Original Article

The Clinical Spectrum of Fibrocalculous Pancreatic Diabetes in Kashmir Valley and Comparative Study of the Clinical Profile of Fibrocalculous Pancreatic Diabetes and Type 2 Diabetes Mellitus

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Abstract

Background: Fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes, described from several tropical countries, including India. We described the existence of this entity in the subtropical region-the Kashmir valley of the Indian subcontinent and compared the clinical characteristics of these patients with type 2 diabetes mellitus (T2DM) patients. **Aim:** The present study aimed to compare the clinical characteristics of patients with FCPD and those with T2DM to identify the characteristics distinctive of FCPD. **Materials and Methods:** A total of 124 patients with FCPD were compared with 124 patients with T2DM matched for age and duration of diabetes. Biochemical parameters and microvascular and macrovascular complications were assessed in all patients. Multivariate regression analyses were performed to study the determinants of microvascular complications in both groups. **Results:** FCPD patients had significantly lower serum cholesterol, serum triglyceride, and serum calcium levels but higher glycosylated hemoglobin levels compared to T2DM patients. FCPD participants were significantly leaner. The prevalence of retinopathy, neuropathy, and nephropathy was similar between the two. Five T2DM patients had documented cardiovascular disease compared to one in FCPD patients ($P < 0.05$). Multiple logistic regression analysis revealed glycosylated hemoglobin and duration of diabetes to be significantly associated with retinopathy and nephropathy in T2DM. Among FCPD patients, glycosylated hemoglobin showed a strong association with retinopathy as well as nephropathy. BMI showed a significant negative association with nephropathy in FCPD patients. Age and age at onset showed a strong association with neuropathy in FCPD patients while the duration of diabetes showed the association with neuropathy ($P = 0.015$) in T2DM. **Conclusion:** There are several differences in the phenotype, biochemical parameters, and prevalence of diabetic complications between patients with FCPD and T2DM.

Keywords: Coronary artery disease, diabetic nephropathy, diabetic retinopathy, fibrocalculous pancreatic diabetes, type 2 diabetes mellitus

Introduction

Fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes mellitus due to chronic nonalcoholic calcific pancreatitis. Apart from pancreatic calculi on imaging, young age of onset, progressive disease, non-ketotic diabetes, and a high risk of pancreatic cancer are the characteristic features that distinguish it from other types of diabetes mellitus.

The classical features of marked emaciation, parotidomegaly, distended abdomen, and a peculiar cyanotic hue of the lips described in earlier literature are seldom seen nowadays.[1] In addition, the previous description of the disease as recurrent attacks of pain abdomen in the first or second decade and

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diabetes mellitus by the third decade is not commonly seen at present times.[2] The disease now occurs in older people, with the mean age at presentation being nearly a decade later than reported. Tropical chronic pancreatitis (TCP) which was the most common cause of pancreatic diabetes is decreasing; pancreatitis due to alcohol and probably other environmental toxins is on the rise.[3-5]

The etiopathogenesis of FCPD is still poorly understood. Earlier hypotheses attributing the disease to protein-calorie malnutrition and cassava (tapioca) intake have not been substantiated.[6,7] The demonstration of familial clustering of FCPD and positive association of serum protease inhibitor Kazal type 1 (SPINK1), cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and chymotrypsinogen C with FCPD points to the possible role of genetic predisposition.[7,8]

The characteristic symptoms of pain abdomen and steatorrhea along with lean built and absence of features of insulin resistance/metabolic syndrome differentiates it from the most common type i.e., type 2 diabetes mellitus (T2DM).

FCPD occurs mainly in developing countries and the majority of cases have been reported from southern India.[2] Initially, considered to be a disease of the tropics and termed tropical pancreatic diabetes, FCPD has been reported to occur in temperate and sub temperate regions including the Kashmir valley, which is located in the sub Himalayan range.[9] Distinguishing FCPD from T2DM is important because patients with FCPD are likely to require insulin at an earlier stage than those with T2DM. They also require enzyme replacement for exocrine pancreatic deficiency and regular screening for pancreatic malignancy. Hence, the objective of the present study was to compare the clinical characteristics of patients with FCPD and T2DM and to identify the characteristics distinctive of FCPD that can aid in its early diagnosis.

Materials and Methods

The study was conducted in the Department of Endocrinology SKIMS Srinagar, a tertiary care hospital in northern India. A total of 124 consecutive FCPD patients, presenting to outpatient clinics of the department, were enrolled in the study after taking informed consent. An equal number of age, sex, body mass index (BMI), and duration of diabetes matched patients with T2DM seen in the Department during the same time period were used for comparison. The study was approved by the Institutional Ethics committee.

All patients were subjected to detailed history with focus on clinical features at the time of presentation, presence of abdominal pain and steatorrhea, the date of diagnosis of diabetes and of insulin initiation, and initial and current treatment. Complete examination including anthropometry and evaluation of complications was done. The patients were categorized into different BMI categories according to Asian cutoff given by WHO.[10] Laboratory workup included kidney function test, liver function test, lipid profile, calcium, the most recent glycated hemoglobin (HbA1c) measurement, fasting and post-prandial blood glucose, USG abdomen, and plain X-ray abdomen. The standard criteria were used for diagnosis of FCPD.[11]

1. Diagnosis of diabetes mellitus as per the American Diabetes Association criteria
2. Evidence of fibrocalculous pancreatopathy from radiological evidence of ductal calcifications. Absence of pancreatic calculi on non-contrast CT abdomen was considered to be non-diagnostic for FCPD
3. Absence of other known causes of pancreatitis including history of chronic alcohol intake, biliary tract stones, hypertriglyceridemia, hypercalcemia, and anatomical abnormalities of the pancreas.

Patients were evaluated at the time of presentation for microvascular complications. Fundus examination was performed by direct ophthalmoscopy by a trained ophthalmologist. Nephropathy was diagnosed on 24 h urinary protein concentration (>150 mg-proteinuria) or estimated glomerular filtration rate.[12] Peripheral neuropathy was assessed by symptoms, foot appearance, foot ulcers, ankle reflex, Semmes-Weinstein monofilament test, and the 128-Hz tuning fork test.

Statistical-analysis

Statistical analysis was done using IBM SPSS version 22 (SPSS Inc, Chicago, IL). The description of quantitative (numerical) variables was performed in the form of mean ± standard deviation. The analysis of numerical variables was performed using the independent Student's t test. The comparison of categorical data parameters was performed by using the Chi-square test. A P value < 0.05 was considered statistically significant. Multiple logistic regression analysis was carried out using diabetic complications as the dependent variable while age, age at onset of diabetes, BMI, duration of diabetes, glycosylated hemoglobin, serum cholesterol, High density lipoprotein cholesterol (HDL), Low density lipoprotein cholesterol (LDL), and serum triglycerides were taken as the independent variables.

Results

A total of 124 patients with FCPD were assessed in the current study. Males were affected more than the females in the ratio of 1.4:1. Most of the patients (63%) had diagnosis of disease below the age of 30 years, 20% below 20 years, whereas 17% of patients presented first time above 40 years of age. Majority (66%) of patients were of normal weight, whereas 23% were underweight and 11% overweight. Approximately, 9.6% patients had a family history of diabetes mellitus. Osmotic symptoms leading to diagnosis of diabetes mellitus was the initial presentation in 44% of cases followed by abdominal pain in 33% [Table 1]. Only 22% of patients had the triad of pain abdomen, steatorrhea, and diabetes mellitus. Glycemic control was poor in most of the patients; 50% had

HbA1c >9%, 36% between 7–9%, whereas only 14% patients had HbA1c below 7%. Neuropathy was the most common complication followed by nephropathy and retinopathy. Tripathy was seen in 6%. SPINK-1 mutation was done in five patients; out of which, two were positive. The mean serum CA 19-9 level was 15.30 ± 40.74 IU/ml with levels ranging from 0.8 to 396 IU/ml. Patients with serum CA 19-9 level more than 300 IU/ml (10 patients) were evaluated for evidence of pancreatic malignancy, however, none of them had malignancy. One hundred seventeen FCPD patients (94.3 %) required insulin for stabilization of the diabetes and none had evidence of ketonuria. Majority of the patients (71%) were managed medically only, whereas 29% additionally required various forms of surgical management (25 patients had undergone Frey's procedure, 7 had pancreaticojejunostomy, and 3 had subtotal pancreatectomy) to get relief from the symptoms.

The characteristics of the FCPD patients (n = 124) were compared with the same number of age, sex, BMI, and disease duration-matched patients with T2DM [Table 2]. FCPD patients had an earlier age at onset of diabetes (36.3 ± 15.1 years vs. 46.0 ± 10.0 years; P = 0.031). BMI, waist circumference, serum cholesterol, triglyceride, and LDL cholesterol levels were significantly lower among FCPD patients than theT2DM patients. Glycated hemoglobin levels (HbA_1C) were significantly higher in patients with FCPD. There was no statistically significant difference in prevalence of microvascular complications including retinopathy, neuropathy, or nephropathy among the two groups. Two T2DM and one FCPD patient had established coronary artery disease [Table 2].

Multiple logistic regression analysis revealed glycosylated hemoglobin [odds ratio (OR) = 1.26, P = 0.048] and duration of diabetes (OR = 1.42, P < 0.001) to be associated with retinopathy in T2DM. Among FCPD patients, only glycosylated hemoglobin (OR = 1.21, P= 0.031) showed a strong association. The risk factors for nephropathy among T2DM patients were glycosylated hemoglobin (OR = 1.49, P = 0.002) and duration of diabetes (OR = 1.42, P = 0.009). In patients with FCPD, glycosylated hemoglobin (OR = 1.31, P = 0.010) and body mass index (OR = 0.78, P = 0.009) were the risk factors for nephropathy. Age (OR = 1.29, P = 0.005) and age at onset (OR = 1.24, P = 0.014) showed association with neuropathy in FCPD patients, whereas duration of diabetes showed the association with neuropathy (OR = 1.23, P = 0.015) in T2DM. BMI (OR = 0.78, P = 0.009) showed a negative association with nephropathy in FCPD patient.

Table 1: Clinical and radiological presentation of FCPD patients

	Frequency (n)	Percentage
Positive family history	18	15%
Acanthosis Nigricans	6	4.8%
Skin tags	9	7.3%
Osmotic symptoms	53	42.7%
Chronic diarrhoea	30	
Abdominal pain	41	33%
Pancreatic calculi on radiology	124	100%

Discussion

FCPD is a unique form of pancreatic disorder characterized by irreversible destruction and fibrosis of the pancreatic parenchyma, leading to exocrine pancreatic insufficiency and progressive endocrine failure resulting in diabetes mellitus. Although hyperglycemia sets in by early adulthood is severe and usually insulin requiring, ketosis is rare. The prevalence of FCPD is low, and peculiar clinical features mandate strong clinical suspicion to diagnose and subsequent multispecialty management to take care of varied clinical manifestations.[12] However the macrovascular complications are low as compared to T2DM patients.[13]

Table 2: Comparative description of anthropometric, clinical, and biochemical characteristics of FCPD group vs.T2DM group

	T2DM group (mean±SD) (n=124)	FCPD group (mean±SD) (n=124)	P
Age in years (Range)	35±8.5 (16-65)	35±9.4	0.35
Duration of DM in years (range)	7.30±5 (1-25)	7.38±5	0.90
Family history	72 (58%)	12 (9.6%)	0.00*
BMI (kg/m^2)	25.4±3.3	20.8±3.3	0.00*
Serum calcium (mg/dl)	9.49±0.57	9.23±5.2	0.00*
HbA1c (%)	8.8±2.1	10.0±2.9	0.02*
Serum total cholesterol (mg/dl)	172±38	146±35	0.00*
Serum TG (mg/dl)	214±135	148±59	0.00*
HDL Cholesterol (mg/dl)	37±6.6	38±12	0.34
LDL Cholesterol (mg/dl)	105±26	90±26	0.00*
Neuropathy n (%)	41 (33)	40 (35)	0.88
Nephropathy n (%)	16 (16)	23 (18)	0.38
Retinopathy n (%)	7 (6)	8 (7)	0.34
CAD	2	1	0.01*
Stroke	3	0	0.00*

*Significant

We describe a cohort of 124 patients with FCPD from the Kashmir valley, a subtropical Himalayan region. The study by Zargar *et al*., was the first and the only study to report the presence of FCPD in this part of north India.[9] In present study, males were affected more than the females in the ratio of 1.4:1, which is in agreement with earlier studies on FCPD patients.[9,14,15] The reason for predominant affliction of males is not known. The onset of symptomatic diabetes mellitus was at younger age, mostly before 30 years of age, which is in accordance with the available literature.[9,14,16]

Majority of patients were of normal weight (66%) with 11% being overweight and only 23% were underweight. The presence of obesity, already a known phenomenon in patients of FCPD denotes the changing trend in the presentation of the disease, which is in contrast to conventional phenotype of lean, thin, and emaciated patients.[16,17] Like other studies, current study also undermines the earlier hypothesis that malnutrition is the primary cause of FCPD, although it may well be a promoting factor.[18,19]

The cardinal triad of FCPD described in the literature is abdominal pain, pancreatic calculi, and diabetes mellitus. The presentation of the disease, however, has become more heterogeneous, with only about 10–15% of patients presenting with the classical picture of FCPD.[20] Clinical characteristics in our study group showed that most (44%) of the patients presented with typical symptoms of diabetes mellitus, only one-third had abdominal pain and 24% had steatorrhea.

Hyperglycemia in FCPD is said to be severe, difficult to control, and is usually insulin requiring. This may be because of progressive nature of destruction of pancreatic tissue owing to fibrosis as well as insulin resistance.[21] In our study, markers of insulin resistance like acanthosis nigricans and skin tags were present in 4.8% and 7.3% patients, respectively. Majority of the patients in our study had poor glycemic control, with mean HbA1c of 10.0 ± 2.9%; 86% of patients had HbA1c >7%; and only 14% of the study group had HbA1c of <7%. This is in agreement with the findings reported in literature by other investigators.[22,23]

Specific complications of diabetes are now considered to be as frequent in FCPD as in other types of diabetes contrary to earlier belief that because FCPD is a secondary form of diabetes, and specific diabetic complications were uncommon. Table 3 compares the prevalence of micro- and macro-angiopathy among subjects with chronic pancreatitis in different studies.

The prevalence of neuropathy is higher in our patients than other studies. In the present study, 35% patients had symptoms or signs of peripheral neuropathy and 18% had nephropathy. These results are in agreement with the results demonstrated in other studies involving FCPD patients, however, Singla *et al*., reported neuropathy in 12.9% and nephropathy in 12.9% of their cases, which is lower than in the current study.[9,15,21] Retinopathy was seen in 9% of patients, which was slightly less than reported in previous studies who reported retinopathy from 12.9% to 37% of FCPD patients, respectively.[21,24-26] The risk factors for retinopathy in this study population were the duration of diabetes and glycosylated hemoglobin in case of T2DM and HbA1c for FCPD patients.

Macrovascular complications are rare in FCPD patients not withstanding isolated case reports of myocardial infarction, gangrene, and peripheral vascular disease.[27,28] One FCPD and two T2DM patients in our study had Coronary artery disease (CAD). This could be owing to the relative youth, low body mass index, and low lipid levels of these patients.

Distinguishing FCPD from T2DM is important because patients with FCPD are likely to require insulin at an earlier stage than those with T2DM. An overlap in the age of diagnosis of the two forms of diabetes, absence of gastrointestinal symptoms in many patients with FCPD, and the fact that glycemic control can be achieved by oral anti-diabetic drugs in some cases of FCPD with limited pancreatic damage may potentially result in FCPD being misdiagnosed as T2DM.[29] A recent study from the UK suggested that over 85% of patients with type 3c diabetes mellitus (pancreatic diabetes) were misdiagnosed as T2DM.[30]

When FCPD patients were compared with age, sex, and disease duration-matched patients with T2DM, FCPD patients had a lower age at onset of diabetes and were lean as compared to T2DM patients. Waist circumference, serum cholesterol, serum triglycerides, and LDL cholesterol levels were significantly lower among FCPD subjects than type 2 diabetic subjects, whereas glycated hemoglobin levels were significantly higher. These results are consistent with results from other studies.[24,29] There was no statistically significant difference in prevalence of microvascular complications between two groups as was demonstrated by Kanta *et al*.[24] In contrast to our results, Shivaprasad *et al*., in their study demonstrated that retinopathy was significantly higher in the T2DM patients, whereas the prevalence of distal symmetric polyneuropathy was significantly lower.[29]

Table 3: Comparision of clinical features and complications of our FCPD patients with patients reported from other centers

Ref.	*n*	Country	Age (years)	Duration of diabetes (years)	HbA_1C (%)	Retinopathy (%)	Nephropathy (%)	Neuropathy (%)	CAD± (%)	PVDδ (%)	Type of diabetes
Barman *et al*.[24]	277	India	47±11	11±10	10.7±2.5	36.1	10.1	20.9	5.8	4.7	FCPD*
Mittal *et al*.[25]	80	India	33±11	4±5	8.1±3.1	15	26	19	-	-	FCPD
Braini *et al*.[26]	86	Italy	52±9.9	12.4±6.8	7.3±1.2	37	23.8	-	-	-	CP**
Present study	124	India	35±9.4	7.38±5	10.0±2.9	9	18.5	32	1.6	-	FCPD

±Coronary artery disease; δPeripheral vascular disease; *Fibrocalculous pancreatic diabetes; **Chronic pancreatitis

There are several differences in the clinical and biochemical parameters and prevalence of diabetic complications between patients with FCPD and T2DM. Apart from diabetes mellitus, FCPD patients also have exocrine insufficiency and an increased risk of pancreatic malignancy. Timely diagnosis may have implications in the follow-up and management of patients.

The strengths of our study included a large sample size and a detailed clinical and biochemical assessment.

Limitations of our study include cross-sectional nature of the study, possible referral bias in view of hospital-based study, and lack of objective assessment of exocrine functions in FCPD patients.

Conclusion

Although the prevalence of FCPD is low, this diagnosis must be kept in mind in countries where its occurrence has been reported. The clinical significance of FCPD is that most of the patients require insulin to manage their hyperglycemia and patients also have the burden of complications related to pancreatitis. Management of recurrent abdominal pain, steatorrhea, and fat-soluble vitamin deficiency warrants multispecialty care. Longer survival of FCPD patients also mandates periodic screening for possible risk of pancreatic adenocarcinoma.

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Conflicts of interest

There are no conflicts of interest.

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