Pancreatic C-Peptide Response to Oral Glucose in Fibrocalculous Pancreatic Diabetes

Improvement After Treatment

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β-Cell function (plasma C-peptide) in 17 fibrocalculous pancreatic diabetic (FCPD) subjects (14 newly diagnosed) was not different at presentation from that in 14 matched insulin-dependent diabetic subjects. After insulin treatment and improvement in the patients' nutritional and metabolic status, fasting and postglucose plasma C-peptide concentrations showed a significant increase (fasting 0.06 ± 0.01 to 0.17 ± 0.03 nM, peak 0.11 ± 0.02 to 0.29 ± 0.06 nM, mean ± SE; $P < 0.01$ for both). Thus, severely diminished β-cell function in FCPD is partially reversible after treatment. This could contribute to the clinical metabolic peculiarities of this group of patients. *Diabetes Care* 13:525–27, 1990

Fibrocalculous pancreatic diabetes (FCPD) is a subtype of the so-called malnutrition-related diabetes mellitus prevalent in several tropical countries (1). β-Cell function in FCPD is variable (2,3), but residual function is thought to be responsible for the ketosis resistance of these patients. Previous studies of β-cell function in FCPD have been only cross sectional (2–5). We therefore investigated the β-cell function (C-peptide) in our FCPD subjects, at presentation and again after a variable interval of appropriate antidiabetic treatment, to improve understanding of the natural history of this condition.

RESEARCH DESIGN AND METHODS

The 17 FCPD subjects studied were all those seen by C.S.Y. at Sassoon General Hospital between September 1984 and February 1986 (median age 21 yr [range 12–45 yr], 11 male, body mass index [BMI] 14.9 kg/m² [11.2–24 kg/m²], fasting plasma glucose 11.4 mM [4.6–36.5 mM], HbA_1 99 μM fructose standard [40–232 μM]). Of these, 14 were newly diagnosed and untreated, and 3 had been diagnosed previously (2 were on insulin treatment). Diagnosis of FCPD was made in these diabetic individuals (by World Health Organization criteria, 1985) from the history of chronic abdominal pain typical of pancreatitis and demonstration of pancreatic calculi by plain X ray of abdomen and confirmed by ultrasonography. There was no history of alcohol intake in any of the patients, and ultrasonography did not reveal any hepatobiliary disease. None of the FCPD subjects showed ketonuria or ketosis at presentation or subsequently, despite stopping insulin for weeks. The data from 14 insulin-dependent diabetes mellitus (IDDM) patients (mean age 24 yr [range 8–35 yr], 10 male, BMI 16.2 kg/m² [13.2–20.6 kg/m²], fasting plasma glucose 16.5 mM [6.3–27.7 mM], HbA_1 122 μM fructose standard [64–155 μM]) and 13 young normal-weight subjects without a family history of diabetes are included for comparison. IDDM subjects had either presented in ketoacidosis or shown significant ketonuria (>40 mg/dl, Ketostix, Ames) in the absence of an obvious cause; 11 of these developed diabetic ketosis after stopping insulin treatment for 2–4 days during subsequent follow-up. Ten of these IDDM subjects were studied within 4 wk of diagnosis and 4 within 6 mo. Classification was made clinically before C-peptide results were available.

All subjects underwent an oral glucose tolerance test (OGTT; 75 g glucose, 1.75 g/kg for children <15 yr old), and plasma was stored at −70°C until transported on dry ice to Newcastle upon Tyne (UK) for plasma C-peptide assay. Special care was taken to preserve the samples; all batches arrived frozen and were immediately stored at −70°C until assayed, within 3 wk. HbA_1 was measured by a chemical method (6) with a normal range 30–50 μM fructose standard, and C-peptide was measured by Novo kit (M 1231). Intra-assay coefficient of variation for C-peptide was <5% and for interassay was <8%.

Eleven FCPD subjects were studied again 2 mo to 1 yr later. All had received insulin treatment after the initial OGTT, with the maximum dose during initial stabilization ranging from 60 to 280 U/day (median 110 U/day). Five underwent surgery (lateral pancreatojejunostomy). At the time of the second OGTT, seven subjects were taking insulin regularly (70 U), two were only on dietary treatment because of repeated hypoglycemia on very small doses of insulin, and two had stopped insulin against medical advice. Of the 6 FCPD subjects who could not be restudied, two were dead (1 of pulmonary tuberculosis, 1 of hypoglycemia), and four were lost to follow-up because of migration or socioeconomic reasons.

Nonparametric tests of significance (Mann-Whitney *U* and Wilcoxon as appropriate) were used. Correlations were done by Spearman's rank correlation (*r*).

RESULTS

Age, BMI, duration since diagnosis, fasting plasma glucose, and HbA_1 were similar in FCPD and IDDM subjects. Fasting plasma C-peptide in FCPD (0.04 nM [0.02–0.38 nM]) was similar to that in IDDM (0.09 nM [0.02–0.28 nM]). After glucose, plasma C-peptide showed a small but significant rise in both groups (Fig. 1); there

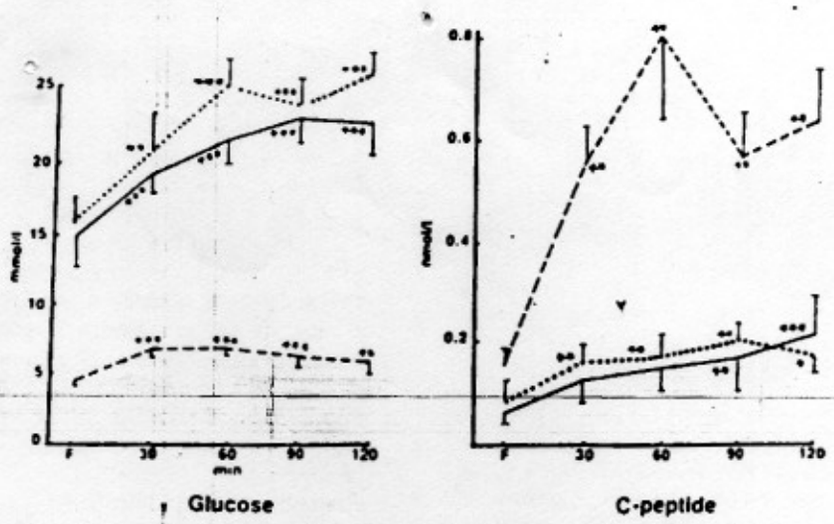

FIG. 1. Plasma glucose and C-peptide concentrations during oral glucose tolerance test. Means ± SE are shown. *Solid line*, fibrocalculous pancreatic diabetes; *dotted line*, insulin-dependent diabetes mellitus; *dashed line*, control. $^{**}P < 0.01$, $^{***}P < 0.001$, differences from fasting value at each point.

was no difference between the two groups at any time, but both were significantly lower than control subjects at all times, including fasting. Peak C-peptide concentrations in both groups were inversely related to HbA_1 ($r_s = -0.6$, $P < 0.05$).

FCPD subjects showed a significant improvement in BMI (from 15.0 to 17.5 kg/m², $P < 0.01$) and a fall in plasma glucose and HbA_1 ($P < 0.05$) at the second OGTT. There was a significant increase in fasting and peak C-peptide compared with the first OGTT (Fig. 2). Increases in C-peptide did not correlate with changes in body weight, plasma glucose, or HbA_1. Despite a similar tendency, eight IDDM subjects, similarly treated and restudied 1 yr later, failed to show a significant improvement in C-peptide concentrations (Fig. 2).

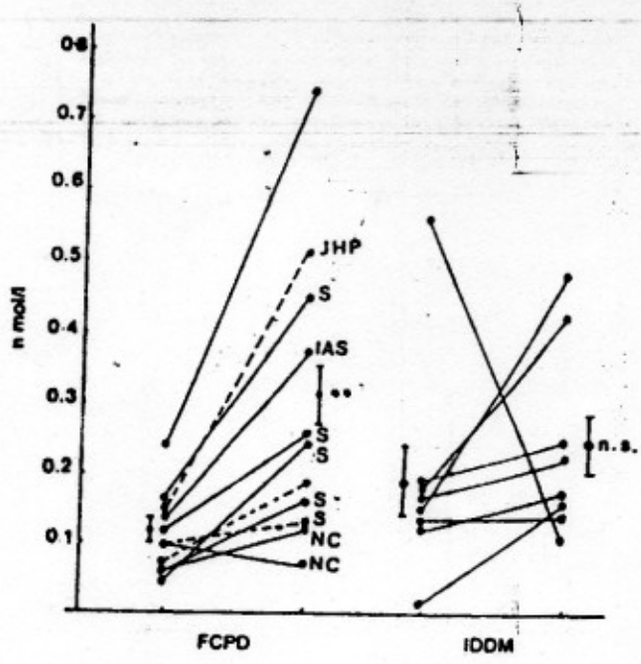

FIG. 2. Plasma peak C-peptide concentrations during 2 oral glucose tolerance tests. Means ± SE also shown for 2 groups. S, subjects who had undergone surgery; NC, noncompliers; IAS and JHP, patients only on dietary treatment because of repeated hypoglycemia on small doses of insulin. $^{*}P > 0.05$, $^{**}P < 0.01$, differences between 2 oral glucose tolerance tests. *Solid lines*, newly diagnosed fibrocalculous pancreatic diabetes (FCPD); *dashed lines*, previously diagnosed FCPD.

DISCUSSION

There are only a few reports of β-cell function in FCPD (2–5). β-Cell function is generally believed to be preserved better in FCPD than in IDDM. We observed concentrations of plasma C-peptide at least as low among FCPD subjects at presentation as among IDDM subjects, possibly because many of our patients were newly diagnosed, untreated, severely hyperglycemic, and had a long history of symptoms. Most had severe pancreatic loss (low serum immunoreactive trypsin), which could diminish β-cell mass severely (7). None of the FCPD subjects showed even mild ketonuria, even though their β-cell function was no different than that of the IDDM subjects. It appears that factors other than β-cell function also contribute to the ketosis resistance of FCPD subjects.

Serial studies of β-cell markers in FCPD subjects have not been reported. β-Cell function had improved by our second study, demonstrating a potential for recovery of β-cell function even in subjects with severely impaired function. Two subjects without much improvement in C-peptide concentrations had stopped insulin treatment against medical advice and remained severely hyperglycemic. This may indicate that improvement in β-cell function is partly related to better glycemic control (8). Pancreatic drainage surgery could be a factor in some

patients, but even those who had not undergone surgery showed similar improvement in β-cell function (Fig. 2). Improved nutrition could also contribute to the improvement in β-cell function. Eight IDDM subjects, as a group, failed to show significant improvement in β-cell function 1 yr after diagnosis. It appears that the improvement in β-cell function in FCPD persists for long periods, possibly because β-cells are not primarily affected. Ramachandran et al. (9) have demonstrated an increase in insulin-receptor affinity in FCPD subjects after metabolic control. Improved β-cell function and insulin-receptor affinity could contribute to the reduced insulin requirements in these subjects, similar to the honeymoon phase in IDDM subjects.

It will be of interest to study β-cell function repeatedly in FCPD subjects to establish the natural history over a longer period.

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