0.122
C-peptide (fasting)	-1.429	0.240 [0.008–6.012]	0.409
Fecal elastase	-0.603	0.547 [0.233–1.284]	0.166
Duration of diabetes	0.238	1.269 [1.039–1.550]	**0.020**
Calculus size	-0.282	0.754 [0.548–1.039]	0.094
Body fat percent	0.071	1.073 [0.944–1.221]	0.279

Binary logistic regression was initially performed with all parameters, which are likely to influence the occurrence of end-organ damage [age, sex, body mass index (BMI), duration of diabetes, basal C-peptide count, fecal elastase levels, size of largest pancreatic calculi on ultrasonography, HbA1c, lipid parameters]. Parameters with $P<0.2$ were included into the final model as elaborated in the table; Exp (B): exponentiation of the B co-efficient, change in odds ratio with 1 unit change in predictor variable; Numbers in bold indicate values of statistical significance

Table 6: Binary logistic regression analysis showing factors that independently predict the need for insulin for glycemic control in patients with fibrocalculous pancreatic diabetes

Variable	β	Exp(B) [95% Confidence Interval]	*P*
Age	-0.124	0.883 [0.779–1.001]	0.059
C-peptide (fasting)	-0.770	0.463 [0.076–+2.813]	0.403
Fecal elastase	-0.298	0.742 [0.591–0.932]	**0.010**
Duration of diabetes	0.209	1.232 [0.944–1.607]	0.124
Body fat percent	-0.269	0.764 [0.631–0.925]	**0.006**

Binary logistic regression was initially performed with all parameters, which are likely to influence the occurrence of end-organ damage [age, sex, body mass index (BMI), duration of diabetes, basal c-peptide count, fecal elastase levels, size of largest pancreatic calculi on ultrasonography, HbA1c, lipid parameters]. Parameters with $P<0.2$ were included in the final model as elaborated in the table; Exp(B): exponentiation of the B co-efficient, change in odds ratio with 1 unit change in the predictor variable; Numbers in bold indicate values of statistical significance

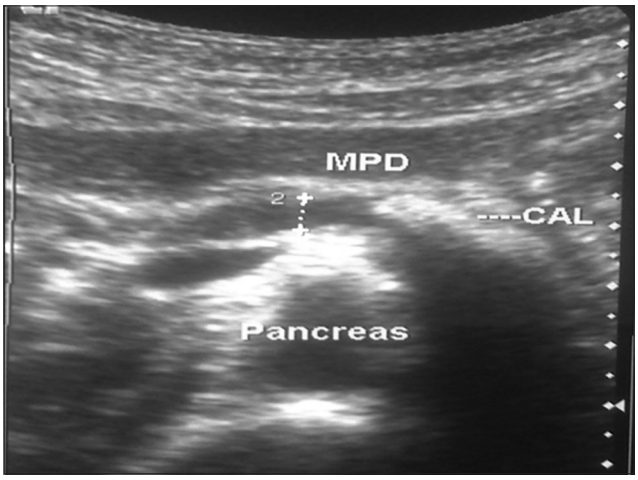

Figure 1: Ultrasound showing features of chronic calcific pancreatitis (Main Pancreatic Duct MPD dilatation, intraductal calculus)

Figure 2: Pancreatic calculi removed during Frey's procedure from a patient with chronic calcific pancreatitis

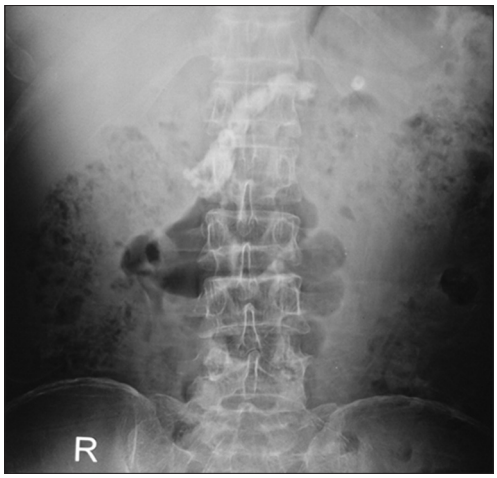

Figure 3: X ray abdomen showing intraductal pancreatic calculi in a patient with Fibrocalculous pancreatic diabetes

27 patients (26.7%) with FCPD had neuropathy which was comparable to the type-2 diabetes cohort (30%), 16 patients had moderate neuropathy (25–42 mV), and 11(>42 mV) had severe neuropathy. Mohan *et al*. had reported peripheral neuropathy in 20.9% of FCPD patients (n = 277).[22] The prevalence of retinopathy in our cohort of FCPD patients was 6.93% compared to type-2 diabetes (20%). The occurrence of microvascular complications in FCPD and T1DM was lower as compared to T2DM.

Data on the burden of CAN in patients with FCPD is limited. In a cohort of patients with long-standing FCPD of almost 16 years, Mohan *et al*. reported 60% of them to have cardiac autonomic dysfunction.[23] In another cohort of 30 FCPD patients, from Vellore India, having median disease duration of 2.4 years; 63.3% and 13.3% of patients had abnormal cardiac autonomic function tests and borderline autonomic function tests, respectively.[11] The occurrence of CAN was lower in our study compared to these previous studies, with 40% and 13.3% of patients having abnormal autonomic function tests, and borderline autonomic function tests, respectively [Table 3]. Published data on the occurrence of CAN in other forms of diabetes is highly variable. The occurrence of CAN in T1DM has been reported to vary from 17–60%.[24,25] Different methods and criteria used to diagnose cardiac autonomic neuropathy in different studies may contribute to this difference. Our study highlighted that FCPD patients with CAN had more advanced disease (as shown by lower fecal elastase; worse glycemic control), and significantly higher occurrence of end-organ damage (neuropathy, nephropathy, retinopathy) [Table 4]. Malnutrition, iron deficiency, and vitamin-B12 deficiency has been linked with CAN.[26,27] Nutritional deficiencies, malnutrition, and low BMI may contribute to the increased occurrence of CAN in FCPD. Our study has highlighted the high prevalence of CAN (53.3%) in a large cohort of FCPD patients, with parasympathetic dysfunction being the predominant type of CAN. Limitations of this study include its cross-sectional nature and lack of evaluation for CAN in the control groups. Binary logistic regression analysis showed the duration of diabetes to be significantly correlated with the occurrence of these complications [Table 5]. Macrovascular complications, on the other hand, were reported to be less common in the previous studies, perhaps owing to the relative youth of the patients, their leanness, and low cholesterol levels. In our study, we had one patient with ischaemic heart disease and he succumbed to diabetic nephropathy.

FCPD has been linked with a disproportionately higher occurrence of pancreas carcinoma.[28] In our study three of our FCPD patients had pancreas carcinoma. Anorexia, weight loss, and jaundice were the presenting features in these patients. Since the risk of developing pancreatic carcinoma in patients with FCPD is postulated to be >100 fold,[28] it will be prudent to screen patients with unexplained weight loss, jaundice, and sudden worsening of glycemic control for the development of carcinoma. The number of deaths during the period of this study was six. Two patients had died of diabetic nephropathy and two of pancreatic carcinoma. The other two had died of disseminated tuberculosis. This finding is concomitant with the study by Mohan *et al*. wherein the two major complications namely pancreatic carcinoma and diabetic nephropathy were cited as the most important causes of mortality in patients with FCPD.[29] Although this was a cross-sectional observational study, we mention this finding as these patients were under regular follow-up in our clinic.

Conclusion

To summarize, this study highlights several important clinical and biochemical facets of FCPD with regards to T1DM and T2DM. Exocrine pancreas defect, which is universal and more severe in FCPD, is also a significant problem in T1DM and T2DM. Beta-cell reserve in FCPD is better than in type-1 DM but worse than type-2 DM. Diabetes complications, especially peripheral neuropathy, and cardiac autonomic neuropathy contribute to significant morbidity in FCPD. Unexplained weight loss, jaundice, and sudden deterioration in glycemic control warrant evaluation for the development of pancreatic carcinoma in this high-risk cohort.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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