Insulin Secretion after Pancreatoduodenectomy

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ALMOST FORTY YEARS HAVE ELAPSED since a successful series of pancreatoduodenectomies was reported.[2,14] In this decade, the results of this procedure have revealed a fairly large number of long-term survivors,[4,6,8,9,12] however, prognosis of pancreatoduodenectomized patients still remains poor. Unknown metabolic disorders are assumed to occur after pancreatoduodenal resection. The present paper deals with an observation on insulin secretion during the oral glucose tolerance test, since little is known about endocrine function after partial resection of the pancreas, this is the first requirement to elucidate metabolism after removal of a non-functioning tumor of the pancreas.

Materials and Methods

Ten pancreatoduodenectomized patients not requiring any particular treatment in daily life were investigated. This group included 8 males and 2 females, ranging from 42 to 72 (mean 56.6) years of age. In each patient the pancreas had been resected at the junction of its head and body with the whole duodenum and an anal third of the stomach *en bloc*. Five weeks to 39 months (mean 20 mos) after the surgery the oral glucose tolerance test was carried out. Clinical findings of these patients are presented in Table 1.

Twelve gastrectomized patients without a preoperative diabetic disposition were used as the control group of sham operation, in whom partial gastrectomy with gastrojejunostomy after the fashion of Billroth II was performed 2 to 204 (mean 26) months prior to the examination (Fig. 1). Included were 10 males, and 2 females, ranging from 18 to 73 (mean 43.8) years of age.

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Twelve healthy adults serving as the group of normal subjects were examined. There were 9 males and 3 females, ranging from 25 to 55 (mean 39.2) years of age.

In this series, there was no familial history of diabetes or over-weight.

After over-night fasting, 100g of glucose was administered orally.

Blood samples were collected into heparinized syringes from antecubital veins, at 15 minutes before and just before glucose load as controls. After glucose ingestion, at every half hour for the first two hours and then three hours, blood samples were obtained. The blood plasma was separated by centrifugation and was frozen within 15 minutes after blood had been drawn. This was stored under −20° C until the time of assay.

Plasma glucose was determined by the potassium ferricyanide reduction method as adapted to Auto-Analyser.[1]

Plasma non-esterified fatty acids (NEFA) were determined by the modified colorimetric micro-method of Itaya-Ui[7] within 24 hours after the samples had been obtained.

Plasma immunoreactive insulin (IRI) was determined by the double antibody technique.*

Results

Plasma Levels of Glucose (Fig. 2.)

Fasting plasma levels of glucose were within normal limits in both pancreatoduodenectomized patients and gastrectomized patients. There were mean peaks of

* Insulin immunoassay kit was obtained from CEA-IRE-SORIN association, France.

TABLE 1. *Summary of Pancreatoduodenectomized Patients*

Case	Age (yrs)	Sex	B. W. (Kg)	Height (cm)	Lesions	Surgical Procedures*	After Operation
1. T.O.	42	M	52	165	Cancer of head of the pancreas	Child	3 yrs 9 mos
2. T.K.	59	M	54	168	Cancer of ampulla	Child	3 yrs 1 mo
3. I.E.	65	M	51	164	Cancer of papilla of Vater	Cattell	2 yrs 10 mos
4. T.S.	67	M	50	161	Cancer of ampulla	Child	2 yrs 1 mo
5. M.Y.	48	M	48	163	Rhabdomyoma of papilla of Vater	Child	1 yr 5 mos
6. Y.H.	57	F	32	145	Cancer of ampulla	Whipple	8 mos
7. S.I.	48	M	56	172	Cancer of papilla of Vater	Cattell	5 mos
8. Z.O.	72	M	42	159	Cancer of ampulla	Child	2 mos
9. K.O.	52	M	50	162	Cancer of ampulla	Child	2 mos
10. M.Y.	56	F	35	159	Cancer of ampulla	Child	5 weeks

* Following pancreatoduodenectomy and cholecystectomy, the series of anastomoses (choledochojejunostomy, pancreatojejunostomy and gastrojejunostomy) was made in all cases. This column indicates adopted types of the reconstruction (for details, see Partipilo, A. V.: Surgical Technique and Principles of Operative Surgery 6th Ed., Philadelphia, Lea & Febiger, p. 691–692).

132.7 mg/dl (S.E. ± 7.6) and 155.3 mg/dl (S.E. ± 6.4) at 30 minutes in normal subjects and gastrectomized patients respectively. As expected, the levels decreased rapidly reaching under 100 mg/dl after 90 minutes in both groups; however, in pancreatoduodenectomized patients the plasma levels of glucose increased soon after glucose ingestion and remained elevated throughout the test; mean peak of 181.0 mg/dl (S.E. ± 11.3) at 60 minutes, 120.4 mg/dl (S.E. ± 20.0) even at 180 minutes. Statistical differences between the groups are presented in Table 2.

Plasma Levels of Non-esterified Fatty Acids (Fig. 3.)

There was no statistical difference of fasting plasma NEFA levels between the groups. After glucose ingestion, plasma NEFA levels decreased rapidly, and were enhanced after 90 minutes in both normal subjects and gastrectomized patients. In pancreatoduodenectomized patients, however, these levels progressively declined up to 120 minutes. Statistical differences between the groups are presented in Table 3.

Plasma Levels of Immunoreactive Insulin (Fig. 4.)

Although fasting plasma IRI levels in pancreatoduodenectomized patients were low in comparison with those in normal subjects and gastrectomized patients, there was not statistical difference between the groups. After glucose ingestion, plasma IRI levels in normal subjects rapidly increased and returned to control gradually; mean peak value was 74.9 μU/ml (S.E. ± 9.5) at 30 minutes. The levels in pancreatoduodenectomized patients increased slightly; mean peak value was 43.9 μU/ml (S.E. ± 14.3) at 90 minutes. On the other hand, levels in gastrectomized patients increased significantly after glucose ingestion. Following the mean peak of 166.8 μU/ml (S.E. ± 28.2) at 30 minutes, the levels remained elevated until 120 minutes. Statistical differences between the groups are presented in Table 4.

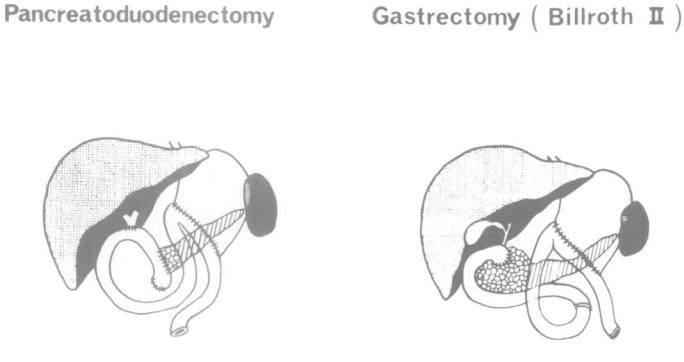

FIG. 1. Schema of pancreatoduodenectomy and sham operation—gastrectomy after the fashion of Billroth II. Reconstruction of the alimentary tract in the former is similar to that of the latter.

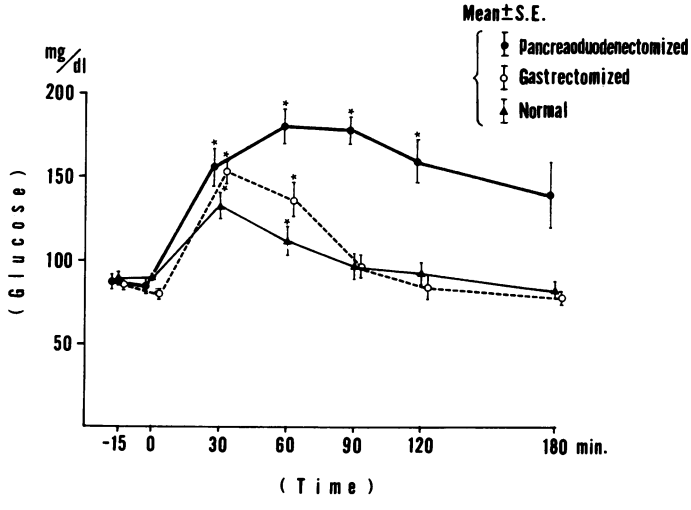

FIG. 2. Plasma levels of glucose during OGTT (100g). *Statistically significant differences as compared with both values before the glucose load ($p < 0.05$).

TABLE 2. *Plasma Glucose Levels during OGTT (100g)*

Time (min)	−15	0	30	60	90	120	180
Normal Subjects							
n	8	12	12	12	12	12	12
Mean (mg/dl)	88.9	89.6	132.7††	112.2*	96.8†	93.2‡	81.5
S.E. (mg/dl)	±3.5	±2.2	±7.6	±8.8	±8.0	±5.6	±3.7
Pancreatoduodenectomized Patients							
n	10	10	10	10	7	10	10
Mean (mg/dl)	87.0	84.1	156.2	181.0*	177.7†	159.3**	120.4
S.E. (mg/dl)	±5.1	±3.6	±11.2	±11.3§	±8.1‖	±14.5‡	±20.0
Gastrectomized Patients							
n	12	12	12	12	12	12	12
Mean (mg/dl)	84.6	81.6	155.3††	137.8§	97.8‖	86.6**	80.8
S.E. (mg/dl)	±2.5	±2.9	±6.4	±9.7	±7.4	±6.4	±3.5

Statistically significant differences;
* $p < 0.001$, † $p < 0.001$, ‡ $0.01 < p < 0.02$
§ $0.001 < p < 0.01$, ‖ $p < 0.001$, ** $0.001 < p < 0.01$
†† $0.01 < p < 0.02$

Discussion

A number of observations[3,4] have been reported on lack of glucose tolerance in pancreatoduodenectomized patients in whom fasting blood sugar levels were within normal limits. On the other hand, it has been also reported that abnormal glucose tolerance curves were not noted even after 75% caudal resection of the pancreas was performed due to blunt trauma.[13] There are no clinical criteria for the minimum requirement of pancreas without producing glucose intolerance. It is difficult to form a criterion, since information concerning use of glucose in pancreatoduodenectomized patients still remains obscure. There are many factors which influence glucose metabolism in humans, however, investigations concerning these factors are surprisingly few among metabolic studies after pancreatoduodenal resection.[10,11,15]

One of the objectives of this study was to elucidate endocrine function of the remnant of the pancreas after pancreatoduodenal resection due to the non-functioning tumors of the pancreas. With uniform materials, 10 pancreatoduodenectomized patients were examined; in whom at least a caudal half of the pancreas had been preserved. These patients are functioning well in daily life without the need of any particular treatment. Objective physical examination revealed them to be healthy and routine laboratory examinations do not present any abnormal findings. The fasting blood sugar levels are within normal limits and urinary sugars cannot be detected. There is no statistically significant difference of fasting plasma levels of glucose, NEFA, and of IRI between pancreato-

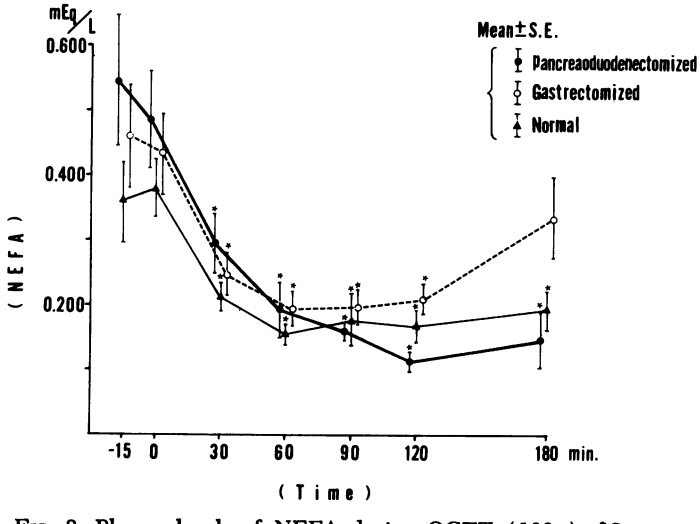

FIG. 3. Plasma levels of NEFA during OGTT (100g). *Statistically significant differences as compared with both values before the glucose load ($p < 0.05$).

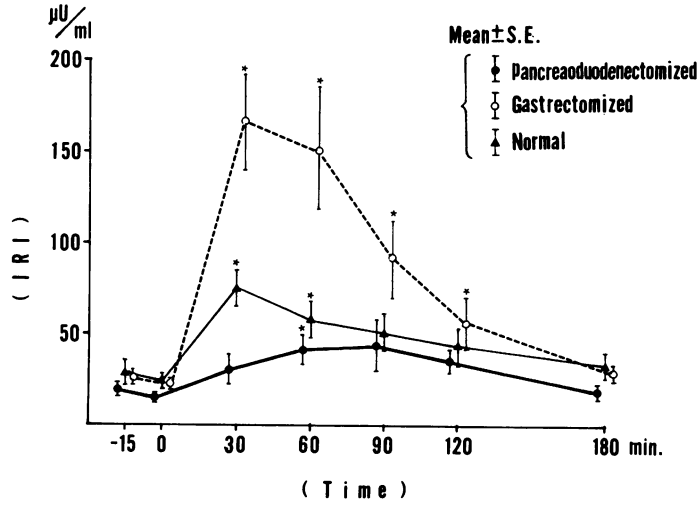

FIG. 4. Plasma levels of IRI during OGTT (100g). *Statistically significant differences as compared with both values before the glucose load ($p < 0.05$).

TABLE 3. *Plasma NEFA Levels during OGTT (100g)*

Time (min)	−15	0	30	60	90	120	180
Normal Subjects							
n	7	12	12	12	12	12	12
Mean (mEq/L)	0.366	0.380	0.212	0.157	0.179	0.168	0.195*
S.E. (mEq/L)	±0.045	±0.045	±0.021	±0.013	±0.031	±0.021	±0.030
Pancreatoduodenectomized Patients							
n	9	9	9	9	6	9	9
Mean (mEq/L)	0.545	0.479	0.295	0.195	0.161	0.114†	0.151‡
S.E. (mEq/L)	±0.104	±0.071	±0.044	±0.033	±0.017	±0.016	±0.046
Gastrectomized Patients							
n	12	12	12	12	12	12	12
Mean (mEq/L)	0.460	0.433	0.258	0.192	0.196	0.208†	0.344*
S.E. (mEq/L)	±0.082	±0.067	±0.035	±0.029	±0.028	±0.038	±0.063‡

Statistically significant differences;
* $0.001 < p < 0.01$
† $0.02 < p < 0.05$, ‡ $0.02 < p < 0.05$

duodenectomized patients and normal subjects. For these reasons, evaluation of endocrine function of the remnant of the pancreas can not be clarified when estimating fasting plasma levels alone.

The oral glucose tolerance test was carried out for the following reasons: 1) physiological loading, 2) absorption of glucose through the alimentary tract can be investigated. In pancreatoduodenectomized patients, glucose intolerance is clearly revealed, that is, in these patients prolonged hyperglycemia and the slow return of blood sugar levels to a normal range are noted. Regarding the relationship between glucose and NEFA during the oral glucose tolerance test, plasma NEFA levels are suppressed until plasma glucose levels decline in pancreatoduodenectomized patients. So-called "caloric homeostasis"[5] appears to be well maintained even among these patients. There is no statistically significant difference in glucose plasma levels at 30 minutes among these patients or normal subjects. This suggests that in these patients absorption of glucose is not disturbed. In normal subjects, plasma levels of IRI are significantly increased according to the initial elevation of plasma levels of glucose, then rapidly decreased. On the other hand, while plasma levels of glucose increased soon after glucose ingestion and remain elevated, plasma levels of IRI do not increase. Also, in these patients IRI plasma levels are significantly higher than those at fasting only at 60 minutes ($0.02 < p < 0.05$). Regarding statistical differences among IRI plasma levels between normal subjects and the patients, there is only a difference at 30 minutes ($0.001 < p < 0.01$). On the basis of such evidence, it can be concluded that the ability of the pancreas to secrete insulin in response to hyperglycemia is impaired in pancreatoduodenectomized patients.

Reconstruction of the alimentary tract such as is performed in pancreatoduodenal resection may play some role in the glucose intolerance of pancreatoduodenectomized patients. Plasma levels of IRI in gastrectomized patients increased significantly, responding to the initial hyperglycemia up to 120 minutes. The 90 minute blood sugar level stayed within normal limits. From this observation, it can be concluded that oral glucose ingestion

TABLE 4. *Plasma IRI Levels during OGTT (100g)*

Time (min)	−15	0	30	60	90	120	180
Normal Subjects							
n	7	12	12	12	12	12	12
Mean (μU/ml)	27.7	24.2	74.9*	57.6‡	50.8	43.8	33.1
S.E. (μU/ml)	±6.0	±4.0	±9.5†	±10.4	±10.3	±8.7	±7.2
Pancreatoduodenectomized Patients							
n	10	10	10	10	7	10	10
Mean (μU/ml)	18.5	14.7	31.2*	41.3‖	43.9	34.9	18.2
S.E. (μU/ml)	±3.6	±2.1	±8.5§	±9.4	±14.3	±6.3	±3.8
Gastrectomized Patients							
n	12	12	12	12	12	12	12
Mean (μU/ml)	25.9	21.7	166.8§	151.1‖	97.1	55.8	28.5
S.E. (μU/ml)	±3.8	±3.1	±28.2†	±34.8‡	±21.9	±12.9	±4.0

Statistically significant differences;
* $0.001 < p < 0.01$
† $0.01 < p < 0.02$, ‡ $0.02 < p < 0.05$
§ $p < 0.001$, ‖ $p < 0.001$

is an effective stimulation for the pancreas when investigating insulin secretion and could also be utilized for the patients who have undergone gastrectomy with gastrojejunostomy. With regard to plasma levels of glucose among gastrectomized and pancreatoduodenectomized patients there is no statistical difference either at fasting or 30 minutes. This fact suggests that absorption of glucose has not been disturbed in these two groups. At 60, 90 and 120 minutes, blood sugar levels of pancreatoduodenectomized patients are significantly higher than those of gastrectomized patients. On the other hand, statistical differences of plasma IRI levels between the gastrectomized and the pancreatoduodenectomized are clearly demonstrated (Table 4). In the gastrectomized, hypersecretion of insulin is noted whereas in the pancreatoduodenectomized, a hyposecretion is evident. It is consequently concluded that reconstruction of the alimentary tract in pancreatoduodenal resection does not contribute to glucose intolerance or to hyposecretion of insulin in pancreatoduodenectomized patients.

From the preceding facts it is reasonable to presume that insufficient secretion of insulin from the remnant of the pancreas is one of major causes of glucose intolerance during the oral glucose tolerance test in pancreatoduodenectomized patients.

Summary

Pancreatoduodenectomized patients in whom at least caudal half of the pancreas had been preserved were subjected to an oral glucose tolerance test. Fasting plasma levels of glucose, NEFA and of IRI were within normal limits, however, glucose intolerance was obvious following glucose ingestion. Estimation of plasma levels of glucose, NEFA and of IRI throughout the test strongly suggest that impaired insulin secretion from the remnant of the pancreas is one of major causes of glucose intolerance among these patients. On the other hand, from the results of the oral glucose tolerance test in gastrectomized patients, it is concluded that reconstruction of the alimentary tract in pancreatoduodenal resection does not contribute to glucose intolerance.

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