International Journal of Pancreatology, vol. 20, no. 3, 169–175, December 1996

0169-4197/96/20:169–175/$6.75

Correlation Between Pancreatic Endocrine and Exocrine Function and Characteristics of Pancreatic Endocrine Function in Patients with Diabetes Mellitus Owing to Chronic Pancreatitis

Teruo Nakamura, Ken-ichi Imamura, Kazuo Takebe, Akinori Terada, Yuki Arai, Yusuke Tandoh, Naoko Yamada, Masataka Ishii, Koji Machida, and Toshihiro Suda*

Third Department of Internal Medicine, Hirosaki University School of Medicine, Hirosaki-shi, Aomori, Japan

Summary

Conclusion. Pancreatic endocrine capacities are remarkably disturbed in patients with pancreatic diabetes owing to calcific pancreatitis as opposed to those owing to noncalcific pancreatitis. Insulin secretion in calcific pancreatitis resembled that in insulin-dependent diabetes mellitus (IDDM), whereas insulin secretion in noncalcific pancreatitis resembled that in non-IDDM (NIDDM). The involvements of acinar cell and ductal cell function closely correlate with endocrine function (insulin and glucagon secretions) in chronic pancreatitis (pancreatic diabetes).

Background. We sought to clarify the differences of pancreatic endocrine function between pancreatic diabetes and primary diabetes, and to verify the correlations between pancreatic exocrine and endocrine dysfunction in patients with chronic pancreatitis.

Methods. Urinary C-peptide (CPR) excretion and fasting plasma glucagon levels in patients with pancreatic diabetes owing to calcific pancreatitis (19 cases) and owing to noncalcific pancreatitis (14 cases) were studied in comparison with those in patients with insulin-dependent diabetes mellitus (IDDM, 23 cases), noninsulin-dependent diabetes (NIDDM, 18 cases), and in healthy controls (11 cases). In addition, pancreatic exocrine function was investigated in patients with chronic pancreatitis (calcific and noncalcific) and in healthy controls. The correlation between pancreatic exocrine and endocrine function was studied.

Results. The urinary CPR excetion in controls was 94.9 ± 20.5 μg/d. The urinary CPR excretion in calcific pancreatitis was 12.8 ± 7.4 μg/d and it resembled that in IDDM (9. 4 ± 5.8 μg/d). The urinary CPR excretion in noncalcific pancreatitis was 41.5 ± 30.1 μg/d, being similar to that in NIDDM (49.3 ± 21.0 μg/d).

The plasma glucagon level in calcific pancreatitis was 64.1 ± 15.9 ρg/mL, which was significantly lower than the values in IDDM (111.2 ± 50.2 ρg/mL) and NIDDM (96.7 ± 21.9 ρg/mL). The plasma glucagon level in calcific and noncalcific pancreratitis (88.4 ± 29.6 ρg/mL) were significantly lower than that in controls (129.8 ± 21.6 ρg/mL).

The residual capacities of acinar cells and ductal cells were strongly correlated with urinary CPR excretion and plasma glucagon concentration.

Key Words: Chronic pancreatitis (calcific, noncalcific); β-cell and α-cell function; pancreatic diabetes; pancreatic exocrine and endocrine function.

Received February 15, 1996; Revised August 26, 1996; Accepted August 28, 1996.

*Author to whom all correspondence and reprint requests should be addressed: Third Department of Internal Medicine, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki-shi, Aomori, 036, Japan.

Introduction

It has been pointed out that metabolic characteristics in secondary diabetes, or pancreatic diabetes due to chronic pancreatitis, differ from those in primary

Table 1
Clinical Features in Patients with Pancreatic Diabetes

Type of diabetes	Age, yr	Alcoholic, cases	Duration of DM, yr	Insulin, U/d	BMI, kg/m^2	HbA$_1$/ A$_1$C, %
Calcific pancreatitis (n = 19)	50.1±8.7	17	8.4±5.4	25.6±11.1	18.4±2.1	10.5±1.7/8.3±1.5
Noncalcific pancreatitis (n = 14)	54.9±8.9	11	5.6±4.3	16.3±6.5	19.9±1.6	10.4±2.3/8.5±2.2
IDDM (n = 23)	30.1±11.1		9.0±6.2	33.9±11.4	20.3+2.4	11.9±2.7/8.5±2.2
NIDM (n = 18)	53.7±11.6		5.9±3.4	15.9±5.0	23.6±2.7	9.9±1.3/7.0±1.3
Control (n = 11)	44.7±12.7				22.7±1.9	

* $p < 0.05$. ** $p < 0.01$.

diabetes. For example, in pancreatic diabetes, diabetic ketoacidosis is uncommon *(1,2)* and amino acid metabolism is different *(3,4)*, whereas insulin-induced hypoglycemia readily occurs *(5)*.

It is believed that disturbances both of insulin secretion from the β-cells in the pancreas and of glucagon secretion from α-cells could be responsible for these differences.

Although some studies have found no relationship between the decrease in pancreatic exocrine and endocrine functions *(6)*, other authors have clarified the relationship between the diminution of exocrine function and decreased pancreatic endocrine function in chronic pancreatitis *(7–9)*.

In the present study, we re-examined the relationship between pancreatic exocrine and endocrine function in calcific and noncalcific chronic pancreatitis. In addition, we investigated whether insulin and glucagon secretions differ in different types of pancreatitis, namely calcific and noncalcific. We studied the characteristics of insulin and glucagon secretion in pancreatic diabetes in comparison with those in insulin-dependent (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM).

Finally, pancreatic exocrine function was investigated in patients with chronic pancreatitis (calcific and noncalcific) and in healthy controls. The correlation between pancreatic exocrine and endocrine function was studied.

Materials and Methods

As shown in Table 1, the study involved a total of 85 cases, classified as follows: 19 cases of calcific pancreatitis, in which calcification in the pancreas was confirmed by simple abdominal radiography, abdominal computed tomography (CT), and endoscopic retrograde cholangiopancreatography (ERCP) *(10)*; 14 cases of noncalcific pancreatitis, in which calcification in the pancreas was not detected in spite of marked abnormalities in the pancreatic duct as shown by ERCP *(11,12)*, but pancreatic exocrine dysfunction was recognized by secretin test; 23 cases of IDDM; 18 cases of insulin-treated NIDDM as diabetic controls; and 11 cases of healthy controls. As shown in Table 2, criteria used to determine IDDM were proneness to ketosis (including 13 cases with ketoacidosis), sudden onset of diabetes in youth, and

Table 2
Correlation Between Pancreatic Exocrine and Endocrine Function in Patients with Chronic Pancreatitis and in Healthy Controls

Correlation coefficiencies between pancreatic exocrine and endocrine function				
		Volume output (mL/kg)	Maximal bicarbonate concentration, (mEg/L)	Amylase output, (U/kg)
Pancreatic endocrine function	Urinary CRP excretion (μg/d)	$r = 0.568^a$ ($n = 44$)	$r = 0.778^a$ ($n = 44$)	$r = 0.803^a$ ($n = 44$)
	Plasma glucagon concentration (ρg/mL)	$r = 0.520^a$ ($n = 44$)	$r = 0.706^a$ ($n = 44$)	$r = 0.606^a$ ($n = 44$)

$^a p < 0.01$.

extreme low values of urinary CPR (<20 μg/d). Criteria used to establish NIDDM were onset in adulthood, absence of ketosis, and a familial history of diabetes. Chronic pancreatitis was excluded in these two types of primary diabetes by ultrasonography of the pancreas and/or abdominal CT imaging. There was no evidence of autonomic neuropathy in IDDM and NIDDM patients. All patients were treated with insulin. The duration of diabetes was 5.6–9.0 yr on the average in all study groups. Diabetic control evaluated by HbA_1 (normal < 8.0%) was poorer in the IDDM group. Also, the daily insulin requirement was significantly higher (mean 33.9 U/d) compared with the other three groups. The insulin requirement was higher in calcific pancreatitis than in noncalcific pancreatitis. Body mass index (BMI) was lower (mean 18.4 kg/m^2) in calcific pancreatitis, and the patients belonging to this group were significantly emaciated in comparison with those in IDDM and NIDDM with primary diabetes.

Twenty-eight out of 33 of the pancreatitis cases have an alcohol etiology (80 g ethanol/d, >10 yr consumption). The pancreatic exocrine and endocrine function tests were performed within a month. The results of liver function tests were normal, except in four cases. Only two cases showed liver cirrhosis (one case HCV antibody-positive, and another case alcoholic) diagnosed by laparoscopy and liver biopsy. In all subjects in this study, urinary CPR excretion was measured for three consecutive days, and the mean value was taken as the daily CPR excretion. The assay of CPR immunoreactivity in urine was performed as described elsewhere *(13)* (C-peptide kit, Daiichi, Tokyo, Japan). Fasting plasma glucagon was assayed by a double-antibody radioimmunoassay with pancreatic glucagon antiserum (glucagon kit, Daiichi).

Exocrine pancreatic function in patients with chronic pancreatitis and in healthy controls was evaluated by pancreozymin-secretin test or secretin test according to Sun and Shay *(14)*. Volume output, maximal bicarbonate concentration, and amylase output were expressed as mL/kg, mEq/L, and U/kg, respectively.

All patients and healthy controls consented to participate in these tests. The protocol was approved by the Human Investigation Committee of Hirosaki University.

Statistical analysis was made by Tukey multiple comparison test and simple regression test, and the values were expressed as mean ± S.D.

Results

Endocrine Function

As shown in Fig. 1, the urinary CPR excretion in each type of diabetes group was significantly lower than in controls (94.9 ± 20.5 μg/d). The urinary CPR excretion in calcific pancreatitis was 12.8 ± 7.4 μg/ d, which was significantly lower than in noncalcific pancreatitis (41.5 ± 30.1 μg/d) and NIDDM (49.3 ± 21.0 μg /d), and resembled the value in IDDM (9.4 ± 5.8 μg/d). The urinary CPR excretion in noncalcific pancreatitis was significantly higher than in calcific pancreatitis and IDDM, and resembled that in NIDDM.

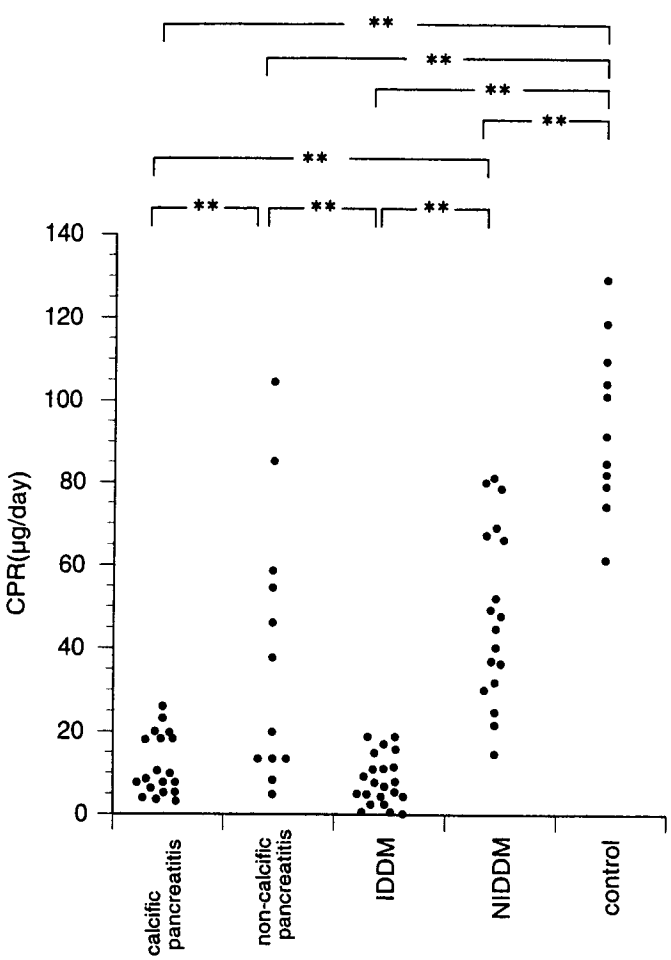

Fig. 1. Urinary c-peptide excretions in patients with pancreatic diabetes (**$P < 0.01$).

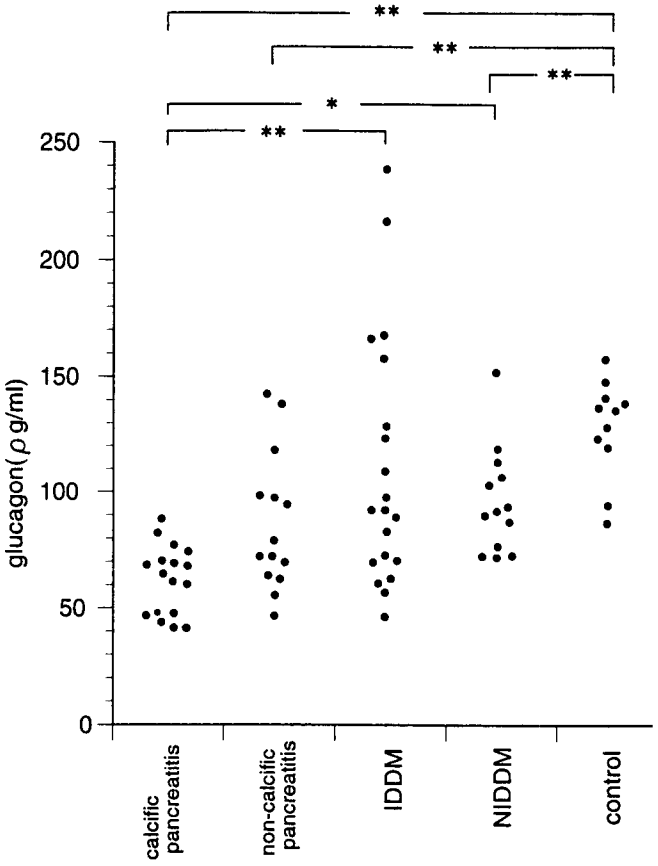

Fig. 2. Plasma glucagon levels in patients with pancreatic diabetes (*$P < 0.05$, **$P < 0.01$).

The plasma glucagon level in each type of diabetes group except for IDDM (112.2 ± 50.2 ρg/mL) was significantly lower than in controls(129.8 ± 21.6 ρg/mL). The plasma glucagon level was the lowest in calcific pancreatitis(64.1 ± 15.9 ρg/mL), which was significantly low when compared with IDDM and NIDDM (97.6 ± 21.9 ρg/mL) (Fig. 2). Thus, in diabetes secondary to calcific pancreatitis, insulin secretion was markedly deficient and similar to that seen in IDDM. Basal glucagon secretion was also disturbed, suggesting that α-cells of the Langerhans islets in the pancreas are also affected. On the other hand, in diabetes secondary to noncalcific pancreatitis (plasma glucagon level 88.4 ± 29.6 ρg/mL), both insulin and glucagon secretions resembled those of NIDDM cases, and the insulin secretion was only mildly diminished.

Correlation Between Pancreatic Exocrine and Endocrine Function

As shown in Fig. 3, pancreatic exocrine function (volume output, maximal bicarbonate concentration, and amylase output) showed significantly low values ($P < 0.01$) both in calcific and noncalcific pancreatitis compared to normal controls, and these parameters showed significantly low values in calcific pancreatitis compared to noncalcific pancreatitis (volume 1.2 ± 0.7 vs 1.7 ± 0.6 mL/kg [$P < 0.05$]), maximal bicarbonate 33.6 ± 15.9 vs 61.6 ± 17.9 mEq/L [$P < 0.01$]), and amylase output 506.9 ± 386.3 vs 1538.3 ± 927.8 U/kg [$P < 0.01$]).

Correlation coefficients between pancreatic exocrine and endocrine function both in patients with chronic pancreatitis (including calcific and noncalcific) and in healthy controls are shown in Table 2.

There was a strong correlation between amylase output and daily CPR output in urine (Table 2, Fig. 4). The correlation was also strong between pancre-

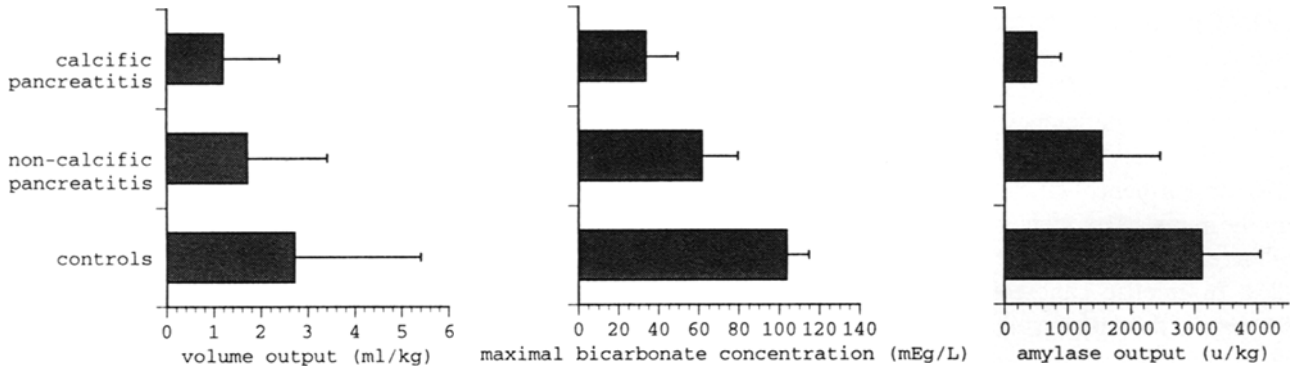

Fig. 3. Pancreatic exocrine and endocrine function in patients with chronic pancreatitis and in healthy controls.

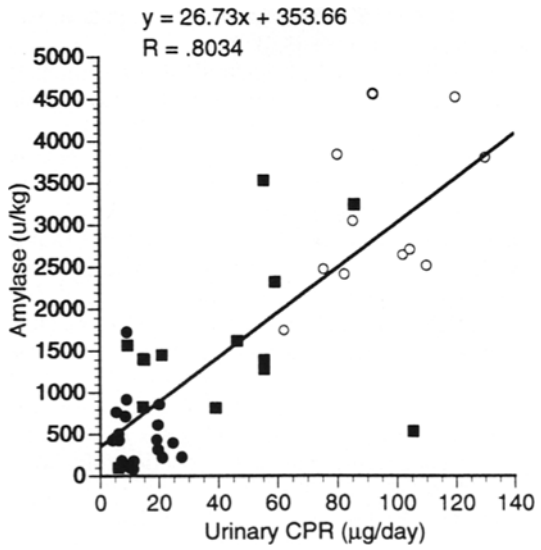

Fig. 4. Correlation between amylase output and urinary CPR excretion. ●, calcific pancreatitis; ■, non-calcific pancreatitis; ○, control.

atic bicarbonate concentration and daily CPR output in urine. In addition, there was a strong correlation between bicarbonate concentration and plasma fasting glucagon concentration.

Discussion

Since only two cases showed liver cirrhosis, we did not take liver cirrhosis into consideration as for pancreatic exocrine and endocrine function.

In pancreatic diabetes, there is a disturbance in insulin and serum CPR secretions in response to stimulants, such as oral glucose tolerance test (GTT), glucagon, tolubutamide, and arginine *(15,16)*. Both glucagon loading test and serum CPR level indicate that a relationship exists between serum CPR level and urinary CPR excretion *(13,15)*. Therefore, we evaluated urinary CPR excretion as endogenous insulin secretion capacity. Urinary CPR excretion evaluated as insulin secretion was disturbed to the same extent in pancreatic diabetes due to calcific pancreatitis and IDDM. On the other hand, endogenous insulin secretion was moderately disturbed in pancreatic diabetes owing to noncalcific pancreatitis and NIDDM. Thus, with respect to urinary CPR excretion, calcific pancreatitis was considered to resemble IDDM *(17,18)*, whereas noncalcific pancreatitis resembled NIDDM.

It has been widely reported that although plasma glucagon response caused by insulin-induced hypoglycemia or arginine loading is lowered in pancreatic diabetes, the basal secretion level is maintained *(19–21)*. In this study, basal glucagon secretion was markedly lowered in patients with pancreatic diabetes owing to calcific pancreatitis as was also found in patients with total pancreatectomy *(22)*. The basal glucagon level in calcific pancreatitis was significantly lower compared with the other groups, suggesting that calcific pancreatitis differs from primary diabetes (IDDM, NIDDM). Studies using the canine duct-ligated pancreatitis model show that dysfunction of the α-cell in response to hypoglycemia seems to precede that to hyperglycemia in diabetes secondary to pancreatolithiasis *(23)*. Basal pancreatic glucagon concentration has been found to be reduced in humans *(24)*.

Both insulin and glucagon secretions were involved more strongly in calcific pancreatitis than in noncalcific pancreatitis. These results reflect the higher fre-

quency of insulin-treated diabetes owing to calcific pancreatitis rather than to noncalcific pancreatic endocrine impairment *(1)*. Moreover, these results suggest that glucagon deficiency may lead to severe hypoglycemic attack in patients with pancreatic diabetes *(24)*. Impairment of glucagon secretion would account for the increased tendency to hypoglycemia, as well as relative rarity of ketoacidosis, in pancreatic diabetes *(25)*. In calcific pancreatitis, the histopathological findings of the pancreas show progressive fibrosis and sclerosis of the exocrine cells, and in some cases, quantitative and qualitative changes in the endocrine cells *(27,28)*. Focal accumulation of islets in the fibrosis is observed in overt pancreatic diabetes.

It is suggested that in calcific pancreatitis there is actual damage to the islet cells (β-cell) and glucagon-producing (α-cell) cells, whereas in noncalcific pancreatitis, there might be some sort of ischemia or functional derangement of the islets, with impairment of glucose diffusion rather than true impairment of endocrine cells. That is, the factors, such as altered pancreatico-portal flow, impaired nerve innervation of islets, and impaired paracrine regulatory mechanisms involving other islet cells *(26)*, might be contributory to the decrease in insulin and glucagon secretions in the patients with noncalcific pancreatitis.

In the present study, we obtained almost the same results, showing a close correlation between amylase output and maximal bicarbonate concentration, and the decrease in urinary CPR excretion and low level of plasma glucagon. These correlations support the contention that there may be more or less parallel destruction of islets and acinar cells (and ductal cells) in the course of pancreatitis *(7,17,29)*.

The residual capacity of acinar cells and the insulin release from β-cells are concomitantly disturbed. Also, plasma glucagon from α-cells and the residual capacity of ductal cells are involved in patients with chronic pancreatitis.

From the above results, we conclude that:

1. Patients with pancreatic diabetes owing to calcific pancreatitis resemble IDDM;
2. Those owing to noncalcific pancreatitis resemble NIDDM with respect to pancreatic endocrine function; and
3. Acinar cell and ductal cell involvements in diabetic patients owing to chronic pancreatitis correlate with residual capacities of insulin release and glucagon secretion.

References

1 Bank S, Marks IN, Vinik AI. Clinical and hormonal aspects of pancreatic diabetes. *Am J Gastroenterol* 1975; 64: 13–22.

2 Del Prato S, Riva F, Devide A, Nosadini R, Fedele D, Tiengo A. Glucagon levels and ketogenesis in human diabetes following total or partial pancreatectomy and severe chronic pancreatitis. *Acta Diabetol Lat* 1980; 17: 111–118.

3 Muller WA, Berger M, Suter P, Cuppers JH, Reiter J, Wyss T, Berchtold P, Schmidt FH, Assal J-P, Renold AE. Glucagon immunoreactivities and amino acid profile in plasma of duodenopancreatectomized patients. *J Clin Invest* 1979; 63: 820–827.

4 Boden G, Master RW, Rezvani I, Palmer JP, Lobe TE, Owen OE. Glucagon deficiency and hyperaminoacidemia after total pancreatectomy. *J Clin Invest* 1980; 65: 706–716.

5 Joffe BI, Bank S, Marks IN. Hypoglycemia in pancreatitis.(letter) *Lancet* 1968; II: 1038.

6 Peters N, Dick AP, Hales CN, Orrell PH, Sarner M. Exocrine and endocrine pancreatic function in diabetes mellitus and chronic pancreatitis. *Gut* 1966; 7: 277–281.

7 Kalk WJ, Vinik AI, Jackson WPU, Bank S. Insulin secretion and pancreatic exocrine function in patients with chronic pancreatitis. *Diabetologia* 1979; 16: 355–358.

8 Domschke S, Stock KP, Pichl J, Schneider MU, Domschke W. Beta-cell reserve capacity in chronic pancreatitis. *Hepatogastroenterol* 1985; 32: 27–30.

9 Keller U, Szöllösy E, Varga L, Gyr K. Pancreatic glucagon secretion and exocrine function (BT-PABA test) in chronic pancreatitis. *Dig Dis Sci* 1984; 29: 853–857.

10 Kasugai T, Kuno N, Kizu M, Kobayashi S, Hattori K. Endoscopic pancreato- cholangiography II. The pathological endoscopic pancreatocholangiogram. *Gastroenterology* 1972; 63: 227–234.

11 Axon ATR. Endoscopic retrograde cholangiopancreatography in chronic pancreatitis. *Radiol Clin North Am* 1989; 27: 39–50.

12 Sarner M, Cotton PB:Definitions of acute and chronic pancreatitis. *Clin Gastroenterol* 1984; 13: 865–870.

13 Kuzuya T. Matsuda A, Saito T, Yoshida S. Human C-peptide immunoreactivity (CPR) in blood and urine—Evaluation of a radioimmunoassay method and its clinical applications. *Diabetologia* 1976; 12: 511–518.

14 Sun DCH, Shay H. Pancreozymin-secretin test. The combined study of serum enzymes and duodenal contents in the diagnosis of chronic pancreatitis. *Gastroenterology* 1960; 38: 570–581.

15 Matsuda A, Kamata I, Iwamoto Y, Sakamoto Y, Kuzuya T. A comparison of serum C-peptide response to intravenous glucagon, and urine C-peptide, as indices of insulin dependence. *Diabetes Res Clin Prac* 1985; 1: 161–167.

16 Larsen S, Hilsted J, Tronier B, Worning H. Pancreatic hormone secretion in chronic pancreatitis without residual beta-cell function. *Acta Endocrinol* 1988; 118: 357–364.

17 Andersen RN, Krarup T, Pedersen NT, Faber OK, Hagen C, Worning H. β cell function in patients with chronic pancreatitis and its relation to exocrine pancreatic function. *Diabetologia* 1982; 23: 86–89.

18 Malfertheiner P, Büchler M. Correlation of imaging and function in chronic pancreatitis. *Radiol Pancreas* 1989; 27: 51–64.
19 Persson I, Gyntelbery F, Helding LG, Boss-Nielsen J. Pancreatic glucagon-like immunoreactivity after intravenous insulin in normals and chronic pancreatitis patients. *Acta Endocrinol* 1971; 67: 401–404.
20 Assan R, Tiengo A. Comparison des secretions de glucagon dans les diabetes sucres avec ou sans pancreatopati organique acquise. *Pathol Biol* 1973; 21: 17–25.
21 Larsen S, Hilsted J, Philipsen EK, Tronier B, Christensen NJ, Nielsen DM, Worning H. Glucose counterregulation in diabetes secondary to chronic pancreatitis. *Metabolism* 1990; 39: 138–143.
22 Muller WA, Brennan MF, Tan MH, Aoki TT. Studies of glucagon secretion in pancreatectomized patients. *Diabetes* 1974; 23: 512–516.
23 Okumura N. Hayakawa T. Sakakibara A, Noda A, Kondo T. Plasma pancreatic glucagon response to blood glucose in experimental pancreatolithiasis in dogs. *Diabetologia* 1983; 25: 510–513.
24 Linde J, Nilsson LH, Barany FR. Diabetes and hypoglycemia in chronic pancreatitis. Scand J Gastroenterol 1977; 12: 369–373.
25 Donowitz M, Hendler R, Spiro HM, Binder HJ, Felig P. Glucagon secretion in acute and chronic pancreatitis. *Ann Intern Med* 1975; 83: 778–781.
26 Sjoberg RJ, Kidd GS. Pancreatic diabetes mellitus. *Diabetes Care* 1989; 12: 715–724.
27 Klöppel G, Bommer G, Commandeur G, Heitz Ph. The endocrine pancreas in chronic pancreatitis—Immunocytochemical and ultrastructural studies. *Virchows Arch A (Pathol Anat and Histol)* 1978; 377: 157–174.
28 Yeo CJ, Bastidas JA, Schmieg RE Jr, Walfisch S, Course N, Olson JL, Andersen DK, Zinner MJ. Pancreatic structure and glucose tolerance in a longitudinal study of experimental pancreatitis-induced diabetes. *Ann Surg* 1989; 210: 150–158.
29 Larsen S, Hilsted J, Tronier B, Worning H. Metabolic control and β cell function in patients with insulin-dependent diabetes mellitus secondary to chronic pancreatitis. *Metabolism* 1987; 36: 964–967.