Fibrocalculous Pancreatic Diabetes

Ranjit Unnikrishnan • Viswanathan Mohan
Madras Diabetes Research Foundation and Dr. Mohan’s Diabetes Specialities Centre, WHO Collaborating Centre for Noncommunicable Diseases Prevention and Control, IDF Centre of Education, Chennai, India

Abstract
Fibrocalculous pancreatic diabetes is an uncommon form of diabetes secondary to chronic nonalcoholic calcific pancreatitis found in tropical parts of the globe. The etiology of this condition remains unknown, although environmental and genetic factors have been postulated. In its classical form, this disease is characterized by recurrent abdominal pain in childhood, followed by exocrine pancreatic dysfunction and diabetes by early adulthood. Pancreatic pathology is characterized by fibrosis of the gland and stone formation preferentially in the large ducts. Diagnosis can be made by imaging studies such as X-ray, ultrasound or CT scanning; tests of exocrine pancreatic function are also useful. Diabetes is usually severe and needs insulin for control; microvascular diabetic complications are also frequent. The most dreaded long-term complication is the development of pancreatic carcinoma.

Introduction
Pancreatic disease is a rare cause of secondary diabetes. Various forms of pancreatic pathology can result in diabetes, the chief ones being chronic pancreatitis, cystic fibrosis, hemochromatosis and malignancy. Chronic pancreatitis is defined as a continuing inflammatory disease of the pancreas, characterized by irreversible morphological changes and leading to permanent loss of function, which can manifest as exocrine insufficiency or diabetes. Alcohol abuse remains the most common cause of chronic pancreatitis in the Western world, and the condition thus produced is called ‘alcoholic chronic pancreatitis’. However, in certain parts of the world there exists a distinct form of chronic calcific pancreatitis which can present with diabetes in adolescence or early adulthood, and which is not associated with excessive alcohol intake.

In 1959, Zuidema [1] reported on a series of 45 patients with diabetes from Indonesia who were poor and protein-energy malnourished and had features of chronic pancreatitis including pancreatic calcification in spite of no or minimal
intake of alcohol. In the subsequent years, more cases of this kind were reported from parts of tropical Africa (Uganda, Nigeria, Zambia and Madagascar), Asia (India, Bangladesh and Sri Lanka) and South America (Brazil). The largest series of such cases was published by Geervarghese et al. [2] from Kerala, India, in the 1960s and 1970s.

The term ‘tropical pancreatitis’ or ‘tropical chronic (calcific) pancreatitis’ (TCP) was subsequently introduced to describe this entity, and the term ‘fibrocalculous pancreatic diabetes’ (FCPD) was applied to those patients with TCP who developed diabetes. TCP can thus be defined as a form of idiopathic nonalcoholic chronic pancreatitis found in tropical regions of the world, characterized by abdominal pain, pancreatic calculi (fig. 1) and, later, diabetes mellitus (FCPD).

While the earlier series reported on by Zuidema and Geervarghese had all the classical features of FCPD, including malnutrition, subsequent studies from other parts of India such as Chennai showed that there was a striking heterogeneity in the clinical presentation of these patients [3]. For instance, not all of them came from poor socio-economic backgrounds, not all of them were malnourished, and a few could even be controlled for a time with oral antidiabetic agents without the need for insulin.

Epidemiology

There is wide geographic variation in the prevalence of TCP and FCPD. Most of the cases have been reported in tropical parts of Asia, Africa and South America, or in individuals who originated from these areas. Highly endemic areas for TCP/FCPD include the states of Kerala and Tamil Nadu in South India. In 1994, Balaji et al. [4] found the prevalence of TCP to be 1 in 793 individuals in Kerala. A study from Chennai
between 2001 and 2003 showed the prevalence of FCPD among self-reported diabetic subjects to be 0.36%, while it was 0.019% among the general population [5].

However, there have been some striking changes in the epidemiology of FCPD over the past few decades. In a clinic-based study from Chennai, the prevalence of FCPD was found to have decreased from 1.6% (for the years 1991–1995) to 0.2% (during the years 2006–2010). This study also showed that there was a significant increase in mean age at onset of FCPD over the years, as well as an increase in mean BMI of the patients [6]. The exact reasons for these changes in the epidemiology of FCPD are not clear, but improvements in socioeconomic status and nutrition are likely to have played a major role.

**Etiopathogenesis**

In contrast to alcoholic chronic pancreatitis, the etiology of TCP is as yet not completely understood. The following hypotheses have been proposed:
1. Malnutrition
2. Role of cassava and other dietary toxins
3. Familial and genetic factors
4. Oxidative stress and trace element deficiencies

**Malnutrition**

The earliest studies on TCP/FCPD focused on malnutrition as the chief causative factor of this disease entity. The earliest series of TCP patients described by Zuidema [1] and Geervaghese et al. [2] consisted almost exclusively of malnourished individuals. Also, the decrease in prevalence of FCPD in many parts of India has coincided with economic development and consequent improvement in nutritional status. However, the fact that the disease is rare in parts of Africa where malnutrition is most profound (such as Ethiopia and Somalia) argues against malnutrition as a direct etiological factor in this condition. Also, studies from India have shown that not all patients with FCPD are malnourished or come from a low socioeconomic class [3]. This has led some authors to postulate that malnutrition is an effect, and not the cause, of the disease.

**The Cassava Hypothesis**

This theory was put forward by McMillan and Geervaghese [7], who noted that cassava (manioc, tapioca) was commonly consumed as a staple food by the poorer sections of society in Kerala, where the prevalence rates of FCPD were the highest. Cassava contains cyanogenic glycosides such as linamarin and lotaustralin. Cyanide is usually detoxified in the body to thiocyanate, the conversion requiring an ample
supply of sulfur-containing amino acids. When individuals deficient in these amino acids consume cassava, cyanides accumulate, leading to pancreatitis and FCPD. Mc-Millan and Geevarghese also showed that rats develop transient hyperglycemia on cyanide ingestion. However, none of the rats developed pancreatitis or permanent diabetes.

Also, it has been noted that TCP is not found in other cassava-consuming regions of the world, and that it is prevalent in many parts of India and Africa where cassava is not a staple. More recent studies have failed to show any association between cassava consumption and TCP/FCPD [8].

Genetic Factors

TCP occasionally affects several members of the same family. While this may imply the presence of shared environmental risk factors, the role of genetic factors has also received close attention. Initial studies in this respect looked at whether FCPD shares common susceptibility genes with type 1 or type 2 diabetes (particularly the Reg gene), but they have drawn a blank [9]. Other genes studied include cathepsin B, anionic trypsinogen, chymotrypsin C, calcium-sensing receptor and cystic fibrosis transmembrane conductance regulator, the last of which has shown some promise.

The first gene to be positively associated with TCP was the SPINK1 (serine protease inhibitor, Kazal type 1) gene [10]. It is considered to be involved in a major protective mechanism preventing inappropriate activation of the pancreatic enzyme cascade. However, the current consensus is that this gene might play, at best, a modulatory role in the etiopathogenesis of TCP [11].

Oxidative Stress and Trace Element Deficiency

Oxidative stress has been linked to chronic pancreatitis in White populations [12]. It is plausible that malnutrition and trace element deficiencies can impair the body’s ability to detoxify free radicals, which can then go on to inflict damage on the pancreas. Studies on Indian patients with TCP showed low levels of the antioxidants, beta carotene and vitamin C, lending further credence to this theory [13].

Pathology

Gross Appearance

The pancreas is usually atrophic in late stages of the disease and may be as small as the little finger of one’s hand. The surface is nodular and the consistency firm, fibrous or
Fig. 2. Calculi of different sizes and shapes from patients with TCP.

gritty. Calculi are found throughout the gland, and they may vary in size from small sand particles to 4.5 cm in length and may weigh up to 20 g. The larger stones are located in the body of the gland and the smaller ones near the tail. The stones are predominantly lodged in the large pancreatic ducts. They are of varying shapes and chalky white or dirty white in color (fig. 2). Chemical analysis indicates that the stones are composed of 95.5% calcium carbonate and small amounts of calcium phosphate. The nidus of the calculus is rich in iron, chromium and nickel, and the periphery is rich in calcium [14]. Traces of magnesium, urate and oxalate have also been found. ‘Soft stones’ are formed of noncalcified protein plugs and caseous material.

Microscopy

The pancreatic capsule is thickened and there is widespread inter- and intralobular fibrosis. There is marked dilatation and fibrosis of the main pancreatic duct, collecting duct and ductules. There is also infiltration of lymphocytes and plasma cells surrounding the ducts. Immunohistochemical examination shows a decrease in the number of alpha and beta cells [15]. Nesidioblastosis may be present in some cases.

Clinical Features

The classic patient with TCP is a lean or malnourished young adult of either sex, residing in a tropical country and hailing from a poor socioeconomic background. There is often bilateral parotid enlargement, a distended abdomen and a ‘cyanotic hue’ of the lips. However, the clinical presentation of the disease has gradually changed over the years, a process which may have been influenced by improvements in
nutritional status [6]. While the majority of patients continue to be lean, frank malnutrition is uncommon and a few are of ideal body weight or even obese. Most patients are aged between 10 and 30 years at the onset of diabetes, but onset in infancy, childhood and the elderly is not unheard of.

The classic triad of clinical features of TCP consists of:
1. Abdominal pain
2. Malabsorption leading to steatorrhea
3. Diabetes

Abdominal pain is usually the first symptom to occur and can start even in childhood. The pain is usually episodic, severe and localized to the upper abdomen with radiation to the back. The patient often assumes a prone position or sits stooping forward in an attempt to relieve the pain. The frequency and severity of pain tend to decrease with time and it usually disappears by the time diabetes develops. Severe exocrine pancreatic insufficiency leads to fat malabsorption with the passage of bulky, oily and frothy stools which are difficult to flush away. Frank steatorrhea is, however, rare in these patients, because their diets are generally low in fat.

Diabetes is a late consequence of TCP, and is termed FCPD. It usually develops a decade or two after the first episode of abdominal pain. Patients may present with classical symptoms of hyperglycemia (polyuria, polydipsia and polyphagia) or may be totally asymptomatic with regard to diabetes. Although FCPD is characterized by extremely high levels of blood glucose, patients usually do not develop ketosis even if insulin is withdrawn. This may be due to [16]:
1. Partial preservation of beta cell function; patients have enough endogenous insulin to prevent ketogenesis, but not to maintain euglycemia
2. Decreased glucagon reserve; the destructive process involves the alpha cells as well
3. Reduced availability of nonesterified fatty acids, the substrate for ketogenesis, due to lack of subcutaneous fat

Most patients with FCPD require insulin for control of glycemia. The occasional patient may be able to maintain good glycemic control with oral antidiabetic agents over varying periods of time. Rarely, some patients become truly insulin dependent in that they develop ketoacidosis on withdrawal of insulin (fig. 3).

While the symptoms attributable to chronic pancreatitis are similar in alcoholic chronic pancreatitis and TCP, the two conditions differ in certain other important respects. These are listed in table 1.

Diagnosis

Several clinical criteria have been put forward for the diagnosis of FCPD. Among the most widely used are the criteria given by Mohan et al. [17] (table 2). In the presence of pancreatic calculi on plain radiographs of the abdomen, the diagnosis is straightforward (fig. 1). However, calculi may develop only after several years of
Fig. 3. Spectrum of diabetes in FCPD.

Table 1. Differences between alcoholic chronic pancreatitis and TCP

<table>
<thead>
<tr>
<th>Alcoholic chronic pancreatitis</th>
<th>TCP</th>
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<tbody>
<tr>
<td>Almost exclusively in males</td>
<td>Male-female ratio 70:30</td>
</tr>
<tr>
<td>Onset in 4th and 5th decades</td>
<td>Onset in 2nd and 3rd decades</td>
</tr>
<tr>
<td>Occurs in all socioeconomic strata</td>
<td>Mostly in poorer sections of society</td>
</tr>
<tr>
<td>Diabetes occurs in 50% of cases</td>
<td>Diabetes occurs in 90% of cases</td>
</tr>
<tr>
<td>Pancreatic calculi in 50–60% of cases</td>
<td>Pancreatic calculi in 90% of cases</td>
</tr>
<tr>
<td>Small speckled calculi mainly in the smaller ducts and tail region</td>
<td>Large dense calculi mainly in the larger ducts and in the head region</td>
</tr>
<tr>
<td>Fibrosis and ductal dilatation less marked</td>
<td>Fibrosis and ductal dilatation more marked</td>
</tr>
<tr>
<td>Incidence of pancreatic cancer higher than in general population</td>
<td>Markedly higher incidence of pancreatic cancer</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic criteria for FCPD [17]

1. The patient should be from a tropical country
2. Diabetes should be present
3. Evidence of chronic pancreatitis must be present – pancreatic calculi on abdominal X-ray or at least 3 of the following:
   a) abnormal pancreatic morphology on sonography/CT scan;
   b) recurrent abdominal pain since childhood;
   c) steatorrhea;
   d) abnormal pancreatic function test
4. Absence of other causes of chronic pancreatitis
disease, and some patients never develop calculi at all. In some of these cases, ultrasonography of the pancreas may be helpful in documenting atrophy of the gland and in confirming intraductal location of calculi, if there are any. Smaller stones can be picked up by CT scanning. Other investigations that can be used to assess pancreatic morphology include endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography.

Tests of pancreatic function help in assessing the extent of pancreatic damage due to the inflammatory process and may assist in assessing the necessity for, and expected response to, treatment. A variety of tests have been used to assess exocrine pancreatic function. Analysis of pancreatic juice collected following stimulation by secretin and pancreozymin (secretin-pancreozymin test) shows a gross reduction in volume, bicarbonate, trypsin and lipase content [18]. ‘Tubeless’ tests for exocrine pancreatic function include the BT-PABA (N-benzoyl-l-tyrosyl-p-aminobenzoic acid) test, fecal chymotrypsin assay and fecal elastase assay. The fecal chymotrypsin assay has a lower sensitivity than the BT-PABA test, but it has equivalent specificity and is much cheaper and easier to perform [19]. Of late, the fecal elastase assay has emerged as the ‘gold-standard’ indirect pancreatic function test.

Endocrine pancreatic function is best assessed using measurement of C-peptide. Patients with FCPD have partial preservation of beta cell function, as shown by C-peptide levels that are lower than those found in type 2 diabetes but higher than those in type 1 diabetes [20].

Complications

It was long held that patients with FCPD rarely developed chronic diabetic complications. However, studies from Chennai in the 1980s showed the presence of even advanced stages of diabetic retinopathy in these patients [21]. Nephropathy, neuropathy [22] and autonomic neuropathy [23] have also been reported in these patients. However, macrovascular complications are rare. This could be due to the relative youth, low BMI and low lipid levels of these patients.

A study comparing the prevalence of long-term complications of diabetes in FCPD and type 2 diabetic patients matched for age, sex and duration of diabetes showed that while the prevalence of all microvascular complications was equal in the two groups, macrovascular complications were significantly less common in the FCPD group [24].

Patients with FCPD can also develop complications due to the pancreatic pathology per se. Perhaps the most dreaded complication of FCPD is pancreatic carcinoma. Studies from Chennai indicate that the risk of malignancy in TCP is increased up to 100-fold [25]. Unlike de novo ductal pancreatic cancer, malignancy in TCP can arise from the body and tail of the gland as well as from the head. Diagnosis of malignancy in TCP is often difficult. Unexplained weight loss or sudden worsening of pain in a patient with FCPD whose glucose levels are well controlled should
prompt a search for malignancy. Development of obstructive jaundice is often a late sign. CA 19-9 is a useful tumor marker, but false-positive and negative results limit its utility. Other complications include pseudocysts, pseudoaneurysms, venous thrombosis, common bile duct obstruction, pancreatic fistulae and ascites. Patients may also develop a deficiency in fat-soluble vitamins (A, D, E and K) as a consequence of fat malabsorption.

**Natural History**

In the 1960s, Geervarghese et al. [2] noted that patients with TCP develop abdominal pain in childhood and diabetes by adolescence, and that they die by young adulthood or in the prime of their lives. Survival of patients with TCP has improved markedly over the last five decades. In a cohort of 370 FCPD patients, it was found that 80% were alive 35 years after the first episode of abdominal pain [26]. The mean survival after diagnosis of diabetes was 25 years. The main causes of death were diabetic complications (particularly nephropathy and infections) and pancreatic cancer.

**Management**

*Abdominal Pain*

The abdominal pain in TCP is severe and often difficult to treat. Nonopioid analgesics are preferred wherever possible, although particularly severe episodes may necessitate the use of opioids. Fortunately, the severity of pain tends to abate with time. Pancreatic enzyme supplements and antioxidants have not shown consistent benefit in reducing pain in TCP.

In certain cases, the pain may be so intractable as to require surgery. The procedures adopted include ductal decompression, drainage procedures (side-to-side pancreaticojejunostomy and distal pancreaticojejunostomy) and ablative procedures (partial or subtotal pancratctomy). Extracorporeal short-wave lithotripsy and endoscopic stone removal are often successful in alleviating pain. Nerve ablation procedures like celiac plexus block, neurolysis and splanchnicectomy have also been tried.

*Steatorrhea*

A low-fat diet can reduce the incidence of steatorrhea. Fat-soluble vitamins should be supplemented appropriately. Pancreatic enzyme supplements may help to reduce steatorrhea and improve quality of life in these patients.
Diabetes

The occasional patient with FCPD is able to maintain good control of glucose levels with oral antidiabetic agents, but the majority ultimately requires insulin. Some patients have brittle diabetes, with wide fluctuations in their blood glucose levels, and are quite difficult to control. The use of subcutaneous insulin infusion pumps may be considered in such cases, since they provide a more physiological mode of insulin delivery. A more liberal calorie and protein intake should be advised to combat malabsorption and malnutrition.

Conclusions

FCPD is a unique form of diabetes secondary to chronic calcific pancreatitis, found exclusively in tropical regions of the world. Although the etiology of this condition remains obscure, it is heartening that there has been a significant improvement in its prognosis over the past half century. Much more, however, remains to be learnt if we are to offer these patients a quality of life equivalent to that of patients with type 2 diabetes.

References


Dr. V. Mohan, MD, FRCP (London, Edinburgh, Glasgow, Ireland), PhD, DSc, FNASc, FASc, FNA
President and Chief of Diabetes Research, Madras Diabetes Research Foundation
Chairman and Chief Diabetologist, Dr. Mohan’s Diabetes Specialities Centre
WHO Collaborating Centre for Noncommunicable Diseases Prevention and Control, IDF Centre of Education
1, Conran Smith Road, Gopalapuram, Chennai 600 086 (India)
E-Mail drmohans@diabetes.ind.in

Unnikrishnan • Mohan