Pancreatic Polypeptide: A Marker for Lean Non-insulin-dependent Diabetes Mellitus?

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Both basal and postprandial pancreatic polypeptide (PP) concentrations were exaggerated twofold in lean NIDDM patients, whereas they were normal in lean IDDM and obese NIDDM patients who were hyperglycemic as a result of partial insulin withdrawal. Insulin infusion from an artificial endocrine pancreas, which resulted in fasting euglycemia and near-normoglycemia postprandially, had no effect on PP responses in any of the diabetic patients. No postprandial PP responses were observed in totally pancreatectomized (TPX) patients. Excessive basal and postprandial concentrations of PP in diabetes appear to be related to both leanness and residual beta cell function and, therefore, potential markers for lean NIDDM. DIABETES CARE 1985; 8:349–53.

Although the regulation of pancreatic polypeptide (PP) in healthy man has been well studied, knowledge of its concentrations in pathophysiologic states is incomplete. PP responses have been reported to be increased in diabetes,[1,2] blunted[3,4] or normal[5] in obesity, and destructive processes of the pancreas.[6–8] Excessive PP responses to meal ingestion[9] or insulin-induced hypoglycemia[10] have been found in lean diabetic patients with residual insulin secretion. In addition, excessive PP responses in diabetes have been reported to improve after improved glucose control.[2,11] It is not known whether leanness or residual insulin secretory capacity or both are the basis for the exaggerated PP responses in diabetes or whether hypersecretion of PP may be restored to normal by achievement of euglycemia. To assess the effects of leanness, residual insulin secretory capacity, pancreatectomy and euglycemia, postprandial PP responses were measured in insulin-dependent (IDDM), lean and obese non-insulin-dependent (NIDDM), and totally pancreatectomized (TPX) diabetic patients during partial insulin withdrawal and again during near-normoglycemia due to an artificial endocrine pancreas.

METHODS

Nineteen insulin-treated diabetic patients, six IDDM, five lean NIDDM, five obese NIDDM, and three who had undergone total pancreatectomy and duodenectomy, as well as 20 healthy nondiabetic (ND) subjects (10 lean and 10 obese) provided written informed consent (Table 1). All were studied in the General Clinical Research Center (GCRC) of the Mayo Clinic. The IDDM and NIDDM patients satisfied the criteria of the National Diabetes Data Group.[12] None had clinical evidence of autonomic neuropathy. The gastric inhibitory polypeptide responses in most of these patients have been previously reported.[13]

Each was studied after an overnight fast before and for 4 h after the consumption of a standard mixed meal (6 kcal/kg IBW) distributed as 50% carbohydrate, 30% fat, and 20% protein prepared in the research kitchen of the GCRC. Meals were presented at time and ingested within 20 min to avoid the effect of the cephalic phase on PP secretion.[14] The TPX patients took the prescribed doses of pancreatic enzymes before and during ingestion of the test meals.

Nondiabetic subjects were studied once. Diabetic patients were studied twice: once during moderate hyperglycemia achieved by a 50% reduction of their usual subcutaneous (s.c.) insulin doses on the day before and on the day of study and again after euglycemia had been maintained overnight and during ingestion of the test meal using an artificial endocrine pancreas (AEP) (Biostator Glucose Controller, Life Science Instruments, Elkhart, Indiana).

Plasma glucose was determined with a YSI Model 23A Glucose Analyzer (Yellow Springs Instruments, Yellow Springs, Ohio). Blood samples for PP and C-peptide[15] were collected in tubes containing EDTA and trasylol (500 kallikrein inhibitor U/ml; Sigma Chemical Co., St. Louis, Missouri), whereas blood for glucagon[16] and free insulin[17] was collected in tubes containing benzamidine (0.1 M) instead of trasylol. All samples for hormone determinations were centrifuged at 4°C, after which the plasma was frozen until assay.

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TABLE 1
Characteristics of diabetic patients and nondiabetic subjects

	M/F	Age (yr)	% IBW	Duration of diabetes (yr)
Nondiabetic, lean	4/6	39 ± 3	105 ± 2	—
Nondiabetic, obese	2/8	39 ± 3	160 ± 6	—
Pancreatectomy	2/1	49 ± 9	97 ± 5	4 ± 1
IDDM	4/2	33 ± 4	97 ± 5	16 ± 7
NIDDM, lean	4/1	55 ± 1	103 ± 6	8 ± 4
NIDDM, obese	2/3	47 ± 6	175 ± 12	5 ± 2

Plasma PP was measured by a double-antibody radioimmunoassay using the method of Chance et al.[18] Purified PP was used as standard (human) and tracer (bovine). The rabbit anti-hPP serum was lot no. 615-1054B-248-19 and standard hPP was lot no. 615-2054B-200-8. The limits of detection, intraassay, and interassay coefficients of variation for the plasma internal reference standards were 30 pg/ml, 5%, and 13%, respectively. No cross-reactivity was detected with glucagon, gastric inhibitory polypeptide, highly purified cholecystokinin, secretin, vasoactive intestinal peptide, motilin, or gastrin in concentrations ≤10 ng/ml. Because of the presence of PP antibodies, PP could not be measured in two IDDM patients.

STATISTICAL METHODS

Data in the text and figures are given as mean ± SE. Student's two-tailed *t*-test was used for statistical significance.[19] Area under the curve was calculated as responses above basal concentrations.

RESULTS (TABLE 2 AND FIGURE 1)

Nondiabetic Subjects

Although basal and peak postprandial plasma glucose, insulin, and C-peptide were greater for the obese than for the lean ND subjects, the differences reached statistical significance ($P < 0.05$) only for C-peptide. Neither basal (110 ± 19 versus 116 ± 14 pg/ml, respectively) nor integrated postprandial PP (27.9 ± 8.8 versus 30.8 ± 7.1 ng · ml^{-1} · 240 min^{-1}, respectively) differed significantly between the obese and lean ND subjects. Plasma PP, whether basal or postprandial, was not significantly influenced by age or gender.

Diabetic Patients

Insulin-deficient diabetic patients. Basal and peak postprandial plasma glucose of the TPX and IDDM patients treated with s.c. insulin exceeded ($P < 0.01$) those of the lean ND subjects. Basal C-peptide in TPX and IDDM patients was significantly lower ($P < 0.01$) than that of lean ND subjects and did not change postprandially. Although the basal plasma free insulin did not differ significantly among TPX and IDDM patients and the lean ND subjects, the peak postprandial free insulin after s.c. insulin was significantly less ($P < 0.01$) in TPX and IDDM patients than in ND subjects.

There were no significant increments in postprandial plasma glucagon (1.4 ± 0.7 ng · ml^{-1} · 240 min^{-1}) for the TPX patients from low basal concentrations (75 ± 14 pg/ml).

Basal plasma PP of the TPX patients and lean ND subjects (138 ± 68 versus 116 ± 14 pg/ml, respectively) did not differ statistically. After meal ingestion there were no PP responses in the TPX patients in contrast to the PP increases in lean ND subjects (−1.1 ± 0.6 versus 30.8 ± 7.1

TABLE 2
Results from s.c. and AEP treatments

	Basal				Postprandial			
					Peak			Integrated
	PG (mg/dl)	Free IRI (μU/ml)	CPR (ng/ml)	PP (pg/ml)	PG (mg/dl)	Free IRI (μU/ml)	CPR (ng/ml)	PP (ng · ml^{-1} · 240 min^{-1})
Nondiabetic subjects								
Lean (10)	94 ± 2	9 ± 1	2.3 ± 0.2	116 ± 14	129 ± 6	59 ± 9	4.5 ± 0.4	30.8 ± 7.1
Obese (10)	100 ± 3	12 ± 2	3.3 ± 0.3	110 ± 19	135 ± 8	84 ± 15	5.8 ± 0.5	27.9 ± 8.8
Diabetic subjects								
S.c. insulin								
TPX (3)	182 ± 34*	9 ± 2	0.7 ± 0.1*	138 ± 68	277 ± 41*	24 ± 7*	1.0 ± 0.2*	−1.1 ± 0.6*
IDDM (4)	230 ± 52*	5 ± 2	1.0 ± 0.1*	76 ± 26	281 ± 44*	19 ± 6*	1.0 ± 0.2*	22.9 ± 7.3
Lean NIDDM (5)	145 ± 8*	20 ± 4*	2.8 ± 0.6	200 ± 29*	230 ± 10*	58 ± 11	4.0 ± 0.7	83.1 ± 16.8*
Obese NIDDM (5)	241 ± 42*	40 ± 10*	3.7 ± 1.1	99 ± 18	313 ± 45*	74 ± 26	4.4 ± 1.2	23.4 ± 3.0
AEP								
TPX (3)	90 ± 5	11 ± 1	0.7 ± 0.1	134 ± 61	150 ± 26*	65 ± 23	0.7 ± 0.1*	0.5 ± 1.5*
IDDM (4)	98 ± 3	13 ± 4	0.6 ± 0.2	75 ± 26	157 ± 7*	64 ± 12	0.9 ± 0.2*	34.9 ± 12.7
Lean NIDDM (5)	103 ± 2	28 ± 7*	1.9 ± 0.5	195 ± 42*	167 ± 7	207 ± 63*	3.1 ± 0.8	95.7 ± 18.6*
Obese NIDDM (5)	105 ± 3	75 ± 15*	1.8 ± 0.2	110 ± 21	157 ± 11	361 ± 93*	2.8 ± 0.8	33.5 ± 10.7

*$P < 0.05$ compared with weight-matched nondiabetic subjects. Basal and peak postprandial concentrations of plasma glucose, free insulin, C-peptide, as well as basal and integrated postprandial concentrations of pancreatic polypeptide are shown for the nondiabetic subjects and diabetic patients studied during partial withdrawal of s.c. insulin and again during insulin replacement from an artificial endocrine pancreas.

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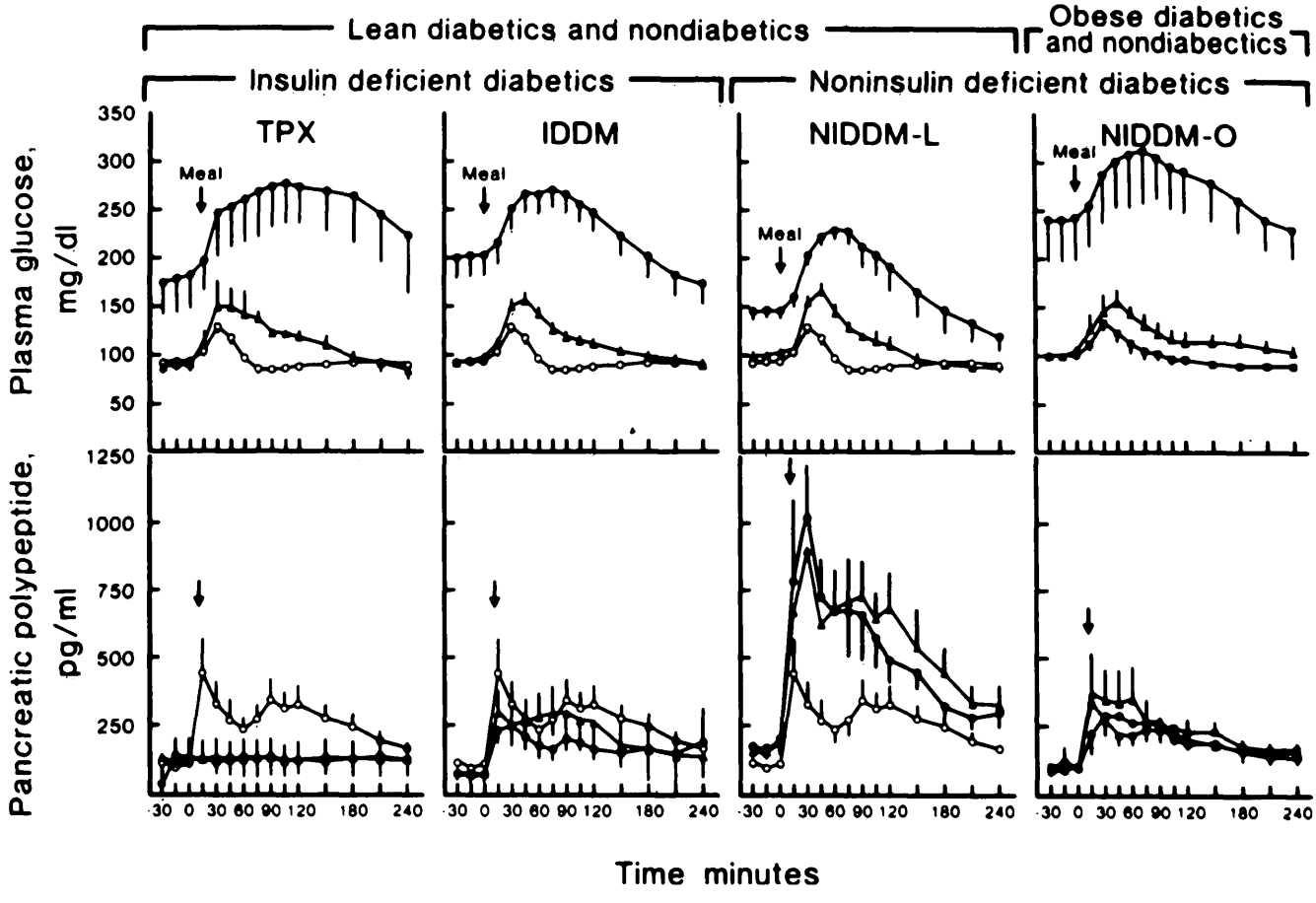

FIG. 1. Plasma glucose and pancreatic polypeptide responses to a mixed meal were measured in three totally pancreatectomized (TPX), four insulin-dependent (IDDM), and five lean (NIDDM-L) and five obese (NIDDM-O) non-insulin-dependent diabetic patients who were hyperglycemic after partial insulin withdrawal (solid circles) and again during artificial endocrine pancreas treatment (solid triangles). Ten lean (open circles) and 10 obese (solid squares) nondiabetic subjects were also studied.

ng · ml^{-1} · 240 min^{-1}, respectively, $P < 0.01$). Basal and integrated postprandial plasma PP (76 ± 26 pg/ml and 22.9 ± 7.3 ng · ml^{-1} · 240 min^{-1}, respectively) in the IDDM patients did not differ significantly from those in the lean ND subjects.

Overnight insulin infusion from the AEP restored basal plasma glucose in the TPX and IDDM patients to those of the lean ND subjects. Peak postprandial plasma glucose during AEP was significantly ($P < 0.01$) improved over s.c. insulin but was not completely normalized, $P < 0.01$. Basal and peak postprandial plasma free insulin in the TPX and IDDM patients during AEP did not differ significantly from those of lean ND subjects. Basal PP (138 ± 68 versus 134 ± 61, and 76 ± 26 versus 75 ± 26 pg/ml, respectively) and integrated postprandial PP (−1.1 ± 0.6 versus 0.5 ± 1.5 and 22.9 ± 7.3 versus 34.9 ± 12.7 ng · ml^{-1} · 240 min^{-1}, respectively) in TPX and IDDM patients did not differ significantly between s.c. insulin and AEP.

Non-insulin-deficient diabetic subjects. Both basal and peak postprandial plasma glucose of the lean and obese NIDDM patients during s.c. insulin exceeded ($P < 0.01$) those of the weight-matched ND subjects. Despite the presence of hyperglycemia, neither the basal nor peak postprandial plasma C-peptide of the lean and obese NIDDM patients was significantly different from that of the weight-matched ND subjects. Although basal plasma free insulin of the NIDDM patients exceeded ($P < 0.05$) those of weight-matched ND subjects, peak postprandial plasma free insulin did not differ significantly. Basal and integrated postprandial plasma PP of the obese NIDDM patients (99 ± 18 versus 110 ± 19 pg/ml and 23.4 ± 3.0 versus 27.9 ± 8.8 ng · ml^{-1} · 240 min^{-1}, respectively) did not differ from obese ND subjects. In contrast, basal and integrated postprandial plasma PP of the lean NIDDM patients exceeded those of lean ND subjects (200 ± 29 versus 116 ± 14 pg/ml, $P < 0.02$, and 83.1 ± 16.8 versus 30.8 ± 7.1 ng · ml^{-1} · 240 min^{-1}, $P < 0.02$, respectively) as well as those in all other groups of diabetic patients ($P < 0.02$).

Fasting concentrations of PP have been reported to increase with age[1,2,8,21–24] in healthy subjects. Because the exaggerated PP levels in the lean NIDDM patients could have been related to their greater age (55 ± 1 yr) than the lean ND (39 ± 3 yr), a control group of five lean healthy subjects matched by age (56.2 ± 2.2 yr) to the lean NIDDM patients was studied.

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Both basal (200 ± 29 versus 68 ± 9 pg/ml, $P < 0.01$, respectively) and integrated (83.1 ± 16.8 versus 42.2 ± 7.8 ng · ml^{-1} · 240 min^{-1}, $P < 0.05$, respectively) PP levels of the lean NIDDM patients exceeded those of the age-matched lean control subjects.

Achievement of basal euglycemia and near-normoglycemia postprandially in the lean and obese NIDDM patients during AEP was associated with significantly higher ($P < 0.05$) postprandial plasma free insulin concentrations than in weight-matched ND subjects. However, basal PP (195 ± 42 versus 200 ± 29 and 110 ± 21 versus 99 ± 18 pg/ml, respectively) and integrated postprandial plasma PP (95.7 ± 18.6 versus 83.1 ± 16.8 and 33.5 ± 10.7 versus 23.4 ± 3.0 ng · ml^{-1} · 240 min^{-1}, respectively) did not differ between s.c. insulin and AEP.

DISCUSSION

We have found twofold increases in basal and threefold in postprandial PP concentrations in lean NIDDM patients who were hyperglycemic as a result of partial insulin withdrawal compared with lean nondiabetic subjects. These elevated PP levels remained unchanged during near-normoglycemia, which was achieved by use of an artificial endocrine pancreas. In contrast, basal and postprandial PP concentrations in lean IDDM and obese NIDDM patients during both hyperglycemia and near-normoglycemia did not differ from those in nondiabetic subjects. Our findings are consistent with previous reports of greater PP responses to hypoglycemia[10] or meal ingestion[9] in lean diabetic patients with residual beta cell function. The excessive basal and postprandial PP concentrations in our lean NIDDM patients cannot be ascribed solely to residual beta cell function; the obese NIDDM patients had residual beta cell function and normal PP concentrations. Since hyperglycemia has been reported to blunt PP levels, the higher basal and peak postprandial plasma glucose concentrations of the obese NIDDM patients compared with the lean NIDDM patients may have obscured differences between the groups.[1] However, the failure of near-normoglycemia to alter basal and postprandial PP concentrations in any of the diabetic patients makes this possibility unlikely. Autonomic neuropathy, both diabetic and nondiabetic, blunts PP responses.[24,25] The following hypotheses are required to implicate autonomic neuropathy as a basis for our findings: (1) PP responses are excessive in IDDM and NIDDM patients and (2) autonomic neuropathy was present in our IDDM and obese NIDDM patients but absent in the lean NIDDM patients. This seems improbable because no clinical evidence for autonomic neuropathy was present in any of the diabetic patients. Although subclinical neuropathy may have been undetected in the IDDM patients who had longer duration of diabetes than the NIDDM patients, diabetes was of shorter and equal duration for the lean and obese NIDDM patients, respectively.

Hyperplasia of the PP-secreting cells appears to be an unlikely explanation for our findings, since the mass of PP cells of NIDDM and IDDM patients has not been found to differ from nondiabetic cases.[26]

Fasting PP levels have been reported to increase with age in nondiabetic subjects.[1,2,8,20–23] The average increment per decade from the third through the sixth decades in nondiabetic subjects has been reported to be small (approximately 25–30 pg/ml.[1,8,20,23] Age-related differences in fasting PP concentrations in diabetic patients have been reported at the extremes of age and not in the fourth, fifth, and sixth decades.[2]

Because the greater age of the lean NIDDM patients than the original control group of lean ND subjects could have contributed to the exaggerated basal and postprandial PP levels in the former, an age-matched group of lean ND subjects was studied. However, an effect of age was eliminated by the observation that excessive basal and postprandial PP concentrations were still observed in the lean NIDDM patients in contrast to the age-matched lean ND subjects.

The lack of PP postprandial change in TPX patients is consistent with the pancreas being the primary site of PP secretion.[26] The presence of normal basal concentrations of PP suggests that PP may be secreted from extrapancreatic sites or that pancreatectomy was incomplete. The latter explanation appears unlikely in view of the complete absence of postprandial responses of C-peptide and glucagon. Indeed, PP-secreting cells have been identified in the colon and rectum.[22] If an extrapancreatic site is the source for basal concentrations of PP, it appears not to be responsive to the stimulus of meal ingestion.

Some[3,4] but not all[5] investigators have reported decreased PP levels in obese subjects; the current study did not confirm this observation. The use of a fixed nutrient load by others,[3,4] rather than one based on subjects' ideal weights, may account for this discrepancy.

In summary, basal and postprandial PP concentrations were found to be normal in IDDM and obese NIDDM patients but exaggerated in lean NIDDM patients. Studies in larger numbers of patients are required to determine whether elevated PP levels are indeed a characteristic of lean NIDDM patients and whether hypersecretion or delayed clearance of PP is the mechanism for the high levels. Lack of postprandial response of PP in TPX patients is consistent with the surgical absence of the pancreas. Postprandial PP concentrations are not influenced by the state of glucose control or by obesity.

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