β-Cell Function and Insulin Sensitivity in Tropical Calcific Pancreatitis From North India

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Tropical calcific pancreatitis (TCP) is a variant of chronic pancreatitis, occurring only in developing countries. It frequently leads to diabetes at a young age. To determine the pathogenesis of glucose intolerance, β-cell function and insulin sensitivity were measured in 11 TCP patients with normal glucose tolerance (TCP-NGT), six TCP patients with mild hyperglycemia [TCP-DM] median fasting plasma glucose, 6.1 mmol/L), and 16 healthy control subjects. The technique of continuous infusion of glucose with model assessment (CIGMA) was used to calculate β-cell function (%B) and insulin sensitivity (%S), based on plasma glucose and insulin levels achieved after an intravenous infusion of glucose. %S was similar in both groups of TCP patients and controls. In contrast, %B was significantly lower in TCP-DM patients (median, 53; interquartile range, 41 to 62) compared with controls (90; 65 to 143; $P < .01$) and with TCP-NGT patients (119; 91 to 159; $P < .01$). TCP-NGT and control subjects had similar β-cell function. Among patients with TCP, %B negatively correlated with the duration of pancreatitis ($r = -.63$, $P < .05$). Our results suggest that patients with TCP develop diabetes due to a diminution in beta-cell function, and that insulin resistance does not play a significant role in its pathogenesis.

TROPICAL CALCIFIC pancreatitis (TCP) is a unique cause of diabetes in developing countries.[1,2] These patients present with abdominal pain in childhood and often develop diabetes before they are 30 years of age.[3,4] Most patients require insulin for glycemic control, but do not develop ketosis with stoppage of insulin.[3] The pathogenesis of TCP is still unknown, but it is not related to alcohol.[1,2] Protein-calorie malnutrition and intake of cyanogenic glycosides have been proposed as etiologic candidates.[5]

Previous studies have found a variable reduction in β-cell function in patients with TCP who develop diabetes.[4,6-11] In addition, reduced sensitivity to insulin has also been demonstrated.[12,13] However, these studies have been performed in severely hyperglycemic insulin-requiring subjects. In these circumstances, it is difficult to distinguish between the primary pathophysiological abnormalities and effects of glucose toxicity.[14]

The aim of the present investigation was to study β-cell function and insulin sensitivity simultaneously in TCP patients with either normal glucose tolerance (TCP-NGT) or mild hyperglycemia, using the technique of continuous infusion of glucose with model assessment (CIGMA).

SUBJECTS AND METHODS

Subjects

Nineteen consecutive North Indian patients with TCP were studied. Of these, only one was previously known to have glucose intolerance. TCP was suspected on the basis of a history of abdominal pain since childhood, and was confirmed by the demonstration of pancreatic ductal calcification on abdominal ultrasonography. No patient reported a history of alcohol intake. Hypercalcemia, hypertriglyceridemia, and biliary tract stones were ruled out by appropriate investigations. All patients had normal liver and renal function. No patient had an episode of acute pancreatitis for at least 3 months before the study. Seventeen volunteers of North Indian origin, matched for age and body mass index ([BMI] kg/m^2) with the TCP patients and without a family history of diabetes, were used as controls. All subjects provided informed consent, and the study was approved by the institutional ethics committee.

All patients and controls underwent a 75-g oral glucose tolerance test (OGTT). Before the OGTT, all patients were on oral pancreatic enzyme supplementation and consuming a diet with at least 250 g carbohydrates. Using World Health Organization criteria,[15] patients were classified into three groups: TCP with normal glucose tolerance ([TCP-NGT] n = 11), TCP with impaired glucose tolerance (n = 2), and TCP with mild hyperglycemia ([TCP-DM] n = 6). In view of the small number of TCP patients with impaired glucose tolerance, these were not included in our analysis. All control subjects had normal glucose tolerance.

CIGMA Test

CIGMA is a mathematical model for simultaneous evaluation of β-cell function and insulin sensitivity.[16] The test is based on the principle that after a slow infusion of intravenous glucose, a steady state is reached in which plasma levels of glucose and insulin depend on the feedback loop between the pancreas, liver, and peripheral glucose-metabolizing tissues.

The CIGMA test was performed within 1 week of the OGTT, using the protocol previously described.[16] Three arterialized venous plasma samples for measurement of glucose and insulin levels were drawn in a fasting state. A 10% glucose solution was then infused for 1 hour at a rate of 5 mg/kg ideal body weight/min using an infusion pump. Samples were again drawn at 50, 55, and 60 minutes, and the mean achieved glucose and insulin values were used to obtain an estimate of β-cell function (%B) and insulin sensitivity (%S). These were expressed as percentages of the values obtained in a reference young lean population, for whom the model has been calibrated at 100%. In addition to the CIGMA-derived %B, the achieved plasma insulin corrected for the basal plasma insulin (plasma achieved/basal insulin) was used as a measure of β-cell function.[17]

Assays

Plasma glucose level was measured by the glucose oxidase technique (Boehringer Mannheim, Mannheim, Germany) on a UV-265 Shimadzu spectrophotometer (Shimadzu, Kyoto, Japan). Plasma insulin was

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determined by radioimmunoassay (Diagnostic Products, Los Angeles, CA). The assay had a sensitivity of 1.4 μU/mL, and the intraassay and interassay variations were 6.7% and 6.6%, respectively. Pancreatic exocrine function was assessed by measuring the fecal chymotrypsin (FCT) level using an enzymatic technique (Boehringer Mannheim). Hemoglobin A_{1c} was determined by ion-exchange chromatography (Biorad, Hercules, CA).

Statistical Analysis

Clinical characteristics of the patients are presented as the mean ± SD. Comparison between groups was made by one-way ANOVA and the unpaired Student's *t* test. The results of the CIGMA test did not conform to a normal distribution and are presented as the median and interquartile range. The Kruskall-Wallis test and Wilcoxon's rank-sum test were used for comparisons. The chi-square test was used to compare categorical variables. Correlations were determined using Spearman's rank correlation test. A two-tailed *P* value less than .05 was considered significant.

RESULTS

Clinical characteristics of the two patient groups and healthy controls are listed in Table 1. TCP patients were lean, but their BMI did not differ from that of the control subjects. Patients with TCP-NGT and TCP-DM had a similar duration of illness, as measured by the time elapsed since the first episode of pain. FCT levels were significantly lower in the two groups of TCP patients compared with controls, but TCP-NGT and TCP-DM patients had similar levels.

Patients with TCP-NGT did not differ from control subjects in either fasting or achieved plasma glucose (Table 2). TCP-DM patients had significantly higher levels of both fasting and achieved plasma glucose when compared with the other groups. However, TCP-DM patients had only mild hyperglycemia, as reflected by the fact that five of six patients had a fasting plasma glucose level of less than 7.8 mmol/L (median, 6.1; interquartile range, 5.9 to 6.5) and a hemoglobin A_{1c} of 5.0% (4.5% to 5.3%; normal range, 4.2% to 5.9%). Despite the higher fasting plasma glucose levels, fasting plasma insulin levels were similar in patients with TCP-DM and the other two groups. Both indices of β-cell function (%B and achieved/basal plasma insulin) were reduced significantly in TCP-DM compared with TCP-NGT patients ($P < .01$) and controls ($P < .01$). %B was less than 50% in four of six patients with TCP-DM, in comparison to none of 11 patients with TCP-NGT ($P < .01$). TCP-NGT patients did not differ from control in either of the indices of β-cell function. Insulin sensitivity (%S) was similar in control subjects and the two groups of TCP patients.

Among patients and controls, %S had a negative correlation with fasting plasma insulin ($r = -.55$, $P < .05$), whereas %B had a significant correlation with achieved/basal plasma insulin ($r = .82$, $P < .01$). Among patients with TCP, %B had a significant negative correlation with the duration of pain ($r = -.63$, $P < .05$), but not with the age of the patients or the age at onset of pain. FCT levels did not show any significant correlation with either %B or %S.

Table 1. Clinical Features of TCP Patients

Characteristic	Controls	TCP-NGT	TCP-DM
No. of subjects	16	11	6
Age (yr)	28.6 ± 3.4	25.6 ± 7.3	23.8 ± 2.9
Sex (M/F)	10/6	6/5	3/3
BMI (kg/m²)	20.2 ± 2.0	19.4 ± 2.4	19.8 ± 2.7
Pain duration (yr)	—	4.7 ± 4.8	6.2 ± 3.9
FCT (U/g)	16.9 ± 14.7*	1.7 ± 1.9	1.7 ± 1.6

NOTE. Results are the mean ± SD.
*$P < .05$ *v* TCP-NGT and TCP-DM.

DISCUSSION

When compared with other methods for determination of insulin sensitivity and β-cell function, CIGMA has the advantages of being simple to perform and of requiring infrequent blood sampling. The CIGMA-derived parameters have previously been found to have an excellent correlation with insulin resistance measured by the euglycemic-hyperinsulinemic clamp ($r = .87$) and with β-cell function determined by the hyperglycemic clamp ($r = .87$) and with β-cell function determined by the hyperglycemic clamp ($r = .64$).[16] CIGMA has been used previously to study diverse diseases associated with abnormal glucose tolerance.[17-19] Since CIGMA has not been previously used in North Indians, all comparisons were made with a control group of the same ethnic background. We found a good correlation between independent measures of insulin sensitivity (fasting insulin) and β-cell function (achieved/basal plasma insulin) and %S and %B, respectively. This provided indirect evidence that CIGMA-derived values can be used in the Indian population.

We found that TCP-NGT patients had β-cell function and insulin sensitivity that were indistinguishable from those of controls. In contrast, TCP subjects with mild hyperglycemia were characterized by a reduction in β-cell function, although this was not accompanied by a reduction in insulin sensitivity. This suggests that in TCP, diabetes develops due to decreased β-cell function, and that impaired insulin sensitivity does not play a significant role in its pathogenesis. In this regard, TCP more closely resembles well-controlled type I diabetes, wherein insulin sensitivity is normal,[20] rather than type II diabetes, wherein most subjects develop insulin resistance at an early stage.[21] It is also consistent with the pathological findings in TCP of severe parenchymal fibrosis with β-cell atrophy and disruption of blood supply to the islet.[22]

Previous studies have shown that in TCP, worsening of glucose tolerance is associated with a deterioration in β-cell function.[6,11] Consistent with this, %B was reduced by only 40% in our TCP-DM patients with mild hyperglycemia compared with control subjects. In contrast, severely hyperglycemic, insulin-dependent subjects have C-peptide responses similar to those of patients with type I diabetes,[6-11] although the levels are higher in TCP patients whose diabetes is treated with diet or oral hypoglycemic agents.[4] β-Cell function may be in part related to the duration of pancreatitis. This is underscored by the negative correlation we found between %B and duration of pain. Unlike a previous study,[6] we found no correlation between FCT and β-cell function. This may be because exocrine function is severely reduced at a much earlier stage than β-cell function, or because the processes leading to β-cell impairment and to exocrine insufficiency may be different.

Although the results of our study suggest that it is unlikely

Table 2. β-Cell Function and Insulin Sensitivity in TCP

Parameter	Controls	TCP-NGT	TCP-DM	P
Plasma glucose 0 min (mmol/L)	4.8 (4.5-5.3)	5.0 (4.6-5.1)	6.1 (5.9-6.5)*	<.01
Plasma insulin 0 min (μIU/mL)	4.5 (3.9-5.8)	5.6 (5.1-6.1)	5.1 (4.9-11.5)	NS
Plasma glucose 60 min (mmol/L)	9.3 (8.9-9.8)	9.4 (9.1-9.6)	11.9 (11.0-13.2)*	<.01
Plasma insulin 60 min (μIU/mL)	19.6 (12.8-39.0)	32.0 (22.7-47.3)	16.9 (10.7-26.0)	NS
%S	64 (33-107)	44 (29-59)	56 (34-85)	NS
%B	90 (65-143)	119 (91-159)	53 (41-62)†	<.01
Plasma insulin 60 min/0 min	5.1 (2.7-6.8)	5.4 (4.1-7.3)	2.6 (1.8-3.3)†	<.01

NOTE. Results are the median (interquartile range).

*$P < .001$ *v* controls and TCP-NGT.

†$P < .01$ *v* controls and TCP-NGT.

that reduced insulin sensitivity plays a role in the pathogenesis of the early stages of diabetes in TCP, glucose toxicity may lead to insulin resistance when diabetes is uncontrolled.[14] Using the insulin tolerance test, Mohan et al[12] found that poorly controlled, insulin-dependent TCP subjects had a reduced glucose disposal rate. The same investigators also demonstrated a reduced insulin binding to erythrocyte insulin receptors, which improved with better control of diabetes, suggesting that the binding defect was secondary to the hyperglycemia.[13]

TCP differs from chronic alcoholic pancreatitis (CAP) in many respects.[23] TCP subjects are much younger, and may have an increased frequency and severity of diabetes. Associated chronic liver disease, which may lead to insulin resistance, is common in CAP but is not found in TCP.[22] As in TCP, β-cell function in CAP varies with the severity of glucose intolerance.[24-28] Some studies have found evidence of impaired insulin sensitivity,[26] but this has not been confirmed by others.[29]

In conclusion, we have found that TCP patients with mild hyperglycemia have diminished β-cell function, but insulin sensitivity is not reduced.

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