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Tropical pancreatic diabetes in South India: heterogeneity in clinical and biochemical profile

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Summary. Clinical and biochemical studies were carried out in 33 patients with diabetes secondary to chronic calcific, non-alcoholic pancreatitis (tropical pancreatic diabetes) and in 35 Type 2 (non-insulin-dependent) diabetic patients and 35 non-diabetic subjects. Despite lower body mass indices, only 25% of patients with tropical pancreatic diabetes had clinical evidence of malnutrition. There was no history of cassava ingestion. Mean serum cholesterol concentration was significantly lower in the tropical pancreatic diabetic patients ($p < 0.01$) in comparison with the Type 2 diabetic patients or non-diabetic subjects, due to a significantly decreased concentration of LDL cholesterol ($p < 0.01$) and VLDL cholesterol ($p < 0.05$). Basal and post-glucose stimulated concentrations of serum C-peptide were highest in those pancreatic diabetic patients ($n = 11$) who responded to oral hypoglycaemic drugs, intermediate in the majority ($n = 17$), who were insulin dependent and ketosis resistant and negligible in a small sub-group ($n = 5$) who were ketosis prone. The occurrence of microangiopathy in pancreatic diabetic patients was common and similar to that in Type 2 diabetic patients. Thus, tropical pancreatic diabetes in South India appears to be heterogenous with respect to level of nutrition, severity of glucose intolerance, B-cell function, response to therapy and the occurrence of microvascular complications.

Key words: Tropical pancreatic diabetes, heterogeneity, ketosis-resistant, C-peptide, microangiopathy.

While classical Type 1 (insulin-dependent) diabetes and Type 2 (non-insulin-dependent) diabetes are two well characterized entities of the diabetic syndrome, there are certain types of diabetes which do not fit into either of these categories. In tropical countries, diabetes associated with malnutrition, such as J-type diabetes [1, 2] and tropical pancreatic diabetes [3-6], have been described. Earlier studies have suggested the following characteristics of tropical pancreatic diabetes [5, 6]: (1) Patients belong to the lowest socio-economic strata of society and appear grossly emaciated with signs of severe protein-calorie malnutrition. (2) They have severe insulin-dependent diabetes and often require large doses of insulin for stabilization of the diabetes. However, they are resistant to ketosis on withdrawal of insulin even for several weeks. (3) A history of cassava ingestion is very common.

Recently, an explanation for the ketosis-resistant nature of tropical pancreatic diabetes has been put forward [7]. The present study demonstrates an interesting clinical and biochemical spectrum of tropical pancreatic diabetes as seen in the state of Tamilnadu (Madras) in South India.

Subjects and methods

Subjects studied were attending the M. V. Hospital for Diabetes, Madras, a large referral centre for diabetes in South India.

The following criteria were used for diagnosis of tropical pancreatic diabetes: (1) a history of recurrent abdominal pain from an early age; (2) the presence of pancreatic calculi seen on plain abdominal X-ray and confirmed by ultrasonography; (3) the absence of alcoholism, gall-stones or hyperparathyroidism; and (4) diabetes. The study population consisted of 33 patients with tropical pancreatic diabetes seen consecutively during 1983 and 1984, who satisfied all the above criteria. There were 23 men and 10 women in the age group 16-47 years. Their mean age was 32 ± 1 years and the mean age at diagnosis of diabetes was 25 ± 1 years. Twenty-nine had no family history of diabetes, and in only three did a first degree relative have diabetes. Ten patients had evidence of steatorrhoea. A detailed medical and family history of diabetes was recorded. A specific enquiry about the ingestion of cassava (tapioca) was made in every case.

Thirty-five patients with Type 2 diabetes matched for duration of diabetes were also studied. Eighteen had a family history of diabetes. Three were hypertensive. The mean duration of hypertension was 4.5 years and blood pressure ranged between 150/100 and 190/120 mmHg.

Thirty-five non-diabetic subjects matched for age and sex with the two groups of diabetic patients were also studied. None had a family history of diabetes. The clinical details of the study groups are summarized in Table 1. Informed consent was obtained from all subjects and approval of the study was obtained from the Hospital Ethical Committee.

Study design

All patients underwent a thorough clinical examination. Body mass index was calculated (kg/m^2). Hypertension was defined as blood pressure > 140/95 mmHg. All patients had a resting ECG taken. Ischaemic heart disease was considered to be absent unless there was a clear history of angina pectoris or myocardial infarction or ischaemia, infarction or left bundle branch block was present in the ECG. All ECG's were reviewed by a cardiologist and they were assessed in accordance with the Minnesota code adapting the WHO study questionnaire for macrovascular disease [8]. Deep tendon jerks and vibration sense were tested and peripheral pulses in the feet were recorded clinically and by doppler ultrasound (Medasonics, Mountain View,

USA). Neuropathy was defined as the absence of ankle jerks bilaterally or gross sensory disturbance in both feet. The criteria for peripheral vascular disease were those of the WHO Multinational Study of Vascular Complications [9]. Peripheral vascular disease was deemed to be present if there was a history of intermittent claudication or if one or more peripheral pulse (dorsalis pedis or posterior tibial) was absent. A plain X-ray examination of the abdomen and a PA view of the chest were taken. In patients with tropical pancreatic diabetes the presence of pancreatic calculi and fibrosis was confirmed by ultrasonography.

The fundi were examined by an ophthalmologist both by direct and indirect ophthalmoscopy. Diabetic retinopathy was classified as either background or proliferative according to the classification of Kohner et al. [10].

Biochemical investigations

A 75-g oral glucose tolerance test was carried out in all subjects. We used the recommendations of the WHO Expert Committee for the diagnosis of diabetes and classification into Type 2 diabetes [11]. The diagnosis of diabetes was accepted if either the fasting venous plasma glucose was >8 mmol/l or the 2 h value was >11 mmol/l. Plasma glucose was estimated by the orthotoluidine method [12]. Glycosylated haemoglobin (HbA_1) was estimated by a colorimetric method [13].

Table 1. Clinical details of the subjects studied

	Patients with tropical pancreatic diabetes ($n=33$)	Type 2 diabetic patients ($n=35$)	Non-diabetic subjects ($n=35$)
Male: female	23:10	24:11	24:11
Age (years)	32±1 (16-47)	35±2 (23-48)	32±1 (20-47)
Age at onset (years)	25±1	28±2	-
Duration of diabetes (years)	7±1 (1-15)	7±1 (2-15)	-
Body mass index (kg/m^2)			
Men	17.0±0.4	23.5±4.6	22.3±2.1
Women	18.8±1.2	22.5±1.5	21.2±1.5
Fasting plasma glucose[a] (mmol/l)	13.0±0.7	10.8±0.8	6.4±0.4
Post-prandial plasma glucose (mmol/l)	21.3±0.7	17.3±0.9	8.3±0.5
HbA_1 (%)[b]	12.6±0.3	11.7±0.3	6.9±0.2

Values are expressed as mean ± SEM with ranges in parentheses.
[a] Plasma glucose values for the diabetic subjects are before the control of diabetes; [b] normal value for HbA_1: 5-8%

Serum triglyceride [14], total serum cholesterol [15], HDL-cholesterol [16], and VLDL and LDL-cholesterols [17] were determined in the fasting state. Blood urea, serum creatinine [18] and creatinine clearance were determined in all the patients. Proteinuria was assessed by estimating the 24-h urinary protein excretion by the sulphosalicylic acid method [19]. Those with values >500 mmol, in the absence of urinary tract infection or severe hypertension, were considered to have nephropathy. Renal insufficiency was defined as a serum creatinine >133 μmol/l.

Serum C-peptide levels were assayed by radioimmunoassay [20] using M1230 antiserum (Novo, Copenhagen, Denmark). The serum samples were extracted with equal volumes of 30% polyethylene glycol to remove insulin antibodies and proinsulin according to the procedure of Kuzuya et al. [21].

Statistical analysis

The data are expressed as mean ± SEM and comparison between sets of data was made using the Student's t-test.

Results

The mean body mass index was lower in both men and women with tropical pancreatic diabetes when compared with age- and sex-matched Type 2 diabetic patients or non-diabetic subjects. While most of the tropical pancreatic diabetic patients were underweight (71%), overt evidence of protein-calorie malnutrition was seen only in 25%. Nine patients (25%) were anaemic, the skin changes of malnutrition were seen in two (6%) and one patient each had evidence of parotid gland enlargement, abdominal swelling and pedal oedema. Cyanotic hue of the lips was not seen in any patient. There was no history of cassava ingestion in any patient.

Serum lipids

Serum lipid concentrations in the three groups are shown in Table 2. The mean serum total cholesterol, LDL-cholesterol and VLDL-cholesterol concentrations were significantly lower in tropical pancreatic diabetic patients compared with Type 2 diabetic patients or non-diabetic subjects ($p<0.01$). Women with tropical pancreatic diabetes also had lower levels of HDL-cholesterol ($p<0.01$). Mean serum triglyceride levels were normal in all the tropical pancreatic diabetic patients.

Table 2. Serum lipid concentrations in patients with tropical pancreatic diabetes compared with Type 2 diabetic patients and non-diabetic subjects

Serum lipids (mmol/l)	Males			Females		
	Patients with tropical pancreatic diabetes ($n=23$)	Type 2 diabetic patients ($n=24$)	Non-diabetic subjects ($n=24$)	Patients with tropical pancreatic diabetes ($n=10$)	Type 2 diabetic patients ($n=11$)	Non-diabetic subjects ($n=11$)
Total cholesterol	3.9±0.1[a]	5.2±0.2	5.4±0.0	4.2±0.2[a]	5.6±0.1	5.2±0.2[a]
HDL-cholesterol	1.3±0.1	1.3±0.0	1.3±0.0	1.1±0.1[a]	1.4±0.1	1.5±0.1[a]
LDL-cholesterol	2.3±0.1[a]	3.0±0.1	3.2±0.2	2.7±0.2[b]	3.3±0.2	3.0±0.2[b]
VLDL-cholesterol	0.3±0.1[a]	0.8±0.1	0.9±0.1	0.4±0.1[c]	0.9±0.1	0.8±0.1[c]
Triglycerides	1.1±0.1	1.2±0.1	1.1±0.1	1.0±0.3	1.2±0.1	1.0±0.0

Results are expressed as mean ± SEM. [a] $p<0.01$ compared with non-diabetic subjects or Type 2 diabetic patients; [b] $p<0.01$ compared with Type 2 diabetic patients; [c] $p<0.05$ compared with non-diabetic subjects or Type 2 diabetic patients

Table 3. Basal and post-glucose peak levels of serum C-peptide levels in patients with tropical pancreatic diabetes

	Duration of diabetes (years)	C-peptide (pmol/ml)	
		Basal	2-h post load
Non-diabetic subjects ($n=35$)		0.61 ± 0.04	1.53 ± 0.13
Type 2 diabetic patients ($n=35$)	7.0 ± 0.9	0.36 ± 0.05	0.98 ± 0.18
Tropical pancreatic diabetic patients			
Group A ($n=5$) (insulin-dependent and ketosis-prone)	9.8 ± 4.1	0.07 ± 0.01	0.09 ± 0.04
Group B ($n=17$) (insulin-dependent and ketosis-resistant)	5.9 ± 0.9	0.13 ± 0.06	0.23 ± 0.05[a]
Group C ($n=11$) (responding to oral therapy)	6.2 ± 1.6	0.17 ± 0.04[a]	0.48 ± 0.16[a]

Values expressed as mean ± SEM. [a] $p < 0.05$ compared with group A

Table 4. Vascular complications in patients with tropical pancreatic diabetes and Type 2 diabetes

Diabetic complications	Number with complications			
	Tropical pancreatic diabetes ($n=33$)		Type 2 diabetes ($n=35$)	
	n	%	*n*	%
Retinopathy ($n=28$)	11	39	15	43
Background	9	32	11	31
Proliferative	2	7	4	12
Nephropathy	4	7	5	14
Renal insufficiency	2	17	3	9
Peripheral neuropathy	11	33	14	40
Ischaemic heart disease	1	3	4	12
Peripheral vascular disease	0	0	1	3

Serum C-peptide analysis

The basal and glucose stimulated levels of serum C-peptide in tropical pancreatic diabetic patients, Type 2 diabetic patients and non-diabetic subjects are shown in Table 3. Tropical pancreatic diabetic patients could be classified into three groups based on their clinical characteristics.

Group A: ($n=5$) These patients were insulin-dependent and showed evidence of ketosis when insulin injections were stopped for periods even as short as 2–3 days. Basal and stimulated levels of C-peptide were lowest in this group.

Group B: ($n=17$) This group consisted of the majority of the tropical pancreatic diabetic patients. They required insulin for the control of hyperglycaemia, but when the insulin injections were withdrawn even for several weeks, there was no evidence of ketosis. The C-peptide concentrations were intermediate in this group (group B versus group A, $p < 0.05$).

Group C: ($n=11$) This group of patients responded to oral therapy and had the highest C-peptide levels (group C versus group A, $p < 0.05$).

Prevalence of diabetic complications

Microvascular and macrovascular complications in tropical pancreatic diabetic patients are shown in Table 4. Retinopathy was the most common, occurring in 39% of patients (32% had background; 7% had proliferative retinopathy). Nephropathy was present in 11% of patients; 31% had peripheral neuropathy. Only one patient (3%) had ischaemic heart disease and none had peripheral vascular disease. The prevalence of all complications was only marginally lower than in the Type 2 diabetic patients.

Discussion

Most of the earlier literature on tropical pancreatic diabetes in southern India has been from the state of Kerala [5, 22, 23] where cassava (tapioca) is consumed by poor people as a staple food instead of cereals; this has been proposed as the cause of this condition [24]. In Tamil Nadu, cassava is rarely consumed. We found no history of cassava ingestion in any patient with tropical pancreatic diabetes in the present series. However, the possibility of other unidentified toxins in foodstuffs cannot be ruled out.

Though the majority of patients with tropical pancreatic diabetes were lean, only 25% showed clinical signs of malnutrition. Nine were of ideal body weight and one was slightly overweight. This suggests that malnutrition, hitherto considered an important aetiological factor for tropical pancreatic diabetes might not be as important as was believed. Using routine X-ray examination of the abdomen, we were able to identify patients with possible tropical pancreatic diabetes.

Most cases of tropical pancreatic diabetes reported in the literature are insulin-dependent. We have previously reported two patients who responded to oral therapy [25]. In this study we found that among tropical pancreatic diabetic patients there is a sub-group who responded to oral hypoglycaemic therapy and they had the highest basal and post-load glucose-stimulated serum C-peptide levels. The insulin-dependent and ketosis-prone group had very low C-peptide levels, similar to those found in Type 1 diabetes. In agreement with our earlier report [7], we found that patients who were insulin-dependent but ketosis-resistant, had significantly higher C-peptide levels than patients with Type 1 diabetes. Thus, response to treatment in tropical pancreatic diabetic patients seems to depend on the C-peptide levels, which in turn, probably depend on the amount of viable islet cell mass. Pancreatic fibrosis, the characteristic pathology in this condition [24], appears to occur more slowly in some individuals. Thus, two tropical pancreatic diabetic patients at our centre only have impaired glucose tolerance and are treated with diet alone.

Patients with tropical pancreatic diabetes have low serum cholesterol concentrations compared with Type 2 diabetic patients or non-diabetic subjects. This appears to be due to the low LDL-cholesterol level in men and low LDL- and HDL-cholesterol levels in women. The observation that young women with tropical pancreatic diabetes have significantly lower HDL-cholesterol levels is interesting because the opposite is true of young non-diabetic women and young women with Type 2 diabetes [27]. This may be a result of endocrine abnormalities which are frequently seen in female patients with tropical pancreatic diabetes [28].

There is very little data available on the vascular complications in tropical pancreatic diabetes although earlier reports have suggested that microangiopathy was extremely rare [29]. In this series, 39% had retinopathy and 7% had proliferative retinopathy. Nephropathy and renal insufficiency also occurred in these patients. These prevalence rates are only marginally lower than in the Type 2 diabetic patients. Thus, microvascular, in contrast to macrovascular, complications are not uncommon in tropical pancreatic diabetes. Admittedly, the numbers are small and large prospective studies are needed for more accurate figures on vascular complications in this condition.

To summarize, the present study shows certain peculiarities and clinical variations compared with earlier reports [5, 6, 22–24]. Protein-calorie malnutrition and cassava ingestion do not appear to be essential aetiological factors as believed previously. The extent of damage to the pancreatic B cells appears to be variable and the response to therapy is dependent on this. Microangiopathy, even in a severe form, does occur in tropical pancreatic diabetes. The clinical profile of tropical pancreatic diabetes appears to show heterogeneity even within South India.

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