Pancreatic hypofunction in extrahepatic portal venous obstruction

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SUMMARY Pancreatic function was studied in 29 patients with extrahepatic portal venous obstruction, and 30 age-matched controls. The aetiology of the portal venous obstruction was known in 20 out of 29 patients. No patient had a history of pancreatitis. Serum trypsin, both fasting and for 120 minutes after a Lundh meal, was significantly lower in the patients than in controls ($P < 0.005$). 5/28 (18%) patients had reduced fasting serum trypsin levels and in 5/14 trypsin was abnormal after a Lundh meal. Mean fasting serum glucose (3.8 ± 0.49 mmol/l) was significantly higher than in control subjects (mean 3.4 ± 0.42 mmol/l) ($P < 0.05$). After 100 g glucose orally, mean serum glucose at 180 minutes (5.26 ± 1.58 mmol/l) was higher than the control value (3.96 ± 1.45 mmol/l) ($P < 0.05$), and 30 and 60 minutes serum C-peptide values were significantly lower ($P < 0.005$). Pancreatic hypofunction found in these patients probably results from an abnormal portal circulation in association with mild pancreatic damage secondary to chronic venous congestion.

Patients with obstruction to the main portal vein, but with normal liver structure, have venous congestion throughout the splanchnic area. The major clinical effect is the development of a portal systemic collateral circulation with subsequent bleeding, usually from oesophageal varices. Deprivation of portal blood flow to the liver leads to mild hepatic dysfunction which progresses as age advances.¹ The effect of portal venous obstruction on pancreatic function, both exocrine and endocrine, has not been studied in man. We have therefore investigated pancreatic exocrine function by serum trypsin measurements both fasting and after a Lundh test meal, and endocrine function by the plasma glucose, insulin, and C-peptide levels. The effect of portal-systemic bypassing on pancreatic endocrine and exocrine secretions has also been considered.

Results in 29 patients with extrahepatic portal venous obstruction have been compared with those in 30 age-matched control subjects.

Methods

Twenty-nine patients aged from 16 to 63 years and 30 age matched control subjects were studied. The aetiology of the portal vein obstruction was known in 20 out of the 29 patients (Table). Liver biopsy

in all patients showed normal hepatic architecture and blood urea and creatinine levels were normal in all patients and controls. No patient had a history of diabetes or steatorrhoea and only one suffered from abdominal pain. The diagnosis of extrahepatic portal venous obstruction was confirmed by portal venography. The controls were volunteers, medical or laboratory staff, or hospital inpatients with no history of gastrointestinal or endocrine disease.

Fifteen patients and 18 controls, after an overnight fast, received a Lundh test meal.² Venous blood was drawn for analysis of trypsin levels at 0, 30, 60, 90, and 120 minutes after ingestion of the meal. The serum trypsin was measured by radioimmunoassay (Hoechst RIA—gnost trypsin, Behringwerke, Marburg). In 13 additional patients the fasting trypsin level was measured. Nineteen patients and 12 controls, with no previous history of gastric surgery or endocrine disease, after 24 hours bed rest in hospital and an overnight fast received 100 g glucose orally. Venous blood was taken for glucose, C-peptide and insulin estimations before and 30, 60, 90, 150, and 180 minutes after glucose ingestion. Plasma insulin and C-peptide levels were measured by radioimmunoassay.^{3,4}

In 22 patients the pancreas was scanned by grey-scale ultrasonography.

Twenty-six of the 28 patients' weights fell within 10% ideal body weight, including the 19 patients

Table Results of pancreatic function in patients with extrahepatic portal venous obstruction

	Age (yr)	Aetiology	Fasting trypsin ($\mu\text{g/l}$)	Trypsin (Lundh)	Amylase (Lundh)	Glucose tolerance test	
1	22	Unknown	78	L	L	D*	D†
2	49	PRV	70	L	H	—	—
3	49	Unknown	160	L	H	—	—
4	23	Umbilical sepsis	91	L	N	—	—
5	30	Unknown	189	L	N	—	—
6	49	Cholelithiasis	—	—	—	D*	—
7	21	Umbilical sepsis	182	N	H	—	—
8	63	TPM	283	N	N	—	—
9	19	Unknown	205	N	N	N	—
10	22	Umbilical sepsis	290	N	N	N	—
11	25	Umbilical sepsis	205	N	N	D*	—
12	18	Unknown	212	N	N	—	—
13	21	Umbilical sepsis	162	N	N	N	—
14	46	Unknown	398	N	N	N	—
15	23	Neonatal septicaemia	194	N	N	—	—
16	49	Unknown	350	N	N	—	—
17	29	Umbilical sepsis	120	—	—	N	—
18	31	Umbilical sepsis	123	—	—	N	—
19	31	Appendicitis	129	—	—	N	—
20	20	Liver abscess	137	—	—	N	—
21	38	Appendicitis	235	—	—	D*	D†
22	60	CBD fibrosis	183	—	—	D*	—
23	52	Abdominal trauma	220	—	—	D*	—
24	16	Unknown	180	—	—	D*	D†
25	25	Appendicitis	195	—	—	D*	—
26	20	Choledochal cyst	150	—	—	N	—
27	16	Exchange transfusion	200	—	—	N	—
28	25	Cholelithiasis	215	—	—	N	—
29	22	Unknown	245	—	—	N	—

PRV: polycythaemia rubra vera. CBD: common bile duct. TPM: thrombophlebitis migrans. L: value 2 standard deviations below control mean. M: value 2 standard deviations above control mean. N: normal. D*: diabetic glucose tolerance test (Joslin Clinic criteria⁵). D†: diabetic glucose tolerance test (American Diabetic Association criteria⁶).

who had an oral glucose tolerance test.

Values given in the text are mean $\pm$ S.D.

Results were analysed by Student's test for unpaired data.

Results (Table)

The mean fasting serum trypsin for the patients ($196 \pm 76 \mu\text{g/l}$) was significantly lower than for controls ($269 \pm 71.4 \mu\text{g/l}$) ($P < 0.005$, Fig. 1) and this difference was maintained after a Lundh meal (Fig. 1). Five of the 28 patients (18%) had a fasting trypsin below the normal range. After a Lundh meal

the serum trypsin fell in the patient group and rose in the control group (Fig. 1). Five of the 14 patients had reduced trypsin levels (Fig. 2). The mean fasting serum glucose for the patients ($3.8 \pm 0.42 \text{ mmol/l}$) was significantly greater than the control mean ($3.41 \pm 0.42 \text{ mmol/l}$, $P < 0.05$, Fig. 3). After 100 g of glucose orally, the mean serum glucose for the two groups did not differ till 180 minutes when the patient mean was 5.26 ± 1.58 and the control mean was $3.96 \pm 1.45 \text{ mmol/l}$ ($P < 0.05$). Eight patients and two controls were diabetics according to the Joslin clinical criteria⁵ of a blood glucose greater than 8.89 mmol/l after 100 g oral glucose. Only three patients

Fig. 1 Serum trypsin concentrations after a Lundh meal in extrahepatic portal venous obstruction and control subjects. Values are mean $\pm$ SEM (fasting: $P < 0.05$; 30 minutes: $P < 0.005$; 60 minutes: $P < 0.025$).

Fig. 2 Serum trypsin concentration after a Lundh meal in patients with extrahepatic portal venous obstruction. Vertical bars represent control mean $\pm$ 2SD. A normal range was not established for the 90 minute value.

Fig. 3 Blood glucose after 100 g oral glucose in extrahepatic portal venous obstruction and in control subjects. Values are mean $\pm$ SEM.

Fig. 4 C-peptide response after 100 g oral glucose in extrahepatic portal venous obstruction and control subjects. Values are mean $\pm$ SEM (30 minutes: $P < 0.001$; 60 minutes: $P < 0.005$).

and one control were diabetic if the American Diabetic Association⁶ rules of a blood glucose greater than 8.89 mmol/l at one hour and 7.77 mmol/l at two hours after 100 g oral glucose were applied. The mean fasting C-peptide for the patients and the controls was the same, whereas at 30 and 60 minutes after the oral glucose the patients' values were lower ($P < 0.001$, $P < 0.005$, Fig. 4).

Grey-scale ultrasonography of the pancreas was normal in 21 patients. One patient (No. 23, Table) who was diabetic according to Joslin Clinical Criteria had an ultrasound scan suggestive of chronic pancreatitis. The fasting serum trypsin was normal in this patient.

Discussion

Serum trypsin is a useful screening test for pancreatic disease.⁷⁻⁹ If levels are subnormal then chronic pancreatitis or carcinoma of the pancreas is usually present.⁷ However, patients with chronic pancreatitis can have a normal serum trypsin.⁷⁻⁹ The low results found in five of our patients suggest pancreatic dysfunction. An enteropancreatic circulation for trypsin was originally demonstrated in rabbits^{10,11} and probably exists in man as large amounts of trypsin are found in portal blood.¹² If this is so, then interruption of the portal circulation could affect the serum trypsin value. This might explain the low fasting levels in our patients. The same mechanism

might also be expected to influence serum trypsin levels after pancreatic stimulation. However, pancreatic hyposecretion would also explain the fall in serum trypsin which occurred in the patients after a meal, compared with the small rise in controls. Pro-insulin is cleaved in the pancreatic B-cell to insulin and C-peptide, which are released into the circulation in equimolar quantities.¹³ C-peptide is not degraded by the liver and peripheral levels are a good reflection of pancreatic insulin secretion. The low values in our patients suggest that pancreatic insulin secretion is reduced. Peripheral insulin levels were also lower than control values, although the difference was not significant. Ligation of pancreatic venous drainage in dogs results in pancreatitis.¹⁴ Abnormalities in pancreatic pathology including hyperaemia, fibrosis and fat necrosis have been described after portal vein obstruction in man.¹⁵ Mass. Gen. Hosp. Case No. 38272 (1952). This results from chronic pancreatic venous congestion.¹⁶

In addition, the obstruction in the main portal vein may extend into the intrapancreatic veins and so lead to minor degrees of fibrosis and pancreatic dysfunction. The abdominal pain associated with extrahepatic portal venous obstruction could be explained in this way.¹⁷ Chronic pancreatitis can cause portal vein obstruction.¹⁸ However, this is an unlikely cause as 20/29 patients had a known alternative aetiology for their portal venous obstruction. In the remaining nine, the clinical features did not support the diagnosis of primary chronic pancreatitis.

Invasive pancreatic investigations were not considered to be justified in symptom-free volunteer patients and endoscopic pancreatography was not performed. Similarly, duodenal intubation with measurement of trypsin output was not performed, as many of the patients had documented oesophageal varices. Duodenal intubation is an insensitive test of pancreatic function and will not detect pancreatic hypofunction of minimal degree. Furthermore, in minimal pancreatic disease, pancreatic secretion is increased.¹⁹ Normal grey-scale ultrasonography excluded gross pancreatic pathology.

Thus the changes observed in these patients could be the result of the abnormal portal circulation or mild pancreatic damage secondary to chronic venous congestion. An intact portal circulation is necessary for glucose homeostasis in both man²⁰ and animals²¹ and may also be necessary for trypsin homeostasis.

Over 75% of the pancreas needs to be destroyed²² and pancreatic lipase output to fall below 10% of normal¹⁹ for clinical pancreatic insufficiency to develop, and it is not surprising that our patients showed none of the usual features of chronic pan-

creatitis. However, minimal pancreatic dysfunction has been demonstrated. Patients with extrahepatic portal venous obstruction who suffer from severe abdominal pain, steatorrhoea, or failure to thrive should have their pancreatic function fully investigated.

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