## Special Topic

### Malnutrition-Related Diabetes Mellitus

# Diagnosis And Treatment

by C.S. Yajnik

**IN BRIEF**

*Most often doctors expect to find fibrocalculous pancreatic diabetes (FCPD) only if the patient is young, severely malnourished, from a poor socioeconomic background, and has a history of abdominal pain. Such a classic picture is now seen in only a few patients and represents the extreme end of a spectrum. FCPD can occur in the absence of these features. In fact, some patients with FCPD belong to well-to-do families. It is, therefore, not surprising that some are treated as having primary diabetes until the underlying condition is diagnosed. A high index of suspicion is the key to diagnosis. Management of these patients consists of the treatment of diabetes and exocrine pancreatic deficiency, and other general measures.*

Diabetes, hypertension, and coronary artery disease, the so-called diseases of civilization are traditionally attributed to "overnutrition." It was, therefore, a matter of interest when workers from tropical developing countries reported an association between diabetes and malnutrition. Despite lack of conclusive evidence from prospective studies, it was assumed that malnutrition led to diabetes, and the concept of "nutritional diabetes" evolved. Ahuja and colleagues in Delhi and Tripathy and colleagues in Orissa (northeast India) reported on many such patients during the 1960s and 1970s. About the same time, Geevarghese reported a large study of "pancreatic diabetes," which was secondary to tropical calcific pancreatitis (TCP) in a cassava-eating population from southern India. These patients with pancreatic diabetes share some of the clinical and biochemical features of nutritional diabetes, although the relationship between the two is unclear.

The present definition of malnutrition-related diabetes mellitus, which is based on low body weight at diagnosis, is open to criticism. The so-called protein-deficient pancreatic diabetes could be a *forme fruste* (a partial or arrested form of disease) of insulin-dependent diabetes mellitus (IDDM or type I). The classic descriptions of fibrocalculous pancreatic diabetes (FCPD) were based on advanced cases, and diagnosis based on only such clinical criteria would fail to diagnose many patients. Many FCPD patients at the King Edward Memorial Hospital Research Center in Pune, India, are from relatively affluent families and do not exhibit the nutritional stigmata described in classic reports.

Recent retrospective studies in the United Kingdom have demonstrated an interesting association between low birth weight and diabetes, hypertension, lipid abnormalities, and deaths from coronary heart disease in adult life. It appears that an altered intrauterine environment (including nutritional deficiencies) at crucial periods in development could have far-reaching effects on the incidence and pattern of disease in adult life (1). Animal studies (see Hoet and colleagues' article later in this section) have highlighted the deleterious effects of intrauterine and early postnatal protein deficiency on the insulin-glucose metabolism in later life. The relevance of these findings to the etiology of malnutrition-related diabetes mellitus and FCPD needs to be investigated in carefully planned prospective studies. This novel concept differs entirely from the present-day concept of malnutrition-related diabetes mellitus, which is based on obvious undernutrition at diagnosis.

### Diagnostic Criteria

Diagnosis of nutritional diabetes is usually by Ahuja's criteria (see Table 1), although no specific marker has yet been described. The suggested characteristic feature is malnutrition (reduced body mass) at the time of first visit (i.e., diagnosis). It is tacitly assumed that this malnutrition reflects poor dietery intake, which is etiologically important in the pathogenesis of diabetes. Ahuja believed pancreatic fibrosis and calculi to be a result of the same pathological process. He did not attach much importance to the exocrine pancreatic component in "nutritional diabetes."

In 1985 a World Health Organization (WHO) Study Group argued that malnutrition-related diabetes mellitus deserved recognition as a major subclass of diabetes in tropical developing countries because of its "clinical

distinctiveness and severity." The study group further proposed that malnutrition-related diabetes could be subclassified into *1*) protein-deficient pancreatic diabetes (PDPD) and *2*) FCPD, depending, respectively, on the absence or presence of pancreatic calculi. This was an attempt to group together special varieties of diabetes in the tropical countries under one umbrella. These suggestions have stimulated much debate and controversy and have prompted further research in the field. Criteria for diagnosis of FCPD were compiled by Mohan (see Table 2). He rightly stressed the importance of the exocrine pancreatic component in this condition and deemphasized the malnutrition and other clinical peculiarities highlighted in the older reports.

Many experts doubt the existence of PDPD as a distinct entity. It has been suggested that PDPD represents an incomplete form of IDDM, perhaps as a result of nutritional or other environmental factors. Clinical, genetic, and metabolic studies of such patients in Ethiopia by Lester and by Abdulkadir support such a thesis. There are few studies of a similar kind from other countries. I have seen few patients who could be categorized as PDPD. On the other hand, we treat many patients with FCPD. Indeed, the majority of recent scientific publications from India in this field concern the FCPD variety.

### Clinical Features of FCPD

The first doctor visit of a patient with tropical calcific pancreatitis may be for problems related to pancreatitis or for diabetes. Diabetes usually manifests itself after years of progressive pancreatic destruction. From the classic descriptions of FCPD and its classification under malnutrition-related diabetes mellitus, doctors expect to find FCPD only if the patient is young, severely malnourished, from a poor socioeconomic background, and has a history of abdominal pain. Studies in Pune and Madras have shown that such a classic picture is seen in relatively fewer patients than before and represents the extreme end of a spectrum. It is important to remember that FCPD can occur in the absence of these features. For example, one-third of our patients were diagnosed after 30 years of age, 20% did not remember any episodes of pancreatic-type pain, 40% had a body mass index (BMI) > 19 kg/m², and only 10% showed severe malnutrition. More than 75% of our type I patients had a BMI <19 kg/m² at diagnosis, suggesting that diabetes-related malnutrition contributes significantly to the weight loss. A number of our patients belong to well-to-do families. It is, therefore, not surprising that some of them were treated for primary diabetes until we diagnosed the underlying condition. A high index of suspicion is the key to correct diagnosis.

*Patients with FCPD in Pune, India.*

The severity of diabetic symptoms and hyperglycemia is variable. The progression from normal to impaired glucose tolerance and diabetes is seen over a number of years. Many patients see the doctor only when blood glucose levels have risen very high after a long time of neglecting their symptoms. This neglect is usually related to socioeconomic conditions, lack of awareness, and a relative immunity from metabolic disasters (i.e., ketoacidosis or hyperosmolar coma). Note that we have not yet seen diabetic ketoacidosis or hyperosmolar coma in these patients despite very severe hyperglycemia. It may be, however, that in remote areas such severely ill patients die before proper diagnosis.

Diabetic tissue damage (neuropathy, retinopathy, and nephropathy) is at least as common in FCPD as in primary varieties of diabetes. Macrovascular disease has been reported in only a few of the FCPD patients because of the relatively young age of the patients in most of the series.

### Exocrine Pancreas Tests

Sensitive tests of pancreatic function and newer imaging techniques can be used to diagnose pancreatic involvement at an early stage when stones are not demonstrable on plain X-rays of the abdomen. We studied serum immunoreactive trypsin, stool chymotrypsin, and sonography and CT scans of the pancreas in diabetic patients as well as nondiabetic control subjects. The results suggest that asymptomatic exocrine

Table 1
*Ahuja's criteria for nutritional diabetes*

1. Onset before 30 years of age.
2. Body mass index (BMI) <19 kg/m²
3. Ketosis-resistance under adverse conditions
4. Insulin requirement > 2.0 U·kg⁻¹·day⁻¹
5. Poor socioeconomic status (and childhood malnutrition)

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Table 2
*Mohan's criteria for fibrocalculous pancreatic diabetes*

1. Occurrence in a tropical country
2. Diabetes by WHO (1985) criteria
3. Evidence of chronic pancreatitis: pancreatic calculi on X-ray or at least three of the following:
   - ► Abnormal pancreatic morphology by sonography or CT scan
   - ► Chronic abdominal pain
   - ► Steatorrhea
   - ► Abnormal pancreatic function test
4. Absence of other causes of chronic pancreatitis, i.e., alcoholism, hepatobiliary disease, or primary hyperparathyroidism, etc.

*The Diabetes Annual 4:46-55, 1988*

*Clinical malnutrition, young age at onset, and absence of ketosis are useful adjuncts but not diagnostically essential.*

pancreatic involvement, the so-called "subclinical pancreatopathy," is common in our population. Serum levels of pancreatic enzymes were also abnormal in many patients with type I or type II diabetes. In some, such early pancreatic involvement could be a forerunner of progressive pancreatic destruction; in others, it might persist as a mild exocrine abnormality. The relationship of such patients to the classic tropical calcific pancreatitis awaits clarification. The effects of such early exocrine involvement on the endocrine pancreas, if any, remain to be studied.

**Treatment**

Management of these patients consists of the treatment of diabetes and exocrine pancreatic deficiency, and other general measures.

Approximately 10% of our patients (those with milder diabetes) could be treated by dietary adjustment, and some have received oral sulfonylureas. The majority, however, were treated with insulin. Insulin treatment may prove difficult in some patients because of poor economic or educational status and conflicting social beliefs. Some may be hesitant to use insulin because of the relative freedom from acute metabolic complications that these patients enjoy. Such factors combine to make the doctor's job difficult. A free supply of insulin, reuse of plastic disposable syringes (without sterilization), and home visits by medical social workers to ensure compliance have improved the treatment of many of our patients. Nonetheless, for some patients compliance remains irregular, and a substantial number are lost to follow-up.

Insulin resistance is said to be a feature of malnutrition-related diabetes mellitus. It is difficult to judge the insulin requirement of such patients. A few of our patients admitted to the wards received quite high doses of insulin during the initial few days of treatment (up to 10 $U \cdot kg^{-1} \cdot day^{-1}$). In most patients the insulin requirements progressively fell, and some could be managed without insulin for some time (the honeymoon phase). After the initial fluctuations, most patients settled on reasonable doses of insulin. The mean doses of insulin in FCPD and type I patients in our clinic were not significantly different (0.8 $U \cdot kg^{-1} \cdot day^{-1}$ vs. 1.0 $U \cdot kg^{-1} \cdot day^{-1}$, respectively).

Because of the cost, treatment of exocrine pancreatic deficiency by oral enzymes is possible only in a few cases. We reserve it for those with severe persistent steatorrhea despite dietary fat restriction and in those with poor weight gain even with good diabetes control. Pancreatic drainage surgery offers relief to those troubled by severe pain.

Twelve of our first 55 patients are dead (nine died within three years of diagnosis). Five died of infection complicated by metabolic and nutritional problems; five died of metabolic problems; one died of end-stage renal disease; and one of unrelated causes.

## Islet Function in FCPD

It is generally believed that β-cell function in FCPD patients is better preserved than that in patients with type I diabetes. We found that β-cell function was normal in patients with tropical calcific pancreatitis and normal or mildly impaired glucose tolerance. In diabetic (FCPD) patients there was a spectrum of plasma C-peptide levels, which was reflected in the level of glycemia. In patients with severe hyperglycemia, plasma C-peptide levels were very low, comparable only to those in patients with type I diabetes. Interestingly, β-cell function (plasma C-peptide) was directly related to exocrine reserve (serum immunoreactive trypsin). This suggests that β-cell loss in FCPD is secondary to progressive exocrine loss. On the other hand, plasma glucagon levels were normal and showed a paradoxical rise after oral glucose. α-cell function appeared preserved even when β-cell loss was severe. This finding begs an explanation because islet damage secondary to exocrine pancreatitis would be expected to destroy α- and β-cells simultaneously.

**Reference**

1. Fetal and Infant Origins of Adult Diseases. D.J.P. Barker, Ed. *Br Med J* 1992.

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