Exocrine Pancreatic Function after Upper Abdominal Surgery

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SUDA, Y., SHIRASO, M. and SATO, T. *Exocrine Pancreatic Function after Upper Abdominal Surgery*. Tohoku J. exp. Med., 1975, 115 (4), 307-317 — Daily pancreatic flow and daily outputs of bicarbonate and amylase in pure pancreatic juice were observed in 15 postoperative patients who underwent upper abdominal surgery. Exocrine pancreatic secretion under the stimulation by endogenous or exogenous hormones was well correlated with the extent of pancreatic fibrosis estimated by the histometrical treatment. Exocrine pancreatic secretion in Billroth II type of gastrectomy was depressed to 60-70% of the patients' with Billroth I type of gastrectomy. In distal pancreatectomy the depression in the exocrine pancreatic secretion almost corresponded with the resected volume of pancreas. Exocrine pancreatic secretion in pancreatoduodenectomy was highly depressed beyond the expected value from the resected volume and fibrosis of the pancreas. This was interpreted as partly due to the elimination of hormonal mechanism by duodenectomy and partly due to the denervation of the secretory fibers by surgical manipulation. — exocrine pancreatic secretion; pancreatic fibrosis; pancreatoduodenectomy; distal pancreatectomy; gastrectomy

Although many studies have been performed on the physiology or pathophysiology of exocrine function of pancreas, most of them were animal experiments or carried out on patients with morbid pancreatic fistulae encountered during the postoperative period. The present study deals with the comparison of the exocrine functions in patients who underwent upper abdominal surgery of several types with the external pancreatic duct drainage. The effects of pancreatic or gastric resection and pancreatic fibrosis on the exocrine pancreatic function were investigated by the histometrical treatment of the tissue and the quantitative measurement of pure pancreatic juice.

MATERIALS AND METHODS

The control cases were tabulated in Table 1. Pancreatic and hepatic functions in these cases were proved to be within normal limits by pancreozymin-secretin test and routine liver function tests performed preoperatively. The other cases studied were tabulated in Tables 2 and 3. The effect of pancreatic fibrosis on the exocrine secretion was investigated in Case 5. The influence of duodenal passage of gastric content upon the exocrine secre-

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TABLE 1. *Control cases*

Case	Age & sex	Diagnosis	Operation performed
1	61♂	Cholecystocholedocholithiasis	Cholecystectomy, choledocholithotomy, T-tube drainage
2	55♀	Cholecystolithiasis	Cholecystectomy, T-tube drainage
3	55♀	Intrahepatic gallstone	Cholecystectomy, partial hepatectomy, T-tube drainage
4	30♂	Hepaticolithiasis	Cholecystectomy, choledocholithotomy, T-tube drainage

TABLE 2. *Cases of pancreatic fibrosis and gastrectomies*

Case	Age & sex	Diagnosis	Operation performed
5	52♀	Cholecystolithiasis, chronic pancreatitis	Cholecystectomy, T-tube drainage
6	51♂	Gastric cancer	B I gastrectomy
7	26♂	Membranous mucosal folding of duodenum	B II gastrectomy, cholecystectomy
8	39♂	Gastric cancer	Total gastrectomy, jejunal interposition
9	43♂	Gastric cancer	Total gastrectomy, esophagojejunostomy Roux en Y
10	50♂	Gastric cancer	Total gastrectomy, esophagojejunostomy, distal pancreatectomy

TABLE 3. *Cases of pancreatoduodenectomy*

Case	Age & sex	Diagnosis	Operation performed
11	44♂	Localized pancreatitis of the head of pancreas	Pancreatoduodenectomy
12	51♀	Insulinoma of the head of pancreas	Same as above
13	64♂	Cancer of common bile duct	Same as above
14	61♂	Same as above	Same as above
15	55♂	Cancer of the head of pancreas	Same as above

tion was studied in Cases 6, 7, 8 and 9. The effect of distal pancreatic resection on the exocrine pancreatic secretion was examined in Case 10 using Case 9 as control, and that of proximal pancreatic resection was examined in Cases 11 to 15, taking into consideration the fibrotic change of the remnant pancreata.

After transduodenal minor sphincterotomy, pancreatic duct drainage was exteriorized through the jejunal loop with a polyethylene tube of 2 mm in caliber.

Pancreatic juice was collected every 6 hr into a bottle in an ice bucket. Checking its volume at the bedside, bicarbonate and amylase concentrations were measured for an aliquot according to the methods of Van Slyke et al. (1919) and Caraway (1959) and expressed as total dialy output, i.e. the sum of 4 six-hr outputs. The average daily output on the 7th to 14th postoperative day was used for the purpose of comparison, since the patients recovered so as to have ordinary meals on the 7th to 10th postoperative day. For the purpose of exogenous stimulation, secretin of 0.02 unit/min/kg was infused and pancreozymin of 1 unit/kg was administered by a single injection after the pancreatic

Fig. 1. Point counting method. Intra-acinar and interacinar connective tissue overlapping with the crossings of micrometer was counted. The parenchymal ratio was expressed as a quotient of the parenchymal points by the total crossings. Photo shows the histology of Case 10 with the parenchymal ratio 94.24%.

flow of a few consecutive collections reached plateau. As the parameters for the comparison of exocrine pancreatic function, the above-mentioned flow rate, bicarbonate output and amylase output are used in the following description.

The histological examination was performed in the specimen from the cut-surface and mid-portion of the resected pancreas by hematoxylin-eosin stain and Masson's trichrome stain. In the case whose pancreas was not operated, the specimen of wedge resection from the head of pancreas was used instead. The point counting method (Weibel et al. 1966) was applied to investigate the parenchymal ratio in the tissue. As shown in Fig. 1, a glass disc incising 21×21 crossings of lattice was equipped under the ocular lens of microscope. Including the small vessels and intra-acinar connective tissue, non-parenchymal portion overlapping with the crossings of micrometer was counted in randomized 50 views, i.e. $21 \times 21 \times 50$ points, as a whole, on the histology slide. Parenchymal ratio was then expressed as a quotient of the parenchymal points over total crossings.

In 15 microscopically normal pancreata the parenchymal ratio was calculated histometrically, the obtained value being $92.77 \pm 1.31\%$. It was postulated that pancreas with normal histology had its parenchyma of approximately over 90% in its tissue.

In usual pancreatoduodenectomy, pancreas is resected on the left side of the superior mesenteric vessels. The cadaver pancreata with normal histology in a middle age were weighed by separating the head portion from the body and tail as usual pancreatoduodenectomy. The average weights of both in 21 cadaver pancreata were 35.00 ± 10.15 g in cephalic portion and 38.09 ± 10.88 g in caudal portion. Thus, the weight ratio of cephalic to caudal pancreas under ordinary pancreatoduodenectomy was approximately 1:1. In distal pancreatectomy often combined with total or proximal gastrectomy for cancer, the pancreas is usually resected at the stem of the splenic artery to dissect the regional lymph nodes along the splenic artery. The mean weights of cadaver pancreata transected at this line were 38.54 ± 10.22 g in cephalic portion and 24.45 ± 7.48 g in caudal portion, showing the approximate ratio of 3:2. Thus, 40% of the total organ is resected and the remaining 60% would be preserved in this distal pancreatectomy.

RESULTS

Daily secretion in normal and fibrotic pancreata

Daily flow of pancreatic juice in controls with normal histology ranged from 833.9 to 958.5 ml, the average value being 891.6 ml (Table 4). Daily bicarbonate output ranged from 79.45 to 93.63 mEq with the average of 85.79 mEq. Daily amylase output was 25323 units on the average. Pancreatic parenchyma in 4 controls occupied from 90.47 to 93.96% (mean; 92.58%) of the total tissue. In contrast, daily flow of pancreatic juice and daily outputs of bicarbonate and amylase in Case 5 were 587.7 ml, 59.75 mEq and 15682 units, respectively. The histology of Case 5 was shown in Fig. 2. The histometrical ratio of this tissue was 70.95% of parenchyma. Since the mean control parenchymal ratio in this series was 92.58%, the parenchymal reduction in Case 5 was corrected to 70.95/92.58 or 76.63%. Comparing the parameters of secretory function in Case 5 with control, the extents of reduction in daily flow and daily outputs of bicarbonate and amylase were 65.9%, 69.6% and 61.9%, respectively. Although these values did not

TABLE 4. *Exocrine pancreatic secretion in controls and pancreatic fibrosis*

Case	Flow (ml/day)	Bicarbonate (mEq/day)	Amylase (units/day)	Parenchymal ratio (%)
1	958.5	86.059	28351.3	93.70
2	928.9	84.059	23419.9	92.19
3	845.2	93.634	24458.0	90.47
4	833.9	79.450	25062.4	93.96
Mean	891.6	85.790	25322.9	92.58
5	587.7	59.746	15682.7	70.95

Fig. 2. Histology of Case 5. Parenchymal ratio was estimated at 70.95%.

exactly coincide with the degree of reduction in parenchyma of 76.6%, the above three parameters were depressed at a similar rate.

Daily pancreatic secretion after gastric resection

The parameters of pancreatic exocrine function in the cases of gastric resection were shown in Table 5. Case 6 underwent gastric resection with gastroduodenostomy (Billroth I) for gastric cancer and Case 7 underwent the same with gastrojejunostomy for the membranous mucosal folding at the 2nd portion of duodenum. Histological investigation of pancreas was not performed in Case 6, but the gross finding was normal in appearance and consistency at the time of operation. In comparison with the control values, daily output of bicarbonate in Case 6 was slightly decreased at a rate of 88.9% but daily flow and daily output of amylase in this case remained in the control range at the rates of 97.7% and 91.2%, respectively. Comparing the three parameters of Case 6 (Billroth I gastrectomy) with those of Case 7 (Billroth II gastrectomy), all parameters in Case 7 were depressed at the similar rates, i.e., 65% in flow, 66% in bicarbonate and 68% in enzyme outputs. By the comparison of these two cases, it was suggested that there might be a difference in postoperative exocrine pancreatic function between Billroth I gastrectomy and Billroth II, that is, between duodenal passage and diversion; the secretion was depressed to 60 to 70% in the latter.

TABLE 5. *Exocrine pancreatic secretion in gastrectomies*

Case	Flow (ml/day)	Bicarbonate (mEq/day)	Amylase (units/day)	Parenchymal ratio (%)
6	871.2	76.227	23104	*
7	567.9	50.605	15854	93.93
8	875.8	47.997	14480	*
9	581.3	32.981	7655	90.76
10	376.5	18.378	4949	94.24

* No specimen for histology. Gross finding was normal.

Similar comparison was made between Cases 8 and 9 in total gastrectomy. The alimentary tract after total gastrectomy was reconstructed by jejunal substitution for stomach in Case 8 and by esophagojejunostomy combined with Roux en Y jejunojejunostomy in Case 9. Namely, the duodenal passage was preserved in Case 8 but diverted in Case 9. The value of daily pancreatic flow under total gastrectomy with jejunal interposition was similar to control, showing 98.23% of the control value. The bicarbonate and enzyme outputs, however, showed a considerable depression to 55.9% and 57.2% of controls, respectively. As compared with Case 8, Case 9 showed a depressed daily flow to 66.3%. This seemed to be due to the diversion of duodenal passage in Case 9. The declines in bicarbonate and enzyme outputs were 68.7% and 52.8%, respectively. The decrease of 66% and 69% in flow and bicarbonate output under total gastrectomy was almost the same as under subtotal gastrectomy, but the enzyme output was less than the latter.

Daily pancreatic secretion after pancreatectomy

On the assumption that 60% of pancreas was preserved in distal pancreatectomy at the stem of the lienal artery, comparison was made between the cases of total gastrectomy with and without distal pancreatectomy (Table 5). In Cases 9 and 10, the alimentary tracts were reconstructed by esophagojejunostomy and Roux en Y jejunostomy. The former was combined with distal pancreatectomy, but the latter was not. The parenchymal ratios in both cases were within normal range histometrically. The exocrine parameters of Case 10 showed the decrease of 64.76% in pancreatic flow, 55.72% in bicarbonate output and 64.66% in enzyme output against the respective values of Case 9. These corresponded approximately with the ratio of preserved remnant parenchymata.

In ordinary pancreatoduodenectomy as prescribed before, 50% of pancreas parenchyma was preserved. The histology of the pancreatic cut-surface in pancreatoduodenectomy varied with the fibrotic changes for the lesion of the pancreatic head, and the parenchymal ratio ranged from 91.53% to only 2.07%. The parameters of pancreatic exocrine function in 5 pancreatoduodenectomized cases were shown in Table 6 in an ascending order of fibrosis. Case 11 had localized cephalic pancreatitis which was misjudged as carcinoma. The histology of the resected surface was normal and its parenchymal ratio was estimated at 91.53%.

TABLE 6. *Exocrine pancreatic secretion in pancreatoduodenectomy*

Case	Flow (ml/day)	Bicarbonate (mEq/day)	Amylase (units/day)	Parenchymal ratio (%)	Ratio to Case 11
11	282.3	16.375	2858	91.52	—
12	233.9	11.894	2317	82.84	90.52
13	275.5	10.730	2405	78.50	85.77
14	93.1	4.544	1566	36.11	39.46
15	34.6	2.011	83	2.07	2.26

Comparison of the exocrine parameters was made between the pancreatoduodenectomized Case 11 with normal histology and the unresected controls. The values of the former were 31.66% of the controls in flow, 19.08% in bicarbonate output and 11.26% in enzyme output.

Applied Case 11 as the pancreatoduodenectomized control, each exocrine parameter in Case 12 with parenchymal ratio of 82.84% (corrected ratio to Case 11; 90.52%) was depressed in an almost parallel fashion, that is, to 82.8% in flow, 72.6% in bicarbonate output and 81.1% in enzyme output. The data of Case 13 were not exactly comparable with others', since the averages during the 5th to the 10th postoperative day were adopted because of the spontaneous removal of pancreatic duct drainage on the 12th postoperative day. The same comparison was attempted between Case 13 with 85.8% of the corrected parenchymal ratio and Case 11 with the normal histology. The declined ratios were 97.6% in flow,

65.5% in bicarbonate output and 84.1% in enzyme output. These did not correspond with the histological parenchymal ratio except for the enzyme output. The depression rates of parameters in Case 14 with 39.46% of the parenchymal ratio were 32.9% in flow, 27.8% in bicarbonate and 54.8% in enzyme outputs, respectively. In Case 15 of almost complete fibrotic replacement, flow and bicarbonate output were markedly decreased, but as compared with the parenchymal ratio of 2.26% these values were as big as 4 times. On the other hand, the enzyme output of this case was depressed to a similar degree to the parenchymal ratio.

Estimated mean concentrations of bicarbonate and amylase

Mean bicarbonate and amylase concentrations in each case were estimated from the values on the above-mentioned postoperative days. Mean daily bicarbonate concentration in 4 controls ranged from 89.9 to 110.8 mEq/liter, averaging 96.22 mEq/liter. Mean daily amylase concentration in the controls ranged 2521 to 3005 units/100 ml, averaging 2840.1 units/100 ml. Mean bicarbonate and amylase concentrations in Case 5 with the corrected parenchymal ratio of 76.63% were within the control range. In subtotal gastrectomy with Billroth I or II anastomosis, mean bicarbonate concentration was 90 or 92% of the control and mean amylase concentration was 93 or 98%. In total gastrectomy with jejunal interposition or Roux en Y anastomosis, mean bicarbonate concentration was 56 or 58% of the control and amylase concentration was 58 or 46%. So far as the mean bicarbonate and amylase concentrations were concerned, it was assumed that in subtotal or total gastrectomy, these concentrations were influenced by the degree of gastric resection, but not so much affected by the mechanical duodenal passage under the ordinary intake of diet. The difference in mean concentration from the daily amylase output, therefore, seemed to be due to the presence or absence of stomach, or surgical manipulation such as denervation of the secretory fibers.

From the comparison between Cases 9 and 10 on which distal pancreatectomy was performed, no distinguished difference was observed. Mean bicarbonate concentration in pancreatoduodenectomy ranged from 38.95 to 58.12 mEq/liter, averaging 50.95 mEq/liter. These values accounted for 40 to 60% decrease against the control, but no clear-cut correlation with the fibrotic change of remnant pancreata. Decrease in mean amylase concentration ranged from 35 to 6%, and the lower the parenchymal ratio, the less the amylase concentration was.

Secretory responses to exogenous secretin and pancreozymin

The above-described data were on the secretory responses to so-called endogenous stimulation of diet. Responses to the exogenous stimulants were as shown in Table 7. Bicarbonate concentration under the secretin infusion was increased up to 115 to 200%, as compared with the unstimulated values. Flow of pancreatic juice in the fibrotic pancreas under secretin infusion was lower than control. Similar results on bicarbonate concentration were obtained in the fibrotic

TABLE 7. *Exocrine pancreatic secretion under exogenous stimulations*

Case	Secretin infusion			Pancreozymin stimulation		Parenchymal ratio (%)	Decrease ratio to controls (%)
	Flow (ml/10 min)	Bicarbonate (mEq/10 min)	Amylase (units/10 min)	Amylase (units/10 min)	Increase ratio (%)		
4	21.7	2.381	194.30	336.6	173.2	92.19	99.37
5	10.9	1.429	93.33	227.6	158.8	70.95	76.48
6	23.0	2.782	222.58	380.2	170.8	*	—
14	6.9	0.688	21.80	23.9	109.9	36.11	38.92
15	1.0	0.062	4.19	5.7	136.3	2.07	2.23
Mean of normals (N=18)	22.87 ±6.03	2.590 ±0.760	181.50 ±57.29			92.77 ±1.31	100

* No specimen for histology. Gross finding of pancreas was normal.

pancreas remnant under pancreatoduodenectomy. In Case 5 with 76.6% of the corrected parenchymal ratio, however, the change in bicarbonate concentration was minimal.

The ratio of percent increase in amylase concentration under pancreozymin stimulation was 110 to 160% in the present series. On the other hand, the ratios in flow of juice and bicarbonate concentration were around 110%. Compared with each amylase concentration in the cases studied under pancreozymin stimulation, the percent increase after stimulation was correlated with fibrotic replacement. It was concluded, therefore, that the changes in water and enzyme secretion seemed to be correlated with the pancreatic fibrosis, even under these corresponding hormonal stimulations.

DISCUSSION

Early postoperative exocrine pancreatic function after upper abdominal surgery was studied by White and co-workers (Elmslie et al. 1964; Tournut and White 1972). Daily flow of pancreatic juice is not constant in the literature, ranging from 700 to 4000 ml. The flow in the controls with normal pancreatic ductography and histology was 830 to 958 ml a day in the present study, which was comparable with the value of Tournut and White (1972). As reported previously by one of the present authors (Shiraso 1973), a gradual increase in pancreatic secretion was observed in the early convalescent period after surgery. But the pancreatic flow and the concentrations of bicarbonate and enzyme showed constant values after the 7th to 10th postoperative day. Therefore, the values for one to two weeks after surgery were available for the present comparative study. Duodenal passage of gastric content is considered to liberate endogenous stimulants to pancreas. In comparison of different anastomotic types after subtotal or total gastrectomy, cases of diverted duodenum showed 60 to 70% depression in pancreatic secretion. Clinically, better nutritional absorption in Billroth I

gastrectomy than in Billroth II was also reported in the postoperative balance study (MacLean et al. 1954; Kaneko 1971). Annis and Hallenbeck (1952) reported from their animal experiments of Billroth I and II gastrectomy, that a clear difference was noticed by dietary stimulation, though the exocrine change was not observed after secretin stimulation or duodenal acidification. White et al. (1963) showed that the duodenal response to the exogenous stimulants was depressed by about 30% in Billroth I patients and by about 60% in Billroth II patients as compared with the normal. Placing a suction tube at the papilla of Vater, however, no considerable difference in duodenal aspirate was noticed between Billroth I and II gastrectomies. They suggested, therefore, that it might be due to the absorption of enzyme in the duodenal loop (Lenninger et al. 1965). From the results of the present study, the difference in secretory response between Billroth I and II gastrectomies was considered more likely due to the lack in the endogenous duodenal stimulation caused by the diversion of gastric contents.

In order to investigate the exocrine function after pancreatoduodenectomy, two major factors, i.e. the volume of resected pancreas and the eliminated duodenal loop, should be taken into consideration. The volume of resected pancreas in ordinary pancreatoduodenectomy was roughly estimated as 50% of the total organ. Assuming the effect of the duodenal diversion as 60 to 70% decrease in pancreatic secretion of the control, the remnant pancreas without fibrotic change in pancreatoduodenectomy would secrete 30 to 35% of the control. In the present series of pancreatoduodenectomy, the secretory depressions in the pancreatic remnant without fibrosis were 31.7% in pancreatic flow, 19.1% in bicarbonate and 11.3% in enzyme output against the control. Namely, the pancreatic flow corresponded to the expected estimation, but the outputs of bicarbonate and enzyme were lower than the expected values. Several factors such as the lack of endogenous stimulation for duodenectomy, upper jejunal diversion for pancreato-jejunostomy and exchange mechanism (Janowitz and Dreiling 1962) for the depressed pancreatic flow would contribute to the secretory depression.

The secretory changes in distal pancreatectomy were examined in two cases of total gastrectomy with the same reconstructive anastomosis. Their decreases were almost the same as the parenchymal reduction of 40%.

The correlation between function and histological changes in the corresponding gland has been generally accepted and the exocrine function in experimentally produced pancreatic lesion has been studied by many investigators (Wang et al. 1950; Feldman et al. 1962; White and Magee 1962). Wang et al. (1950) ligated the pancreatic duct in rabbits to examine the subsequent histological changes and pancreatic function under the maximal stimulation of pancreozymin and secretin. They concluded that the pancreatic function was deteriorated to the extent of histological changes. As for the gastric function, the same correlation was also reported between parietal cells and acid secretion (Ragins et al. 1957; Marks et al. 1960). However, few literatures have been reported in which pancreatic parenchyma was quantitatively estimated and its correlation with

exocrine function was studied. Only the report of Hansky et al. (1963) on the relationship between the canine pancreatic weight and function was comparable with the present study.

Since it was confirmed in the present study that the pancreas parenchyma without microscopical lesion occupied 90.47 to 93.97% of the total organ, pancreas with over 90% parenchyma might be considered as functionally normal. The fibrotic pancreas with 70.95% of parenchymal ratio showed the corresponding decrease in the flow of juice, outputs of bicarbonate and amylase. As for the residual parenchyma and its secretory function after pancreatoduodenectomy, a similar correlation was found when compared with the histologically normal remnant. Namely, the cases with 90.52, 85.77 and 39.46% of the corrected parenchymal ratios against Case 11 with normal histology showed considerably parallel depressions of their exocrine parameters. In the case with parenchyma of 2.26%, exocrine secretion was extremely low and any numerical correspondence was not obtained. Since the residual parenchymal cells would be still scattered even in an extraordinarily fibrotic pancreas, measurement of parenchyma should be made in the overall organ as possible. As mentioned above, however, under the conditions of diffuse lesion it would be postulated that a quantitatively parallel correlation exists between pancreatic parenchyma and exocrine function in the endogenous stimulation of diet.

Since the so-called endogenous stimulation of diet in the present study was not uniform as the stimulant to each patient, the exogenous stimulation with secretin or pancreozymin, though in small numbers, was attempted to confirm the relationship between secretory activity and parenchyma. Under secretin infusion, a decrease in bicarbonate output was coincident with the parenchymal ratio in fibrotic pancreas. The parameters of exocrine function also tended to decrease in a parallel fashion within $\pm 10\%$ divergency, and the more parenchymal reduction resulted in the less secretory outputs. Under pancreozymin stimulation the same tendency was observed. Although there might be arguments for and against that the dose of secretin or pancreozymin used in this study was not appropriate for submaximal stimulation comparable with each individual, it was suggested that the secretory output was affected by the histological changes and the volume of pancreas remnant even under the exogenous stimulation of secretin and/or pancreozymin.

The percent increase in enzyme secretion under pancreozymin stimulation was much higher in the non-resected pancreas than in the pancreatoduodenectomized. Interaction of neurological or endogenous factors during the exogenous infusion of stimulants should be taken into consideration. Further studies are required for this matter. Although some questions on the sequel of fibrotic pancreas or pancreatic remnant after pancreatoduodenectomy are still remained, the present study will show a clue for the rational treatment or substitution of enzymes after upper abdominal surgery.

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