Malnutrition-related diabetes mellitus (MRDM) has been included in the classification of diabetes mellitus by the WHO Study Group due to its increasing incidence in some of the developing countries\textsuperscript{1}. The new category of diabetes comprises of the types previously known as tropical diabetes, pancreatic diabetes, pancreatogenic diabetes, endocrine pancreatic syndrome and ketosis-resistant diabetes of the young. Two sub-classes have now been suggested: fibrocalculus pancreatic diabetes (FCPD) and protein deficient pancreatic diabetes (PDPD)\textsuperscript{2-4}. Although a large number of cases of MRDM have been reported from India, Bangladesh, Sri Lanka, Indonesia, Thailand, Jamaica, Brazil, Madagaskar, Ghana, Nigeria, Uganda, Zaire and Zambia\textsuperscript{5,6}, MRDM has so far not been reported from Pakistan. We present two cases diagnosed as fibrocalculus pancreatic diabetes (FCPD).

Case 1
A 24 year old male with IDDM diagnosed at the age of 15 years presented at the outpatient clinic of the Diabetic Association of Pakistan, Karachi. A month before diagnosis, he had developed mild polyuria, polydipsia and polyphagia and the diagnosis of ketoacidotic coma was made when he was hospitalised in an unconscious state. Insulin therapy was started which he continued regularly for two and a half years. He then stopped insulin and took herbal medicines for six months when he noticed gradual loss of weight, polyuria and polydipsia. His blood sugar fluctuated between 11.5-13 mmol/L with no ketonuria. Insulin was restarted which relieved the symptoms and his daily requirement was 32 units. At the time of presentation there was a past history of 6 to 7 episodes of recurrent upper abdominal pain followed by mild jaundice between the ages of 9 and 14 years. Mild abdominal discomfort and steatorrhoea after taking fats was also noted. A detailed dietary work up revealed deficient animal protein intake with no history of cassava or alcohol consumption. There was no family history of diabetes or recurrent abdominal pain, the physical examination was unremarkable except for bilateral cataract with no retinopathy and a body mass index of 17.6. The plain x-ray abdomen showed coarse calcification in antero- posterior view at the level of D12-L1, lying obliquely across the midline. In the supine lateral shoot-through film, the calcification was situated posteriorly in the abdomen in the region of the pancreas (Figure I).
Ultrasonography revealed areas of high echogenicity and marked calcification throughout the pancreas, consistent with extensive fibrosis and calcification. The body of the pancreas measured 1.1 cm anteroposteriorly which is small for this age. ERCP was performed by passing a duodenoscope and the ampulla of Vater was catheterized. The pancreatic and biliary ductular systems were selectively injected and visualised and the x-rays showed a dilated and irregular pancreatic duct with multiple calculi (Figure 2).
The fasting and 90 minutes post-prandial C-peptide levels were 0.44 ng/ml and 0.80 ng/ml respectively, both being much below the normal range of 2-4 ng/ml and 6-9 ng/ml.

Case 2
A 41 year old male was diagnosed as IDDM at the age of 25 years, when he had developed polyuria,
polydipsia, polyphagia and weight loss of 8 months duration. He was underweight and had moderately severe hyperglycaemia (fasting blood sugar 15 mmol/L and 2 hour post breakfast 19 mmol/L) with no ketonuria. Treatment was started with insulin which relieved his symptoms. Since then, the patient omitted insulin therapy for 1-4 months on four occasions without developing ketosis. His present insulin requirement was 68 units per day. The dietary history revealed that as a child in India, the food was prepared largely from cassava, millet and oats. Milk and meat was scarce. There was no past complaint of recurrent abdominal pain but recently he had episodes of upper abdominal pain and steatorrhoea which was relieved by taking pancreatic extract preparations. There was no history of alcohol intake and no history of diabetes in the family. Physical examination was normal except for a low BMI (BMI = 18.4). The plain x-ray abdomen in the antero-posterior view showed dense calcification in the region of the head of the pancreas at the level of 11-3. Ultrasound examination reported the pancreas to measure 1.9 cms, with dense calcification in the region of the head. On ERCP the ampula was catheterized with the catheter entering the pancreatic duct for 3 ems only. The dye reached the distal part of pancreatic duct and refluxed, suggesting obstruction due to a large intraductal calculus in the region of the head of the pancreas. Catheterization of minor ampula was not successful. The fasting and 90 minutes post-prandial C-peptide levels were 0.33 ng and 0.80 ng/ml respectively, again lower than the normal range.

**Discussion**

Fibrocalculous pancreatic diabetes, one of the two sub-types of MRDM has been described in several tropical countries. An estimated 30-55% of diabetics below the age of 30 years, may show evidence of pancreatic calcification, thus indicating the common occurrence of FCPD. History of recurrent abdominal path is frequently present though not always. Men out-number women by 3:1. Patients with PCPD are grossly underweight and other stigmata of past or present malnutrition may be noted. There is also evidence of exocrine pancreatic insufficiency. The main metabolic features are moderate to severe hyperglycaemia requiring high doses of insulin for control and in the absence of stress as trauma and infection, tendency to resist ketosis on withholding insulin therapy. The characteristic absence of ketosis is explained by the fact that despite extensive damage to pancreatic islets, the residual insulin production, though greatly diminished, is sufficient to suppress lipolysis and ketogenosis but inadequate to control hyperglycaemia. The rise in post-prandial C-peptide levels demonstrates some residual endogenous insulin production. This distinguishes these patients from IDDM in whom insulin response to food or carbohydrate load is reported to be virtually absent. The absence of ketosis in FCPD has also been attributed to a concomitant glucagon deficiency, due to destruction of alpha islet cells. Diagnosis of FCPD is based upon the characteristic, clinical features and supported by radiographic demonstration of calculi in the pancreatic ducts. Pancreatic calcification can be detected in 75% of patients with FCPD. With ultrasonography and computerised tomography, calcification can be seen in nearly 90% of cases. ERCP locates the site of the calculi formed. There is no parenchymal calcification in these cases. Microscopically the most typical features are diffuse interlobular and periductular pancreatic fibrosis with progressive acinar and islet replacement by fibrofatty tissue. There is little or no evidence of inflammatory pancreatic fibrosis and there is no reported association between FCPD gall-bladder disease and excessive alcohol intake. Epidemiological observations strongly suggest a relation between the global distribution of fibrocalcubus pancreatic diabetes and the consumption of cassava root (tapioca, manioc). Cassava root contains several cyanogenic glucosides, of which linamarin is the most important as it liberates hydrocyanic acid on hydrolysis. Cyanide is detoxified by several pathways, mainly those involving sulphur containing amino acids. The main end product is thiocyanate, which is excreted in the urine. High cassava intake combined with inadequate
intake of proteins, particularly if deficient in sulphur-containing amino acids, creates conditions for the accumulation of cyanide in the body\textsuperscript{3,4}. Other foods such as sorghum, sweet potato, maize and some varieties of beans may also be source of dietary cyanide\textsuperscript{3} and high intake of these and other toxic food factors such as nitrosamines may act similarly when combined with malnutrition\textsuperscript{8}. Having detected only two cases in the patient population of DAP, it could be presumed that the incidence of FCPD is low in Pakistan. The two most important contributory factors for this are absence of cassava and better nutrition and animal protein consumption as compared to some parts of India, Indonesia, Thailand and other developing countries.

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