Basal and postprandial serum concentrations of pancreatic polypeptide in pancreatitis and after pancreaticoduodenectomy

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Summary
Basal and postprandial serum concentrations of pancreatic polypeptide (PP) were measured in 22 normal subjects, in 6 patients with a history of acute pancreatitis, in 21 patients with chronic pancreatitis and in 6 patients with previous pancreaticoduodenectomy. Eighteen of the 21 with chronic pancreatitis and all 6 with pancreaticoduodenectomy had abnormally low serum PP-responses to the standard test meal, while all patients with a history of acute pancreatitis had normal postprandial increases in serum PP. The impaired serum PP-responses to food in patients with chronic pancreatitis were not related to the aetiology of pancreatitis, to glucose tolerance, to exocrine pancreatic function (absorption of fat) or to pancreatic calcifications. It is concluded that impaired postprandial serum PP responses in patients with pancreatitis indicate damage to the pancreas.

Introduction
Pancreatic polypeptide (PP) is a 36 amino acid polypeptide hormone with a molecular weight of 4200. This peptide was originally isolated as a by-product of the purification of insulin from the pancreas (Chance and Jones, 1974; Kimmel, Pollock and Hazelwood, 1968). In man, PP is confined almost totally to the pancreas (Adrian et al., 1976). PP-containing cells have been found by immunohistochemical techniques to be distributed throughout the pancreas; they are present at the islet periphery, in the exocrine parenchyma, and in the epithelium of small and medium-sized ducts (Larsson, Sundler and Hakanson, 1976). PP is released into the circulation after ingestion of food (Adrian et al., 1976, 1977; Diemel and Lamers, 1980; Floyd et al., 1977; Lamers, Diemel and Roefen, 1978). Its secretion is thought largely to be due to vagal cholinergic stimulation (Schwartz et al., 1976, 1978) and, in part, to stimulation by gastrointestinal hormones (Adrian et al., 1977; Lonovics et al., 1980) or by food products (Taylor et al., 1980).

It is conceivable that the secretion of PP after feeding reflects the number of functional PP cells present in the pancreas. Impaired PP release after feeding might, therefore, be a manifestation of destruction of the pancreas.

In the present study the authors measured basal and postprandial serum PP concentrations in patients with a history of acute pancreatitis, in patients with chronic pancreatitis, in patients with previous pancreaticoduodenectomy and in normal control subjects.

Patients and methods
Basal and postprandial serum concentrations of PP were measured in 6 patients with a history of acute pancreatitis (3 male), mean age 40 years with a range of 17–56 years; in 21 patients with chronic pancreatitis (16 male), mean age 41 years, range 16–73 years; in 6 patients with pancreaticoduodenectomy (4 male), mean age 52 years, range 33–71 years; and in 22 normal subjects (12 male), mean age 45 years, range 26–73 years. The diagnosis of acute pancreatitis was based upon clinical symptoms and raised circulating and urinary amylase concentrations and was confirmed at surgery in the single patient operated upon. None of these patients had a clearly abnormal pancreaticography or symptoms of pancreatic insufficiency or glucose intolerance. Chronic pancreatitis was diagnosed at surgery in 8 patients and by pancreaticography in 7 patients. All remaining 6 patients had malabsorption of fat (fat absorption coefficient between 45 and 82%) responding to oral replacement therapy with pancreatic enzymes. Of these 6, 2 had cystic fibrosis, one had pancreatic calcifications, and 3 had impaired glucose tolerance tests. The aetiology of chronic pancreatitis was alcoholic in 12 patients, cystic fibrosis in 2, familial in 2, and unknown in 5 patients. Glucose tolerance tests were normal in 8, impaired in 7 and diabetic in 6 of the patients with chronic pancreatitis. Sixteen patients with chronic pancreatitis were treated by enzyme replacement (fat absorption 45–82%), while 5 patients had no enzyme replacement therapy (fat absorption 91–98%). Four
of the 21 patients with chronic pancreatitis were studied after pancreaticoduodenectomy. The patients studied after pancreaticoduodenectomy (Whipple procedure) were operated upon because of pancreatic carcinoma in 3, carcinoma of the papilla of Vater in one and chronic pancreatitis in 2. Five of the 6 patients with pancreaticoduodenectomy had diabetes mellitus.

After an overnight fast, the patients ingested a standard test meal consisting of one slice of bread, 50 g cheese, one boiled egg and 200 ml milk, corresponding to 30 g protein, 25 g carbohydrate and 20 g fat. Serum samples for measurement of PP were drawn before and 15, 30, 45, 60, 90 and 120 min after feeding. Serum PP was measured by radioimmunoassay as described by Lamers et al. (1978).

Results are expressed as mean ± s.e. mean. Statistical analysis was performed using Student's t-test for paired and unpaired data.

Results

Fasting serum PP concentrations in 22 normal subjects, in 6 patients with a history of acute pancreatitis, in 21 patients with chronic pancreatitis and in 6 patients with previous pancreaticoduodenectomy are shown in Fig. 1. Basal serum PP (30.8±4.1 pmol/l) were not significantly different from normal. The 6 patients with pancreatoduodenectomy had a tendency to lower serum PP concentrations (24.3±1.9 pmol/l) when compared with the group of normal subjects (P = 0.10). Fasting serum PP concentrations in the 4 groups of patients studied showed considerable overlap (Fig. 1).

Ingestion of the standard test meal induced significant increases in serum PP concentrations in normal subjects (P < 0.0001) and in patients with a history of acute pancreatitis (P < 0.005). Patients with chronic pancreatitis had slight but significant (P < 0.005) serum PP responses to feeding, while serum PP concentrations in patients with pancreaticoduodenectomy were not influenced by feeding.

![Fig. 2. The effect of ingestion of a standard test meal on serum concentrations of pancreatic polypeptide (PP) in 22 normal subjects (●●●), in 6 patients with a history of acute pancreatitis (○○○), in 6 patients with chronic pancreatitis (△△△), and in 6 patients with pancreaticoduodenectomy (A—A). Asterisks indicate significant (P < 0.05—P < 0.0005) differences from normal.](http://pmj.bmj.com/PostgradMedJ/files/10.1136/pgmj.57.672.617)

(24.3 ± 1.9 pmol/l) after 15 minutes, while the normal controls had a peak of 60.8 ± 4.7 pmol/l after 60 minutes. The mean peak serum PP concentration in the 6 patients with chronic pancreatitis was 25.7 ± 3.5 pmol/l, which was significantly lower than in the normal control group (Fig. 2).

**Fig. 1.** Basal serum concentrations of pancreatic polypeptide (PP) in 22 normal subjects, 6 patients with a history of acute pancreatitis, 21 patients with chronic pancreatitis, and 6 patients with pancreaticoduodenectomy (Whipple’s procedure). Unfilled circles indicate patients with chronic pancreatitis and pancreaticojejunostomy.

Concentrations in 21 patients with chronic pancreatitis (23.2 ± 1.7 pmol/l) were significantly lower (P < 0.005) than the PP levels in 22 normal subjects (39.6 ± 4.8 pmol/l). Fasting serum PP concentrations in 6 patients with a history of acute pancreatitis (25.7 ± 3.5 pmol/l) were significantly lower than in the normal control group (Fig. 2). All postprandial serum PP concentrations in patients with chronic pancreatitis or with pancreaticoduodenectomy were significantly (P < 0.0005) lower than in the normal control group. Peak serum PP increments to feeding in patients with a history of acute pancreatitis (103 ± 30 pmol/l) were not significantly different from the normal controls (132 ± 19 pmol/l; Fig. 3). The peak serum PP response to feeding in patients with chronic pancreatitis (15.4 ± 3.5 pmol/l) was significantly lower than in the normal control group.
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(P < 0.0001) reduced when compared with normal control subjects (Fig. 3). In 18 of 21 patients with chronic pancreatitis, the peak serum PP response to food was below the lowest response in the control subjects (Fig. 3). Peak serum PP increments in patients with a history of acute pancreatitis overlapped completely with the results obtained in the normal subjects (Fig. 3). None of the 6 subjects studied after pancreaticoduodenectomy showed postprandial increases in serum PP concentrations (Fig. 3).

![Graph](image)

Fig. 3. Peak serum PP increments to a standard test meal in 22 normal subjects; in 6 patients with a history of acute pancreatitis; in 21 patients with chronic pancreatitis; and in 6 patients with pancreaticoduodenectomy. Unfilled circles indicate patients with chronic pancreatitis and pancreaticojejunostomy.

In the group of patients with chronic pancreatitis there were no significant differences in basal or postprandial serum PP concentrations between patients with and without previous pancreaticojejunostomy (Figs 1 and 3). The impaired serum PP responses to food in patients with chronic pancreatitis were not related to the aetiology of pancreatitis, to glucose tolerance, to exocrine pancreatic function (absorption of fat) or to pancreatic calcifications (Table 1).

Discussion

This study showed that both basal and postprandial serum PP concentrations in patients with chronic pancreatitis were significantly lower than in normal control subjects. However, only 4 of 21 patients with chronic pancreatitis had basal serum PP concentrations below the lowest level in 22 normal control subjects. This indicates that the sensitivity of measurement of basal serum PP concentrations in the diagnosis of chronic pancreatitis was very low (19%). In contrast, 18 of 21 (86%) patients with chronic pancreatitis had postprandial increases in serum PP below the lowest response in 22 control subjects. These results are in agreement with those of Adrian et al. (1979b) and Valenzuela, Taylor and Walsh (1979) who also showed that measurement of postprandial serum PP concentrations is more helpful in the separation of patients with chronic pancreatitis and normal subjects than determination of basal serum PP concentrations. Andersen et al. (1980), however, found that estimation of basal PP was as efficient as postprandial PP in distinguishing between patients with chronic pancreatitis and control subjects. The sensitivity of determination of the serum PP response to feeding in the diagnosis of chronic pancreatitis in the study of Andersen et al. (1980) was 71% for severe chronic pancreatitis, 25% for moderate chronic pancreatitis and 0% for mild chronic pancreatitis. Valenzuela et al. (1979) found that 76% of patients with chronic pancreatitis had serum PP concentrations above the normal range. Adrian et al. (1979b) reported abnormally low postprandial serum PP concentrations in 90% of patients with chronic pancreatitis and steatorrhoea, while postprandial serum PP levels were normal in patients with chronic pancreatitis without overt pancreatic insufficiency. The relatively high sensitivity of measurement of postprandial serum PP responses in the diagnosis of chronic pancreatitis in the present study (86%) can probably be attributed to the investigation of a large proportion of patients with chronic pancreatitis and severe exocrine insufficiency. It might be argued whether or not the 3

<table>
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<th>Group</th>
<th>Serum PP (pmol/l)</th>
<th>Basal</th>
<th>Incremental</th>
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<tr>
<td>Alcoholic pancreatitis (n=12)</td>
<td>22.7 ± 2.3</td>
<td>13.6</td>
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<td>Non-alcoholic pancreatitis (n=9)</td>
<td>24.1 ± 3.1</td>
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<td>3.7</td>
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<td>Subclinical diabetes mellitus (n=7)</td>
<td>23.0 ± 3.2</td>
<td>15.3</td>
<td>5.7</td>
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<td>Normal glucose tolerance test (n=8)</td>
<td>23.4 ± 3.0</td>
<td>17.2</td>
<td>6.4</td>
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<td>Enzyme replacement (n=16)</td>
<td>23.3 ± 2.1</td>
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<td>3.9</td>
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<tr>
<td>(fat absorption 45-82%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No enzyme replacement (n=5)</td>
<td>25.4 ± 2.0</td>
<td>15.2</td>
<td>5.3</td>
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<tr>
<td>(fat absorption 91-98%)</td>
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<tr>
<td>Pancreatic calcifications (n=11)</td>
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<td>10.6</td>
<td>2.4</td>
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<tr>
<td>No pancreatic calcifications (n=10)</td>
<td>25.2 ± 2.7</td>
<td>19.7</td>
<td>5.9</td>
</tr>
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</table>

responses to feeding below the normal range.
patients with chronic pancreatitis and normal postprandial serum PP concentrations had severe destruction of the pancreas. Unfortunately, none of these 3 patients was operated upon and pancreaticography was performed in only one of them showing slight abnormalities of the pancreatic duct. None of the 3 patients had pancreatic calcifications or diabetes mellitus. The diagnosis in these 3 patients was based upon malabsorption of fat (45–78%) with a favourable clinical response to replacement therapy with pancreatic enzymes. It might be possible that localized pancreatitis of the pancreatic head has led to a stricture of the pancreatic duct resulting in exocrine pancreatic insufficiency without gross destruction of the pancreas.

It has been assumed that impaired postprandial serum PP responses in patients with chronic pancreatitis indicate damage to the pancreas (Adrian et al., 1979b). Surprisingly, the number of PP cells in chronic pancreatitis was not found to be decreased but, on the contrary, hyperplasia of PP cells was reported (Klöppel et al., 1978). If this finding is confirmed in future studies, it has to be assumed that chronic pancreatitis affects either the responsiveness of PP cells to stimuli, possibly by damage to nerves, or the secretory function of the PP cells. Since PP cells are present both in the pancreatic islets and in the exocrine parenchyma (Larsson et al., 1976), determination of serum PP concentrations will give information different from that obtained by a glucose tolerance test or by exocrine pancreatic function tests. In this study there was no relation between abnormally low postprandial serum PP responses and glucose intolerance or malabsorption of fat. Six of 8 patients with normal glucose tolerance tests and all 5 patients without overt exocrine pancreatic insufficiency had abnormally low serum PP responses to the test meal. Similarly, both Valenzuela et al. (1979) and Andersen et al. (1980) were unable to show significant correlations between an impaired serum PP release after the meal and glucose intolerance in patients with chronic pancreatitis. Furthermore, Valenzuela et al. did not find a correlation between the serum PP increment in response to food and the exocrine pancreatic function, while Andersen et al. found only a very weak correlation. Impaired PP release from the pancreas in chronic pancreatitis has not only been reported after feeding, but also in response to other stimuli, such as secretin (Adrian et al., 1979b; Glaser et al., 1980; Stern, Hansky and Korman, 1980) or insulin hypoglycaemia (Sive et al., 1978).

Basal and postprandial serum PP concentrations in patients with a history of acute pancreatitis were not different from normal, probably indicating the absence of destruction of pancreatic tissue. Valenzuela et al. (1979) found that 3 of 11 patients with recurrent pancreatitis had abnormally low serum PP responses to food, while Sive et al. (1980) observed normal basal serum PP concentrations in the active phase of acute pancreatitis. As the PP response to a standard test meal is consistent from day to day in any one individual, monitoring of this PP response to a standard meal over time may give a measure of the rate of pancreatic destruction in an individual patient (Valenzuela et al., 1979).

Patients with previous pancreaticoduodenectomy did not show any serum PP response to feeding. This may be due to the small number of PP cells present in the pancreatic tail (Orci et al., 1978) or to impaired vagal innervation of the remaining pancreas. It has been shown that a background of vagal activity is needed for stimulation of PP release from the pancreas (Adrian, Besterman and Bloom, 1979b; Modlin, Lamers and Jaffe, 1980). Accordingly, impaired PP release from the pancreas has been observed in patients with truncal vagotomy (Schwartz et al., 1976) or diabetic autonomic neuropathy (Levitt et al., 1980).

Infusion of physiological amounts of PP in man inhibits exocrine pancreatic function and gastric bladder contraction (Greenberg et al., 1979). It seems, however, unlikely that the impaired PP release in patients with chronic pancreatitis or in patients with previous pancreaticoduodenectomy will have important metabolic consequences.

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