Fibrocalculous Pancreatic Diabetes (FCPD) in India

V Mohan*

ABSTRACT

FCPD is a unique form of diabetes secondary to tropical calcific pancreatitis. FCPD usually affects the poorer strata of society and patients are lean and often frankly malnourished. The hall-marks of the disease are the occurrence of pain in abdomen in childhood and pancreatic calculi associated with dilatation of the pancreatic duct and fibrosis of the gland in adolescence. Diabetes sets in by early adulthood, is severe and usually insulin requiring although ketosis is rare. Specific diabetic complications do occur on long term follow-up. The aetiology of FCPD still remains unclear.

KEY WORDS

Tropical Calcific Pancreatitis,. Tropical Diabetes, Malnutrition Diabetes, Chronic Pancreatitis, Pancreatic Calculi, Fibrocalculous Pancreatic Diabetes, Secondary Diabetes.

Terminology

Tropical Calcific Pancreatitis (TCP) is a unique form of juvenile onset, non-alcoholic, chronic pancreatitis peculiar to tropical countries. The highest known prevalence of TCP in the world is in Southern India. Diabetes is one of the common end points of TCP. Various terminologies have been proposed for this form of diabetes including Pancreatic Diabetes, Pancreatogenous Diabetes, and Tropical Pancreatic Diabetes. Recently the term Fibrocalculous Pancreatic Diabetes (FCPD) was introduced for this form of diabetes by the World Health Organization Study Group Report on Diabetes [1]. FCPD is one of the two forms of malnutrition related diabetes mellitus (MRDM), the other type being protein deficient diabetes mellitus (PDDM) which will not be discussed further in this article. The terms TCP and FCPD will be used to denote the pancreatitis and the diabetes secondary to TCP respectively in the rest of this article.

Historical perspective

Isolated reports of tropical calcific pancreatitis first appeared in the early part of this century. However, it was after Zuidema's paper from Indonesia [2] and that of Shaper from Uganda [3] that the entity assumed great significance. Subsequent reports from several tropical developing countries including Brazil, Congo Nigeria, Madagascar, Kenya, Zimbabwe, Zambia, Thailand, Sri Lanka, Bangladesh, Singapore, New Guinea and India have confirmed the existence of diabetes secondary to calcific pancreatitis [4,5]. The largest numbers of patients to data have been reported from the south-western state of Kerala, where Geevarghese, has seen over 1700 cases [5,6]. Large series of patients have also been reported from the states of Tamil Nadu [7,8], Orissa [9] and Karnataka [10]. Reports of FCPD have also been published from Andhra Pradesh [11], Bombay [12], Pune [13], Nagpur [14], Tripura [15], and New Delhi [16].

Prevalence of FCPD

There is only one population based study on the prevalence of tropical chronic pancreatitis. Balaji [17] made a systematic survey of 6079 families of Quilon district, Kerala. A population of 28,507 was studied. Twenty-eight cases of chronic calcific pancreatitis (CCP) and 8 cases of non-calcific pancreatitis (NCP) were identified. Thus 1 in 1020 subjects had CCP (0.09%).

The prevalence of FCPD in diabetic clinic populations varies widely. Reports from Africa showed that in Zimbabwe [18] 1 per cent of diabetic patients had FCPD and in Nigeria 8.6 per cent of patients had FCPD [19]. In South Africa FCPD was found to be rare [20]. In Thailand, 14 out of 253 (5.5%) "young" diabetic patients, (defined as those with age at diagnosis below 30 years) had FCPD [21]. In Kerala, FCPD constituted 29.3% of the total diabetic cases registered and 1.3% of all inpatient admissions at the Kottayam Medical College in 1964. However, this figure later dramatically reduced to 0.03% in 1971 and 0.009% in 1980 [6]. It is not clear whether this is due to a true decline in the incidence of FCPD or merely represents a change in the priorities for admission at this hospital. In Indonesia also there has been decline in the incidence of FCPD and at one centre no new cases have been detected since 1983 [21]. At our centre at Madras, we currently see between 50-60 new patients with FCPD every year, which represents about 1% of
all diabetics and 4% of "young" diabetics, defined as those with age at diagnosis below 30 years seen at our centre [22].

Clinical Features

In its classic form as described by Geevarghese, FCPD has several distinct characteristics.

** M. V. Diabetes Specialities Centre, Royapettah, Madras-600 014.*

Diagnosis of diabetes is made in the majority of patients between the ages of 10 years and 40 years. There is a marked male predominance. Extreme emaciation, a peculiar cyanotic hue of the lips, bilateral parotid enlargement and distension of the abdomen are some of the classic clinical feature [4,5,23]. Recently, however, there appears to be a change in the clinical features of the disease, perhaps because of the better nutritional status of the people. In our series, malnutrition was observed only in 25% of patients, although 70 per cent were lean [24]. Nowadays, patients are seen from the middle and upper strata of society as well [24,25]. Many patients give a past history of abdominal pain in childhood or adolescence. The pain is usually severe, epigastric in location and characterised by periods of remission and exacerbation. It radiates to the back on either side and is typically relieved by stooping forward or lying in a prone position. The pain usually abates by the time diabetes sets in. About one-third of patients complain of passing bulky or oily stools. The low frequency of steatorrhoea has been attributed to the low fat content of the diet. When the fat content of the diet was experimentally increased, steatorrhoea occurred in over 90 per cent of patients [26].

Nature of Diabetes

The diabetes is usually severe. Most patients require insulin for control of their diabetes. Interestingly despite requiring insulin for control of diabetes, patients with FCPD rarely develop ketoacidosis even if the insulin injections are withdrawn for prolonged periods [5, 7]. This phenomenon is discussed at some length below. We [22,27] have recently observed a spectrum of glucose intolerance in tropical calcific pancreatitis. Although the majority of patients with TCP ultimately develop overt diabetes, in earlier stages of the disease, a stage of impaired glucose tolerance (IGT) may be seen and, at a still earlier stage, the glucose tolerance can be normal. Even among those with overt diabetes, there is a spectrum ranging from those who can be treated with diet and oral agents to the occasional patient who is ketotic [22]. There appears to be a good correlation between the response to treatment and the pancreatic B-cell function assessed by serum C-peptide levels [24]. Yajnik et al [28] recently reported on the spectrum of pancreatic endocrine and exocrine function in TCP and have confirmed the existence of an IGT phase in TCP.

Radiological features

The classic radiological finding in FCPD is the presence of pancreatic calculi on a plain X-ray of the abdomen [4,5]. The calculi are mostly situated to the right of the first or second lumbar vertebrae, but may occasionally overlap the spine. In some patients the whole pancreas may be studded with calculi. It is extremely rare to find isolated calculi to the left of the vertebrae [6]. The calculi tend to be large and rounded and are invariably intraductal in location.

Imaging techniques

Ultrasonography of the pancreas is a useful tool in the diagnosis of FCPD. Shrinkage of the gland, increased echogenicity (‘fibrosis’) and ductal dilatation can be made out in these patients [29]. Ultrasonography helps to localize the calculi to the pancreas and document other features of chronic pancreatitis, e.g. ductal dilatation. Yajnik [13] has reported on the usefulness of CT scan in pancreatic imaging in FCPD. His CT studies showed that the pancreatic mass was preserved in the early stages of the disease although swelling of the parenchyma was seen. In more advanced stages the pancreas shows varying degrees of atrophy. In extreme cases little pancreatic parenchyma is visible, its place being taken by a "bag of stones". In some cases fat infiltration is prominent, which can be easily demonstrated by CT scan. Endoscopic retrograde cholangiopancreatography (ERCP) studies were performed by Balakrishnan and colleagues in patients with tropical chronic pancreatitis [30]. It was seen that in the presence of pancreatic calculi there were marked ductal changes; ductal changes were less prominent, where calculi were absent.

Lipid Studies

We [24] have reported that total cholesterol, low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL) cholesterol were significantly lower among FCPD patients compared with NIDDM patients or non-diabetic control subjects. However, serum triglyceride levels were normal.

Specific Diabetic Complications in FCPD

It was formerly believed that FCPD being a secondary form of diabetes, specific diabetic complications were uncommon. We [31] have shown recently that the sight-threatening forms of retinopathy, namely proliferative retinopathy and maculopathy, do develop in FCPD when followed for long periods. Neuropathy [32], nephropathy [24] and left ventricular dysfunction [33] also occurred in our patients. Geevarghese [6] has confirmed the occurrence of sight-threatening retinopathy in FCPD patients on long term follow-up. In contrast, macrovascular complications were less common [34], perhaps owing to the relative

youth of the patients, their leanness and the low cholesterol levels [24]. Other complications frequently seen in FCPD are tuberculosis, urinary tract infections and cataract [4,5].

Ketosis Resistance

Earlier studies to explain the ketosis resistance in MRDM has suggested a number of mechanisms such as low adipose tissue mass and delayed mobilization of free fatty acids from adipose tissue [35,36]. Recent studies have offered other explanations. In one study it was shown that although the plasma glucagon levels in IDDM patients rose after administration of oral glucose, in patients with malnutrition diabetes (PDDM variety) there was a paradoxical fall in the glucagon levels [37]. Thus low glucagon levels were suggested as one of the mechanisms for the resistance to ketosis. We [38] have recently reported that pancreatic A-cell function is blunted in FCPD patients and the lack of glucagon response may be one of the factors responsible for protection against ketoacidosis.

Our studies on pancreatic B-cell function using C-peptide as a marker have shown that FCPD patients have some residual beta cell function [39]. The C-peptide levels in FCPD are intermediate between those seen in patients with NIDDM and IDDM. Thus, FCPD patients appear to have sufficient insulin to protect them from developing ketosis. These findings have been confirmed by other workers [40, 41, 42]. Yajnik et al [28] measured B-cell function in TCP patients with different degrees of glucose tolerance. Plasma C-peptide concentration were normal in those with normal glucose tolerance and IGT, whereas the overtly diabetic subjects as a group showed diminished concentrations. In fact in 75% of these patients the C-peptide levels were indistinguishable from IDDM patients. Interestingly, none of these FCPD patients with negligible C-peptide levels had presented with ketosis, suggesting that mechanisms in addition to partially preserved B-cell function are involved in their "ketosis-resistance". Yajnik et al [28] further noted an inverse correlation between peak plasma C-peptide concentrations during the glucose tolerance test and HbA1 concentrations, suggesting that B-cell function was an important determinant of blood glucose control in TCP. Even more significantly, C-peptide and serum immunoreactive trypsin concentrations were directly correlated. Thus, for the first time a direct relationship between exocrine and endocrine measurements in TCP has been described. A follow-up study [43] showed that clinical improvement after anti-diabetic treatment was associated with improved B-cell function.

Yajnik [13] has recently summarised the various hypotheses to explain the ketosis resistance in malnutrition related forms of diabetes. They are as follows:

1. Residual B-cell function adequate to prevent ketosis [16, 39- 42].
2. Concomitant destruction of A-cells and thus loss of glucagon, a major ketogenic hormone [1 ,37,38].
3. Subcutaneous fat loss and therefore, reduced supply of nonesterified fatty acids (NEFA) - the "fuel" for ketogenesis.
4. Resistance of subcutaneous adipose tissue lipolysis to adrenaline [36, 37, 44].
5. Carnitine deficiency [45] affecting transfer of NEFA across the mitochondrial membrane.

Exocrine Pancreatic Function

The paucity of data on exocrine pancreatic function in TCP is mainly due to the unpleasantness and inconvenience of the "older" pancreatic function tests (stool fat and tube tests). Recently, measurements of specific pancreatic enzymes (serum immunoreactive trypsin) showed a spectrum of exocrine pancreatic involvement [28,46]. In early cases serum immunoreactive trypsin was subnormal in only a few subjects. In advanced cases serum immunoreactive trypsin was subnormal in most cases and severely diminished in over two-thirds. Stool chymotrypsin measurements showed similar results [47].

The Secretin-pancreozymin test done on a small number of patients showed that pancreatic enzyme output was severely diminished, trypsin being more affected than amylase [48,49]. Balakrishnan made the interesting observation that even some of the control subjects from South India showed evidence of early pancreatopathy [50]. Yajnik [46] has recently reported that elevated serum immunoreactive trypsin concentrations occur in our population in the absence of clinical or radiological evidence of TCP. Yajnik thus speculates that a "subclinical pancreatopathy" occurs in the tropics which may have an environmental aetiology and that the fullblown picture of TCP with calculi is the extreme end of the spectrum (44, 51, 13).

Pathology of Pancreas

The pathology of TCP has been reported from surgical biopsies obtained at surgery and autopsies. Little information is available in the early stages. Detailed reviews of pathology are available [13, 51-53].

Fibrosis starts early and classically leads to "cirrhosis of the pancreas". In some cases, extensive fat infiltration without much fibrosis is seen [51-

53]. Ducts and ductules show degenerative changes, and the lining epithelium may show goblet or squamous cell metaplasia. Ductules crowd together due to loss of intervening acinar tissue and also show true proliferation. Nesidioblastosis has been described.

The visible islets of Langerhans appear intact and "untouched". There is no "insulitis". Hypertrophy as well as atrophy are seen. Nesidioblastosis is a well described feature [53]. Immunoperoxidase staining has shown normal insulin and glucagon content in the cells [53]. The islets are probably destroyed due to surrounding fibrosis ("strangulation") and possibly also by disruption of circulation and also deranged fuel-mediated modulation of islet function. There are no studies of islet number of TCP but extensive loss of pancreatic mass suggests that the total number must be severely diminished with progression of the disease.

Pitchumoni and colleagues [54] have analysed the composition of pancreatic stones from FCPD patients by X-ray diffractiometry, scanning electron microscopy and energy dispersive X-ray fluorescence: they found that the nidus of the stone contained only iron, chromium and nickel, whereas the outer shell contained calcium and 17 other elements. These authors postulate that the formation of the pancreatic calculi takes place in numerous layers and stages. Formation of the inner protein nidus in the form of cobweb is the first stage, then the calcite is deposited on this fibrous network as tiny crystals. Because of the large surface area and high surface activity of the calculi, metallic ions are incorporated through co-precipitation, absorption and/or lattice substitution. It is fascinating that; irrespective of the aetiology of chronic pancreatitis, the structure and composition of pancreatic calculi are the same, suggesting that there could be a final common pathway for lithogenesis in tropical and alcoholic pancreatitis.

Management of Chronic Pancreatitis in FCPD

Steatorrhoea, when present, can be reduced, but not totally alleviated, by the use of pancreatic extracts and various enzyme preparations [55], Pain is a major problem in the initial stages of the disease and may require narcotic analgesics and parenteral anti-spasmodics. If the pain is severe and intractable and recurrent it may require surgical intervention. A variety of surgical procedures have been employed, reflecting the inadequacy of the available techniques [5,6]. Thomas et al [56] have recently reported on a large series of operated cases and have also reviewed the literature on the subject. The Puestow - Gillesby procedure of longitudinal pancreato-jejunostomy is one of the most useful procedures. Other drainage procedures including the Duval type of distal pancreato-jejunostomy, have been tried by others with varying degrees of success. Pancreatogastrostomy, trans-duodenal sphincteroplasty and various degrees of pancreatectomy have been used by other workers. Pain invariably decreases after these surgical procedures. However, surgery does not influence the course of the disease nor does the insulin requirements come down very markedly [55]. Many patients have recurrence of pain after surgery.

Aetio - Pathogenesis of FCPD

The aetiology of FCPD is still far from clear. The following have been suggested as pathogenic factors:

Undernutrition

The clinical evidence of protein-energy malnutrition in FCPD patients has often been used to cite undernutrition as an aetiological factor. However, this could well be the effect rather than the cause, because chronic pancreatitis with consequent maldigestion and malabsorption could itself lead to protein-energy malnutrition. The exact role of malnutrition in the pathogenesis of FCPD is thus far from clear. It is also possible that subclinical malnutrition (e.g. micronutrient deficiency) may contribute to pancreatic tissue damage in FCPD and this needs further investigation.

Cassava Hypothesis

McMillan and Geevarghese [57] put forward the "Cassava hypothesis" to explain the occurrence of FCPD. The geographic distribution of FCPD coincides with the areas of consumption of cassava. Cassava is known to contain cyanogenic glycosides, linamarin and lotaustralin. Cyanide is normally detoxified in the body by conversion to thiocyanate. The detoxification requires sulphur which is derived from sulphur-containing amino acids. Experiments in rats [57] showed that ingestion of cyanide led to transient hyperglycaemia. It was therefore concluded that ingestion of cyanide is linked to FCPD. It must however, be noted that none of the rats in the above experiments developed permanent diabetes. Moreover, the effects were seen only with potassium cyanide and not with cassava. Thus the relevance of these experiments to the human situation is far from clear. Finally, although the cassava hypothesis might explain the occurrence of FCPD in areas where the tuber is consumed, it does not explain its occurrence in other areas (e.g. Madras) whe~e it is not. The possibility exists that

other foodstuffs such as sorghum, ragi, jowar or certain varieties of peas may contain cyanide and other toxic substances.

Other Dietary Factors

Studies on the dietary intake of TCP patients have been done by Balakrishnan's group in collaboration with Sarles in Marseille [50,58]. The mean protein intake in the diet was 53 g per day in FCPD patients, which was not different from that of the controls. However, the fat intake of the diet of both TCP patients and controls in India was very low (27 g per day). The authors speculate that a low fat intake could be one of the factors responsible for the occurrence of TCP but this finding need to be confirmed.

Familial and Genetic Factors

Familial occurrence of FCPD is not uncommon and Pitchumoni [59] was the first to report on a large series of familial cases of FCPD. Familial aggregation has also been noted by Geevarghese [6] and Balakrishnan [58]. In a recent report we [60] showed that about 10% of FCPD cases have a familial aggregation. It is of interest that, where aggregation of FCPD occurs in some families, in others FCPD overlaps with NIDDM, and in the remaining families FCPD occurs in a sporadic manner. Familial occurrence suggests, but does not necessarily prove, a hereditary aetiology for FCPD. Several family members could be exposed to the same environmental factors that could produce the disease. However, support for a genetic predisposition to FCPD comes from a recent study of gene markers using the restriction fragment length polymorphism (RFLP) techniques [61]. It was found that FCPD shares susceptibility genes in common with NIDDM (class 3 of the insulin gene) and IDDM patients (HLA-DQ gene). This provides evidence for the first time of a genetic basis for FCPD.

Micronutrient Deficiency and Oxidant Stress

Chronic pancreatitis in Caucasians has been linked to "heightened oxidative detoxification reactions" conducted by cytochrome P450, within the pancreas and/or liver [62]. Recent collaborative studies between our centre and Dr. Braganza's group at the University of Manchester, UK, have revealed low intake of antioxidants like Vitamin C, Vitamin E and beta carotene [63]. Furthermore, theophylline clearance (a measure of cytochrome P 450, activity in vivo) was faster in patients with FCPD than in controls [64]. These studies suggest that oxidant stress may predispose to tropical pancreatitis through free radical injury.

Heterogeneity in tropical chronic pancreatitis and FCPD

The studies mentioned above highlight the heterogeneous nature of the chronic pancreatitis seen in developing countries. This has been reviewed recently by Yajnik [65].

Table-1 summarizes the evidence for the heterogeneity which is seen with respect to the clinical, biochemical, ERCP and histopathological features of tropical chronic pancreatitis. Indeed, the presence or absence of diabetes is itself an evidence of the heterogeneous nature of this disease.

Table-1: Heterogeneity in tropical chronic pancreatitis [Ref. 22]

1. Symptoms	Asymptomatic Marked symptoms	[6, 7]
2 Carbohydrate intolerance	Normal OGTT IGT Overt diabetes	[22, 28]
3. B-cell reserve	Good Poor Negligible	[24]
4. Response to therapy	Diet alone Oral agents Insulin	[24]
5. Proneness to ketosis	Ketosis-resistant Ketosis-prone	[24, 6]
6. Exocrine dysfunction	Only after provocative tests Clinical steatorrhoea	[4, 5]
7. ERCP	Absent to mild ductal changes Marked ductal changes	[30]
8. Histopathology	Mild changes: calculi absent or small Marked changes: extensive fibrosis ductal dilatation multiple calculi	[51 , 53]

Criteria of FCPD

Despite excellent clinical descriptions of the disease, no definite criteria have been laid down as yet for the diagnosis of FCPD. Mohan et al (66) have proposed the following criteria for the diagnosis of FCPD, based on their own studies and extensive review of the literature (Table 2).

Table 2 - Diagnostic criteria for fibro-calculous pancreatic diabetes (FCPD) [Ref. 66]

1. Occurrence in a "tropical" country.
2. Diabetes by WHO Study Group [1] criteria.
3. Evidence of chronic pancreatitis: pancreatic calculi on X-ray or at least three of the following:
   a) Abnormal pancreatic morphology by sonography
   b) Chronic abdominal pain since childhood
   c) Steatorrhoea
   d) Abnormal pancreatic function test.
4. Absence of other causes of chronic pancreatitis. i.e. alcoholism, hepatobiliary disease or primary hyperparathyroidism etc.

Features like clinical malnutrition, young age at onset and absence of ketosis are useful clues but are not diagnostic criteria by themselves.

REFERENCES

1. WHO Study Group Report on Diabetes Mellitus. WHO technical report series 727, WHO, Geneva 1985.

2. Zuidema PJ. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Geog Med 1959; 11:70-4.

3. Shaper AG. Chronic pancreatic disease and protein malnutrition. Lancet 1960; ii: 1223-4.

4. Pitchumoni CS. In: Pancreatitis - concepts and classification. "Tropical" or "nutritional pancreatitis" - an update. Gyr KE, Singer MV, Sarles H, Eds., Elsevier, Amsterdam. 1984, 359.

5. Geevarghese PJ. Pancreatic diabetes. Bombay: Popular Prakashan, 1968.

6. Geevarghese PJ. Calcific pancreatitis. Bombay, Varghese, 1985.

7. Viswanathan M. Pancreatic diabetes in India: an overview In: The spectrum of the diabetic syndromes. Podolsky S., Viswanathan M, Eds., Secondary Diabetes. Raven Press, New York. 1980; 105.

8. Moses SGP, Kannan V. The clinical profile of undernourished diabetics aged 30 years or less with associated complications in Madras, India. In: Diabetes Mellitus in Asia. Baba S, Goto Y, Fukui I, Eds., Excerpta Medica, Amsterdam. 1976, 259.

9. Tripathy BB. Diabetes with exocrine pancreatic disease. In: Diabetes in developing countries. Bajaj JS, Ed., Interprint New Delhi. 1984, 135.

10. Hedge JS, Kituri KH, Channappa NK. Pancreatic diabetes in Hubli area (N. Karnataka). J Assoc Phys Ind 1976; 24:305-7.

11. Rao SV, Choudhurani CPD, Sathyanarayana S. Pancreatic calculi with diabetes. Diabetes in the tropics. Patel JC, Talwalkar NG, Eds., Diabetic Association of India, Bombay. 1966, p. 234.

12. Ratnam VS, Bhandarkar SJ, Bapat RD, Rais N, Rao PN. Diabetes with pancreatic calcification. In: Diabetes in developing countries. Bajaj JS, Ed., Interprint, New Delhi. 1984, 147.

13. Yajnik CS. Diabetes secondary to tropical cakific pancreatitis. Bailliere's Clinical Endocrinology and Metabolism 1992; 6:777-97.

14. Pendsey SP, Doongaji SK, Vaidya MG. Clinical profile of fibrocalculous pancreatic diabetes (FCPD) from Vidarbha region. J Diab Assoc Ind 1990; 30:7-10.

15. Bhattacharyya PK., Mohan V., Ramachandran A., Viswanathan M. Fibrocalculous pancreatic diabetes in Tripura. Antiseptic 1990; 87:161-5.

16. Ahuja MMS., Sharma GP. Serum C-peptide content in nutritional diabetes. Horm Metab Res 1985; 17:267-8.

17. Balaji LN. The problem of chronic calcific pancreatitis. PhD Thesis, All India Institute of Medical Sciences, New Delhi, 1988.

18. Gefland M. Forbes J. Diabetes mellitus in the Rhodesian African. S Afr Med J 1953; 32:1208-13.

19. Osuntokun BO, Akinkugbe FM, Francis TI, Reddy S, Sountokun O, Taylor GOL. Diabetes Mellitus in Nigerians. A study of 832 patients. W Afr Med 1971; 20:295-312.

20. Omar MAK, Asmal AC. Profile of diabetes mellitus in young Africans and Indians in Natal. Trop Geog Med 1984; 36:133-8.

21. Wiyono P, Ahmed H, Asdie H. Clinical profile of diabetes mellitus in young patients with pancreatic calcification in Yogyakarta. In: Childhood and juvenile diabetes mellitus. Mimura G., Ed., Excerpta Medica, Amsterdam. 1985, p 70.

22. Mohan V, Alberti KGMM. Diabetes in the tropics. In: International Textbook of Diabetes Mellitus. Alberti KGMM, Defronzo H, Keen H, Zimmet P, Eds., John Wiley & Sons Ltd., Chichester. 1991 , p 177.

23. Viswanathan M, Sampath KS, Sarada S, Krishnaswami CV. Etiopathological and clinical profile of pancreatic diabetes from Madras. J. Assoc Phys Ind 1973; 21 :753-9.

24. Mohan V, Mohan R, Susheela et al. Tropical pancreatic diabetes in South India: heterogeneity in clinical and biochemical profile. Diabetologia. 1985; 28:229-32.

25. Narendranathan M. Chronic calcific pancreatitis of the tropics. Trop Gastroenterol 1981; 2:40-5.

26. Ramachandran M, Pai KN. Clinical features and management of pancreatic diabetes. In: Diabetes Mellitus. Bhaskar Rao Ed., Arnold Heinemann, New Delhi. 1977, p 239.

27. Mohan V, Chari S, Viswanathan M, Madanagopalan N. Tropical calcific pancreatitis in southern India. Proc Roy Coll Phys Edin 1990; 20:34-42.

28. Yajnik CS, Katrak A, Shelgikar KM, Naik SS, Alberti KGMM, Hockaday D. Pancreatic C-peptide response to oral glucose in fibrocalculous

pancreatic diabetes: improvement after treatment. Diabetes Care 1990; 13:525-7.

29. Mohan V, Sreeram D, Ramachandran A, Viswanathan M, Doraiswamy KRI. Ultrasonography of the pancreas in tropical pancreatic diabetes. Acta Diab Lat 1985; 22:1438.

30. Balakrishnan V, Hariharan M, Rao VRK, Anand BS. Endoscopic pancreatography in chronic pancreatitis of the tropics. Digestion 1985; 32:128-31.

31. Mohan R, Rajendran B, Mohan V, Ramachandran A, Viswanathan M. Retinopathy in tropical pancreatic diabetes. Arch Ophthalmol 1985; 103:1487-9.

32. Ramachandran A, Mohan V, Kumaravel TS, et al. Peripheral neuropathy in tropical pancreatic diabetes. Acta Diab Lat 1986; 23:135-40.

33. Ramachandran A, Mohan V, Snehalatha C et al. Left ventricular function in fibrocalculous pancreatic diabetes. Acta Diab Lat 1987; 24:81-4.

34. Mohan V, Ramachandran A, Viswanathan M. Two case reports of macrovascular complications in fibrocalculous pancreatic diabetes. Acta Diab Lat 1989; 26:345-9.

35. Hagroo AA, Verma NPS, Datta P, Ajmani NK, Vaishnava H. Observations on lipolysis in ketosis resistant growth onset diabetes. Diabetes 1974; 23:268-75.

36. Ahuja MMS, Viswanathan K. Differential mobilisation of nonesterified fatty acids and insulin reserve in various types of diabetes mellitus in India. Ind J Med Res 1967; 55:870-83.

37. Rao RH, Vigg BL, Rao KSJ. Suppressible glucagon secretion in young ketosis resistant, type "J" diabetic patients in India. Diabetes. 1983; 32:1168-71.

38. Mohan V, Snehalatha C, Ramachandran A, Chari S Madanagopalan N, Viswanathan M. Plasma glucagon responses in tropical fibrocalculous pancreatic diabetes Diabetes Res Clin Pract 1990; 9:97-101.

39. Mohan V. Snehalatha C, Jayashree R, Ramachandran A Viswanathan M. Pancreatic beta cell function in tropical pancreatic diabetes. Metabolism 1983; 32:1091-2.

40. Sood R, Ahuja MMS, Karmarkar MG. Serum C-peptide levels in young ketosis resistant diabetics. Ind J Med Res 1983; 78:661-4.

41. Vannasaeng S, Nitiyanan W, Vachayanrat A, Ployburr S Harnthong S. C-peptide secretion in calcific tropical pancreatic diabetes. Metabolism 1986; 35:814-17.

42. Samal KC., Das S., Parija CR., Tripathy BB. C-peptide response to glycaemic stimuli J Assoc Phys Ind 1987; 37:262-4.

43. Yajnik C.S., Shelgikar KM, Sahasrabudha A R. et al The Spectrum of pancreatic exocrine & endocrine (Beta cell) function in tropical calcific pancreatitis. Diabetologia 1990; 33 417-21.

44. Krishnan RB, Sachdev S, Chopra A and Karmarkar MG Biochemical characterization of ketosis-resistant young diabetics of Northern India. In vivo effects of i.v. glucose s.c. epinephrine and i.v.glucagon and in vitro effects o anti-insulin serum on adipose tissue. Acta Diabetologi: Latina. 1984; 21:141- 51.

45. Khan L and Bamji MS. Plasma carnitine levels in childrer with protein-calorie malnutrition, before and afte rehabilitation. Clinica Chimica Acta 1977; 75:163-6.

46. Yajnik CS, Katrak A, Kanikar SV et al. Serum im munoreactive trypsin in tropical fibrocalculous pancreatic diabetes syndrome. Ann Clin. Biochem 989; 26 : 69-73.

47. Mohan V, Snehalatha C, Ahmed MR et al. Exocrine pancreatic function in tropical fibrocalculous pancreatic diabetes. Diabetes Care 1989; 12:145-7.

48. Tripathy BB, Samal KC. Chronic calcific pancreatitis with diabetes in the young in developing countries. In: Chronic Pancreatitis in India. Balakrishnan V, Ed., Indian Society of Pancreatology, Trivandrum. 1987.

49. Punnose J, Balakrishnan V, Bhadran A. Exocrine pancreatic function in chronic pancreatitis with and wiihout calcification. Ind J Gastroenterol 1987; 6:85-6.

50. Balakrishnan V, Sauniere JH, Hariharan M et al. Diet, pancreatic function and chronic pancreatitis in South India and France. Pancreas 1988; 3:30-5.

51. Nagalotimath SJ. Pancreatic pathology in pancreatic calcification with diabetes. In: Secondary diabetes: the spectrum of the diabetic syndrome. Podolsky S, Viswanathan M. Eds., Raven Press, New Delhi. 1980, p. 117- 45.

52. Pitchumoni CS. Pathology of the pancreas in the tropics, In: Proceedings WHO workshop on malnutrition related diabetes. Alberti KGMM, Keen H, Parry E, Eds., Oxford University Press. (In press).

53. Nair B and Laiha P. Pancreas in chronic calcific pancreatitis. In: Chronic pancreatitis in India. Balakrishnan V Ed., Indian Society of Pancreatology, Trivandrum. 1988, p 113.

54. Pitchumoni CS, Viswanathan KV, Geevarghese PJ, Banka PA. Ultrastructure and elemental

composition of human pancreatic calculi. Pancreas 1987; 2:152-8.

55. Balakrishnan V. Chronic calcifying pancreatitis in the tropics. Ind J Gastroenterol 1984; 3:65-7.

56. Thomas P.G., Augustine P, Ramesh H, Rangabashyam N. Observations and Surgical Management of Tropical Pancreatitis in Kerala and Southern India. World Journal of Surgery 1990; 14:32- 42.

57. McMillan D, Geevarghese PJ. Dietary cyanide and tropical malnutrition diabetes. In: Secondary Diabetes: The spectrum of the diabetic syndromes. Podolsky S, Viswanathan M Eds., Raven Press, New York. 1980: p 239.

58. Balakrishnan V. Tropical pancreatitis (pancreatic tropicale). In: Maladies du pancreas exocrine. Bernades P, Hugler M Eds., Doin, Paris. 1987.

59. Pitchumoni CS, Geevarghese PJ. Familial pancreatitis and diabetes mellitus. In: Proceedings of the World Congress on Diabetes in the Tropics. Patel JC, Talwalkar NG, Eds., Diabetic Association of India, Bombay. 1966, p 240.

60. Mohan V, Chari S, Hitman GA et al. Familial aggregation in tropical fibrocalculous pancreatic diabetes. Pancreas 1989; 4:690-3.

61. Kambo PK, Hitman GA, Mohan V et al. The genetic predisposition to fibrocalculous pancreatic diabetes. Diabetologia 1989; 32:45-7.

62. Braganza JM. In: Free radicals: chemistry, pathology and medicine. Free radicals and pancreatitis. Rice-Evans C, Dormands T Eds. Rechelieu Press, London. 1988, p 357.

63. Braganza JM, John S, Padmalayam I et al. Xenobiotics and tropical chronic pancreatitis. Int J Pancreatol. 1990:231-5.

64. Chaloner C, Sandle LN, Mohan V, Snehalatha C, Viswanathan M, Braganza JM. Evidence for induction of cytochrome P-450 patients with tropical chronic pancreatitis. Int J Clin Pharm Ther Toxicol. 1990; 28:235-40.

65. Yajnik CS. Diabetes in tropical developing countries. In: The Diabetes Annual 6. Alberti KGMM, Krall LP, Eds., EIsevier, Amsterdam. 1991 , p 62.

66. Mohan V, Ramachandran A, Vishwanathan M. Diabetes secondary to tropical pancreatopathy. In: Diabetes secondary to pancreatopathy. Tiengo A, Alberti KGMM, Delprato S, Vranic Eds., Elsevier Science Publishers, Amsterdam. 1988, p 215.