Diabetologia 16, 355–358 (1979)

Diabetologia

Originals

Insulin Secretion and Pancreatic Exocrine Function in Patients with Chronic Pancreatitis

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Summary. The relationship between insulin responses to oral glucose and pancreatic exocrine function were examined in 15 patients with chronic pancreatitis. Good correlations were found between the insulin responses and exocrine pancreatic function measured as the concentrations of pancreatic enzymes in duodenal juice after intravenous cholecystokinin-pancreazymin (CCK-PZ). There appears to be a roughly parallel loss of endocrine and exocrine function in the course of chronic pancreatitis.

Key words: Cholecystokinin-pancreazymin, diabetes, insulin, pancreatitis, pancreatic function tests, secretin.

The serum insulin (IRI) responses to an oral glucose load are frequently normal or marginally sub-normal in patients with chronic pancreatitis [1, 2]. In contrast, the insulin responses to intravenous glucose have been reported to be grossly subnormal by Kalk et al. [3] and relatively normal by Raptis et al. [2]. Although the glucose intolerance in pancreatitis is thought to be due to a quantitative diminution in insulin secretion caused by destruction of pancreatic beta cells [4], recent observations suggest a selective or qualitative impairment of the responses of the beta cells to glucose administration but maintenance of the insulin response to various "enterohormones" [3]. There is also some evidence that the insulin responses to oral glucose in chronic pancreatitis are dependent on the severity of exocrine pancreatic dysfunction [5, 2].

Because of the apparent lack of parallel changes in pancreatic endocrine and exocrine function several indices of pancreatic exocrine function and the insulin responses to oral glucose in patients with chronic pancreatitis were examined. We report here a good correlation between the insulin responses to oral glucose and exocrine pancreatic function, measured as the concentration of pancreatic enzymes in duodenal juice after intravenous injection of cholecystokinin-pancreozymin (CCK-PZ).

Patients and Methods

Fifteen patients with chronic pancreatitis were studied. There were 12 males and 3 females, 21–61 years old. Pancreatitis was associated with chronic alcoholism in 14 and with gallstones in one female. No patient was obese and none had family history of diabetes. At the time of testing none of the patients was receiving insulin or oral antidiabetic agents or other drugs known to affect insulin secretion.

Ten patients had the typical clinical features of recurrent pancreatitis associated with high serum amylase concentrations [6]. The diagnosis of pancreatitis was confirmed by surgery in 5 patients, by the presence of radiologically demonstrable pancreatic calcification in 4, and by the radiological demonstration of pancreatic pseudocysts in another 4 patients; one patient developed ascites with high levels of amylase-"pancreatic ascites." Eight patients had either clinically significant hepatomegaly or serum albumin concentrations below 3.5 g/dl, or both.

Pancreatic Exocrine Function

All patients had tests of pancreatic exocrine function in the interval between acute attacks [7]; after an overnight fast two nasogastric tubes were positioned-one in the stomach to remove gastric acid and one in the duodenum. Thereafter, intravenous secretin (Karolinska Institute, Sweden) (1.0IU/kg body weight) was injected. Three 20 minute aspirations of duodenal juice were collected. At 60 minutes 1.5 IU/kg body weight of CCK-PZ (Karolinska Institute) was injected intravenously and further collections of duodenal contents were made for 20 minutes. The total volume of pancreatic secretion was measured and bicarbonate, amylase, trypsin, chymotrypsin and lipase activity were estimated in each collection of pancreatic fluid. Amylase was estimated by an amyloclastic method [8]. Trypsin and chymotrypsin were measured by a spectrographic method [9] using as substrates N-benzoyl-L-arginine ethyl HCL (BAEE) and N-acetyl-L-tyrosine ethylester monohydrate (ATEE) respectively. Lipase was measured by the method of Weber [10], modified for duodenal juice.

Total volume and mean values of bicarbonate and amylase and peak concentrations of the other enzymes after the CCK-PZ injection were used in the calculations.

0012-186X/79/0016/0355/$01.00

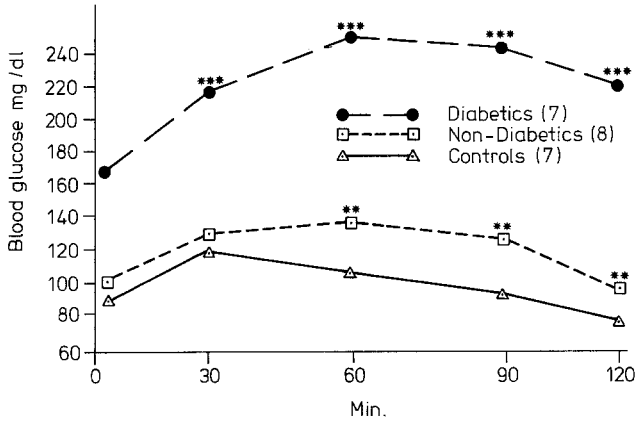

Fig. 1. Blood glucose responses to 50 g oral glucose in diabetic and non-diabetic patients with chronic pancreatitis and in controls. Fasting glucose values were significantly higher ($p < 0.05$) in diabetic patients than in controls. ** $p < 0.025$ vs controls, *** $p < 0.005$ vs non-diabetics and controls

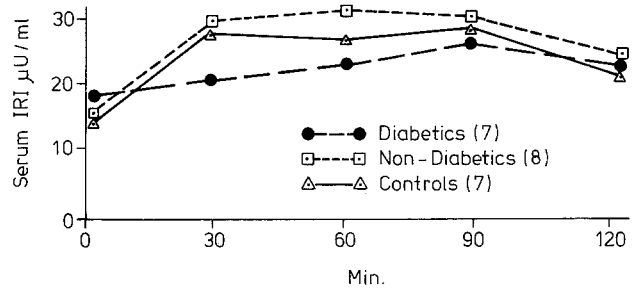

Fig. 2. Serum insulin responses to 50 g oral glucose in diabetic and non-diabetic patients with chronic pancreatitis and in controls. Mean values were not significantly different at each time

Glucose Tolerance Tests

The 15 patients and 7 controls had a 50 g oral glucose tolerance test; after a basal venous blood sample was taken, 50 g of glucose in 150 ml of water was rapidly ingested and further blood taken at 30, 60, 90 and 120 minutes.

Blood glucose was measured by a ferricyanide method [11] using a Technicon autoanalyser, and serum insulin (IRI) by the method of Hales and Randle [12]. Insulin secretion was computed as the incremental (above basal level) area under the curve. Student's t-test and linear regression analysis were used in the statistical assessments.

Results

All but one patient had a reduction of at least one of the indices of exocrine pancreatic function measured (Table 1); the patient with normal exocrine pancreatic functions had radiologically evident pancreatic calcification.

Seven patients were diabetic by the criteria of Jackson and Vinik [13]; the remaining 8 patients and all controls had normal glucose tolerance, although at 60, 90 and 120 minutes mean glucose levels were lower in the controls (Fig. 1). Five diabetic and three non-diabetic patients had evidence of abnormal liver function (Table 1).

Mean fasting serum IRI levels were similar in diabetic and non-diabetic patients and controls. IRI responses to the oral glucose load were extremely variable: the IRI areas ranged from zero to well within the range of the controls (Table 1). The mean insulin area of the diabetics was significantly lower than that of the non-diabetics ($p < 0.05$) and controls ($p < 0.025$) (Fig. 2). However, in both the diabetic and non-diabetic groups there were patients with either normal or grossly reduced IRI responses.

Mean values of pancreatic juice amylase, chymotrypsin and lipase after CCK-PZ stimulation were lower in the diabetic than in non-diabetic patients (Table 1). Furthermore, levels of these pancreatic enzymes correlated significantly with the IRI responses to the oral glucose (Table 2) and a similar trend was seen with trypsin ($p < 0.05$).

Discussion

Patients with chronic pancreatitis usually have marked pancreatic exocrine insufficiency and may or may not have qualitative or quantitative abnormalities in endocrine pancreatic function [4, 6, 7, 14]. It is however unclear as to whether there is a simultaneous or parallel decline in these functions or if the hormonal function is dependent upon intact exocrine secretions, or vice versa. In this study all patients had normal or high fasting IRI concentrations. The high basal IRI levels were seen especially in the diabetic patients, and may have been associated with significant liver disease in some [15]. All but one patient had an increase in serum IRI concentration in response to a 50 g oral glucose load and every patient was capable of secreting bicarbonate and digestive enzymes in response to secretin and CCK-PZ, known stimulants of the exocrine pancreas. Both the mean IRI response to oral glucose and the digestive enzyme responses to CCK-PZ were significantly reduced in diabetic patients compared to non-diabetics, suggesting that endocrine and exocrine functions are lost together. However, glucose intolerance was not a function of insulinopenia alone, since there was considerable overlap in both pancreatic enzyme and IRI responses in diabetic and non-diabetic patients – as there is when using other stimuli of the endocrine pancreas in patients with chronic pancreatitis [16].

Both the endocrine and exocrine pancreas in our patients were capable of responding to known physiological stimuli, given in somewhat pharmacological amounts. Since oral glucose stimulates IRI secretion partially via gut hormones [17], the inference is that both the pancreatic beta cells and the acinar tissue retained some capacity to respond to hormones released from the gastrointestinal tract, even in the presence of chronic pancreatic destruction. The basic physiological enterohormone mechanisms for both

Table 1. Fasting glucose, and IRI, and integrated IRI areas after oral glucose, and pancreatic exocrine function tests in diabetic and non-diabetic patients with chronic pancreatitis

Subjects	Fasting glucose (mg/dl)	Fasting IRI μU/ml	Incremental IRI response μU/min.	Volume (ml) N >120	HCO_3 (mEq/ml) N >60	Amylase iμ/ml N >5	Trypsin (BAEE μ/ml) N >2000	Chymotrypsin (ATEE μ/ml) N >1000	Lipase (μ/ml) N >300
I. Diabetics									
1[a]	300	24	0	219	50	3.4	1675	817	–
2	250	8	240	66	31	2.8	1042	675	198
3[a]	147	18	495	145	59	4.9	2459	1000	375
4[a]	125	25	705	120	32	1.3	300	142	63
5[a]	82	9	810	247	38	3.4	2042	1575	297
6	105	13	1342	159	35	2.4	2375	792	459
7[a]	139	35	1575	139	50	1.4	5415	875	209
Mean ± SEM	164±30	19±4	738±214	156.4±24.8	42.1±4.4	2.8±0.5	2186±611	839±161	267±58
II. Non-diabetics									
8[a]	112	13.5	622	182	51	3.2	2583	1167	495
9	87	13	660	191	45	5.4	1937	1292	–
10[a]	98	12	1065	121	65	4.7	3417	1200	318
11	93	31	1335	226	99	4.1	2217	1634	218
12	80	15.5	2032	103	38	6.1	4333	2300	881
13	93	12	2532	164	46	3.2	1175	600	229
14	106	14	2640	129	88	10.5	3367	3333	1177
15[a]	85	16	4095	112	34	10.6	3233	2233	1120
Mean ± SEM	94±3.4	16±2	1873±422	153.5±16.6	58.3±9.0	6.0±1.1	2783±354	1720±305	643±158
III. Controls	90±2	15±2	1790±327	–	–	–	–	–	–
Significance I vs. II	$p < 0.05$	NS	$p < 0.05$	NS	NS	$p < 0.025$	NS	$p < 0.05$	$p < 0.05$
Significance I vs. III	$p < 0.05$	NS	$p < 0.025$						

[a] Abnormal liver function

There were no significant differences between groups II and III

Table 2. Correlation coefficients (r), of integrated responses to oral glucose and pancreatic exocrine responses to I. V. secretin and CCK-PZ in 15 patients with chronic pancreatitis

	Volume (ml)	HCO_3 (mEq/l)	Amylase (iμ/ml)	Trypsin (BAEE μ/ml)	Chymotrypsin (ATEE μ/ml)	Lipase (μ/ml)
Correlation coeff. (r)	−0.0288	0.070	0.690	0.398	0.587	0.722
Significance	NS	NS	$p < 0.0025$	$p < 0.05$	$p < 0.0125$	$p < 0.0025$

appear to remain relatively intact, although IRI responses to intravenous glucose alone may be lost [3]. Thus the finding of correlations between the incremental IRI areas after oral glucose and 3 of the 4 enzymes secreted after CCK-PZ stimulation was not unexpected. These correlations support the contention that there may be more or less parallel destruction of islet and acinar tissue in the course of pancreatitis. The ability of the remaining beta cells to secrete insulin in response to oral glucose was clearly retained in nearly all patients despite destruction of the exocrine pancreas, as evidenced by very low bicarbonate and enzyme concentrations in duodenal juice. The finding that some patients had "normal" insulin responses to oral glucose despite severely reduced exocrine pancreatic function is contrary to the hypothesis that beta cell function is dependent on the integrity of the exocrine tissue [2, 5, 18].

In conclusion we have demonstrated correlations between the IRI responses to oral glucose on the one hand, and pancreatic secretion of enzymes in response to intravenous CCK-PZ on the other. We suggest that the significant correlations reflect roughly parallel loss of function of islets and pancreatic acini in the course of pancreatitis. The few patients who did not follow this rule had poor enzyme responses but good insulin release, indicating that endocrine function does not depend upon exocrine integrity. Furthermore, in chronic pancreatitis it appears that the relative retention of the insulin response to oral glucose largely depends on the stimulatory effects of gastrointestinal hormones.

Acknowledgement. This study was supported by a grant from the South African Medical Research Council and we wish to thank the Gastrointesinal Clinic, Groote Schuur Hospital, for permission to study patients under their care and for carrying out the pancreatic function tests.

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Received: February 27, 1978,
and in revised form: September 4, 1978

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