MALNUTRITION RELATED DIABETES-REVIEW

V.C. Mathew Roy

INTRODUCTION

History and distribution

Pancreatic calculi were first described by R. de graaf (1664), and diabetes associated with pancreatic calculi was first reported by Thomas Cawley (1788)[1]. The pathology of chronic pancreatitis was first documented by Riedle in 1896. Assmann (1912) recognized pancreatic calculi radiologically. Elman et al (1929) related changes in serum amylase with pancreatitis, and introduced this as a diagnostic test in inflammatory disorders of pancreas. Zuidema (1955) from Indonesia described the clinical features of patients with malnutrition, calcification of the pancreas and diabetes. From Kerala, Geevarghese (1962) reported a large series of patients with chronic pancreatitis, calculi and diabetes. This initiated a countrywide awareness of calcific pancreatitis and diabetes. Following this, case reports from Karnataka[9], Tamil Nadu[4-6], Orissa[7,8], Maharashtra[62] and again Kerala[9], were published. As early as 1952, Dr. R. Kesavan Nair from Trivandrum presented a paper at the annual meeting of the Association of Surgeons of India describing surgery on twenty three cases of pancreatic calculi. Globally, similar cases of pancreatic diabetes have been reported from Nigeria, Uganda, West Indies, Kenya, Ceylon, Madagascar, Indonesia and Zaire[10]. Various synonyms used for this condition are : tropical diabetes; pancreatic diabetes; tropicai calcific pancreatitis; tropical juvenile pancreatic syndrome; chronic calcific pancreatitis of the tropics; idiopathic chronic calcific pancreatitis of the tropics; non endocrine pancreatic syndrome, non-alcoholic tropical pancreatitis and pancreatogenous diabetes, ketosis resistant diabetes of the young, Z type, J type, M type, etc.

A random population survey in Trivandrum showed the prevalence of diabetes was 1.5-2%[11]. Diabetics comprise 6-7% of all admissions to Medical College Hospital, Trivandrum[12,13]. In 1962, 14.8% of diabetics admitted there had diabetes of pancreatic origin. At the Medical College Hospital, Kottayam, in central Kerala, pancreatic diabetes was found in 29.3% of all diabetics[13]. However, in Kottayam in 1964, it was found only in 1.3% of all admissions in the Medical College Hospital. This fell to 0.03% in 1971 and 0.009% in 1980[14].

Clinical Features

The disease is associated with distinct clinical features. Most of the patients are aged between 10 and 30 years, 50% of them in the second decade[2,15]. There is male preponderance in all the series. Most patients belong to poor socio-economic status. However the disease of late is being recognized in middle class and the upper middle class too. The syndrome commonly presents as diabetes, with polyphagia, polydypsia, polyuria and gross emaciatiation[16].

Professor of Endocrinology, Medical College Hospital, Trivandrum.

Majority of the patients give a history of abdominal pain and this may precede diabetes by many years. Sometimes the pain in abdomen is concurrent with the onset of diabetes or sometimes, may follow it. In one series of 431 cases, 6 instances had onset of disease before the age of 10 and 13 after 40, the remaining 412 (95%) between 11 and 40 yrs. Sex ratio male to females 3:1. Steatorrhoea is not uncommon, but seems to depend on the amount of fat consumed. In severe cases, frankly oily stools are passed. Type of presention was as follows. (Table I).

Table I

Pancreatic Calculi

(431 cases)

Type of presentation :		% age	
Diabetes	Pain	Calculi	49.9
Diabetes	Pain	No calculi	23.9
Diabetes	No pain	Calculi	19.4
No diabetes	Pain	Calculi	6.4

49.9% showed diabetes, abdominal pain and pancreatic calculi. 23.9% showed diabetes and abdominal pain highly suggestivo of panereatic diabetes, but without calculi. 19.4% had diabetes and calculi, but without abdominal pain, and 6.4% showed calculi and abdominal pain but no diabetes; however, most of them later developed diabetes. The severity of the abdominal pain is variable. It is typically severe, epigastric in location with periods of exacerbations and remissions; it radiates to the back on either side and is typically relieved by stooping forwards or lying prone. It may be related to meals, so that the unwary surgeon has sometimes operated upon such patients, with a provisional diagnosis of peptic ulcer to find no ulcer, but pancreatitis with calculi[3]. The remissions may last months and years. Pain is not completely relieved with antispasmodics and may require narcotics.

There is no history of gall bladder disease or gallstones. Similarly, it is very uncommon to elicit history of jaundice, viral hepatitis or mumps in such instances. There is no consumption of alcohol by the subjects under study.

The other predorminant symptoms are a result of neuropathy[17],[18]. Sensory neuropathy with numbness, sensation of pins and needles, episodic sweating, and burning paraesthesia is frequent. Patients may immerse their feet in cold water or cover them with moist cloth for relief. Girdle muscle weakness is also common[19].

Most patients are lean with little subcutaneous fat. T'he development of secondary sexual characters is often lacking[20]. There is a peculiar cyanotic hue of the lips[21]. Parotid gland enlargement may be often obvious[21]. Enlarged parotid glands, seen in 50% of the authors series were not associated- with parotid stones. Varying grades of undernutrition and vitamin deficiencies may be observed. Nutritional

status employing I.C.M.R. proforma is given in Table II. With glossitis, cheilitis; angular stomatitis, dry

Table II

Nutritional assessmeut-ICMR proforma

(100 cases)

	%
Underweight	100
Retarded growth	20
Absent secondary sex characteristics	20
Conjunctival pigmentation	13
Night blindness	16
Bleeding gums and pyorrhoea	28
Caries teeth	17
Loss of lustre and dry skin	7
Angular stomatitis	10
Angular conjunctivitis	3
Ulcerated and fissured tongue	7

lustreless skin, emaciation, hollow cheeks, partial loss of teeth, periodontal disease protuberant belly, the clinical picture is characteristic[16]. The liver is often enlarged, firm, and tender[22] found in 88% of cases under review.

Radiological findings

Radiological demonstration of calculi is the diagnostic feature of calcific pancreatitis. The stones, typically seen on the right side of L_l vertebra may vary in size and shape. Sometimes, they are found throughout the pancreas and at times only opposite L_l or L_2 vertebrae. Solitary stones may be mistaken for gall stones at the lower end of the common bile duct. Large irregular stones are usually seen near the head of the pancreas, the largest one seen being 4.5 cms long. Sometimes, a “string of pearls” appearance is found. ERCP studies show ductal dilation, kinking, tortuosity and diverticulum formation [29,30]. In the post ERCP period, there may be a transient elevation of serum amylase, but without pancreatitis.

Biochemical Investigations

The glycaemic status varies with the severity and stage of the disease. Glucose tolerance tests showed moderate to severe diabetes in most cases. The serum

protein[16] and amylase were normal, the latter even during episodes of abdominal pain suggestive of acute pancreatitis.

Stool examination may show evidence of undigested fat. 80 % of the patients had steatorrhoea as shown by fat balance studies.

I^{131} triolien test was abnormal in 25%, while in 50% it was mildly affected[27]. Oleic acid absorption and D-xylose excretion were normal. Following secretin - pancreozymin test, there was low volume of pancreatic juice, low levels of bicarbonate, amylase and lipase[26] and elevated calcium. They were confirmed by Lundh test[28]. Iron absorption studies showed a normal pattern[32]. Cholecystograms showed a normal biliary system.

Whereas lipoproteins were increased in most of the patients[3l], serum cholesterol was increased only in those with evidence of microangiopathy. The liver function showed no significant alteration except in those with frank cirrhosis[22]. Sialactasis was demonstrated in a few cases[2l]. Hypercalcaemia was seen only in one who turned out to have hyperparathyroidism. One patient had haemochromatosis with associated cardiomyopathy.

Pathology

Pathological lesions are found in the pancreas and extrapancreatic tissues. The pancreas may show changes in the exocrine tissue, ducts, islets and interstitium[33-38]. The acini may show local, focal or diffuse atrophy. Loss of bipolar staining in the acinar cells is an early finding. The atrophic cells may become basophilic and later disappear. Presence of inflammatory cells is significant. The spaces produced by atrophic acini are later replaced by fibrous tissue. Fibrosis may convert the pancreas into pseduo lobules which is best described as “cirrhotic pancreas”[39]. In extreme involvement, the gland may be reduced to a fibrous cord, the size of a finger. There is no parenchymal calcification. The stones are found only in the ducts which show ectasia and on section appear like microcysts. The ductal epithelium may show proliferation with stratification and even squamous metaplasia[39],[40]. The cells may show pseudopapillae or solid buds in the periductal zone. Neoductule formation may be seen. Some of the ductules show a tendency to differentiation into islets known as nesidoblastosis. The islets may show progressive changes like pseudonesidiosis, in which some of the islets increase in size and number (macronesia). This may be followed by nesidiosis which is characterised by proliferation of existing islet cells. These giant islets may be irregular, more solid and as small clusters haphazardly distributed in the fibrous tissue - the so called endocrine dysplasia. Atrophy is the final pathological change. Immunoperoxidase staining has confirmed that the existing islets contain hormonally active B cells, A cells and D cells. The presence of insulin in the cells by immunoperoxidase staining is consistent with the observation of preserved C-peptide in some cases [41-44]. Interstitial changes are characterised by fibrosis, lipomatosis or steatosis with scanty or absent inflammatory cells.

Pancreatic biopsy findings available in 33 instances are indicated in Table III.

Table III

Pancreas Biopsy

(32 cases)

ISLETS	
	%
No changes	0
Complete atrophy	94
Degeneration (mainly vacuolar)	25
Inflammation (chronic)	21
Fibrosis	42
ACINI	
No changes	0
Complete atrophy	7.8
Incomplete atrophy	13.7
Degeneration	31.4
Inflammation	19.6
Fibrosis	27.5
DUCTS	
Not seen	7
Normal size	9.3
Dilatation	28
Inflammation (chronic)	34.9
Lumen : Calcareous deposits	7
Inflammatory exudates	14
STROMA	
Fibrosis	All cases
Degeneration : Hyaline	80
Fatty	15
Inflammation	All cases
Eosinophilic infiltration	5

In long standing cases, atheromatous changes may be seen in the pancreatic artery. The nerve fibres amidst the fibrous tissue may be thickened. Some islets appear to be entrapped in the perineurium of the thickened nerves. The protein plaques in the ductal lumen may be oval, round or cylindrical. The plaques are eosinophilic, having striations or concentric laminations. They tend to aggregate and form the building material for calculi, which vary in size and shape, are usually chalky and friable and rarely bony hard. This may vary from that of gravel, to stones 3 cms. in diameter[45]. Their centre may contain organic material, ductal epithelial cells, blood and blood products. Analysis of the stones by thermoanalytical methods, chemical analysis, atomic absorption spectrometry, infrared spectroscopy, X-ray differaction and scanning electron microscopy reveals that calcium carbonate constitutes 95-98% of stones. The other constituents are Cu, Mg, Cd, Fe, Mn, Zn, Co arid Al; Calcium carbonate exists as calcite. Scanning microscopy shows the presence of amorphous material and crystals arranged rectangularly.

Liver shows glycogen infiltration and fatty changes. Cirrhosis is seen in 22°/ of cases.

Enlarged parotid glands seen in 50% was not associated with stones in the parotid. Sialactasia was demonstated in a few cases. Interstitial round cell infiltration and large acini with swollen cells and normal ducts were the common microscopic findings.

In long standing cases changes of diabetic nephropathy may be seen[46],47.

Aetiology

The etiology of malnutrition related diabetes (MRDM) is still not known. Heredity is sometimes associated. There are cases occurring in twins and siblings[48,49]. Definite history of viral infections is lacking. In a series of 52 patients, antibodies against mumps were seen in 54.3%, against CMW in 61.1% and against mycoplasma pneumonia in 31.6%[50]. Hyperparathyroidism, hyperlipaemia and haemochromatosis cannot be per se incriminated for lack of other clinical evidence.

Autoimmune process is unlikely to be the cause, because round cell infiltration of pancreas is scanty. Antipancreatic antibodies were demonstrated in 60% of cases using indirect haemogglutination test[5l], while islet cell antibodies have not been seen significantly. HLA studies, done in a few cases show no distinctive association[52,53]

The predominant occurrence of the disease in undernourished people suggests a nutritional origin. The currently popular theory incriminates dietary toxins acting on the pancreas and causing the disease in malnourished persons[10,54-56]. Epidemiological evidence is in favour of cyanogenic glycosides in cassava (tapioca) as an incriminating factor. The well known clinical entities connected with cassava toxicity are tropical ataxic neuropathy, endemic goitre and calcific pancreatitis[57]. Tropical ataxic neuropathy is only rarely encountered in Kerala, but nodular lesions of the thyroid are common. Mc Millan and Geevarghese (1979) experimentally produced pancreatitis by chronic cyanide poisoning in rats[54]. The issue of whether nutritional deficiency aggravates or is permissive for the noxious

effects of linamerin, the toxic glycoside of cassava, is unanswered. There are atleast four pathways of cyanide detoxification in the organism that could be interfered by amino acid deficiencies. Methionine deficiency is known to cause pancreatic damage. However, all the patients with pancreatic calculi do not give a history of tapioca ingestion. Other food toxins like aflatoxin have not been investigated. It is common knowledge that stored rice and stored dried tapioca become contaminated by several species of aspergillus.

Congenital anomalies like ductal anomalies and pancreas division have been excluded[36,58,59]. Helminthic pancreatitis is also unlikely because helminthiasis is so common but not many individuals have pancreatitis.

Complications

These patients are relatively resistant to ketotic coma and may be designated ambulant ketotics[13]. Seldom are they admitted in coma.

Skin, respiratory and urinary infections are common. Pulmonary tuberculosis is frequent.

Vascular complications seem to depend on the duration of the illness. However, observations for over fifteen to twenty years showed that many patients go into diabetic nephropathy, thus demonstrating development of microangiopathy in these patients, which were intially thought to be uncommon.

Autonomic neuropathy involving the bladder is common. Hypertension may occur with advanced renal disease. Peripheral dry gangrene is rare. Neither ischaemic heart disease nor stroke has been encountered in the group. Premature loss of teeth with periodontal disease is common. Xanthomas, diabetic dermopathy, necrobiosis lipoidica, Dupturen's contracture and cheiroarthropathy have not been observed. Periarthritis of the shoulder is not infrequent. Infertility, oligomenorrhoea and amenorrhoea are common. In a follow up for 15 years, seven cases of carcinoma of the pancreas superimposed over chronic pancreatitis with diabetes have been observed[58].

Management

Management poses several problems. Most important is the glycaemic control. Many patients require large doses of insulin, which is generally beyond their means. The dose of insulin required may go upto 150-200 units even in the absence of complications, indicating insulin resistance. Brittleness of diabetes, alternating hyperglycaemia and hypoglycaemia is another bothersome problem. Irregular and erratic management leads to retarded physical and sexual development. Steatorrhoea may be relieved by pancreatic extract and low fat diet[60]. For recurrent pancreatic pain due to calculi, surgical intervention may need to be considered. Pancreatic lithotomy, pancreaticojejunostomy, sphincterotomy, choledocho-jejunostomy have all been tried with variable results[38,59]. Pain and diabetes may be temporarily relieved, while insulin requirements are not substantially reduced. Enthusiasm for surgical treatment is on the wane. Few pancreatic diabetics respond to oral sulphonyl urea drugs[61].

The Future

Community based studies in endemic areas to assess the magnitude of the problem is the immediate challenge. X-ray screening of any population sample for demonstration of pancreatic lithiasis is a limiting factor. The aetiological factors of the disease need some indepth studies.

MRDM without pancreatic calcification may closely mimic type I diabetes. Whether protein deficient pancreatic diabetes and fibrocalculous pancreatic diabetes according to WHO classification, are two distinct types of MRDM remains doubtful. They may be only two sides of the same coin. This is substantiated by some cases where there were no calculi to start with but later over the years developed calculi. Screening some of these patients by CT scan has revealed microcalculi that were not otherwise demonstrable by routine radiological examination.

There is scope for studies on early pancreatic lesions by immunoperoxidase methods. The possibility of food toxins, e.g. cyanogens, aflatoxin nitrosamines or chemical toxins from pesticides, needs further elaborate investigations.

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