

Chapter 14

Fibrocalculous pancreatic diabetes

Mohan V

Summary

This article is a state-of-the-art update on fibrocalculous pancreatic diabetes (FCPD). In addition to our studies on the etiopathogenesis and clinical profile of the illness, we also present the results of our work on the natural history as well as the long-term survival analyses of subjects with FCPD. The management of diabetes in FCPD is the same as for the other types of diabetes except that a more liberal calorie and protein intake may be advised because of the associated undernutrition. Oral hypoglycemic agents may be useful in cases with mild diabetes and relatively early in the course of the disease. However, the majority of patients eventually need insulin for control of diabetes and to improve their general health and sense of well-being.

Definition and terminology

Fibrocalculous Pancreatic Diabetes (FCPD) can be defined as a form of diabetes secondary to non-alcoholic chronic pancreatitis of uncertain etiology predominantly seen in tropical developing countries. Several terms had been earlier proposed for this syndrome including tropical calcific pancreatitis, tropical chronic pancreatitis, tropical pancreatic diabetes, nutritional pancreatitis, endemic pancreatic syndrome, etc. As the term Fibrocalculous Pancreatic Diabetes was introduced by the World Health Organization Report (1) this is the preferred term used by diabetologists while the term Tropical Calcific Pancreatitis (TCP) is used by gastroenterologists. We currently use the term tropical calcific pancreatitis (TCP) to denote the pre-diabetic stage of FCPD for which we have also coined the term "pre-FCPD" as shown in Figure 1 (2,3).

Historical background and prevalence

In 1959, Zuidema's (4) landmark paper reported on a series of 45 cases with pancreatic calcification from Indonesia. Zuidema's patients were very poor and consumed a diet deficient in calories and protein. Non-ketotic diabetes mellitus of a severe degree was seen in 16 of 18 patients and insulin resistance were additional features. Marked emaciation, parotid gland enlargement, and hair and skin changes resembling kwashiorkor were the striking clinical features. Reports from several

tropical parts of the world (5-11) have confirmed the widespread occurrence of this syndrome in several developing countries of the world, mostly located in the tropical zone.

The single largest series of cases of (FCPD) reported to date is from the southwestern state of Kerala in India, where Geevarghese (12,13) and Pitchumoni (14,15) observed this disease in endemic proportions in two major medical college hospitals. Indeed, Geevarghese collected one of the largest series in the world (over 1700 patients) and two monographs on the subject were published by him (12,13) and is therefore often referred to as "Father of Pancreatic Diabetes". The clinical features of FCPD and tropical chronic pancreatitis have also been described by other workers in Kerala (16-20), Orissa (21-23), Karnataka (24), Tamil Nadu (25-28), Nagpur (29), Tripura (30) and other places in India (31).

At the M.V. Diabetes Specialities Centre (MVDSC) at Chennai, (formerly Madras) a large referral centre for diabetes in Tamil Nadu state in south India, approximately 50 patients with FCPD are registered annually, which constitutes about 0.7% of all diabetic patients. The distribution of type of diabetes seen at our centre is shown in Table 1. A total of 913 patients with chronic pancreatitis have been registered at our centre of which FCPD consists 624, TCP without diabetes 76, alcoholic chronic pancreatitis 183 and other types 30.

Table 1: Distribution of types of diabetes seen at our centre (n=89180)

Variants	Number	Percentage
Type 2 diabetes mellitus	85163	95.5
Type 1 diabetes mellitus	1365	1.53
Fibrocalculous pancreatic diabetes	624	0.7
Others	2028	2.3
TOTAL	89180	100

Clinical presentation

FCPD patients present with several distinct clinical features. Earlier reports suggested that patients were poor, extremely emaciated, young (over

90% are below 40 years of age at onset), and emphasised the presence of protein calorie malnutrition, bilateral parotid enlargement, distended abdomen and sometimes a cyanotic hue of the lips. However, recent reports suggest a change in the clinical presentation that may be attributed to improved nutritional status. We found that while the majority of patients were lean, severe malnutrition was uncommon, many patients were of ideal body weight (36) and an occasional patient even obese (32). Most of the patients are aged 10-30 years when the diagnosis is made, but FCPD may occur in infancy (33), childhood (34) and the elderly (35). The clinical picture of FCPD consists of the following four cardinal features:

- Abdominal pain (36-39)
- Pancreatic calculi (40)
- Maldigestion leading to steatorrhoea (41) and
- Diabetes

However all features need not be present in every patient.

This article will mainly focus on the diabetes aspects as several other authors will be describing the exocrine aspects of the disease.

Diabetes

Diabetes is an inevitable consequence of the disease, commonly occurring a decade or two after the first episode of abdominal pain (38,39). In lean and undernourished individuals, the diabetes tends to be more severe and polyuria and polydipsia are the major presenting complaints. In the better nourished patients, the symptoms may be insidious and the diagnosis of FCPD is usually made during investigations for pain in the abdomen. Unless there is a high index of suspicion, the diagnosis is often delayed or missed. One of the characteristic clinical features of FCPD is that despite requiring insulin for control, patients rarely become ketotic on withdrawal of insulin. This is attributed to the following factors:

1. Partial preservation of beta cell function as shown by C-peptide studies (42-45).
2. Decreased glucagon reserve (46).

3. Reduced supply of non-esterified fatty acid (NEFA), the fuel needed for ketogenesis, due to the loss of subcutaneous tissue.
4. Resistance of subcutaneous adipose tissue lipolysis to epinephrine.
5. Carnitine deficiency, affecting transfer of NEFA across mitochondrial membrane (47).

While some studies have shown that patients with FCPD have insulin resistance to a similar degree to that seen in type 2 diabetic patients (48), others have not found insulin resistance to be a major factor in FCPD (49).

Diabetes is usually very severe with a fasting blood glucose from 11.1–22.2 mmol/l (200–400 mg/dl) and often requires the use of insulin for control. The mean daily insulin dose in a clinic based study was 40 ± 12 units/day when oral hypoglycemic agents were also used (49,50). However there is a wide spectrum in the clinical presentation of FCPD with patients requiring only diet/oral drug treatment at one end of the spectrum to others who present with ketosis requiring insulin for survival at the other end (Figure 2).

Pathology

FCPD is a progressive disease. Therefore the pathological findings depend on the stage of the disease at which the specimen is obtained. The pathological changes in FCPD are mostly reported from postmortem or surgical specimens and hence represent very late stages of the disease based on which several excellent reviews have been published (51-53) and hence the gross findings and microscopic findings are not discussed here and only brief mention of the immunohistochemistry will be done.

Immunohistochemistry

Immunohistochemistry has shown paucity of alpha cells and beta cells with a decrease in the number of islets in some cases and hyperplasia in others (52,54). Nesidioblastosis may also be present in some patients (Figure 3). There is an overall decrease in insulin positivity in the islets which often correlates with the serum c-peptide levels and inversely with the duration of diabetes (54).

Etiology and pathogenesis

The etiopathogenetic mechanisms of FCPD still remain unclear. There is no satisfactory experimental model for FCPD. The following hypotheses have been proposed based on epidemiological data:

1. Malnutrition theory
2. The cassava hypothesis and other dietary toxins
3. Oxidant stress hypothesis and trace element deficiency states.
4. Familial and genetic factors

The first three have been reviewed extensively (55-57) and hence have not been discussed here. I shall therefore briefly touch upon the familial and genetic factors where some new data has emerged.

Familial aggregation of FCPD

FCPD sometimes affects many members of the same family. One study (58) found 17 families with two or more members having evidence of pancreatitis. In a more recent study, nearly 8% of patients with FCPD were shown to have evidence of a familial aggregation (59). However, many patients also had a family history of Type 2 diabetes. In some families, there was evidence of vertical transmission of FCPD from the parents to the offspring, while in others, there was horizontal distribution of the disease among siblings. Familial aggregation suggests, but does not necessarily prove, a hereditary etiology for FCPD, since several family members could arguably be exposed to the same toxic or other environmental factors. However recent studies suggest that there is a genetic predisposition to FCPD (see below).

Genetic factors

Whatever be the nutritional or toxic factor that predisposes to FCPD, it is clear that only a minority of people exposed to the risk seem to get the disease, suggesting a possible role for genetic factors in the causation of the disease. Our group was the first to suggest a genetic susceptibility to FCPD and in that report we found that FCPD shares common susceptibility genes with both Type 1 and Type 2 diabetes (60).

Many subsequent studies have looked for genetic abnormalities in all forms of chronic pancreatitis following the discovery of genetic mutations in hereditary pancreatitis (60-62). We reported no association between FCPD and the *reg* gene or the trypsinogen gene (63). In a previous study on a small cohort of patients with tropical pancreatitis, the frequency of CFTR mutations was lower than in white subjects (64). However during the last 2-3 years, a number of independent groups have confirmed an association between SPINK 1 mutations and FCPD (65-67).

SPINK 1 mutations

In the normal pancreas, a number of mechanisms work synergistically preventing the premature activation of trypsinogen to trypsin. The central mechanism of acinar cell injury is autodigestion by active trypsin. Pancreatic secretory trypsin inhibitor (PSTI / SPINK 1) is a potent protease inhibitor and thought to be a major protective mechanism preventing inappropriate activation of pancreatic digestive enzyme cascade by inhibiting upto 20% of potential trypsin activity. Mutations of SPINK 1 gene are significantly associated with tropical calcific pancreatitis as demonstrated by Chandak et al (65). Their studies revealed that the frequency of SPINK1 mutations are similar in both TCP and FCPD patients showing that they are probably the same disease.

SPINK 1 mutations was also studied in FCPD subjects from Chennai and Dhaka (66). In the total study group (Bangladeshi and Southern Indian) the N34S variant was present in 33% of 180 subjects with FCPD, 4.4% in non-diabetic subjects and 3.7% in Type 2 diabetes. These results suggest that the N34S variant of SPINK 1 is a susceptible gene for FCPD Bhatia et al (67) also found a strong association with SPINK 1 trypsin inhibitor mutations and a high prevalence of N34S in FCPD and TCP again suggesting that both entities have similar genetic predisposition.

Investigations

Diagnosis of FCPD is made by establishing evidence of chronic pancreatitis in patients who have the typical clinical features described earlier. If pancreatic calculi are present on plain abdominal radiography, the diagnosis is straightforward. Unfortunately, there are still no sensitive and specific non-invasive blood or urine tests to diagnose early stages of chronic pancreatitis. As in other types of chronic pancreatitis, the diagnosis of FCPD

is seldom made in the early stages of the disease. The investigation for a suspected case of FCPD without pancreatic calculi is as follows:

Tests of pancreatic structure

- a. Ultrasonography
- b. Computed tomography
- c. Endoscopic retrograde cholangiopancreatography
- d. Endoscopic ultrasonography
- e. Tests of pancreatic function

Test of Pancreatic Function

1. Tests of exocrine pancreatic function
2. Tests of endocrine pancreatic function.

As most of these sections will be covered by gastroenterologists, the derangement of endocrine function will be discussed here.

Endocrine function

Studies on C-peptide assay (a marker of pancreatic beta cell function) in FCPD patients indicate partial preservation of pancreatic beta cell function, in contrast to classical type 1 patients who have negligible beta cell reserve. Yajnik et al (68) measured beta cell function in TCP patients with different degrees of glucose tolerance and found that plasma C-peptide concentrations were normal in those with normal or mildly impaired glucose tolerance.

In the diabetic group, the C-peptide levels were scattered: they were severely diminished in some while in the rest some beta cell reserve was present. Plasma glucagon responses have been shown to be blunted in patients with FCPD (46). In response to a glucose load, plasma glucagon levels rose sharply in subjects with primary forms of diabetes, whereas glucagon response was absent in the FCPD group.

Complications

Complications secondary to chronic pancreatitis

Complications due to chronic pancreatitis include pseudocysts, pancreatic abscesses, and ascites. Obstructive jaundice may also be occasionally seen, which can be due to common bile duct obstruction or associated carcinoma of the pancreas. This is not discussed further here.

Complications related to diabetes

It was earlier believed that patients with FCPD do not develop long term complications of diabetes. This belief was based mainly on the assumption that being a secondary form of diabetes, patients with FCPD do not live long enough to develop specific diabetes related complications, which normally set in only after 10–15 years of diabetes. However, a series of studies from our group and others have shown that both microvascular and macrovascular complications do occur in patients with FCPD.

Rema et al (69) reported advanced retinopathy in FCPD patients, which has been confirmed by others (70). Nephropathy was seen in 8.9% of our FCPD patients. Renal failure due to diabetic nephropathy has also been reported in other forms of pancreatic diabetes (71). Peripheral neuropathy (72) and autonomic neuropathy (73,74) have also been reported in those with FCPD. Macrovascular complications are, however, rare in FCPD. This is believed to be due to three reasons: the patients are young, lean, and have low lipid levels. However, ischaemic heart disease (75), peripheral vascular disease and cerebrovascular accidents have occasionally been reported (76-79). Recently we did a comparative study on the prevalence of long term complications of diabetes in a large group of FCPD patients and a group of type 2 diabetic patients matched for age, sex, and duration of diabetes. The prevalence of all microvascular complications was found to be equal in both groups but macrovascular complications, particularly coronary heart disease, was significantly lower in the FCPD group (79). The prevalence of complications among the study groups is shown in Table 2.

Table 2: Prevalence of diabetes complications among the study groups (121)

Complication	Type 2 diabetes (n = 277)	FCPD (n = 277)	p value
Coronary artery disease	33 (11.9%)	13 (5.1%)	0.003
Peripheral vascular disease n(%)	12 (4.3%)	13 (4.7%)	NS
Retinopathy n (%)	103 (37.2%)	100 (36.1%)	NS
Neuropathy n (%)	70 (25.3%)	58 (20.9%)	NS
Nephropathy n (%)	42 (15.0%)	30 (10.1%)	NS
Microalbuminuria n (%)	65 (23.5%)	73 (26.4%)	NS

Long term survival analysis

In the 1960s and 70s, it was reported that FCPD patients develop abdominal pain in childhood, diabetes by adolescence, and die of complications of diabetes or chronic pancreatitis by early adulthood. Today, FCPD patients survive much longer, perhaps due to improved nutrition and better control of diabetes. We analysed the survival time of a cohort of 370 FCPD patients, taking the date of first occurrence of abdominal pain and the time of onset of diabetes as the two reference points (80). About 80% of patients were alive 35 years after the first episode of abdominal pain. The mean survival time after the diagnosis of diabetes was 25 years. The majority of deaths were associated with diabetes related causes, with diabetic nephropathy accounting for 40%. Severe infections, pancreatic cancer, and pancreatitis related causes also contribute to the mortality of FCPD patients. However, the overall prognosis of these patients seems to have considerably improved during the last two to three decades.

Natural history

Abdominal pain usually is the first symptom to manifest in the natural history of FCPD. After prolonged periods varying from a few months to several decades, pancreatic calculi may be diagnosed by routine

abdominal radiography. Until this point, both endocrine and exocrine pancreatic function of the subject may be found to be normal.

After some months to years, glucose intolerance and/or exocrine pancreatic dysfunction may set in. Although this is the classical presentation, the first sign of the disease may be detection of pancreatic calculi, diabetes, or steatorrhoea. It is believed by most workers in the field that FCPD is the logical end point of TCP i.e. that TCP is the prediabetic stage of FCPD. However, recent reports from Bangladesh have suggested that TCP and FCPD are two different entities (81,82). Based on long term follow up of large numbers of patients, we believe that FCPD is indeed the later diabetic stage of TCP for the following reasons:

1. TCP patients are younger than FCPD patients (83)
2. TCP patients are also seen at the impaired glucose tolerance stage (83, 84), which is considered to be a prediabetic stage.
3. The presence of SPINK 1 mutations in both TCP and FCPD (67), suggests a common genetic basis.

However, till recently there was no follow up study of patients who were actually followed through to the stage of FCPD. We recently conducted a prospective follow-up study on subjects who had TCP and sex matched controls without TCP (79). Among the subjects with TCP 42.3% (11/26) developed diabetes and 15.4% (4/26) developed IGT on follow-up. Thus, nearly 58% of the TCP patients followed, developed FCPD during the follow-up period compared to 26% of the control subjects. The conversion to diabetes was higher among subjects with more severe exocrine dysfunction, as assessed by lower faecal chymotrypsin levels. It was also found that early surgical intervention prevented progression to diabetes.

Management

- a. **Diabetes:** The basic principles of diet and exercise are the same as for the other types of diabetes except that a more liberal calorie and protein intake may be advised because of the associated

undernutrition. Oral hypoglycemic agents may be useful in cases with mild diabetes and relatively early in the course of the disease. However, the majority of patients eventually need insulin for control of diabetes and to improve their general health and sense of well-being.

- b. Steatorrhea: Pancreatic enzymes help to reduce steatorrhea and also improve quality of life (85). They may occasionally help to improve diabetic control and abdominal pain.

Conclusions

FCPD is a unique form of diabetes secondary to tropical calcific pancreatitis⁸⁶. Work during the last 2-3 decades has thrown considerable light on the clinical features and natural history of this condition. This has also led to improved survival of these patients. However, the etiology still remains a mystery and more work needs to be done on this in the future.

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Fig. 1: Natural history of FCPD showing TCP (Pre-FCPD) and FCPD stages of the disease. Reproduced with permission from publishers (Ref.86).

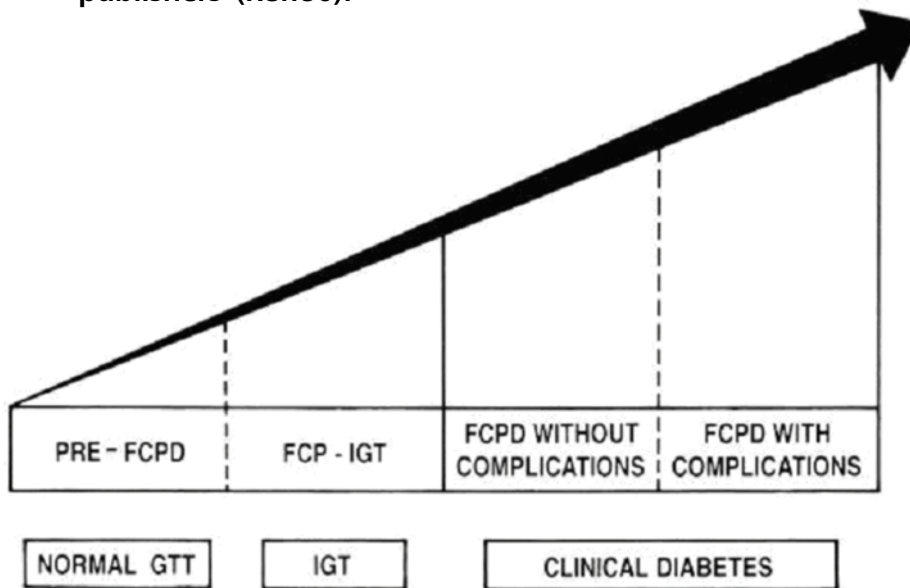


Fig. 2: Clinical spectrum of severity of FCPD: OHA (oral hypoglycemic agents). Reproduced with permission from publishers (Ref.2).

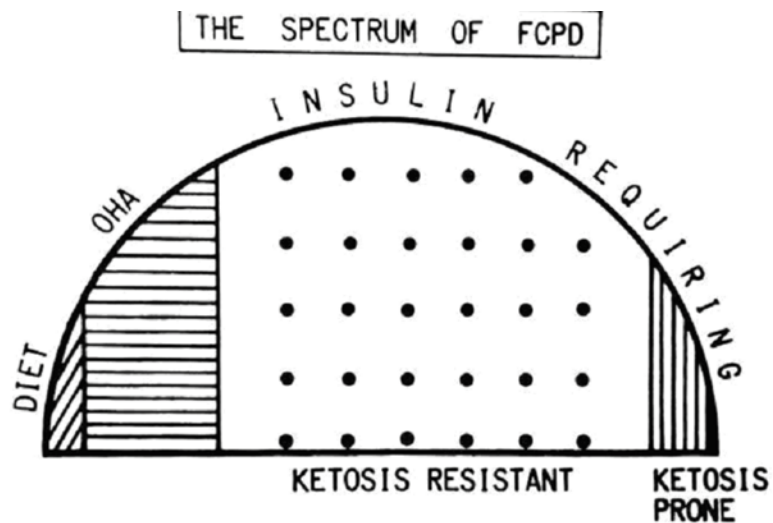
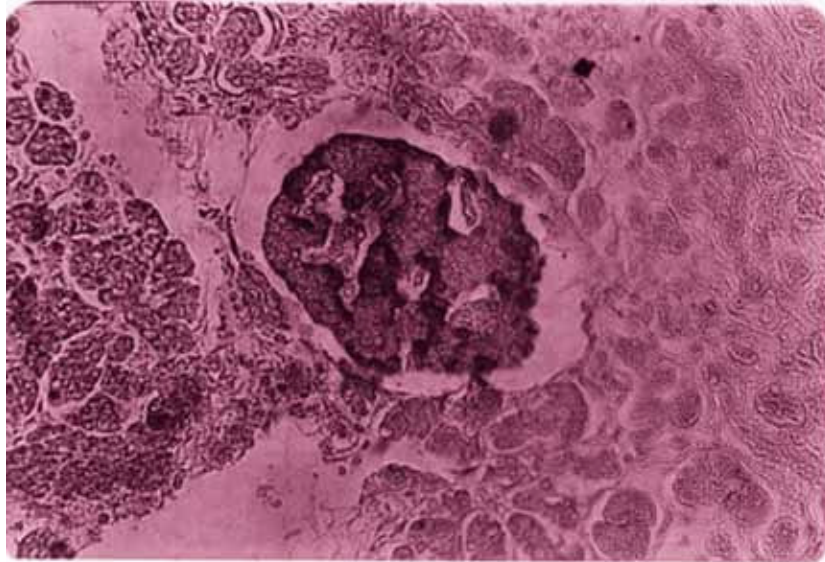


Fig. 3: Histopathology showing “nesiodioblastosis” from a case of fibrocalculous pancreatic diabetes, showing islet tissue arising from ductal remnants (aminoethylcarbazole stain; magnification x40).



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