

Non-tropical fibrocalculous pancreatic diabetes: case reports and review of recent literature

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Abstract

Background: Fibrocalculous pancreatic diabetes (FCPD), an uncommon form of secondary diabetes, is caused by chronic nonalcoholic calcific pancreatitis and primarily occurs in tropical countries.

Objective: To present our first-hand experiences in the diagnosis and management of FCPD in two patients from a non-tropical location.

Case report: Two male Chinese patients (29 and 32 years old) presented with poor insulin function, negative islet cell and glutamate decarboxylase antibodies, and no spontaneous ketosis or abdominal pain. A careful clinical assessment was made and the results were correlated with laboratory findings. Abdominal ultrasound and computed tomography scans further revealed pancreatic calcification, calculi, and pancreatic duct dilation. Differential diagnosis confirmed FCPD and excluded the potential misdiagnosis of type 2 diabetes mellitus. FCPD in these patients was managed with insulin and symptomatic treatment with close monitoring. At the time of submission of this report, the first patient was stable at his last follow-up, but the second had been re-hospitalized for worsening symptoms.

Conclusion: Early differential diagnosis of FCPD based on clinical examination and biochemical and radiological investigations, in tandem with insulin therapy, can help manage FCPD effectively.

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Keywords

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Introduction

Fibrocalculous pancreatic diabetes (FCPD) is a rare type of diabetes mellitus (DM) that occurs in malnourished young individuals.¹ This premalignant-like condition primarily occurs in tropical and developing countries like India,² and reports of nontropical cases have been few in number. The underlying etiology is unclear, but environmental influences and genetic involvement are both suggested.³ FCPD is associated with simultaneous pancreatic endocrine and exocrine dysfunction. The classical clinical features of FCPD are stones in the pancreatic duct, pancreatic calcification, poor glycemic control, and insulin-requiring, ketosis-resistant DM.⁴ The challenges in managing FCPD begin with differential diagnosis of the condition. Despite significant differences in phenotype and laboratory findings, FCPD is often misdiagnosed as DM. Compared with type 2 DM, patients with FCPD have decreased levels of triglycerides, cholesterol, and calcium and increased glycated hemoglobin levels.⁵ FCPD patients were also significantly less affected by coronary artery disease, retinopathy, or stroke.⁶ FCPD patients are reported to have decreased insulin sensitivity and increased impairment of insulin secretion compared with type 2 DM.⁷ A South Indian report highlighted that abnormal cardiac autonomic neuropathy was observed in over 60% of FCPD patients, with isolated parasympathetic dysfunction being the most common abnormality.⁸ Earlier diagnosis of the disease, based on clinical examination and biochemical and radiological investigations, would help

manage FCPD more effectively.⁹ In the current report, we present our first-hand experiences in the diagnosis and management of two patients with FCPD from a non-tropical locality. Such cases are rare outside the tropics.

Case reports

Case 1

A 29-year-old Chinese man, born in the Ningbo City of Zhejiang Province, visited our hospital on 22 February 2017. He had a 5-year history of dry mouth, polydipsia, polyuria, weight loss (6.7 kg), and general weakness. He had type 1 DM but was physically active. He did not consume alcohol or cassava but had a long history of smoking (one pack per day for 10 years). His father had type 2 DM.

Upon presentation, his random blood glucose level was 15.29 mmol/L (normal range: 3.5–7.7 mmol/L). He received 22 and 26 units of insulin aspart 30 at breakfast and dinner, respectively. However, the patient continued to have poor glycemic control and experience progressive weight loss. Further detailed examinations, followed by intensive treatment, was planned.

On admission, the patient underwent a general physical examination. His body weight was 50.6 kg, his height was 170 cm, and his body mass index (BMI) was 17.50 kg/m². He showed signs of chronic disease including weight loss, dry skin, and a scaphoid abdomen. There were no abnormalities observed in his heart, lungs, liver and spleen, no tenderness in the

abdomen, and no lower extremity edema. Laboratory results demonstrated that his fasting blood glucose level was 17.82 mmol/L. Urine sugar was strongly positive, while urinary ketones were negative. His fasting and postprandial (2-hour PP) C peptide levels were 0.14 ng/mL (normal range: 0.37–1.47 ng/mL) and 0.42 ng/mL, respectively. Both islet cell and glutamate decarboxylase antibody tests were negative. Glycated hemoglobin A1c (HbA1c) was 16.7% (159 mmol/mol). Stool analysis revealed fat droplets. Serological tests showed abnormal liver function including elevated levels of alanine aminotransferase (ALT; 199 U/L, normal range: 7–40 U/L) and aspartate aminotransferase (AST; 78 U/L, normal range: 13–35 U/L). Other biochemical tests revealed total protein levels of 55.6 g/L, albumin levels of 29.8 g/L, amylase levels of 31 U/L, carcinoembryonic antigen (CEA) levels of 15.7 ng/mL, and carbohydrate antigen 19-9 (CA19-9) levels of 76.76 U/mL. Biomarkers of autoimmune liver disease and hepatitis were negative.

An abdominal ultrasound revealed dilation of the pancreatic duct with stones and pancreatic atrophy. An abdominal computed tomography (CT) scan revealed pancreatic atrophy with calcification (Figure 1). The lumbar spine was examined using dual-energy x-ray absorptiometry (DEXA) and the bone mineral density (BMD) was -3.1 . The patient's parathyroid hormone (PTH) level was 36.74 pg/mL.

Based on these findings, a diagnosis of FCPD with abnormal liver function and osteoporosis was made. The patient was advised to undergo intensive insulin therapy with aspart 30 (18 units at breakfast, 12 units at lunch, and 16 units at dinner) for 10 days. Vitamin D3 and calcium replacement therapy were indicated for osteoporosis. Upon discharge after 14 days of hospitalization, his blood glucose levels were within the normal range, with a fasting

blood glucose level of 6 to 10 mmol/L and a 2-hour PP blood glucose level of 8 to 13 mmol/L. Following treatment, the patient's ALT was 121 U/L and hist AST was 29 U/L. At a 1-month follow-up, his fasting blood glucose level was 7 mmol/L, his 2-hour PP glucose level was 10 mmol/L, and his HbA1c level was 7.5%. At the last follow-up visit on 8 December 2019, the patient's blood glucose was within normal levels, he had gained 5 kg of body weight compared with baseline, his BMD had improved (-2.8), his liver function had returned to normal, and his tumor index was normal.

Case 2

A 32-year-old Chinese man from the Shangrao City of Jiangxi Province was referred to our hospital on 1 January 2018 with a 2-year history of polyuria, polydipsia, and weight loss (5 kg). His fasting blood glucose level was 27.16 mmol/L (normal range: 3.9–6.1 mmol/L). Urinary ketones were positive. He had previously been diagnosed with type 1 DM with ketosis and was on insulin therapy. The patient received eight units of Humulin R at each meal and 12 units of Detemir per day. Three days prior to admission, his symptoms relapsed when he stopped his insulin medication. He was otherwise healthy and denied having steatorrhea. The patient was a non-smoker but drank occasionally. Both his parents were healthy.

The patient's weight, height, and BMI were 40.4 kg, 156 cm, and 16.60 kg/m², respectively. He suffered from weight loss, chronic dry skin, and developed a scaphoid abdomen. He had no heart or lung abnormalities, no tenderness in the abdomen, no liver or spleen enlargement, and no edema of the lower extremities. His random blood glucose level was 24.22 mmol/L, urine sugar was strongly positive, urinary ketone was

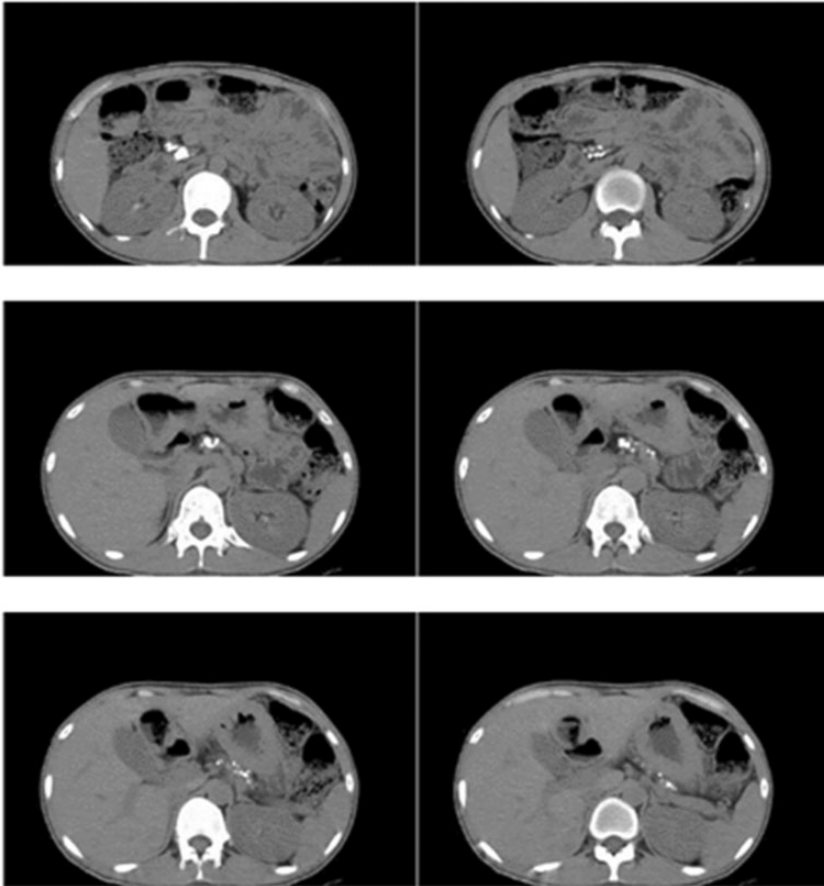


Figure 1. Presence of stones in the pancreatic head, pancreatic body, and pancreatic tail. Pancreatic duct dilation and pancreatic atrophy were observed.

positive, his fasting C peptide was 0.41 ng/mL, and his 2-hour PP glucose was 0.43 ng/mL. Islet cell and glutamate decarboxylase antibodies were negative, and his HbA1c was 17% (162 mmol/L). His CEA level was 11 ng/mL, and his CA19-9 level was 55.01 U/mL. Liver and kidney functions were normal.

CT scans of the upper abdomen showed pancreatic atrophy, pancreatic duct dilation, and multiple calcifications in the head of the pancreas (Figure 2). The lumbar spine was examined using

DEXA and the BMD was -2.9 . His PTH level was normal (22.15 pg/mL).

Based on these findings, a diagnosis of FCPD with osteoporosis was made. The patient was advised to undergo intensive insulin therapy (10 units of Humulin R[®] thrice daily and 14 units of Detemir[®] once daily). The patient was also prescribed vitamin D3 and calcium supplements. Upon discharge on 19 June 2018, his blood glucose levels were within the normal range, with a fasting level of 5 to 9 mmol/L and a 2-hour PP level of 7 to 17 mmol/L. At the

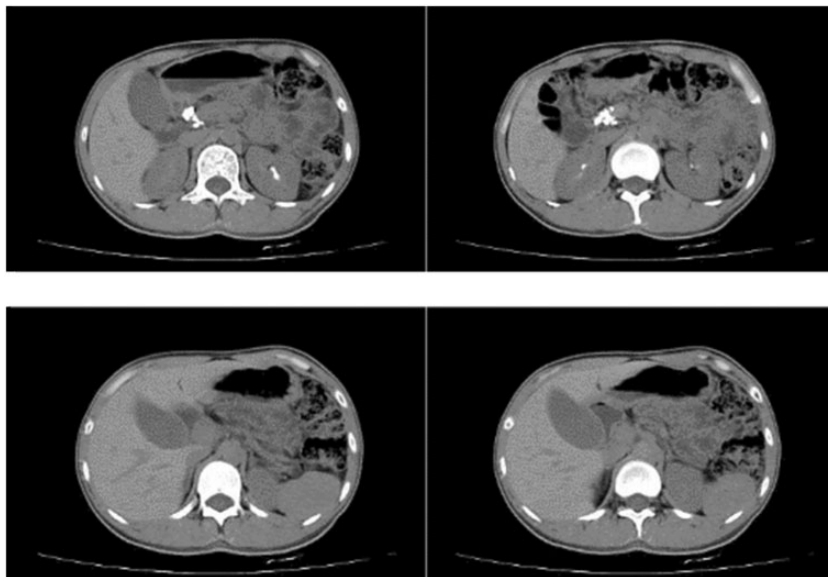


Figure 2. Presence of stones in the pancreatic head with pancreatic atrophy.

follow-up visit 1 week post-discharge, his fasting blood glucose was 7 mmol/L and his 2-hour PP glucose was 10 mmol/L. The patient returned to his hometown. Intermittent telephone follow-ups indicated that the patient had gained 4 kg, his fasting blood glucose was 7 to 8 mmol/L, and his 2-hour PP blood glucose was 8 to 14 mmol/L. On 3 March 2019, the patient was hospitalized again because of worsening symptoms. His fasting blood glucose was 12 mmol/L and his 2-hour PP glucose was 18 mmol/L. His condition was closely monitored. On 20 Jan 2020, his fasting blood glucose was 8 mmol/L and his 2-hour PP blood glucose was 11 mmol/L.

Discussion

The present report described the clinical conditions and manifestations of FCPD, a rare type of secondary DM, in two Chinese male patients. We survey the challenges in diagnosis and management of FCPD in light of the available clinical evidence.

Interestingly, the majority of FCPD patients are malnourished. The classical clinical features of FCPD are mainly observed in young patients with DM and include abdominal pain, pancreatic stones, steatorrhea, and DM. The three diagnostic criteria for FCPD are: (i) occurrence in the tropics, (ii) DM meeting the World Health Organization Study Group criteria, and (iii) presence of chronic pancreatitis confirmed by x-ray findings showing pancreatic calcification. Alternatively, the existence of at least three of the following clinical conditions may help diagnose FCPD: chronic abdominal pain since childhood, abnormal pancreatic morphology observed by CT scan, endoscopic retrograde cholangiopancreatography or ultrasonography, abnormal pancreatic function determined via chymotrypsin tests, or steatorrhea. Other causes of chronic pancreatitis, such as hepatobiliary disease, alcoholism, and primary hyperparathyroidism, should carefully be excluded.^{1,5,10,11}

The pathogenesis and progression of FCPD remain poorly understood.⁴

Multiple causes have been proposed, including malnutrition, dietary toxins present in cassava, genetic factors, autoimmune factors, and micronutrient deficiencies (such as vitamin C and D). FCPD may also be caused by a combination of genetic and environmental factors. However, no Chinese patients have undergone genetic testing and hence it is unknown whether Chinese ethnicity may be associated with FCPD susceptibility genes.

More than half of FCPD cases occur in the tropics, with sporadic incidence in the subtropics. The prevalence of FCPD is 0.36% in patients with DM. Although the prevalence of DM in Chinese adults is 11.6%,¹² only 62 cases of FCPD have been reported to date. Most of them were misdiagnosed as type 1 DM, with one patient being misdiagnosed for more than 30 years. Hence, accurate and timely diagnosis is crucial for patients with FCPD. Unsurprisingly, both patients described in this report were also misdiagnosed with type 1 DM. Differential diagnosis was made based on the following criteria: (i) patients with type 1 DM have ketosis vs. FCPD patients have high blood glucose levels with no ketosis, (ii) the presence of auto-antibodies in type 1 DM vs. their absence in FCPD patients, and (iii) imaging examinations demonstrating pancreatic duct stones in patients with FCPD but not DM.¹³

Type 1 DM can only be treated with insulin therapy. Both cases presented here did not have a history of long-term alcohol abuse. Their blood glucose levels were poorly controlled at disease onset. Their C-peptide levels were deficient; however, there was no diabetic ketoacidosis. Islet cell and glutamate decarboxylase antibodies were negative. Based on the above observations, a diagnosis of FCPD was made. Both patients lived in the subtropics and did not have a history of abdominal pain.

FCPD may be associated with changes in liver function, i.e., increased transaminase levels. However, the precise pathogenic mechanisms remain unclear.¹⁴ The first patient had abnormal liver function when he was hospitalized. However, viral hepatitis markers and autoimmune liver disease antibodies were negative. Imaging examinations showed no liver abnormalities or pimeiosis. These findings suggested that liver damage was not induced by autoimmune liver disease, viral hepatitis, liver cancer, or fatty liver.

Chronic pancreatitis and DM are the main risk factors for pancreatic cancer. Previous studies have reported calcified pancreatitis in patients with pancreatic cancer. The incidence of calcified pancreatitis complicated with pancreatic cancer is around 2% to 25%. Carcinogenesis may be associated with long-term presence of pancreatic stones. In both patients, CEA and CA19-9 levels were significantly elevated, especially in the first case. Special attention should be paid to increased susceptibility to pancreatic cancer in these patients. Close follow-up of FCPD patients is necessary to monitor development of malignancy.

Only a few reports have been published on FCDP patients with osteoporosis. Both of our patients had osteoporosis; however, their PTH levels were normal. Osteoporosis may be caused by pancreatic exocrine dysfunction resulting in fat malabsorption, leading to malabsorption of vitamin D and calcium.^{15,16}

Barman et al.¹⁷ compared 277 FCPD patients with type 2 DM patients. No significant differences in the incidence of retinopathy, nephropathy, or neuropathy were observed. In the two patients presented here, no evidence of microvascular and neurological complications was observed after fundus screening, urine protein tests, and electromyography examinations. Macrovascular complications in FCDP

patients are rare. This may be because the majority of FCPD patients are young, lean, and have low cholesterol levels.

FCPD should be treated with a combination of drugs and surgery. Medicines include oral hypoglycemic drugs and insulin therapy. Most patients suffer from severe damage to pancreatic islets resulting in reduced endogenous insulin release. Surgical options include sphincteroplasty, drainage procedures, celiac plexus ablation, and pancreatic necrosectomy. Surgeries performed during the early stages of the disease are believed to prevent the development of DM.

Unfortunately, FCPD patients have a poor prognosis. The mean survival time following diagnosis of DM is 25 years. The main cause of mortality is chronic kidney disease, accounting for more than 40% of deaths. Pancreatic cancer, malnutrition, and infections are other causes of mortality.

In summary, a high level of vigilance is necessary for early diagnosis and treatment of FCPD patients, even in non-tropical countries. Adequate glycemic control with regular monitoring, pain relief, management of macro- and micronutrient requirements, and monitoring of pancreatic function are essential to improve quality of life in FCPD patients.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate


This study was performed in accordance with the principles laid out in the Helsinki Declaration and was approved by the Ethics Committee of People's Hospital of Beilun District. Written

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