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Original Article

A comparative study of the clinical profile of fibrocalculous pancreatic diabetes and type 2 diabetes mellitus

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ABSTRACT

Aims: The present study aimed to compare the clinical characteristics of patients with fibrocalculous pancreatic diabetes (FCPD) and those with type 2 diabetes mellitus (T2DM) to identify the characteristics distinctive of FCPD.

Methods: A total of 133 patients with FCPD were compared with 665 patients with T2DM matched for 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 and macrovascular complications in both groups.

Results: The mean duration of diabetes was 4.42 ± 5.65 years in the FCPD group and 4.51 ± 3.88 years in the T2DM group. FCPD participants were significantly younger at diagnosis and leaner than patients with T2DM. The FCPD group had higher fasting and postprandial glucose and HbA1c levels than the T2DM group. The FCPD group had significantly lower triglyceride, total cholesterol, low-density lipoprotein cholesterol, serum total calcium, hemoglobin, and serum creatinine values than the T2DM group. The prevalence of coronary artery disease, stroke, and retinopathy was significantly higher in the T2DM patients while the prevalence of distal symmetric polyneuropathy was significantly lower. On multivariate logistic regression analysis, duration of diabetes and HbA1c (OR = 1.17, P = 0 0.04) in FCPD patients and age (OR = 1.04, P < 0 0.001), duration of diabetes (OR = 1.17, P < 0 0.001) and HbA1c (OR = 1.28, P < 0.001) in T2DM patients were associated with microvascular complications.

Conclusions: There are several differences in the phenotype, biochemical parameters, and prevalence of diabetic complications between patients with FCPD and T2DM. Timely diagnosis may have implications in the follow-up and management of patients.

1. Introduction

Fibrocalculous pancreatic diabetes (FCPD) is a form of type 3c (pancreatogenic) diabetes mellitus predominantly seen in the developing tropical countries. It is a complication of non-alcoholic chronic calcific pancreatitis and occurs in lean, young individuals with a male preponderance [1]. A population-based study found an approximately 0.5% prevalence of fibrocalculous pancreatic diabetes among adults with self-reported diabetes [2]. While the exact etiopathology of fibrocalculous pancreatopathy (FCP) is yet to be elucidated, both environmental and genetic factors have been proposed to play a role [3–5].

The classic triad of FCPD comprises of abdominal pain, pancreatic ductal calculi, and diabetes. Diabetes in FCP occurs due to progressive and irreversible destruction of the pancreatic beta cells and is frequently associated with concomitant exocrine pancreatic insufficiency. The uninhibited destruction of the pancreatic alpha and beta cells accompanied with exocrine insufficiency with associated malnutrition contributes to a clinical profile that differs from that of the patients with type 2 diabetes mellitus (T2DM). Furthermore, FCPD is associated with a high risk of developing pancreatic cancer [6].

FCPD was traditionally described as a disease that manifested as “pain in childhood, diabetes in adolescence, and death in the prime of life” [7]. However, recent studies on FCPD have shown the clinical

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picture to be heterogenous with longer survival rates. An overlap in the age of diagnosis of the two forms of diabetes, absence of GI symptoms in a few patients with FCPD, and the fact that glycemic control can be achieved by oral antidiabetic drugs in some cases of FCPD with limited pancreatic damage may potentially result in FCPD being misdiagnosed as T2DM. A recent study from the UK suggested that over 85% of patients with type 3c diabetes mellitus, i.e., pancreatogenic diabetes, were misdiagnosed as T2DM [8].

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 deficiency and regular screening for pancreatic malignancy [3]. The risk of microvascular and macrovascular complications may also be different for these two forms of diabetes. However, data on the comparison of the clinical profile and micro- and macrovascular complications between FCPD and T2DM are limited. 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 diagnosis.

2. Subjects and methods

A total of 133 consecutive patients with FCPD were recruited for the study from the Outpatient Department of Vydehi Institute of Medical Sciences and Research Centre between January 2016 and December 2017. All the patients were on regular follow-up for a minimum of one year. We also recruited five times as many patients with T2DM who were matched for the duration of diabetes and had registered at our centre during the same period (n = 665) as the comparison group. Written informed consent was obtained from all the participants, and the study protocol was approved by the Institutional Ethics Committee of Vydehi Institute of Medical Sciences and Research Centre.

FCPD was diagnosed on fulfilment of the following criteria [3]:

1. Diagnosis of diabetes mellitus as per the American Diabetes Association criteria.
2. Evidence of fibrocalculous pancreatopathy based on 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 duct stones, hypertriglyceridemia, hypercalcemia, and anatomical abnormalities of the pancreas.

Participants found to be on drugs that are known to interfere with plasma glucose levels and serum lipid levels such as glucocorticoids, statins, thiazide diuretics, beta blockers, antipsychotic drugs, and fibrates were excluded from the study.

Detailed history was obtained from all the patients with focus on clinical picture at the time of presentation, presence of abdominal pain and steatorrhea, socioeconomic status, dietary habits with special reference to cassava intake, and history of past or current addictions. We also collected information on the date of diagnosis of diabetes, initial and current treatment, date of insulin initiation, and the most recent glycated hemoglobin (HbA1c) measurement. The National Health Interview Survey criteria were used to assess the smoking status, and we included both current and former smokers [9]. Alcohol status was assessed based on the Alcohol Use Disorders Identification Test (AUDIT). Briefly, the AUDIT includes 11 questions, and meeting any 2 of the 11 questions was considered as abnormal [10]. Information on the presence or absence of the macrovascular complications, namely, coronary artery disease (CAD), stroke, and peripheral vascular disease (PVD), was also collected.

All patients underwent anthropometric assessment. Height and weight were measured using a Harpenden's stadiometer and a portable electronic weighing scale, respectively. Both height and weight were measured twice, and the mean value was taken. Body mass index (BMI) was calculated as the ratio of weight in kilograms to square of height in meters. Blood pressure was measured twice in the right arm with the patient in sitting position after at least 10 min of rest using a clock model aneroid sphygmomanometer [Model-BPDL237, Diamond^{R}, Pune, India). For the purpose of this study, hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

A fasting blood sample was drawn for the biochemical assessment that included fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fasting serum lipid profile, serum calcium, serum creatinine, and hemoglobin. A postprandial plasma glucose (PPG) sample was taken 2 h after breakfast for evaluating the PPG level. A fully automated Beckman Coulter DXC 860i autoanalyzer (Beckman Coulter, California, USA) was used to analyze all the samples.

2.1. Microvascular complications

a. Diabetic nephropathy was defined as a spot urinary protein/creatinine ratio of more than 0.2 after attaining normoglycemia in the absence of urinary tract infection and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage.
b. Diabetic neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) and vibration perception threshold (VPT) testing. VPT was evaluated using a biothesiometer (Dhansai Lab, Mumbai, India) at 7 different sites in both feet, namely, the great toe; first, third, and fifth metatarsals; medial arch; heel; and dorsum, in a graduated mode from 0 V upward. Patients were requested to provide a verbal answer once they could sense the vibration, and a mean value of >15 V was considered as abnormal response. The foot examination part of MNSI, which includes foot appearance and foot ulcers, ankle reflex, Semmes-Weinstein monofilament test, and the 128-Hz tuning fork test, was used to assess diabetic peripheral neuropathy (DPN). The maximum score of the foot examination is ten points, and bilateral limbs are independently scored. An MNSI examination score of >2 was considered abnormal. We defined DPN as VPT >15 and/or MNSI >2 for the purpose of this study.
c. Diabetic retinopathy was evaluated via fundoscopy in all the participants and was diagnosed as per the Early Treatment Diabetic Retinopathy Study system for diabetic retinopathy.

2.2. Macrovascular complications

Macrovascular complications of diabetes were determined using standard procedures as follows:

a. CAD was diagnosed if the participant had symptoms of definite angina pectoris or definite history of past myocardial infarction or electrocardiogram changes that are consistent with previous myocardial infarction.
b. Cerebrovascular disease was recognized via a positive answer to the question “Have you ever had a stroke?” and required confirmation by the interviewing physician.
c. For PVD, peripheral Doppler studies were done using Hadeco's Smartdop 30EX, a bidirectional vascular Doppler with automated cuff inflator and computer interface. The ankle/brachial index (ABI) was computed as the ratio of blood pressure at the

ankle to that of the upper arm (branchial pressure). PVD was diagnosed if the ABI was less than 0.8.

2.3. Statistical analyses

SPSS software, version 23 was used for statistical analysis. Data were represented as mean and standard deviation or percentages as applicable. Independent sample *t*-test was performed to determine the differences in the demographic, anthropometric, and biochemical parameters between the two groups for continuous variables. Categorical variables were compared using Chi-square test or Fischer's exact test. Pearson's correlation analysis was performed to determine the association between HbA1c and the biochemical parameters. Multivariate logistic regression analyses with computation of odds ratio (OR) was performed to identify the determinants of complications of diabetes for both groups individually. Any microvascular or macrovascular complication was used as the dependent variable, while age, duration of diabetes, BMI, HbA1c, lipid parameters, hypertension, and smoking were the independent covariates. A P value < 0.05 was considered significant.

3. Results

3.1. Baseline characteristics

Table 1 shows the clinical and anthropometric characteristics of the study population. A total of 64% of the subjects were men. Both the groups were matched for sex, with a male-to-female ratio of 1.89 for the FCPD group and 1.77 for the T2DM group. The FCPD patients were significantly younger at the time of diagnosis of diabetes than the patients with T2DM (P < 0.05). Patients with FCPD also had lower BMI (P < 0.05), lower positive family history among first-degree relatives (P < 0.05), and lower prevalence of hypertension (P < 0.05) than patients with T2DM. Smoking history was not significantly different between the two groups. A total of 77.4% of patients with FCPD were from Eastern India, and 14.2% were from South India.

In general, 98 (73.6%) FCPD patients complained of steatorrhea, and the mean duration of the complaint was 4.02 ± 4.32 years. The steatorrhea was commonly noticed after a high-fat meal. A total of 83 (62.4%) FCPD participants reported a history of abdominal pain, and the mean duration from the onset of abdominal pain to the diagnosis of FCPD was 4.43 ± 4.45 years. A total of 20 (15.3%) patients complained of diminished night vision, while 11 (8.2%) complained of proximal muscle weakness.

3.2. Biochemical features

The FCPD group had a significantly higher FBS (P < 0.05), PPG (P < 0.05), and HbA1c (P < 0.05) and significantly lower triglycerides (P < 0.05), total cholesterol (P < 0.05), and low density lipoprotein (LDL) cholesterol (P < 0.05) than the T2DM group. The levels of high-density lipoprotein cholesterol was not significantly different between the two groups (Table 2). Serum total calcium, hemoglobin, and serum creatinine were significantly lower in the FCPD patients than the patients with T2DM (P < 0.05). Fig. 1 demonstrates the relation between HbA1c and the duration of the diabetes for the two groups. PPG was more strongly correlated to HbA1c than FPG in FCPD patients (R [2]: 0.67 vs 0.59). Moreover, PPG was found to be a stronger predictor of HbA1c than FPG on regression analysis.

3.2.1. Diabetes complications

The overall prevalence of macrovascular complications was significantly higher in the T2DM patients than that in the FCPD patients (p < 0.001). The frequency of CAD and stroke were significantly higher in the T2DM patients (p < 0.001). Meanwhile, the prevalence of PVD was not significantly different between the two groups (Table 3).

There was no significant difference in the overall prevalence of microvascular complications between the FCPD and T2DM patients (Table 3). However, compared with that in the T2DM patients, the prevalence of DPN was significantly higher (P = 0.002), while the prevalence of diabetic retinopathy (P = 0.03) was lower in the patients with FCPD. There was no significant difference in the prevalence of diabetic nephropathy among the two groups.

3.3. Predictors of complications

In multivariate logistic regression analysis, the duration of diabetes (OR = 1.19, P = 0.02) and HbA1c (OR = 1.17, P = 0.04) were found to be associated with microvascular complications in FCPD patients. Meanwhile, age (OR = 1.04, P < 0.001), duration of diabetes (OR = 1.17, P < 0.001), and HbA1c (OR = 1.28, P < 0.001) were the predictors of microvascular complications in T2DM patients. As regards macrovascular complications in T2DM patients, they were found to be associated with age (OR = 1.033, P = 0.005), duration of diabetes (OR = 1.14, P < 0.001), BMI (OR = 1.22, P < 0.001), and HbA1c (OR = 1.11, P = 0.018).

4. Discussion

The present study highlights some of the salient differences in the clinical features between patients with T2DM and FCPD. Patients with FCPD had a lower BMI, LDL cholesterol, and triglycerides; higher HbA1c; and significantly younger age at diagnosis than the T2DM patients. Dyslipidemia, obesity, and hypertension were more common among T2DM patients. The prevalence of neuropathy was higher in the FCPD patients, whereas macrovascular complications and retinopathy were significantly higher among the T2DM patients.

The classical description of an FCPD patient was that of a lean,

Table 1
Clinical characteristics of the study groups.

Variable	FCPD (n = 133)	Type 2 Diabetes (n = 665)	P value*
Age (years)	34.74 ± 8.49	49.26 ± 10.52	*< 0.05*
Age at diagnosis (years)	30.3 ± 8.87	44.75 ± 10.58	*< 0.05*
Male *n* (%)	87 (65.4)	425 (63.9)	0.476
Duration of diabetes (years)	4.42 ± 5.65	4.51 ± 3.88	0.51
BMI (kg/m2)	18.77 ± 2.82	25.26 ± 4.28	*< 0.05*
Family history *n* (%)	11 (8.2)	230 (34.6)	*< 0.05*
Hypertension *n* (%)	10 (7.5)	180 (27.1)	*< 0.05*
Smoking history *n* (%)	32 (24.1)	109 (16.3)	0.1

P-value < 0.05 considered significant. BMI - body mass index.

Table 2
Comparison of biochemical characteristics of the study groups.

Parameter	FCPD (Mean ± SD) N = 133	T2D (Mean ± SD) N = 665	P Value*
FBG (mg/dl)	204.6 ± 92.6	176.2 ± 78.5	*< 0.01*
PPG (mg/dl)	325.6 ± 115.8	274.3 ± 110.7	*< 0.01*
HbA1c (%)	9.8 ± 2.8	8.6 ± 2.4	*< 0.01*
Calcium (mg/dl)	9.0 ± .6	9.6 ± 5.5	*0.015*
Hemoglobin (g/dl)	12.5 ± 1.8	13.2 ± 1.9	*< 0.01*
Creatinine (mg/dl)	0.7 ± .2	0.8 ± 0.4	*< 0.01*
Total Cholesterol (mg/dl)	165.8 ± 35.8	185.4 ± 70.3	*0.014*
Triglycerides (mg/dl)	158.8 ± 100.8	194.3 ± 129.7	*< 0.01*
HDL (mg/dl)	40.5 ± 8	40.8 ± 10.4	0.73
LDL (mg/dl)	95.3 ± 31.2	114.8 ± 83.0	*< 0.01*

FPG-fasting plasma glucose, PPG-post prandial glucose, HbA1c - glycated hemoglobin, HDL-high density lipoprotein, LDL-low density lipoprotein, P-value < 0.05 considered significant.

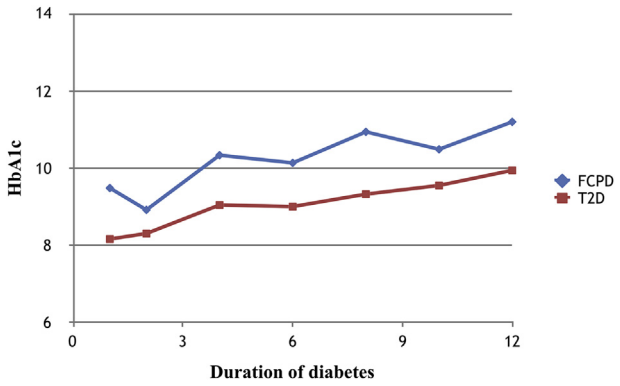

Fig. 1. HbA1c in relation to the duration of diabetes for the two groups.

malnourished young individual coming from a lower socioeconomic background in a tropical country [7]. However, recent data have shown considerable heterogeneity in the clinical picture of FCPD [11,12]. While a high proportion of the FCPD participants were diagnosed during their third or fourth decades, approximately 10% and 15% of the FCPD participants in the present study were diagnosed before the age of 20 years and after the age of 40 years, respectively. Similar findings have been observed in other studies from India [13–15]. Although the mean BMI of the FCPD patients at 18.7 kg/m^2 was significantly lower than that of the T2DM cohort, it is still within the normal reference range for the adult population. In a study by Papita et al. wherein the BMI at presentation of FCPD patients was compared across different decades, a rising trend in BMI was noticed, with a mean BMI of 21.2 kg/m^2 in patients detected during 2006–2010 and a mean of 19.4 kg/m^2 in those detected during 1991–1995 [16].

Abdominal pain is usually the first symptom to occur in FCPD [17]. The pain is usually episodic, starts in childhood, and decreases around the time diabetes develops in most cases. In the present study, only 62.4% of the patients had history of abdominal pain. A total of 73.6% of our FCPD patients reported a history suggestive of steatorrhea. Exocrine insufficiency has been reported to occur in almost 93% of FCPD patients when fecal chymotrypsin levels were estimated [18]. Deficiency of the fat-soluble vitamins A, D, E, and K may be seen in FCPD patients owing to exocrine dysfunction. Approximately 15% of FCPD participants in the present study had symptoms suggestive of nyctalopia and proximal myopathy suggestive of possible vitamin A and D deficiency, respectively. The low serum calcium, hemoglobin, and creatinine levels in the FCPD group can also be explained by the high prevalence of malabsorption in FCPD patients.

Diabetes develops in patients with fibrocalculous pancreatopathy (FCP) secondary to destruction of beta cells, although insulin resistance has also been proposed to play a role [19–22]. The exact pathogenic mechanism responsible for the development of FCP is unknown. Interaction of environmental factors in genetically susceptible individuals is proposed to lead to FCP. Mutations in SPINK1 and PRSS1 have been noted in a significant proportion of patients with FCP [23–25]. Previous studies have explored the roles of malnutrition, cassava intake, micronutrient deficiency, and increased oxidative stress as environmental factors involved in the pathogenesis of FCP [26–30]. None of the patients in the present study had cassava as a part of their diet. Previous studies have reported an association of tobacco smoking with an earlier diagnosis of alcoholic pancreatitis, diabetes, and the presence of calcifications independent of alcohol consumption [31]. In the present study, no association of smoking with FCPD was found. While FCPD has traditionally been described to be genetically related, only approximately 8% of patients had history of diabetes/pancreatitis in their first degree relatives in the present study [32]. By contrast, nearly 45% of T2DM patients had a positive family history of diabetes.

Poorer glycemic control was observed in the FCPD group than

Table 3
Diabetes complications among the study groups.

Complication	FCPD (n = 133)	Type 2 Diabetes (n = 665)	P value*
CAD *n* (%)	4 (3%)	103 (15.4%)	*< 0.001*
Stroke *n* (%)	0	16 (2.4%)	*< 0.001*
PVD *n* (%)	3 (2.2%)	28 (4.2%)	0.27
Overall *n* (%)	6 (4.5%)	138 (20.9%)	*< 0.001*
Diabetic retinopathy *n* (%)	12 (9.02%)	142 (21.3%)	*0.002*
Nephropathy *n* (%)	16 (12.0%)	114 (17.1%)	0.14
Peripheral Neuropathy *n* (%)	45 (33.8%)	166 (24.9%)	*0.03*
Overall *n* (%)	53 (39.8%)	269 (40.4%)	0.89

CAD – coronary artery disease, PVD – peripheral vascular disease, P-value < 0.05 considered significant.

the T2DM group, suggesting a greater degree of beta cell depletion in FCPD patients. In addition, glycemic control was found to be predominantly determined by PPG values in the FCPD patients. Attenuated and delayed insulin secretion in response to food intake could explain the disproportionately higher level of PPG and its higher contribution to HbA1c in FCPD patients. Glucagon deficiency, defective gluconeogenesis and glycogenolysis, and reduced glycogen storage in the liver may result in relatively lower FPG levels in the face of higher PPG in FCPD patients [33].

The fasting serum triglyceride, total cholesterol, and LDL cholesterol levels were higher in the T2DM group. Severe exocrine insufficiency may lead to fat malabsorption, which can explain the low levels of triglycerides and LDL cholesterol in FCPD patients. Meanwhile, metabolic syndrome is a common comorbidity with T2DM, and hypertriglyceridemia is often encountered in T2DM. The higher prevalence of hypertension in the T2DM cohort further substantiates metabolic syndrome as a distinctive feature of T2DM rather than in FCPD. In a study by Mohan et al., both patients with T2DM as well as the normal controls had higher total and LDL cholesterol than the FCPD patients [17].

Three of the FCPD participants in our study had pancreatic carcinoma. The risk of pancreatic malignancy has been estimated to increase by 100-fold in patients with FCPD [8]. In a study by Midha et al., the presence of SPINK1 gene mutations was associated with higher risk for developing pancreatic carcinoma [34]. While CA19-9 may be used as a tumor marker for detecting pancreatic carcinoma, it is highly non-specific; thus, its utility is limited [35]. The presence of obstructive jaundice, sudden weight loss, and pain in an otherwise stable FCPD patient should lead to the suspicion of pancreatic carcinoma. Contrast-enhanced computed tomography of the abdomen is a better modality for detecting pancreatic carcinoma.

The incidence of neuropathy was higher in the FCPD patients than that in the T2DM patients. Malabsorption, high prevalence of micronutrient deficiency, poorer glycemic control, and increased oxidative stress may all contribute to the development of peripheral neuropathy among FCPD patients [29,36,37]. Similar observations have been noticed in a study from north-east India wherein the prevalence of neuropathy was reported to be highest in the FCPD patients than those with other forms of young-onset diabetes [38]. However, few other studies have shown a similar incidence of neuropathy among FCPD and T2DM patients [39,40]. The prevalence of autonomic neuropathy has also been shown to be high (>60%) in patients with long-standing FCPD [41]. Autonomic neuropathy has been reported to occur as early as within two years of diagnosis [42].

The higher incidence of retinopathy in T2DM patients highlights the importance of other comorbidities such as dyslipidemia and hypertension in the development of the complication. Furthermore, the lack of a long preclinical phase in FCPD may contribute to the lower incidence of retinopathy. There was no difference in the prevalence of microvascular complications in a study by Mohan et al. [37]. The result of lower prevalence of macrovascular complications in FCPD participants in our study is consistent with that in other studies [37]. This may be explained by the relatively lower age group of the FCPD cohort and the lower prevalence of dyslipidemia, hypertension, and obesity in them.

HbA1c and the duration of diabetes were found to be significantly associated with microvascular complications in both T2DM and FCPD participants. This finding is consistent with that in previous studies that have shown that poor glycemic control and long-standing diabetes are associated with microvascular complications [37,43,44]. Age was additionally found to be significantly associated with microvascular complications in T2DM patients. The present study highlights some of the salient clinical differences between FCPD and T2DM patients. FCPD participants were younger at the time of diagnosis, leaner with poorer glycemic profile, have clinical and biochemical evidence of malnutrition, and better lipid profiles than T2DM patients. A higher prevalence of DPN and a lower prevalence of macrovascular complications was also observed among them. The strengths of our study included the large sample size and a detailed clinical and biochemical assessment. Meanwhile, our study has few limitations. First, it was a hospital-based study and hence a referral bias could have impacted the results. Second, the study was cross-sectional in nature, and a prospective study is required to confirm the findings. Third, exocrine functions were not objectively assessed in FCPD patients.

In conclusion, the clinical profile of FCPD is different from that of T2DM patients. Efforts have to be made to diagnose FCPD in patients with diabetes with atypical features. A high index of suspicion of FCPD should be considered in patients with diabetes with a low BMI who are diagnosed at a young age, particularly when they are from tropical areas. Patients may not always present with history suggestive of exocrine insufficiency, and thus a detailed history pertaining to steatorrhea and abdominal pain should be obtained. Timely diagnosis of FCPD have multiple implications in patient management such as the need for early initiation of insulin, correction of exocrine dysfunction and malnutrition, and surveillance for pancreatic carcinoma.

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Declarations of interest

None.

Author contribution

Study conception and design: CS, KA.
Acquisition of data: CS, YA, SA, BA, BR.
Analysis and interpretation of data: CS, GA, KA.
Drafting of manuscript: CS, KA.
Critical revision: CS.
All authors have approved the final article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.003.

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