

Complications in Fibro-Calculous Pancreatic Diabetes - The Pune and Madras Experience

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INTRODUCTION

Fibro-calculous pancreatic diabetes (FCPD) is a type of diabetes secondary to tropical calcific pancreatitis. Although described originally by Zuidema in 1959 [1] it has received its due attention only since its recognition as a specific subclass of 'malnutrition related diabetes' (MRDM) by WHO in 1985 [2]. FCPD represents a relatively small proportion of diabetes in tropical countries. Thus, only 4% of 545 consecutive young diabetics (age at onset < 30 yrs) attending a large diabetes centre at Madras were classified as FCPD [3]. The disease is commonly seen in economically poor, younger individuals, predominantly from rural areas, but exceptions to these are common in urban clinics [4]. Earlier workers suggested that FCPD patients do not suffer from diabetic vascular complications [5-9], but it is now known that these patients suffer all the complications known to occur in 'primary' varieties of diabetes. In addition they are at risk of suffering from other problems because of the peculiar age, socio-economic status and underlying chronic pancreatitis.

This article describes the epidemiology and clinical spectrum of such complications, their pathogenesis, diagnosis, treatment and prevention. The information is based on data obtained from two clinics in India (K.E.M. Hospital Research Centre, Pune and M.V. Diabetes Specialities Centre, Madras). The number of FCPD patients studied and followed up so far at Pune is 65 and that in Madras is 393. community based epidemiological data is not available.

Complications in FCPD : The Spectrum

These complications can be classified into 3 broad categories:-

- * Those related to diabetes and its treatment,
- * Those related to exocrine pancreatic involvement,
- * Miscellaneous.

Complications Related to Diabetes and its Treatment

I. Acute metabolic:

Hyperglycaemia, frequently severe and requiring insulin for adequate control, is common in FCPD subjects. However, diabetic ketoacidosis is very unusual. Ketosis resistance has been recognised as an important metabolic feature of FCPD [10]. Ketosis has been reported in < 15% of patients in different series [11 -13]. In the KEM Hospital experience, over the last 10 years we have not treated anyone for ketoacidosis, though one girl died of 'coma' in a peripheral hospital. A number of our patients stopped insulin for months (for lack of money), became severely hyperglycaemic (plasma glucose > 40 mmol/L) but never ketotic, even when suffering severe systemic infections. It is possible that more severe ketotic patients from rural areas die without proper diagnosis (especially if previously undiagnosed) and would be excluded from clinic-based data. In Mohan series however, at least nineteen patients with FCPD have presented with ketosis of which two patients had ketoacidosis.

Ketosis resistance in FCPD appears multifactorial origin. Twenty-eight out of 33 (85%) patients reported by Mohan from Madras were ketosis-resistant and had higher basal and stimulated C-peptide concentrations as compared to the ketosis-prone subject [12]. Thus, relatively preserved B-cell function could account for the ketosis resistance in some patients. However, circulating C-peptide concentrations in ketosis-resistant FCPD patients from Pune were similar to those in newly diagnosed IDDM patients [14]. This suggests that other factors are involved in the phenomenon of ketosis resistance. It appears the hepatic ketogenesis in these patients is not stimulated as much as in IDDM patients even after or medium-chain triglycerides or intravenous intralipid infusion.

One of the frequently emphasized metabolic features of FCPD patients is their proneness to hypoglycaemia with even small doses of insulin [11]. However, our patients hypoglycaemia was not a particular problem, being severe enough to require hospitalization in only 3 patients. It is possible that these patient experience asymptomatic hypoglycaemia during day life, but home monitoring of blood glucose is rare done because of socio-economic reasons. The most commonly given explanation for hypoglycaemia glucagon deficiency that results from the destruction of A cells

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during the process of pancreatitis [15]. This would make counter-regulation defective and would delay recovery from hypoglycaemia. Another factor which might play a role is depletion of hepatic glycogen stores because of chronic malnutrition.

Hyperosmolar non-ketotic diabetic coma and lactic acidosis have not been reported in FCPD.

II. Diabetic vascular complications

a) Microangiopathy: Earlier reports emphasised the rarity of microvascular complications in FCPD (and in other varieties of secondary diabetes) [5-9]. Several studies in the last decade, however, report on the microvascular complications in FCPD.

i) Retinopathy and diabetic eye disease: Although Geevarghese in his 1968 monograph [11] stated that retinopathy was rare in FCPD, in his 1985 monograph [16] he had a separate chapter on retinopathy in FCPD. Both mild background diabetic retinopathy (BDR) and sight-threatening proliferative diabetic retinopathy (PDR) have been observed in patients with FCPD. BDR was present in 6 patients from Pune when first seen, one had maculopathy [4]. These individuals had long standing diabetes (median duration 5 years (range 1.5-30 years)), two patients had PDR requiring laser photocoagulation and one patient was blind in one eye as a result of central retinal artery occlusion. In a detailed study from Madras by Rema Mohan of 40 patients with FCPD diabetic retinopathy was detected in 13 patients [17]. Ten had BDR and 3 PDR requiring laser photocoagulation. Three patients had evidence of diabetic maculopathy. A subsequent report by the same group has described larger series of FCPD patients with retinopathy [18-20].

Cataractogenesis is thought to be accelerated in young, severely diabetic patients in tropics. However, it does not seem to be particularly common in FCPD.

ii) Proteinuria and diabetic nephropathy: Renal failure due to diabetic nephropathy is an important cause of morbidity and mortality in diabetes. Unlike insulin dependent diabetes, not much is known about the epidemiology of nephropathy in FCPD. A recent study by Levitt et al [21] however reported that nephropathy was as common and severe in pancreatic diabetes as compared to IDDM. Microalbuminuria (Urinary albumin excretion rate 20-200 µg/min) was present in 3 patients from Pune when first seen. Dipstick positive proteinuria was

present in two patients. Progressive renal insufficiency developed in 2 of these patients, leading to death. Polycystic kidneys were present in 2 patients, one died of renal failure. the other suffers recurrent urinary infections. High dietary protein intake and hypertension are important determinants of the rate of progression of renal dysfunction in insulin-dependent diabetic patients [22, 23]. It is possible that low dietary protein intake (due to socio-economic reasons) and absence of hypertension in many of FCPD patients could delay the onset of progressive renal insufficiency.

iii) Peripheral Neuropathy: Symptoms suggestive of peripheral neuropathy are commonly observed in patients with FCPD, although objective evidence is less common. Thus, diminished sensations in lower limbs and diminished or absent ankle jerks were found in 16 patients from Pune when first seen. Six of these were newly diagnosed and 10 were known diabetic patients (median duration 9 years, range 1.5 - 30 years).

In a study of 16 patients from Madras [24] with a mean duration of diabetes of 10 yrs, clinical evidence of peripheral neuropathy was present in 6 patients, motor conduction velocity was diminished in 9, vibration sensory threshold was increased in 7 and sensory potential abnormalities were present in 6. These figures were no different from a group of NIDDM patients (n = 16) matched for age, BMI and duration of diabetes. Thus it appears that subclinical neuropathy is as common in FCPD patients as in those with NIDDM. Exocrine pancreatic dysfunction could further contribute to the development of neuropathy in FCPD because of dietary deficiencies and/or malabsorption of important nutrients. Severe painful peripheral neuropathy so characteristically described in PDDM was not seen in our patients. Autonomic neuropathy has however been reported in FCPD patients by Govindan and Das [25].

b) Macrovascular disease: Unlike NIDDM, macrovascular complications are believed to be uncommon in FCPD. This is probably because of the younger age of these patients and absence of 'conventional' risk factors for atherosclerotic vascular disease such as obesity, dyslipidaemia and hypertension. With improved long-term survival, many of these patients could develop macrovascular disease. None of the FCPD patients from Pune had symptoms suggestive of ischaemic heart disease. However, electrocardiographic abnormalities (T wave changes) were observed in 6 subjects when first seen (3 newly diagnosed, 3 known diabetic

with median duration 3 years). None have demonstrated progression of ECG abnormalities during ten years of follow-up. None of the patients had hypertension (blood pressure > 160/ 95 mm Hg and/or antihypertensive treatment) when first seen; one developed severe hypertension during follow-up in association with progressive renal failure culminating in death. None of the patients had significant peripheral vascular disease as recorded by the Doppler blood flow detector.

Prevalence of macrovascular disease is reported to be low in the patients from Madras [12]. However, both ischaemic heart disease and peripheral vascular disease have been reported by Mohan et al [26]. In a study of the left ventricular function assessed by systolic time intervals [27], abnormal PEP/LVET ratios were observed in 5/13 (38%) FCPD patients with mean duration of diabetes 7.4 years. Five out of 19 (26%) matched NIDDM patients also had an abnormal left ventricular function. All were normotensive and had normal ECGs (resting and post-exercise). It is therefore likely that these abnormalities represent 'diabetic' cardiomyopathy, either metabolic or microvascular in origin.

Complications Related to Exocrine Pancreatic involvement

1. Malnutrition: Although described as a subclass of MRDM by WHO criteria [2], the precise relation between malnutrition and FCPD is unclear. Malnutrition in FCPD could be either its cause or, more likely, an effect because of combined exocrine and endocrine deficiency. Insulinopenia leading to uncontrolled diabetes sets in a catabolic cascade that results in weight loss. Similar sequence of events is seen in newly diagnosed IDDM patients; the body mass indices of FCPD and IDDM patients from Pune were identical at diagnosis (median BMI 17.0 kg/m² and 15.7 kg/m² respectively) [4]. This would favour the possibility that malnutrition (low BMI) is the effect rather than the cause of FCPD, and questions the specificity of low BMI as a diagnostic criterion in FCPD. Similar results have been reported by Mohan's group [12-28].

Malnutrition in FCPD is aggravated by exocrine pancreatic dysfunction which leads to malabsorption of essential nutrients. This can develop even in absence of frank steatorrhea. The latter is uncommon because of low fat intake of many of these patients. Protein malnutrition leads to hair changes and muscle wasting. Fat malnutrition is reflected by thin skinfolds which are however not different from IDDM patients [28]. Anaemia is

common because of iron, vitamin B₁₂ and folate deficiency. Low socio-economic status which deprives these patients of a balanced and nutritious diet, ignorance of nutritional principles and frequent chronic infections such as tuberculosis, add to the problem of malnutrition.

II. Carcinoma of the pancreas: It is not clear if patients with primary diabetes are at increased risk of pancreatic cancer. In a large study of 21,447 diabetic patients seen between 1930 and 1959, a standardised mortality ratio of 1.82 was found for pancreatic cancer [29]. Several case reports and a few prospective studies have recorded an association between chronic calcific pancreatitis (mostly 'alcoholic') and pancreatic cancer [30-34], but the significance of this association is unclear. A high incidence of pancreatic cancer has been recently reported in patients with tropical calcific pancreatitis (TCP) as well [35-38]. Chari et al [38] followed 185 patients with TCP at Madras for an average period of 4.5 years. Out of 24 patients who died during the follow-up period, 6 (25%) deaths were due to pancreatic cancer (proven histologically in 3). When compared with the background pancreatic cancer rate (Madras Cancer Registry), the relative risk for pancreatic cancer in patients with TCP was 100 (95% CI = 37-218). The risk was still elevated even under the most stringent assumptions (relative risk = 5, 95% CI = 1.03-14.6). This suggests that TCP is a pre-malignant condition. The exact reason why the prevalence of cancer on TCP is so high is unknown. One could speculate that the larger stones and the younger age at onset (and hence longer duration of the disease) may contribute. This would raise the question of surgery to remove stones to reduce the risk of cancer but these issues are largely speculative at present.

Miscellaneous Complications

I. Infections: Diabetes and malnutrition can both predispose to infections. Infections in turn can worsen diabetes control and malnutrition, thus setting up a vicious cycle. Tuberculosis is particularly common but is often neglected by patients in its early stages. Three FCPD patients from Pune developed pulmonary tuberculosis of whom, one died due to neglect the other two improved after anti-tuberculous treatment. Urinary tract infections and foot infections sometimes leading to amputation, are likewise common. Fatal septicaemia developed in four patients from Pune (following portal vein thrombosis in two chronic diarrhoea in one and perinephric abscess in one).

II. Complications related to surgery: Lateral pancreaticojejunostomy (Peustow's procedure) is performed in FCPD patients to relieve pain and occasionally with the belief that it may ameliorate diabetes and/or exocrine pancreatic dysfunction. Fourteen patients from Pune have undergone surgery for relief of recurrent pancreatic pain. We have not seen any lasting improvement in endocrine or exocrine pancreatic function in these patients after surgery. Some patients continued to get pancreatic pain even after surgery. Two patients developed portal vein thrombosis 6 and 18 months post-operatively and died of resultant septicaemia. One patient died of severe exocrine dysfunction and malnutrition that developed after pancreatectomy.

Causes of Death in FCPD

During ten years of follow-up, 12 FCPD patients from Pune have died. Many of them were young and died within a short time from diagnosis. Details of these patients are shown in Table 1. Infections and metabolic problems accounted for the majority of deaths. Socio-economic factors, resulting in neglect of the disease and delay in seeking medical help, seem to contribute to high mortality.

The causes of death in Madras patients were also analysed (Mohan et al, unpublished observations) Diabetic nephropathy and other diabetes related causes, severe infections and pancreatic cancer were some of the causes of death noted in the Madras cases.

Table 1
Details of FCPD patients who died during follow-up*

S. No	Age at diagnoses	Sex	Age at death	Causes contributing to death
1	10	F	11	Chronic diarrhoea, septicaemia
2	15	F	15	Possible hypoglycaemia
3	14	M	16	Road accident
4	14	F	16	Possible diabetic ketoacidosis
5	19	F	25	Perinephric abscess, septicaemia
6	25	F	27	Chronic malnutrition, neglect
7	35	M	38	Pulmonary tuberculosis
8	28	F	39	Chronic renal failure, polycystic kidneys
9	45	M	46	Possible hypoglycaemia
10	30	F	46	Post operative portal vein thrombosis, septicaemia
11	54	M	57	Post operative portal vein thrombosis, septicaemia
12	34	M	43	Diabetic nephropathy, chronic renal failure

Yajnik et al (4)

Diagnosis, Treatment and Prevention of Complications

These are no different from those in the primary varieties of diabetes. However, socio-economic factors interfere at each stage which result in irregular follow-up and delays in diagnosis and treatment. Many patients are lured away by the claims of practitioners of alternative medicine. Prevention of complications requires intensive patient education, which is not easy in these subjects.

CONCLUSIONS

Complications in FCPD are related to both endocrine and exocrine pancreatic deficiency. Prevalence of diabetic microvascular complications is similar to that in primary varieties of diabetes. Macrovascular complications, though relatively uncommon, are likely to increase with improved patient survival. Malnutrition, aggravated by exocrine pancreatic deficiency, predisposes the patient to serious infections and sets in a vicious cycle. Socio-economic factors contribute substantially to difficulties in diagnosis and treatment. There is a need to undertake intensive patient education for timely diagnosis, treatment and prevention of these complications.

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