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EXOCRINE AND ENDOCRINE PANCREATIC FUNCTION IN MALNUTRITION-RELATED DIABETES MELLITUS (MRDM) IN YOGYAKARTA, INDONESIA

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INDEXING WORDS

MRDM; pancreatic amylase; C-peptide; islet cell antibody

SYNOPSIS

We measured serum C-peptide after fasts and oral glucose loads and pancreatic amylase activity in 10 patients with fibro-calculous pancreatic diabetes (FCPD), 12 with protein-deficient pancreatic diabetes (PDPD), and 11 with non-insulin-dependent diabetes mellitus (NIDDM).

FCPD patients had less pancreatic amylase activity than PDPD patients who in turn had less than NIDDM diabetics or normal subjects. Fasting C-peptide was lower in FCPD than in PDPD or NIDDM; PDPD patients had normal fasting C-peptide levels but abnormally low responses after glucose loading. These differences were significant.

This suggests that FCPD causes severe pancreatic exocrine and endocrine insufficiency, while PDPD causes a partial loss. The pancreatic exocrine in NIDDM remains normal.

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INTRODUCTION

There are two well-characterized types of diabetes, insulin-dependent (IDDM) and non-insulin-dependent (NIDDM). In tropical developing countries, some diabetics fail to meet the criteria of these two types. In 1955, Hugh-Jones reported a form of diabetes in Jamaica that was not either IDDM or NIDDM. These patients were usually young adults, undernourished, requiring large amounts of insulin to control glucosuria and maintain or increase body weight, but who did not develop ketoacidosis even if insulin was withheld. This is type J diabetes.[5] In the same year Zuidema of Indonesia described some cases of disseminated pancreatic calcification and called them pancreatic cirrhosis.[25] Calcium-containing stones became a hallmark of this type which is now known as "pancreatic diabetes" in tropical countries. Since then, numerous cases of pancreatic diabetes have been reported in Asia[4,17,21] and Africa.[7,14,19]

Pancreatic diabetes has been observed in children and young adults from low income groups in many countries where cassava is the main food and people consume a diet deficient in calories and protein. Clinical observations suggested a connection between the consumption of cassava, low protein intake, and pancreatic diabetes. Based on the distinctive clinical features and course, the uncertain etiology (the total absence of any of the well-known causes of chronic pancreatitis), and the great number of such cases in the developing nations, the World Health Organization (WHO) in 1985 created a new classification of diabetes, malnutrition-related diabetes mellitus (MRDM). MRDM has two subclasses: fibrocalculous pancreatic diabetes (FCPD) and protein-deficient pancreatic diabetes (PDPD). MRDM is marked by[24]: (a) an onset of symptoms before the age of 35 commonly between 15 and 25 years, (b) extreme underweight, and the stigmata of current or past malnutrition, (c) resistance to the development of ketosis, (d) resistance to the action of insulin, (e) pancreatic exocrine insufficiency, and (f) pancreatic calcification and recurrent attacks of abdominal pain in the case of FCPD. The diagnosis of FCPD is easily made on finding pancreatic calcification on the abdominal X-ray of a young, underweight, ketosis-resistant diabetic. The clinical profile of PDPD is sometimes confused with

that of non-obese NIDDM. No comparative study of exocrine and endocrine pancreatic function in FCPD and PDPD has been published to our knowledge.

The present study compares exocrine and endocrine pancreatic function in FCPD, PDPD and NIDDM.

PATIENTS AND METHODS

Patients

The study population consisted of 10 patients with FCPD, 12 patients with PDPD, and 11 patients with NIDDM. They came from the hospitals of Yogyakarta. The diagnosis of FCPD depended on : (a) the onset of symptoms before the age of 35, (b) the absence of alcoholism, gallstones, or hyperparathyroidism, (c) the presence of pancreatic calculi on abdominal X-ray, (d) a body mass index (BMI) less than 19, (e) ketosis resistance, and (f) moderate-to-severe hyperglycemia.

There were 2 men and 8 women between the ages of 16 and 32 years with FCPD. Their duration of diabetes was 4.0 ± 0.8 years. Only one patient had a diabetic first-degree relative. The chief complaints of these FCPD patients were weakness and weight loss associated with polyphagia, polyuria, and polydipsia. They had matured normally until diabetes began. Although the FCPD patients had pancreatic calcification, none of them showed symptoms of pancreatitis such as recurrent abdominal pain or pancreatic exocrine insufficiency as manifested by steatorrhea. None of them ate cassava as their main food or admitted any past history of malnutrition.

Twelve patients had PDPD. The diagnosis of PDPD was similar to that of FCPD but without any pancreatic calculi on abdominal X-ray. There were 6 men and 6 women between 15 and 29 years. Their duration of diabetes was 2.6 ± 0.7 years. Their chief complaints were similar to those of FCPD patients. They had matured normally until diabetes began.

We also studied but did not fully examine 4 men and 7 women with NIDDM, aged between 44 and 80 years. Their duration of diabetes was 8.9 ± 2.3 years.

In addition, we studied 11 normal subjects (2 men and 9 women) with no known disease aged between 17 and 21 years.

Study Design

We measured exocrine pancreatic function via fasting total serum amylase and pancreatic amylase activity, measuring the latter with gel electrophoresis and enzyme immunoassay (EIA) using a monoclonal antibody. For endocrine pancreatic function, we used serum C-peptide levels during oral glucose loading, except for NIDDM patients who supplied only fasting levels.

Pancreatic Exocrine Function Test

Total amylase activity was mesured with a chromogenic method using a blue-dyed starch polymer.[3] The results were expressed in Somogyi units per 100 ml. Serum amylase activity was 56.7 - 237.6 Somogyi units/100 ml (mean ± 2SD) in 100 normal persons aged 16 to 50.

Serum amylase isoenzymes were separated by electrophoresis on a thin-layer polyacrylamide gel.[16] Each was identified by a starch-iodine reaction. Amylase activity created a light yellow or transparent band against the dark-blue background. The gels were then scanned with a densitometer. Results for patients with hyper- or hypofunctioning pancreata or salivary glands have suggested that essentially all the isoenzymes in human serum and urine come from the salivary glands and the pancreas.[16] We refered to these isoenzymes as Amylase-1, Amylase-2, etc., starting from the slowest anodic mobility. Human serum and urine amylase was separated into four or five distinct isoenzymes with mobilities consistent with those of the pancreatic isoamylase (Amylase-1, 2 and 4) and the salivary isoamylase (Amylase-3, 5 and 7). No diseases other than pancreatitis have been demonstrated to elevate pancreatic-type isoamylase activity. A low Amylase-1 activity would suggest pancreatic exocrine insufficiency.[6,15,20] Normal serum has 55.1 ± 3.7% (mean ± SE) pancreatic-type isoamylase activity.

Pancreatic Amylase Assay using Monoclonal Antibody

Serum pancreatic (P) amylase was determined by enzyme immunoassay (EIA) with Right Assay P-Amylase kit (Kohjin Co. Ltd., Tokyo, Japan). In this assay system monoclonal antibodies highly specific for P-amylase were coated on microassay plates; it was affected by P-amylase, but not salivary amylase. P-amylase was

determined by protein weight and not by enzyme activity. P-amylase standards or test samples were added to each well of the micro-assay plate, which was incubated and washed to remove the residue of the fluid sample. Mouse anti-P-amylase monoclonal antibody labelled with peroxidase was added to induce a sandwich-type reaction. After a second incubation and washing, an enzyme substrate was added. The resulting absorbance was measured at 492 nm and was proportional to the amount of P-amylase in each sample. Normal serum P-amylase was 40.1 - 144.5 ng/ml (mean ± 2SD : Otsuki et al., unpublished observation).

Pancreatic Endocrine Function Test

Blood for the measurement of serum C-peptide was collected from the antecubital vein both before and after a 50 g glucose load. The sera were stored at -20C until assay. Serum C-peptide was measured with a radioimmunoassay kit (C-peptide RIA Shionogi)supllied by Shionogi Pharmaceutical Co., Osaka, Japan. The kit contains lyophilized standard synthetic human C-peptide in concentrations of 0, 0.2, 0.5, 1, 3, 10 and 30 ng/ml, ^{125}I-labelled human C-peptide and microsepharose coated with rabbit anti-human-C-peptide γ-globulin. Fifty μl of standard C-peptide solution or a test sample, 100 μl ^{125}I-C-peptide solution, and 200 μl of coated microsepharose were mixed thoroughly in a test tube. The tubes were incubated at room temprature for 3 h and centrifuged at 1,500 g for 10 min at 4C. The supernatant was aspirated. The raioactivity of the precepitate was counted in a well-type automatic γ-counter. The assay was performed in duplicate. The normal range of fasting serum C-peptide was 0.5 - 2.5 ng/ml. The C-peptidogenic index was calculated with the following formula;

$$\text{C-peptidogenic index} = \frac{\Delta\text{C-peptide at 1 h}}{\Delta\text{serum glucose at 1 h}}$$

Statistical Analysis

The data were expressed as mean ± SEM and sets of data were compared with Student's t-test.

RESULTS

Our FCPD and PDPD patients did not differ statistically in age, duration of diabetes, body mass index (BMI), fasting blood glucose concentration or total serum protein (Table 1).

Table 1 Clinical profile of subjects

	Age (year)	Duration of diabetes (year)	Body mass index	Fasting blood glucose (mg/100 ml)	Total serum protein (g/100 ml)
Normal subjects (n=11)	19.0 ± 0.3	ND	20.9 ± 0.6	62.4 ± 2.6	7.9 ± 0.1
FCPD (n=10)	23.3 ± 1.5	4.0 ± 0.8	14.5 ± 0.8	310.9 ± 42.5	7.3 ± 0.3
PDPD (n=12)	22.2 ± 1.2	2.6 ± 0.7	15.9 ± 0.4	229.0 ± 29.7	7.2 ± 0.2
NIDDM (n=11)	61.5 ± 4.1	8.9 ± 2.3	ND	166.7 ± 20.5	6.1 ± 0.3

Results shown are mean ± SE of the number of subjects indicated in parentheses.

FCPD, fibrocalculous pancreatic diabetes; PDPD, protein-deficient pancreatic diabetes;

NIDDM, non-insulin-dependent diabetes mellitus; ND, not determined

Mean total serum amylase activity in every group (FCPD, PDPD, NIDDM, and control) was within the normal range (Table 2). The FCPD group had normal total serum amylase activity but significantly low P-amylase as determined by gel electrophoresis or EIA. The P-amylase of some FCPD patients was undetectable by gel electrophoresis but was measureable by EIA. PDPD patients had significantly less P-amylase than NIDDM patients, but significantly more than FCPD patients (Table 2).

Table 2 Serum amylase and fasting serum C-peptide levels and C-peptidogenic indexes of subjects

	Total serum amylase (SU/100 ml)	Pancreatic amylase		Fasting serum C-peptide (ng/ml)	C-peptidogenic index
		by GE (SU/100 ml)	by EIA (ng/ml)		
Normal subjects (n=11)	139.2 ± 14.5	72.7 ± 6.3	157.7 ± 19.1	1.07 ± 0.14	0.1936 ± 0.0359
FCPD (n=10)	145.1 ± 30.7	1.3 ± 0.6[a]	13.2 ± 2.4[a]	0.53 ± 0.05[a]	0.0005 ± 0.0004[b]
PDPD (n=12)	186.5 ± 25.9	18.8 ± 4.6[c]	46.7 ± 9.1[c]	0.99 ± 0.12[c]	0.0042 ± 0.0013
NIDDM (n=11)	107.9 ± 8.0	64.9 ± 5.8	95.8 ± 13.0	2.66 ± 0.46	ND

Results shown are mean ± SE of the number of subjects indicated in parentheses.

SU, Somogyi unit; GE, gel electrophoresis; EIA, enzyme immunoassay; ND, not determined.

[a] $p<0.005$ and [b] $p<0.025$ compared with PDPD; [c] $p<0.005$ compared with NIDDM

Patients with FCPD had the lowest fasting serum C-peptide levels among the four groups and showed abnormally small increases

after glucose loading. Those with PDPD had normal fasting serum C-peptide concentrations but abnormally low increases after glucose loading (Fig. 1). The fasting serum C-peptide and the C-peptidogenic index were significantly lower in FCPD patients than PDPD patients. Fasting serum C-peptide levels in PDPD and in NIDDM were also significantly different (Table 2).

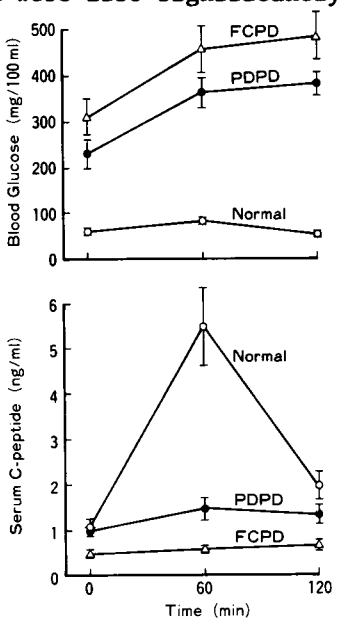

Fig. 1 Blood glucose and C-peptide response after 50 g OGTT in patients with FCPD and PDPD, and normal subjects.

DISCUSSION

Although WHO described FCPD and PDPD in detail in 1985, it failed to give precise criteria for diagnosis. Some researchers fashioned their own criteria based the local characteristics of MRDM. Since these characteristics varied between regions,[11,22] their criteria also differed. For example, Ahuja's criteria[1] differ from Mohan's[11] and McMillan's.[10] Mohan et al. did not include insulin resistance in their criteria because some of their MRDM patients could be controlled by oral hypoglycemic agents. Our present criteria for MRDM did not mention malnutrition, as do McMillan's criteria, or recurrent abdominal pain, as do Mohan's criteria, because our MRDM patients did not show these symptoms. Although our MRDM patients had no recurrent abdominal pain or steatorrhea, they had significantly less serum pancreatic amylase than normal subjects or NIDDM diabetics. This suggests a hetero-

genous clinical profile of MRDM due to local environmental factors. Internationally uniform criteria remain elusive.

Standard procedures showed normal total serum amylase levels in FCPD and PDPD but gel electrophoresis showed very low pancreatic amylase levels. Thus, routine determination of total amylase may be a poor evaluator of pancreatic exocrine function. Pancreatic amylase insufficiency specifically indicates chronic pancreatitis,[6,20] which means that all of our MRDM patients had chronic pancreatitis. They also had MRDM, as confirmed by biochmical testing. Although the PDPD patients' pancreatic amylase determined by EIA in the low end of the normal range, it was significantly less than those of normal subjects and NIDDM diabetics.

FCPD presented a more severe clinical picture than did PDPD, both in biochemical parameters and in outcome. Two FCPD patients died during the year-long course of this study, versus no PDPD patients. Despite being similar to the PDPD patients in age, BMI, duration of diabetes, and fasting blood glucose level, the FCPD patients had significantly less fasting serum C-peptide and serum pancreatic amylase and lower C-peptidogenic index.

PDPD resembles NIDDM clinically but in our sample involved lower fasting serum C-peptide and pancreatic amylse levels. This sort of pancreatic exocrine function test may be useful in distinguishing between these diseases.

The residual insulin secretion in MRDM may explain the lack of ketosis.[2] In the present study, FCPD patients had the lowest serum C-peptide levels among the four groups. However, it was still detectable and increased slightly after glucose loading. Other factors may also be involved in ketosis resistance. Plasma non-esterified fatty acid and acetone levels tend to be low in MRDM. In extremely underweight subjects, body fat is so scarce that no non-esterified fatty acid response to insulin deprivation occurs.[13] Moreover, the plasma glucagon concentration in MRDM is low and decreases after glucose loading.[18] Also, carnitine deficiency, which is associated with malnutrition,[9] may induce ketosis resistance in patients with MRDM. Carnitine is essential for the normal conversion of fatty acids to ketone bodies.

PDPD patients had low C-peptide responses to glucose loads, significantly different from controls and from the delayed response of NIDDM diabetics.[8] However, their normal fasting C-pep-

tide levels may indicate some B cell preservation.

It is tempting to conclude, from the distribution of MRDM in poor countries where people eat mostly cassava and very little protein, that these factors cause MRDM.[24] Linamarin, a cyanogenic glycoside contained in cassava, releases hydrocyanic acid (HCN) on hydrolysis. Ususally, HCN conjugates with SH radicals from sulfuric amino acids such as methionine, cysteine and cystine, and the resulting thiocyanate is excreted in the urine. Malnourished patients, however, may lack sufficient sulfuric amino acids. HCN may accumulate, damaging the pancreas.

Our patients had recently contracted MRDM and were not malnourished. Malnutrition might begin later, perhaps as a consequence of prolonged uncontrolled diabetes and pancreatic exocrine insufficiency. Their overall good nutrition was borne out by their normal growth before onset and the rarity of MRDM in their famillies, who presumably shared the same diet. Nowadays, Indonesians in this area still eat cassava and other roots in small quantities. We cannot eliminate the possibility that our patients experienced prolonged low intake of a toxic agent combined with subclinical protein deficiency, possible causes of FCPD.

Although severe protein deficiency may cause PDPD, our PDPD patients showed no sign of it. One noteworthy possibility is a long subclinical protein deficiency.

We have found one MRDM patient who was positive for islet cell antibodies (ICA),[23] although others have found none.[12] These ICAs may derive from 1) an autoimmune abnormality that causes MRDM, this possibility being supported by the susceptibility of malnourished patients to infection; 2) simultaneous onset of MRDM and IDDM; and 3)islet destruction by toxic agents like HCN from cassava, or by severe malnutrition. Choosing between these alternatives will require further study, including perhaps large-scale HLA determination among MRDM patients.

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