INTRODUCTION

Various types of diabetes associated with undernutrition have been reported since the beginning of this century from several developing countries. In 1985, the World Health Organization (WHO) Study Group on Diabetes Mellitus identified Malnutrition Related Diabetes Mellitus (MRDM) as a separate type of diabetes distinct from type 1 diabetes mellitus (IDDM) and type 2 diabetes mellitus (NIDDM). Under MRDM, two subtypes were recognized, namely Fibrocalculus Pancreatic Diabetes (FCPD) and Protein Deficient Diabetes Mellitus (PDDM). FCPD results from pancreatic damage inflicted by chronic non-alcoholic Pancreatitis. FCPD is seen in developing countries of the world and is characterized by huge pancreatic stones in association with secondary diabetes. PDDM is distinguished by severe malnutrition and diabetes, clinically resembling type 1 diabetes with the exception that they do not develop ketoacidosis if insulin is withdrawn. Pancreatic calculi and chronic pancreatitis are absent by definition in PDDM. In the recent classification of diabetes by the American Diabetes Association (ADA), the class “Malnutrition Related Diabetes Mellitus” has been eliminated and FCPD has been reclassified under “Diseases of exocrine pancreas” as suggested by the workshop held at Cuttack in 1995. This has also been ratified by the World Health Organization consultation group. In this article, we will be dealing only with Fibrocalculus Pancreatic Diabetes.

Definition and Terminology

Fibrocalculus Pancreatic Diabetes (FCPD) is 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
Table 1. Differences between Tropical Chronic Pancreatitis and Alcoholic Chronic Pancreatitis

<table>
<thead>
<tr>
<th></th>
<th>Tropical Chronic Pancreatitis</th>
<th>Alcoholic Chronic Pancreatitis</th>
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</thead>
<tbody>
<tr>
<td>Sex ratio M:F (%)</td>
<td>70 : 30</td>
<td>Almost all male</td>
</tr>
<tr>
<td>Age at onset</td>
<td>2nd and 3rd decades</td>
<td>4th and 5th decades</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>Usually poor, may occur in others as well</td>
<td>All strata of society equally affected</td>
</tr>
<tr>
<td>Course of disease</td>
<td>More aggressive and accelerated</td>
<td>Slower rate of progression</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Occurs in &gt;90%</td>
<td>About 50% of cases</td>
</tr>
<tr>
<td>Pancreatic Calculi</td>
<td>Occurs in &gt;90% description</td>
<td>Usually small and speckled with ill defined margins</td>
</tr>
<tr>
<td>Location of calculi</td>
<td>Always in large ducts</td>
<td>Usually in small ducts</td>
</tr>
<tr>
<td>Ductal dilatation</td>
<td>Usually marked</td>
<td>Usually mild</td>
</tr>
<tr>
<td>Fibrosis of gland</td>
<td>Marked</td>
<td>Less severe</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Absent by definition</td>
<td>Heavy alcohol abuse</td>
</tr>
<tr>
<td>Prevalence of Pancreatic cancer</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

tropical calcific pancreatitis, tropical chronic pancreatitis, tropical pancreatic diabetes, nutritional pancreatitis, endemic pancreatic syndrome, etc. We had earlier used the term “tropical” to describe this disease. However, due to migration of patients from tropical to temperate zones, the disease is occasionally reported from developed countries also.4 Hence Fibrocalcific Pancreatic Diabetes 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) and denote the pre-diabetic stage of FCPD for which we have also coined the term “pre-FCPD” as shown in Figure 1.5,8

In temperate regions of the western world, alcoholism is the commonest cause of chronic calcific pancreatitis7 and alcoholic chronic pancreatitis (ACP) is also seen in India.8 The differences between the clinical profiles of tropical and alcoholic chronic pancreatitis seen in south India have been published by us9,10 and they are summarized in Table 1.

Historical Background and Prevalence

Reports of pancreatic calcification occurring in young people and not associated with alcoholism, have been consistently reported from several tropical countries during the past five decades although most of the large reports are from the southern parts of India. The first case of pancreatic calculi from India was published by Kini11 in 1938. In 1954, Elizabeth and Stephen12 reported cases of pancreatic calculi observed at postmortem from the Christian Medical College, Vellore in South India. In 1959, Zuidema in his landmark paper13 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 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, including Uganda14, Nigeria15, other parts of Africa16, Brazil17 and several countries in Asia such as Thailand18, Bangladesh19 and Sri Lanka20 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 tropical pancreatitis reported to date is from the southwestern state of Kerala in India, where Geevarghese21,22 and Pitchumoni23,24 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 monograms on the subject were published by him.21,22 He is therefore often referred to as "Father of Pancreatic Diabetes." A field study in the same state conducted on 28,567 individuals by Balaji et al.25 showed that the prevalence of tropical chronic pancreatitis to be 1 in 1000. The clinical features of FCPD have also been described by other workers in Kerala26-29, Orissa30-32, Karnataka33, Tamil Nadu34-36, Nagpur37, Tripura38 and other places in India.39

At the Dr. Mohan’s Diabetes Specialities Centre 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 this centre is shown in Table 2. A total of 913 patients with chronic pancreatitis have been registered at the Centre of which FCPD consists 624, TCP without diabetes 76, alcoholic chronic pancreatitis 183 and other types 30.

### Table 2. Distribution of Types of Diabetes seen at our Centre (n = 89,180)

<table>
<thead>
<tr>
<th>Variants</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>85,163</td>
<td>95.5</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>1,365</td>
<td>1.53</td>
</tr>
<tr>
<td>Fibrocalculus Pancreatic Diabetes</td>
<td>624</td>
<td>0.7</td>
</tr>
<tr>
<td>Others</td>
<td>2,028</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>89,180</td>
<td>100</td>
</tr>
</tbody>
</table>

**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. Figure 2 shows the classical appearance of an FCPD patient. 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 weight36 and an occasional patient

![Fig. 2. Classical clinical picture of a patient with FCPD](reproduced with permission from the publishers)
even obese. Most of the patients are aged 10-30 years when the diagnosis is made, but FCPD may occur in infancy, childhood, and the elderly. The clinical picture of FCPD consists of the following four cardinal features:

- Abdominal pain
- Pancreatic calculi
- Maldigestion leading to steatorrhoea and
- Diabetes

However, all the features need not be present in every patient.

Abdominal pain

Abdominal pain is the predominant symptom and usually the presenting complaint in 30-90% of the patients in different series. The pain is typically very severe, upper abdominal in location, radiates to the back and is relieved by stooping forward or lying in a prone position. The severity of the pain tends to decrease and become less frequent as the disease progress and it usually disappears with the onset of exocrine insufficiency and/or diabetes.

Pancreatic Calculi

In over 90% of patients with FCPD, pancreatic calculi may be detected especially in the later stages. The calculi are intraductal in location and are seen mostly to the right of the first and second lumbar vertebra on a plain abdominal radiograph as shown in Figure 3. They may be solitary or multiple and sometimes the entire pancreas may be studded with calculi. The stones tend to be large, dense and rounded with well defined edges in contrast to the small, speckled, ill defined stones in alcoholic chronic pancreatitis.

Maldigestion / Steatorrhoea

Patients with severe exocrine pancreatic insufficiency complain of passing bulky, frothy, or frank, oily stools. However, overt steatorrhoea is only present in about 20% of patients with FCPD. The low frequency of steatorrhoea is attributed to the low fat intake in the diet. When the fat intake of the diet was experimentally increased to 100 g/day from the average intake of 27 g/day, 76% of FCPD patients developed steatorrhoea.

Diabetes

Diabetes is an inevitable consequence of the disease, commonly occurring a decade or two after the first episode of abdominal pain. 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 investigating 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 ketogenic on withdrawal of insulin. This is attributed to the following factors:

1. Partial preservation of beta cell function as shown by C-peptide studies. 50-53
2. Decreased glucagon reserve. 54
3. Reduced supply of non-esterified fatty acid (NEFA), the fuel needed for ketogenesis, due to the loss of subcutaneous tissue.
4. Resistance to subcutaneous adipose tissue lipolysis by epinephrine.
5. Carnitine deficiency, affecting transfer of NEFA across mitochondrial membrane. 55

While some studies have shown that patients with FCPD have insulin resistance to a similar degree to that seen in type 2 diabetic patients, 56 others have not found insulin resistance to be a major factor in FCPD. 57

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. 57-58 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 4).

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. 59-61

Gross findings

The size of the pancreas varies inversely with the duration of the disease and can be as small as the little finger in advanced stages of the disease. The surface is nodular. The shape of the gland is distorted with loss of the normal lobular appearance. The gland is usually firm, fibrous, and gritty. However, depending on the presence of fibrous tissue, cyst, or stone the consistency may vary in different regions of the pancreas. The cut section of the pancreas shows the presence of homogenous areas with early to advanced fibrosis and intraductal calculi of varying shapes and sizes with marked dilation of the ducts and ductules. Areas of dilation and stenosis may be seen in the same gland. The gland may get displaced from its normal location due to uneven shrinkage and fibrous adhesion. Calculi may vary in size, shape, and colour. The size could range from small sand particles to large stones 4.5 cm long and weighing up to 20 grams with the larger ones being located near the head and smaller ones near the tail. The calculi may be smooth, rounded, or staghorn-like in shape and are usually incarcerated in the main pancreatic duct or its major branches. Soft stones are formed by non-calcified protein plugs and caseous material. Sections of calcified stones show epithelial debris, fibrin, and mucinous material. Colour of the stones varies from chalky white to dirty white.

Analysis of the stones

Pancreatic calculi are composed of 95.5% calcium carbonate and small amount of calcium phosphate. In some stones, traces of magnesium, urate, and oxalate have also been identified. The calcium carbonate is predominantly the calcite, and rarely the vaterite, form, as demonstrated by X-ray diffraction studies. 62 Calculi have been found to have an amorphous nidus rich in iron, chromium, and nickel and a cryptocrystalline periphery containing a number of trace elements with a predominance of calcium. 63

Fig. 5. Histopathology showing "nesidioblastosis" from a case of fibrocalculus pancreatic diabetes, showing islet tissue arising from ductal remnants (aminoethylcarbazole stain; magnification x40)
Microscopy

Microscopic examination reveals a thickened capsule and extensive intralobular and interlobular fibrosis not limited to any one zone or area. Interlobular fibrosis is characteristic of early cases and focal, segmental, or diffuse fibrosis of more advanced cases. Marked dilatation with periductular fibrosis is seen in the main duct, collecting ducts, and small ductules with denudation of the ductular epithelium and squamous metaplasia in some areas. The characteristic cellular infiltration of the pancreas is composed of lymphocytes and plasma cells, distributed mainly around the ducts.  

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. Nesidioblastosis may also be present in some patients (Figure 5). 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.

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. Familial and genetic factors

4. Oxidant stress hypothesis and trace element deficiency states.

Malnutrition

Based on the observation that FCPD almost exclusively affects the poor population of developing nations, malnutrition was strongly suspected to be a major etiological factor. It is indeed true that protein-calorie malnutrition is present in many patients with FCPD. The role of undernutrition in the etiology of FCPD has been elegantly reviewed in a number of papers. However, recent observations question the hypothesis of Shaper and Zuidema that FCPD is a protein deficiency disease. Malnutrition could well be the effect rather than the cause of the disease. Since protein-calorie malnutrition is prevalent in many tropical countries, it is likely to be prevalent in many diseases affecting the poor. Further, kwashiorkor seldom leads to permanent pancreatic damage and pancreatic stones are absent even in advanced stages of kwashiorkor. The large pockets of malnutrition in many parts of the world compared to the relative infrequency of FCPD also suggests that malnutrition by itself is unlikely to play an etiologic role. For example, in Ethiopia despite the prevalence of severe malnutrition, FCPD was not detected even when carefully looked for. Secondly, Kerala state with the highest literacy and lowest infant mortality rates in India has the highest prevalence of FCPD. Occurrence of the disease in patients from affluent families in India also challenge the hypotheses. The consensus therefore is that FCPD is not solely secondary to protein malnutrition, although nutritional factors especially micronutrient deficiencies may play a contributory role in the pathogenesis of the disease.

Cassava toxicity (Cyanogen toxicity)

In Kerala state, the geographical distribution of FCPD coincides with the areas of consumption of cassava (Tapioca, Manihot esculenta) which is the staple diet of poor people. Cassava is known to contain cyanogenic glycosides such as linamarin and lotaustralin. Cyanogen toxicity in the presence of malnutrition and antioxidant deficiency has been proposed as an ideal setting for free-radical injury. Cyanide is normally detoxified in the body by conversion to thiocyanate, but this detoxification requires sulfur, which is derived from sulfur containing amino acids like methionine and cystine which are deficient in malnourished states.
McMillan and Geevarghese showed that ingestion of cyanide led to transient hyperglycemia in rats. They concluded that their results supported a role for cyanide in the etiopathogenesis of fibrocalculous pancreatic diabetes. It must, however, be noted that none of the rats in the above experiments developed permanent diabetes. Moreover, the effects were only seen with potassium cyanide and not with cassava. Thus, the relevance of these experiments to FCPD is far from clear. Indeed, recent epidemiologic and experimental studies question the cassava hypothesis. FCPD is prevalent in many parts of India and Africa where cassava is not consumed and is not seen in a rural west African population consuming a high cassava diet. Experimental feeding of cassava in animal models produced conflicting results but these were mainly short-term studies. A recent study on rats kept in cassava diet for up to 1 year did not induce either pancreatitis or diabetes. Thus, it is unlikely that cassava ingestion can explain the majority of cases of FCPD seen worldwide and the current opinion is that cyanogen toxicity is not relevant in its etiopathogenesis.

Other dietary factors

The dietary intake of TCP patients was carefully studied by Balakrishnan. It was found that the protein intake of these patients was 53 g/day, which was the same as in controls. The fat intake of the patients as also of the controls was very low (27 g/day). Whether a low fat intake predisposes to FCPD or not is hypothetical. The predisposition to alcoholic pancreatitis appears to be associated both with low as well as high fat diets. An experimental study showed that monkeys fed high carbohydrate and low protein diet developed inflammatory and vascular changes in the pancreas and the heart. The lesions mimicked those found in FCPD. However, pancreatic calculi were not observed in the study. While the experimental diet used in this study is somewhat identical to the diet of poor third world population, the relevance of these findings to FCPD is not clear.

Familial aggregation of FCPD

FCPD sometimes affects many members of the same family. One study 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. 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 (vide infra).

Micronutrient deficiency and oxidant stress

Chronic pancreatitis in Caucasians has been linked to "heightened oxidative detoxification reactions" induced by cytochrome P450-1 within the pancreas and/or liver. It is possible that several factors, including chronic induction of the cytochrome P450-1 subfamily of monoxygenases by xenobiotics (cigarettes, alcohol, occupational chemicals, dietary corn oil and so forth) may be involved.

One study demonstrated that theophylline clearance (a measure of cytochrome P450-1 activity in vivo) occurs faster in patients with FCPD compared to controls. This suggested that oxidant stress may play a role in its causation. Studies on the antioxidant status of our FCPD patients showed low levels of vitamin C and β-carotene and this may well tilt the balance in favour of oxidant stress.

Malnutrition induces a state of defective ability to scavenge free radicals which could enhance the susceptibility for organ damage. It has been suggested that free radical injury occurs in alcoholic as well as FCPD patients. However, the free radical hypothesis often invoked in the causation of many diseases is by no means proven and merits further studies. It is interesting to note that most of the scavenging enzymes and anti-oxidant vitamins (Vitamin A, β-carotene, C and E) are nutritionally dependent and malnutrition can augment free radical induced injury.

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. Many subsequent studies have looked for genetic abnormalities in all forms of chronic pancreatitis following the discovery of genetic mutations in hereditary pancreatitis. We reported
no association between FCPD and the reg gene or the trypsinogen gene. In a previous study on a small cohort of patients with tropical pancreatitis, the frequency of CFTR mutations was lower than in white subjects. However, during the last 2-3 years, a number of independent groups have confirmed an association between SPINK1 mutations and FCPD.

SPINK1 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 / SPINK1) is a potent protease inhibitor and thought to be a major protective mechanism preventing inappropriate activation of pancreatic digestive enzyme cascade by inhibiting up to 20% of potential trypsin activity. Mutations of SPINK1 gene are significantly associated with tropical calcific pancreatitis as demonstrated by Chandak et al. 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.

SPINK1 mutations were also studied in FCPD subjects from Chennai and Dhaka. In the total study group (Bangladesh and Southern Indian) the N34S variant was present in 33% of 180 subjects with FCPD, 4.4% in non-diabetic and 3.7% in Type 2 diabetic subjects. These results suggest that the N34S variant of SPINK1 is a susceptible gene for FCPD.

Bhatia et al. also found a strong association with SPINK1 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. However, calculi develop after several years of abdominal pain and about 10% of patients do not develop calculi. Hence the need for other diagnostic markers. Unfortunately, there are still no sensitive and specific non-invasive blood or urine tests to diagnose early stages of chronic pancreatitis. Even in the developed nations of the world, the diagnosis of chronic pancreatitis in adults or children is often elusive and usually made very late, only after ductal changes or calculi develop. As in other types of chronic pancreatitis, the diagnosis of FCPD is seldom made in the early stages of the disease. The investigation for suspected cases of FCPD without pancreatic calculi is as follows:

Tests of pancreatic structure
a. Ultrasoundography
b. Computed tomography
c. Endoscopic retrograde cholangiopancreatography
d. Endoscopic ultrasonography

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

By ultrasonography and Computed Tomography (CT) of the abdomen it is possible to evaluate the size of the pancreas and also confirm intraductal location of calculi and the degree of fibrosis and ductal dilatation. Imaging of smaller stones and diagnosis of pseudocyst is better on computed tomography. Endoscopic retrograde cholangiopancreatography (ERCP) studies help to confirm ductal dilatation particularly in the non-calcific causes of TCP. ERCP may show ductal tortuosity and dilatation (Figure 6), stenosis, obstruction, cyst formation, and the presence of calculi in the main pancreatic duct, side branches, and ductules.

Endoscopic ultrasonography is an exciting new tool for diagnosis of chronic pancreatitis, especially at a relatively early stage. The sensitivity and specificity of endoscopic ultrasonography are reported to be 85% and 67% respectively. However, more studies are required before accepting it as a standard diagnostic procedure for chronic pancreatitis.

Exocrine Pancreatic Function

Exocrine pancreatic function in FCPD has been studied by many workers using a variety of tests. Serum immunoreactive trypsin measurements have shown a spectrum of pancreatic involvement. In advanced stages of the disease, there is marked reduction of trypsin level while in early stages it may be subnormal or even elevated due to acute pancreatitis. When Lundh meal tests were performed, 93% of the TCP patients with calcification were reported to have low trypsin activity compared with 27% of the noncalcific variety. Secretin-pancreozymin tests revealed gross reduction in volume, bicarbonate, trypsin, and lipase content of
the pancreatic secretion. The lactoferrin level of the pancreatic juice was found to be considerably higher in both normal controls and FCPD subjects from India compared with their respective European counterparts.\textsuperscript{13}

There are several reports using faecal chymotrypsin as a screening test for evaluating exocrine pancreatic function in FCPD patients.\textsuperscript{97,100,101} We screened three groups of diabetic patients: FCPD, type 1 and type 2 diabetes and found that exocrine pancreatic insufficiency as shown by low faecal chymotrypsin levels (defined as 58 units/g of faecal mass) was present in 87.5% of patients with FCPD, 23.5% with type 1 diabetes, and 4.5% with type 2 diabetes.\textsuperscript{106} Low sensitivity is the only drawback with faecal chymotrypsin as it may not detect many mild cases of chronic pancreatitis, although its specificity is quite high. The usefulness of fecal chymotrypsin was compared with another tubeless test, namely the N-benzoyl L-tyrosyl-para-aminobenzoic acid (BT-PABA) test.\textsuperscript{102} We found that although the fecal chymotrypsin test has a slightly lower sensitivity, it is simpler and considerably cheaper than the PABA test. It is also shown that a new test developed by us, BT-PABA/p-aminosalicylic acid is an excellent test to diagnose FCPD as it has a very high sensitivity and specificity.\textsuperscript{103}

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.\textsuperscript{100} 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.\textsuperscript{22} 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 due 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.

Pancreatic cancer is the most sinister complication of FCPD. The risk of developing pancreatic cancer among patients with temperate zone chronic pancreatitis has been estimated to be 16.5-fold higher than age matched controls.\textsuperscript{105} In FCPD patients the risk appears to be much higher. In one study, 185 FCPD patients were followed up for an average of 4.5 years to assess the risk of pancreatic cancer. During this period, 34 patients died from all causes, and six deaths (25%) were due to pancreatic cancer. When compared with the background pancreatic cancer rate (Madras Cancer Registry), the relative risk for pancreatic cancer in patients with FCPD was 100 (95% confidence interval 37 to 218).\textsuperscript{106} Augustine and Ramesh\textsuperscript{107} have also reported an increased risk of pancreatic carcinoma in TCP. While there are no direct

<table>
<thead>
<tr>
<th>Complication</th>
<th>Type 2 diabetes (n = 277)</th>
<th>FCPD (n = 277)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>33 (11.9%)</td>
<td>13 (5.1%)</td>
<td>0.003</td>
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<tr>
<td>Peripheral vascular disease (%)</td>
<td>12 (4.3%)</td>
<td>13 (4.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>103 (37.2%)</td>
<td>100 (36.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>70 (25.3%)</td>
<td>58 (20.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nephropathy (%)</td>
<td>42 (15.0%)</td>
<td>30 (10.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>65 (23.5%)</td>
<td>73 (26.4%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
comparisons with temperate zone pancreatitis, it appears that the risk of developing pancreatic cancer is higher in TCP than in alcoholic chronic pancreatitis. The only other type of pancreatitis that is highly prone to malignancy is hereditary pancreatitis where the risk ratio is 53 compared with the general population. The duration of exposure to inflammation seems to be the major factor involved in the transition to a malignant condition in chronic pancreatitis and smoking remains the strongest risk factor that is amenable to preventive intervention in temperate zone pancreatitis, while the risk factors for cancer in TCP remain unknown.

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. reported advanced retinopathy in FCPD patients, which has been confirmed by others. 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. Peripheral neuropathy and autonomic neuropathy 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, ischemic heart disease, cerebrovascular accidents and peripheral vascular disease have occasionally been reported. 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. The prevalence of complications among the study groups is shown in Table 3.

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. 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 functions 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 steatorrhea. It is believed by most workers in the field

<table>
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<tr>
<th>Table 4. Standard Surgical Techniques in TCP</th>
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<tr>
<td>1. Longitudinal pancreaticojejunostomy (the Puestow procedure)</td>
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<td>2. Distal pancreaticojejunostomy (Duval procedure)</td>
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<tr>
<td>3. Subtotal pancreatectomy</td>
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<tr>
<td>a. Distal 80-95% pancreatectomy</td>
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<td>b. Less than 80% pancreatectomy</td>
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<td>4. Pancreatic duodenectomy</td>
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<td>5. Total Pancreatectomy (rare)</td>
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<td>6. Local resection of head of the pancreas</td>
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<td>7. Transplantation of the pancreas</td>
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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. Based on long term follow up of large numbers of patients, we believe that FCPD is indeed the late diabetic stage of TCP for the following reasons:

1. TCP patients are younger than FCPD patients.

2. TCP patients are also seen in the impaired glucose tolerance stage, which is considered to be a prediabetic stage.

3. The presence of SPINK 1 mutations in both TCP and FCPD 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. 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 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 fecal 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. They may occasionally help to improve diabetic control and abdominal pain.

c. Pancreatic pain: Often, the pain is severe and intractable and is not relieved even by powerful analgesics. When there is no response to medical treatment, surgical intervention is indicated. Various surgical interventions have been tried with fairly good results. (Table 4). Many of these procedures are beneficial with respect to alteration of pain, although some patients may experience a relapse. There are some reports which suggest that after surgery the mean daily insulin requirement may decrease. However, these changes are usually transient and the diabetic status appears to be largely unaffected by surgery. There is, however, improvement of general health and quality of life, particularly in those with severe intractable pain. Recurrent pain after drainage procedures has often been reported. Stenosis of the anastomosis, retained calculi causing cysts or abscesses and internal post operative herniations some times twisting the roux loop used for the pancreaticojejunal anastomosis are some of the causes identified for recurring pain. Pancreatic cancer, however, is the most important condition to be excluded in any patient with recurrent pain following a drainage procedure.

Extracorporeal shock-wave lithotripsy and stone dissolution and endoscopic stone removal are often successful but the mere removal of stones may not guarantee relief of pain.

CONCLUSIONS

FCPD is a unique form of diabetes secondary to tropical calcific pancreatitis. 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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