Special Topic

MALNUTRITION-RELATED DIABETES MELLITUS

The Indian Perspective

by V. Mohan

IN BRIEF

Both forms of malnutrition-related diabetes mellitus, fibrocalculous pancreatic diabetes and protein-deficient diabetes mellitus, are present in India. Malnutrition alone is unlikely to cause fibrocalculous pancreatic diabetes, but a secondary role cannot be excluded. In contrast to fibrocalculous pancreatic diabetes, people with protein-deficient diabetes mellitus show no demonstrable pancreatic pathology, such as pancreatic calculi or other features of chronic pancreatitis. Special features of this form of diabetes include: onset at a young age, requirement of large doses of insulin to control glycemia (i.e., insulin resistance), ketosis resistance even if insulin is withdrawn, and evidence of protein-calorie malnutrition.

In developing tropical countries of the world certain forms of diabetes associated with undernutrition have been recognized for the past few decades. However, it was due to the brilliant work of J.S. Bajaj that malnutrition-related diabetes mellitus was finally accepted as a separate entity by the World Health Organization (WHO) Study Group on Diabetes Mellitus (1).

In India both forms of malnutrition-related diabetes mellitus, namely fibrocalculous pancreatic diabetes (FCPD) and protein-deficient diabetes mellitus (PDDM), are present.

Fibrocalculous Pancreatic Diabetes

FCPD is a form of diabetes secondary to tropical calcific pancreatitis. It is not due to alcohol consumption and tends to affect younger people.

There is little information on the prevalence of FCPD. Most available data are clinic-based, and thus are subject to referral bias. Balaji's study (2,3) is the only one to have looked at the prevalence of this condition. This study was a systematic survey of 6,079 families in a village in the Quilon district of Kerala state. A population of 28,507 was interviewed, and 518 subjects were identified as having one of the following characteristics: abdominal pain suggestive of pancreatitis, diabetes mellitus, or a history of weight loss (malnutrition). Using a combination of abdominal X-rays, ultrasound, and an NBT-PABA (nitro blue tetrazolium *p*-aminobenzoic acid) test, 28 cases of chronic calcific pancreatitis (CCP) and 8 cases of non-calcific pancreatitis (NCP) were identified. Thus, 1 of 793 (0.12%) patients had chronic pancreatitis (CCP and NCP), and 1 of 1,020 patients had CCP (0.09%).

Geevarghese and Pitchumoni (4) have reported FCPD in large numbers of patients at two medical college hospitals of Kerala state. Large numbers of patients with FCPD have also been reported by Tripathy and colleagues in the state of Orissa and by Viswanathan and colleagues in Tamil Nadu, a southeastern state in India adjoining Kerala state. At our center at Madras in Tamil Nadu, we see from 50 to 60 patients with FCPD each year, which represents about 0.5-1% of all our diabetic patients. Reports from some centers show no decline in the number of cases. FCPD has also been reported from Karnataka and Andhra Pradesh states in southern India and from Nagpur and Tripura. Recently a wealth of original work in this field has come from Yajnik's group (5) in Pune in Maharashtra state. Figure 1 shows the distribution of FCPD in India.

Etiology and Pathogenesis

The etiology and pathogenesis of FCPD is still largely unexplained. Genetic factors have been thought to be unimportant, although familial clustering of FCPD and recent preliminary studies of DNA markers from our own group hint at a possible inherited contribution. Future studies may confirm this finding.

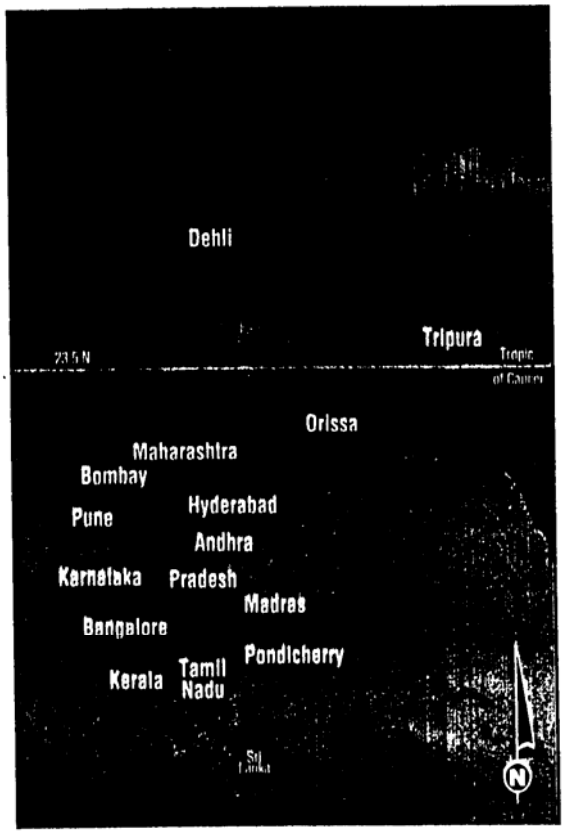
Of the possible environmental agents, protein-calorie malnutrition and cassava (tapioca) ingestion are the two main factors implicated. Malnutrition alone is unlikely to cause FCPD, but a secondary role cannot be excluded. It is more likely that micronutrient deficiency (β-carotene, vitamin C, selenium, etc.) may play a role in making the pancreas vulnerable to toxic agents.

Certain varieties of cassava (tapioca or manihot, a tuber grown in southern India) contain cyanogenic glycosides, which in the presence of protein-calorie malnutrition (particularly deficiency of sulphur-containing amino acids) are believed to lead to toxic pancreatitis and diabetes. Studies in rats by Macmillan and Geevarghese have shown that cyanide administration can lead to transient hyperglycemia but not to permanent diabetes. Although there is some geographical overlap between the areas of cassava consumption and the distribution of FCPD, the occurrence of the disease in noncassava areas suggests that other factors may be involved. The role of other foodstuffs that may contain cyanide merits study.

With the collaboration of Joan Braganza we have studied the role of oxidant stress in producing FCPD. Our studies have shown evidence of oxidant stress and deficient antioxidants (particularly vitamin C and β-carotene) in subjects from southern India. This is obviously an area for future research studies.

Pathology of the Pancreas

The pathological findings in FCPD are striking. The pancreas of a patient with FCPD is small, atrophic, and fibrosed. The pancreatic duct is dilated and usually contains multiple calculi in the major duct or its tributaries. Pitchumoni and colleagues have shown that the calculi are composed mainly of calcium carbonate around a nucleus containing iron, chromium, and nickel. Microscopic examination of the pancreas reveals extensive atrophy of the acini, with their replacement by sheets of fibrous tissue. Periductal fibrosis is also a characteristic feature.



◀ ***Figure 1.*** *Distribution of fibrocalculous pancreatic diabetes in India.*

Clinical Features of FCPD

The following clinical description is compiled from studies on more than 300 subjects with FCPD seen at our unit. In its classic form, the disease is seen in patients from the poorest strata of society. There is a 2:1 male-to-female predominance. FCPD is also a disease of youth: 61% of our patients were diagnosed with FCPD at less than 30 years of age and 93% at less than 40 years.

Patients with classic FCPD usually present with extreme degrees of protein-calorie malnutrition, generalized wasting, decreased muscle mass, sunken eyes, painless bilateral parotid gland enlargement, and a distended abdomen. There may be evidence of multiple vitamin deficiencies, and skin infections are common.

Recently, however, the clinical picture has changed considerably. Overt protein-calorie malnutrition is less common, although most patients are still lean. Many patients now come from the middle or even the upper strata of society.

The classic clinical triad of FCPD consists of abdominal pain, pancreatic calculi, and diabetes, but the occurrence of these is variable. The disease usually starts with recurrent abdominal pain in childhood. In most cases the pain is severe but may be mild or, occasionally, totally absent. After several years pancreatic calculi develop and are usually detected during adolescence by radiographic or ultrasound imaging of the abdomen.

Pancreatic calculi are the hallmark of FCPD and affect up to 90% of patients. These are usually seen to the right of the first or second lumbar vertebrae. They may be solitary or multiple and occasionally occupy the whole pancreas. Figure 2 shows multiple pancreatic calculi to the right of the first and second lum-

bar vertebrae, a characteristic site for these calculi. Ultrasonography can confirm the location of the calculi (which are almost always intraductal) and may identify other characteristic features, such as ductal dilation, irregularity of the gland margins, and increased echogenicity of the parenchyma. Similar appearances may be seen on computerized tomographic scanning. Endoscopic retrograde cholangiopancreatography (ERCP) helps to delineate pancreatic ductal pathology. Figure 3 shows ERCP appearance of a patient with FCPD and a grossly dilated pancreatic duct.

Hyperglycemia in FCPD patients is usually severe, with fasting plasma glucose levels in the range of 15–20 mM. Despite marked hyperglycemia, most patients do not develop ketoacidosis. It has been suggested that ketosis resistance is due to the small adipose tissue mass in patients with FCPD or to delayed mobilization of free fatty acids. We have reported that subjects with FCPD have higher C-peptide levels than those with insulin-dependent diabetes mellitus (IDDM or type I diabetes), indicating that relatively preserved endogenous insulin reserves may be one of the factors responsible for ketosis resistance. Yajnik's studies from Pune show that other mechanisms may also be involved.

Contrary to earlier beliefs, insulin requirements in FCPD are not unusually high. The average insulin dosage in our series was 40 U/day, and true resistance (>200 U/day) is rare.

Specific diabetic microvascular complications were previously thought to be rare and mild in FCPD, as in many other secondary forms of diabetes. Recent studies, however, have shown that complications like those in primary forms of diabetes do occur. Both of the sight-threatening forms of retinopathy, namely proliferative retinopathy and maculopathy, occur in our FCPD patients, as do neuropathy and advanced nephropathy. The frequency of macrovascular complications may be lower than in primary forms of diabetes because the patients tend to be young and lean and have low cholesterol levels.

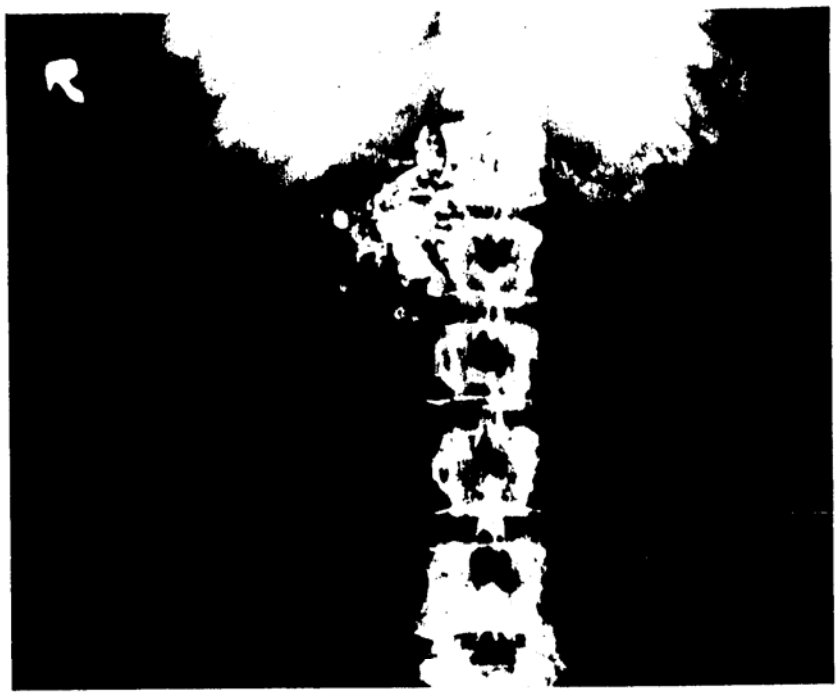


Figure 2.
Extensive pancreatic calculi in patient with FCPD. Note the large rounded calculi typical of FCPD.

Steatorrhea

Steatorrhea, (the passing of large amounts of fat through the feces) is not a prominent feature in FCPD. It affects less than one-third of patients, largely because of their low dietary fat intake. Specialized investigations such as the secretin-pancreozymin, Lundh meal, PABA, or fecal chymotrypsin test can help to document the presence of exocrine pancreatic insufficiency.

Management of FCPD

About 80% of our patients require insulin to control hyperglycemia and the remainder respond to sulfonylureas. This appears to be related to the patient's C-peptide status.

Pain, if severe and intractable, often leads to surgical intervention, and various procedures have been attempted. Pancreatic duct sphincterotomy is of benefit in some cases. Steatorrhea can be reduced by oral administration of pancreatic enzyme preparations.

Protein-Deficient Diabetes Mellitus (PDDM)

In contrast to FCPD, people with PDDM show no demonstrable pancreatic pathology, such as pancreatic calculi or other features of chronic pancreatitis. Special features of this form of diabetes, as originally described by Hugh-Jones in 1955, include the following: onset at young age, requirement of large doses of insulin to control glycemia (i.e., insulin resistance), ketosis resistance even if insulin is withdrawn, and evidence of protein-calorie malnutrition.

In India PDDM has been extensively studied by Tripathy, Samal, and colleagues from Orissa; Bajaj and colleagues and Ahuja's group from Delhi; and several others. Experimental and clinical studies by these researchers have thrown much light on the clinical features and peculiarities of PDDM. The condition is diagnosed in young, insulin-requiring diabetic patients who are extremely lean and malnourished, and despite requiring large doses of insulin, do not develop ketoacidosis when insulin injections are withdrawn.

Figure 3.
ERCP of a patient with FCPD showing grossly dilated pancreatic duct.

A major problem with PDDM is that it is difficult to define accurately: None of the clinical characteristics are highly specific. High insulin requirements are certainly not restricted to PDDM. Ketosis resistance, perhaps the most challenging aspect of malnutrition-related diabetes, also defies accurate description. In Ethiopia, for example, certain patients initially diagnosed as PDDM became ketotic on follow-up, indicating a slowly progressive form of type I diabetes. Furthermore, clinical evidence of protein-calorie malnutrition is not helpful as a clinical sign in societies where poverty is common and where many patients with classic type I or non-insulin-dependent diabetes mellitus (NIDDM or type II diabetes) are also grossly undernourished.

Bajaj has proposed a point-scoring system for diagnosis of malnutrition-related diabetes (6). This certainly helps to eliminate some diagnostic dilemmas and may help to identify individuals with PDDM more accurately. Unfortunately in this scoring system, the two forms of malnutrition-related diabetes, namely FCPD and PDDM, are lumped together. Further refinements of the scoring system and the adoption of an accurate and uniform diagnostic criteria would help in a better understanding of PDDM.

In summary, malnutrition-related diabetes mellitus is now recognized as a separate and major form of diabetes. It deserves further study, not only because of its importance in developing countries, but also because it may improve our understanding of other forms of diabetes as well.

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