Clinical Research Article

Glucose Metabolism After Pancreatectomy: Opposite Extremes Between Pancreaticoduodenectomy and Distal Pancreatectomy

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Abbreviations: AUC, area under the curve; 75gOGTT, 75-g oral glucose tolerance test; BMI, body mass index; BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; DP, distal pancreatectomy; FBG, fasting blood glucose; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; PD, pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy.

Received: 6 October 2020; Editorial Decision: 14 January 2021; First Published Online: 23 January 2021; Corrected and Typeset: 9 February 2021.

Abstract

Context: The rate of glucose metabolism changes drastically after partial pancreatectomy.

Objective: This work aims to analyze changes in patients’ glucose metabolism and endocrine and exocrine function before and after partial pancreatectomy relative to different resection types (Kindai Prospective Study on Metabolism and Endocrinology after Pancreatectomy: KIP-MEP study).

Methods: A series of 278 consecutive patients with scheduled pancreatectomy were enrolled into our prospective study. Of them, 109 individuals without diabetes, who underwent partial pancreatectomy, were investigated. Data were compared between patients with pancreaticoduodenectomy (PD, n = 73) and those with distal pancreatectomy (DP, n = 36).

Results: Blood glucose levels during the 75-g oral glucose tolerance test (75gOGTT) significantly decreased after pancreatectomy in the PD group (area under the curve [AUC] –9.3%, P < .01), and significantly increased in the DP population (AUC + 16.8%, P < .01). Insulin secretion rate during the 75gOGTT and glucagon stimulation test significantly decreased after pancreatectomy both in the PD and DP groups (P < .001). Both groups showed similar homeostasis model assessment of insulin resistance (HOMA-IR) values after pancreatectomy. Decrease in exocrine function quality after pancreatectomy was
more marked in association with PD than DP (P < .01). Multiple regression analysis indicated that resection type and preoperative HOMA-IR independently influenced glucose tolerance-related postoperative outcomes. **Conclusions:** Blood glucose levels after the OGTT differed markedly between PD and DP populations. The observed differences between PD and DP suggest the importance of individualization in the management of metabolism and nutrition after partial pancreatectomy.

**Key Words:** BT-PABA test, distal pancreatectomy, glucose metabolism, insulin secretion, pancreaticoduodenectomy, partial pancreatectomy

The pancreas is a pivotal organ that secretes various hormones and digestive enzymes. Insulin and glucagon, secreted by pancreatic β and α cells, respectively, play a major role in glucose metabolism (1-4). In addition to its endocrine function, the organ also influences nutritional status through exocrine function, including amylase, lipase, elastase, trypsin, and chymotrypsin, which are secreted by acinar cells. Resection of the pancreas (pancreatectomy), therefore, contributes both to endocrine and exocrine pancreatic dysfunction, leading to glucose intolerance and various nutritional disorders (4).

Pancreatectomy is classified into 2 major types: partial and total pancreatic resection. Total pancreatectomy results in complete pancreatic endocrine and exocrine function deficiency, leading to difficulties in achieving glycemic control (5). In contrast, partial pancreatectomy enables the retention of endocrine and exocrine pancreatic system function, and allows for easier blood glucose control than total pancreatectomy. Therefore, there is a general trend toward the use of partial rather than total pancreatectomy, except under specific conditions (6-8). Recent improvements in diagnosis have allowed for the early detection of cancerous lesions, such as intraductal papillary mucinous neoplasm, resulting in an increase in the number of partial pancreatectomies with better prognoses. Gaining an understanding of the changes in patients’ metabolic, endocrine, and exocrine function after partial pancreatectomy is, therefore, important for the provision of optimal metabolism and nutrition-related management.

Partial pancreatectomy is classified into 2 major subtypes: pancreaticoduodenectomy (PD) and distal pancreatectomy (DP); although both are associated with similar resection volumes, the manner in which the stomach and gut as well as residual pancreas are handled and reconstructed markedly differs between them. This suggests the presence of differences in the glucose metabolism-related outcomes, and exocrine and endocrine function, following pancreatectomy. While several studies have investigated patients’ glycemic status after partial pancreatectomy (9-16), the similarities and differences in their endocrine and exocrine function across different resection types have not been well characterized. In this study, we aimed to investigate the changes in the rate of glucose metabolism and endocrine and exocrine function, following PD and DP in patients without diabetes.

**Materials and Methods**

**Participants**

In total, 278 consecutive patients who were scheduled to undergo pancreatectomy at the Kindai University Hospital, Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, between June 2015 and February 2018, were prospectively enrolled into the Kindai Prospective Study on Metabolism and Endocrinology after Pancreatectomy (KIP-MEP study). In the present study, participants who satisfied the following criteria were analyzed: underwent partial pancreatectomy (PD or DP); age older than 20 years; provision of consent to participate; and absence of advanced cancers other than those pertaining to the pancreas. We excluded participants with diabetes mellitus, those who underwent total pancreatectomy, and those in whom participation was deemed inappropriate by the doctors in charge. We also excluded patients with chronic pancreatitis for the avoidance of heterogeneity arising from abnormalities in the preserved pancreas. Eventually, 109 patients were enrolled (73 underwent PD and 36 DP). All patients provided written informed consent. This study was approved by the institutional ethics committee of the Kindai University Faculty of Medicine.

**Surgical Techniques**

For PD, subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) is performed as a standard procedure in our center. Briefly, the stomach was divided 3 cm above the pylorus ring at the pyloric region of the stomach. Reconstruction was performed with end-to-side choledochojunostomy, pancreatogastrostomy, and end-to-side gastrojejunostomy. For DP, distal
pancreatectomy with splenectomy is performed as a standard. After dividing the splenic vessels, the pancreas was transected at the levels of the portal and superior mesenteric vein in most cases.

Data Collection
All patients were admitted to Kindai University Hospital, Department of Endocrinology, Metabolism, and Diabetes, before and after pancreatectomy. “Before pancreatectomy” referred to the period approximately a month before the surgery, whereas “after pancreatectomy” referred to the period less than a month after the surgery and after improvements were observed in the patients’ general condition. General health status was assessed by normalized laboratory data, such as those pertaining to peripheral blood white blood cell and C-reactive protein levels (Supplementary Table 1 [17]), as well as by the normal intake of meals and absence of abdominal symptoms including nausea, vomiting, abdominal pain and cramping, frequent bowel movements, watery diarrhea, and fatty stools. Following pancreatectomy, inspection was initiated at 14.3 ± 6.6 (mean ± SD) days in the PD group and 10.8 ± 4.5 days in the DP group (P < .05). For the detailed assessment of the degree of deterioration in the rate of glucose metabolism and endocrine function after pancreatectomy, we analyzed only patients without diabetes before pancreatectomy. Diabetes was defined, per World Health Organization criteria, as either a fasting blood glucose (FBG) level greater than or equal to 7.0 mmol/L, as detected on 2 or more separate days, or an abnormal FBG level that was detected once and blood glucose level greater than or equal to 11.1 mmol/L as measured 2 hours after a 75-g oral glucose tolerance test (75-gOGTT).

We prospectively investigated the changes in the patients’ glucose metabolism, and pancreatic endocrine and exocrine function, and indicators of nutrition before and after pancreatectomy. Glucose metabolism and endocrine function were assessed using the 75gOGTT and glucagon stimulation test, respectively, and exocrine function by the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test. The 75gOGTT was performed after an overnight fast. Blood samples were drawn at 0, 30, 60, 90, 120, 150, and 180 minutes, and the levels of blood glucose, serum insulin, and C-peptide were measured. The areas under the curve AUCs for glucose, insulin, and C-peptide were calculated using the trapezoidal rule. As an index of early insulin response to glucose, the insulinogenic index was calculated by the increment in the level of serum insulin from 0 to 30 minutes (ΔIRI 30) after a glucose challenge divided by the increment in the blood glucose level from 0 to 30 minutes (ΔBG 30). Glucagon stimulation tests were performed by the intravenous injection of 1-mg glucagon (Novo Nordisk Pharma Ltd). Blood samples were collected at 0 and 5 minutes, and the increment in the level of C-peptide from 0 to 5 minutes (ΔC-peptide) was calculated. As an index of insulin sensitivity, the homeostasis model assessment of insulin resistance (HOMA-IR) value was calculated using the following formula: (fasting insulin [µIU/mL] × fasting glucose [mmol/L])/22.5. Exocrine function was assessed using the BT-PABA test (18). BT-PABA was administered orally, and the rate of urinary PABA excretion was determined 6 hours after administration. The influence of comorbidities on glucose tolerance was assessed using the Charlson comorbidity index (19).

Statistical Analyses
Quantitative data were expressed as mean ± SEM. Differences in the quantitative data were expressed as mean differences and 95% CIs. Categorical variables were expressed as the number (percentage) of patients. All statistical analyses were performed using the Bell Curve for Excel software (Social Survey Research Information Co Ltd). Categorical variables were compared using the chi-square test, and continuous variables using paired or unpaired t tests. Statistical significance was defined as P less than .05. Logistic regression analysis with the forward-backward stepwise selection method was performed for the calculation of the adjusted odds ratio (OR) with its 95% CI for the factors that were potentially independently associated with deteriorations in the degree of glucose tolerance after pancreatectomy. The difference between the AUCs for glucose after pancreatectomy and before pancreatectomy was used as an indicator of the degree of deterioration of glucose tolerance after pancreatectomy, and was selected as a response variable. Preoperative indicators possibly related to the deterioration of glucose tolerance after pancreatectomy were selected as explanatory variables.

Results
Baseline Characteristics
The clinical characteristics of the participants before pancreatectomy are shown in Table 1. Of the 109 patients, 73 underwent PD and 36 DP. None of the participants had diabetes (glycated hemoglobin $A_1c$ [HbA$_1c$] level 40.3 ± 0.46 mmol/mol [5.84 ± 0.04%], FBG level 5.10 ± 0.05 mmol/L). The demographic data were comparable between the PD and DP groups, except for the slight male predominance noted in the PD group.
The BT-PABA test was performed in 89 patients (60 with PD and 29 with DP). The pancreatic enzyme drug was pancrelipase (Mylan EPD G.K.).

Changes in Demographic Parameters and Exocrine Function After Pancreatectomy

The patients’ body weight significantly decreased after pancreatectomy in the PD group (58.9 ± 1.5 vs 53.2 ± 1.3 kg; P < .01); a decreasing tendency was observed in the DP group (54.6 ± 2.0 vs 50.2 ± 1.7 kg; NS) (Table 2). Body mass index (BMI) also significantly decreased in the PD group (22.7 ± 0.43 vs 20.5 ± 0.37 kg/m²; P < .001). BT-PABA test, % significantly decreased in the PD group (16.0 ± 2.4 vs 10.0 ± 1.4, NS) and DP (1.34 ± 0.13 vs 1.12 ± 0.13, NS) groups.

For the evaluation of exocrine function, the BT-PABA test was performed in 89 patients (60 with PD and 29 with DP). The PABA value decreased significantly after pancreatectomy both in the PD (57.2 ± 1.5% vs 38.9 ± 2.3, P < .001) and DP (61.2 ± 2.0% vs 53.9 ± 2.9, P < .05) groups (Table 2). The decrease in the BT-PABA test value was more marked in the PD group than DP group (−32.0% vs −11.9%, P < .01), suggesting that PD has a stronger effect on pancreatic exocrine than DP.

Glucose Tolerance and Insulin Secretion

Pancreaticoduodenectomy

We compared the results of the 75gOGTT (values of 0, 30, 60, 90, 120, 150, and 180 minutes), and AUCs for glucose, insulin, and C-peptide before and after PD (Fig. 1A-1C). The blood glucose levels after PD were significantly lower than those before PD at 30, 60, 90, 120, and 150 minutes, but higher at 0 minutes. Insulin and C-peptide levels after PD were also significantly lower than those before PD at all time points after the 75gOGTT. AUCs for glucose, insulin, and C-peptide decreased significantly after PD (Table 2). The strength of the early insulin response to glucose, as evaluated by the insulinogenic index, decreased significantly after pancreatectomy (16.0 ± 2.4 vs 10.0 ± 1.4, P < .05) (see Table 2).

To better understand the mechanism of insulin secretion, we evaluated the rate of insulin secretion by a glucagon stimulation test, which differs from the OGTT both in the secretagogue used (glucagon vs glucose) and administration route (intravenous vs oral) (see Table 2). The C-peptide values at 0 and 5 minutes decreased significantly...
Table 2. Changes in demographic, glycemic, endocrine, and exocrine parameters after pancreatectomy

|                      | Preoperative | Postoperative | Difference (95% CI) | Preoperative | Postoperative | Difference (95% CI) |
|----------------------|--------------|---------------|---------------------|--------------|---------------|---------------------|
|                      | PD (N = 73)  | DP (N = 36)   |                     |              |               |                     |
| Body weight, kg      | 58.9 ± 1.5   | 53.2 ± 1.3b   | −5.7 (−6.5 to −4.9) | 54.6 ± 2.0   | 50.2 ± 1.7     | −4.4 (−5.2 to −3.5) |
| BMI, kg/m²            | 22.7 ± 0.43  | 20.5 ± 0.37c  | −2.2 (−2.5 to −1.9) | 21.6 ± 0.66  | 19.9 ± 0.57     | −1.7 (−2.0 to −1.4) |
| HbA₁c, mmol/mol      | 40.1 ± 0.60  | 38.3 ± 0.50   | −1.7 (−2.8 to −0.65) | 40.8 ± 0.69  | 40.6 ± 0.63     | −0.18 (−1.1 to +0.75) |
| HbA₁c, %             | 5.82 ± 0.05  | 5.66 ± 0.05c  | −0.16 (−0.26 to −0.06) | 5.88 ± 0.06  | 5.87 ± 0.06     | −0.02 (−0.10 to +0.07) |
| OGTT                 |              |               |                     |              |               |                     |
| Insulinogenic index  | 16.0 ± 2.4   | 10.0 ± 1.4c   | 6.0 (−10.1 to −1.9) | 15.9 ± 2.3   | 9.0 ± 1.1a     | −6.9 (−11.5 to −2.3) |
| AUC glucose, mmol/L × min | 1510.8 ± 35.1 | 1370.1 ± 27.3b | −140.6 (−208.5 to −72.8) | 1474.3 ± 49.9 | 1721.8 ± 59.2b | 247.6 (130.1 to +365.1) |
| AUC insulin, µU/mL × min | 10 451.7 ± 1127.4 | 5304.7 ± 502.9c | −5146.9 (−7343.6 to −2950.3) | 10 589.5 ± 1007.0 | 1721.8 ± 59.2b | −4030.3 (−5854.0 to −2206.7) |
| AUC CPR (nmol/L × min) | 506.7 ± 21.8  | 284.5 ± 27.2c | −222.1 (−265.7 to −178.5) | 495.7 ± 32.1  | 368.0 ± 25.5c | −127.7 (−182.8 to −72.6) |
| Glucagon stimulation test |              |               |                     |              |               |                     |
| CPR at 0 min, nmol/L | 0.57 ± 0.03  | 0.44 ± 0.02c  | −0.13 (−0.17 to −0.08) | 0.54 ± 0.03  | 0.44 ± 0.03d  | −0.09 (−0.13 to −0.05) |
| CPR at 5 min, nmol/L | 1.72 ± 0.09  | 1.03 ± 0.06c  | −0.69 (−0.83 to −0.55) | 1.73 ± 0.11  | 1.13 ± 0.08c  | −0.60 (−0.76 to −0.44) |
| ΔC-peptide, nmol/L  | 1.15 ± 0.08  | 0.59 ± 0.05c  | −0.56 (−0.68 to −0.45) | 1.19 ± 0.10  | 0.68 ± 0.06c  | −0.51 (−0.65 to −0.36) |
| HOMA-IR              | 1.44 ± 0.10  | 1.18 ± 0.10   | −0.26 (−0.45 to −0.08) | 1.34 ± 0.13  | 1.12 ± 0.13   | −0.22 (−0.44 to −0.002) |
| BT-PABA test, %      | 57.2 ± 1.5   | 38.9 ± 2.3c   | −18.3 (−23.0 to −13.6) | 61.2 ± 2.0   | 53.9 ± 2.9d   | −7.3 (−13.2 to −1.4) |

Data are presented as mean ± SEM. The variables were compared using paired t tests between the preoperative and postoperative state. Statistical significance was defined as P less than .05. Differences are expressed as mean differences and 95% CI. Abbreviations: AUC, area under the curve; BMI, body mass index; BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; CPR, C-peptide immunoreactivity; DP, distal pancreatectomy; HbA₁c, glycated hemoglobin A₁c; HOMA-IR, homeostasis model assessment of insulin resistance; NS, not significant; OGTT, oral glucose tolerance test; PD, pancreaticoduodenectomy.

aP less than .05.
bP less than .01.
cP less than .001.
dThe BT-PABA test was performed in 89 patients (60 with PD and 29 with DP).
after PD. The ΔC-peptide value also decreased significantly after PD (1.15-0.59 nmol/L).

Distal pancreatectomy
The blood glucose levels after DP were significantly higher than those before DP at 0, 90, 120, 150, and 180 minutes after the 75gOGTT (Fig. 1D). Consequently, the AUC for glucose increased significantly after DP (see Table 2), in contrast to the significant decrease noted in the PD group. The insulin levels at 0, 30, 60, 120, and 150 minutes after the 75gOGTT and C-peptide levels at all time points after the 75gOGTT were significantly lower after DP than before (Fig. 1E and 1F). The AUCs for insulin and C-peptide decreased significantly after DP (see Table 2). The strength of the early insulin response to glucose, as evaluated by the insulinogenic index, decreased significantly after pancreatectomy (15.9 ± 2.3 vs 9.0 ± 1.1, P < .05).

The rate of insulin secretion, as assessed by the glucagon stimulation test, decreased significantly after DP (see Table 2). The C-peptide values at 0 and 5 minutes were significantly lower after DP than before. The rate of increment in the C-peptide (ΔC-peptide) value also decreased significantly after DP (1.19-0.68 nmol/L) (see Table 2).

Comparison between pancreaticoduodenectomy and distal pancreatectomy groups
Changes in the patients’ metabolic, endocrine, and exocrine function after pancreatectomy are summarized in Fig. 2. The blood glucose levels decreased in the PD group and increased in the DP group (AUC during the OGTT –9% vs +17%, P < .001). The rate of insulin secretion, as assessed by the insulin and C-peptide reactivity response during the OGTT and increments in the C-peptide levels after the glucagon stimulation test, decreased in a similar manner both in the PD and DP groups; body weight and insulin resistance, as assessed by the HOMA-IR, also showed similar decreases across the groups. The degree of exocrine function, as assessed by the BT-PABA test, decreased in both groups, but the decrease was more pronounced in the PD group than the DP group (~32% vs –12%, P < .01).

The changes in the AUCs for blood glucose during the OGTT after pancreatectomy were categorized as 1) marked deterioration (≥ 10% increase), 2) mild deterioration (< 10% increase), 3) mild improvement (< 10% decrease), and 4) marked improvement (≥ 10% decrease). In total, 43.5% (32/73) of the patients showed marked improvement after PD, in contrast to the 8.3% (3/36) observed after DP (Fig. 3). However, 50% (18/36) of the patients
showed marked deterioration after DP, in contrast to the 15.1% (11/73) observed after PD (see Fig. 3), indicating that a larger number of patients with PD had an improved status, whereas those with DP tended to show a deteriorated status after pancreatectomy (P < .001, chi-square test).

Factors affecting glucose tolerance after pancreatectomy

For the clarification of the factors that contribute to the deterioration of glucose metabolism rate after pancreatectomy, we evaluated the factors affecting the AUCs for glucose between the improvement and deterioration groups. Significant differences were observed in terms of sex, BMI, postoperative BT-PABA, preoperative HOMA-IR, and resection type between the improvement and deterioration groups (Table 3). Female predominance was noted in the improvement group. The preoperative BMI, postoperative BMI, and preoperative HOMA-IR values were significantly higher in the improvement group than the deterioration group (see Table 3). In addition, the number of patients with PD was significantly higher in the improvement group (P < .001, chi-square test) (see Table 3).

Multiple regression analysis using the AUCs for blood glucose as dependent variables indicated that DP (OR 8.83; 95% CI, 3.02 to 25.8; P < .001) and preoperative HOMA-IR (OR 0.493; 95% CI, 0.257 to 0.944; P < .05) were independent factors affecting postoperative glucose tolerance-related outcomes (Table 4).

Discussion

In the present study, we observed that despite similarities in the resection volume and level of decrease in the rates of insulin secretion and insulin sensitivity after PD and DP, the blood glucose levels after the OGTT markedly differed between the PD and DP populations, showing a decrease in its association with PD and increase with DP.

While several clinical studies have focused on the development of diabetes mellitus after partial pancreatectomy (10-12, 20-22), most of them had a retrospective observational nature; few studies in this context have targeted populations with weak innate β-cell function, such as Japanese people (23). The strengths of our study are its prospective observational design, enrollment of Japanese people, and detailed assessment of glucose metabolism changes using the 75gOGTT, glucagon stimulation test, and BT-PABA test before and after partial pancreatectomy.

Partial pancreatectomy is associated with deteriorations in the rate of insulin secretion and glucose tolerance (24, 25). The present study, however, clearly demonstrates that the glucose metabolism–related changes observed after partial pancreatectomy are markedly different between PD and DP, with significant improvements in the degree of glucose tolerance observed following PD. The remnant pancreatic volume following PD is approximately 50% (26, 27), while the resected volume in PD (approximately 50%) (26, 27) is similar to or rather larger than that in DP (~30%–40%) (13, 28). The observed decrease in the insulin secretion rate in response both to oral glucose (see Fig. 1...
and Table 2) and intravenous glucagon (see Fig. 2 and Table 2) was similar between the PD and DP groups. The insulin sensitivity degree, as assessed by the HOMA-IR, was also similar between PD and DP, suggesting that factors other than insulin secretion and insulin sensitivity are responsible for the observed difference in the rate of glucose metabolism between PD and DP.

One possible mechanism is the association between pancreatic exocrine function and nutritional status. Our patients’ pancreatic exocrine function, as assessed by the BT-PABA test, was different between the PD and DP groups, with a significantly weaker function observed in association with PD than DP, consistent with a previous report (29). PD includes reconstruction of the residual pancreas and digestive tract, with either pancreaticogastrostomy or pancreaticojejunostomy. All the patients in the present study underwent pancreaticogastrostomy; therefore, the acidic environment in the stomach may have denatured the secreted pancreatic enzymes, leading to a more pronounced degree of exocrine insufficiency in the PD group than the

Table 3. Factors affecting areas under the curve for glucose, stratified by changes in glucose tolerance level after pancreatectomy in all patients

| Variable                                      | Improvement group (N = 57) | Deterioration group (N = 52) | P   |
|-----------------------------------------------|----------------------------|-----------------------------|-----|
| Age, y                                        | 65.7 ± 1.2                 | 66.6 ± 1.2                  | NS  |
| Male, n (%)                                   | 21 (36.8%)                 | 31 (59.6%)                  | <.05|
| Preoperative BMI, kg/m²                       | 23.3 ± 0.46                | 21.3 ± 0.53                 | <.01|
| Postoperative BMI, kg/m²                      | 21.2 ± 0.42                | 19.5 ± 0.42                 | <.01|
| Preoperative BT-PABA test, %a                 | 57.1 ± 1.7                 | 60.0 ± 1.6                  | NS  |
| Postoperative BT-PABA test, %a                | 39.1 ± 2.5                 | 48.8 ± 2.9                  | <.05|
| Preoperative HOMA-IR                          | 1.60 ± 0.11                | 1.20 ± 0.10                 | <.01|
| Postoperative HOMA-IR                         | 1.27 ± 0.11                | 1.04 ± 0.10                 | NS  |
| Preoperative insulinogenic index              | 14.8 ± 2.1                 | 17.3 ± 3.0                  | NS  |
| Postoperative insulinogenic index             | 9.86 ± 1.7                 | 9.46 ± 1.2                  | NS  |
| Type of resection                             | –                          | –                           | .001|
| PD, n (%)                                     | 49 (86.0%)                 | 24 (46.2%)                  |     |
| DP, n (%)                                     | 8 (14.0%)                  | 28 (53.8%)                  |     |
| Type of histology                             | –                          | –                           | NS  |
| Malignant, n (%)                              | 41 (71.9%)                 | 32 (61.5%)                  |     |
| Benign, n (%)                                 | 16 (28.1%)                 | 20 (38.5%)                  |     |
| Charlson comorbidity index                    | 0.58 ± 0.13                | 0.54 ± 0.11                 | NS  |

Data are presented as mean ± SEM.
Categorical variables were compared using the chi-square test, and continuous variables using unpaired t tests between the improvement and deterioration groups. Statistical significance was defined as P less than .05.
Abbreviations: BMI, body mass index; BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; DP, distal pancreatectomy; HOMA-IR, homeostasis model assessment of insulin resistance; NS, not significant; PD, pancreaticoduodenectomy.

Table 4. Multiple regression analysis of areas under the curve for blood glucose in all patients

| Variable                                      | OR   | 95% CI           | P (logistic regression analysis) |
|-----------------------------------------------|------|-----------------|----------------------------------|
| Age, y                                        | –    | –               | –                                |
| Sex                                           | –    | –               | –                                |
| Type of resection on DP                       | 8.83 | 3.02-25.8       | <.001                            |
| Type of histology                             | –    | –               | –                                |
| Preoperative insulinogenic index              | –    | –               | –                                |
| Preoperative HOMA-IR                          | 0.493| 0.257-0.944     | <.05                             |
| Preoperative BMI, kg/m²                       | –    | –               | –                                |
| Preoperative BT-PABA test, %a                 | –    | –               | –                                |
| Charlson comorbidity index                    | –    | –               | –                                |

Statistical significance was defined as P less than .05.
Abbreviations: BMI, body mass index; BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; DP, distal pancreatectomy; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio.

The preoperative BT-PABA test was performed in 89 patients (46 in the improvement group and 43 in the deterioration group).
we did not measure our patients’ GLP-1 levels, the differences in the degree of glucose tolerance after PD and DP were most likely a result of the differences in the resection and reconstruction of the digestive tract and associated changes in the gut hormones, particularly GLP-1, in PD but not DP. Further studies must clarify the contribution of gut hormones to glucose tolerance after pancreatectomy.

Several clinical studies have focused on the deterioration of glucose tolerance and development of diabetes mellitus after partial pancreatectomy (10-12, 15, 16, 20-23). In a recent systematic review and meta-analysis of 37 studies focusing on diabetes after partial pancreatectomy, the incidence of new-onset diabetes was 16% (95% CI, 14%-17%) in PD and 21% (95% CI, 16%-25%) in DP (15). Most studies, however, focused on patients with PD alone, DP alone, or partial pancreatectomy as a whole, in which PD and DP were combined. Deteriorations in the degree of glucose tolerance and diabetes development have been observed in studies on partial pancreatectomy as a whole or DP alone. Burkhardt et al (10) reported that DP was related to a greater risk of diabetes development than PD, while Lee et al (20) showed that patients with DP had lower insulin secretion rates than control participants with a normal glucose tolerance status. After PD, however, both deterioration and amelioration of the patients’ diabetes status have been reported (41). Preexisting diabetes associated with pancreatic lesions was suggested to be ameliorated by the removal of the pancreatic lesion and/or changes in body mass and insulin sensitivity after pancreatectomy. For clarification of the metabolic and endocrine changes that occur after partial pancreatectomy, studies conducted among people without diabetes before surgery are indispensable. The present study, which enrolled people without diabetes before surgery, clearly demonstrated that partial pancreatectomy does not necessarily cause patients’ glucose tolerance status to deteriorate, particularly in PD settings in the short term, within less than a month after pancreatectomy. A previous study demonstrated no changes in patients’ blood glucose levels with decreased fasting insulin and C-peptide levels after PD, concluding that an acute reduction in pancreatic mass does not impair glucose tolerance with insulin sensitivity preservation (42). Our findings are in accordance with those of the aforementioned studies, in that the degree of glucose tolerance was not impaired despite a significant decrease in the rate of insulin secretion. However, in our study, the glucose tolerance degree improved significantly after PD. This difference may be attributed to variations in the evaluation periods (4 days vs less than a month) and the methods used in the evaluation of glucose tolerance (intravenous glucose vs oral glucose). In PD, because the head of the pancreas, duodenum, jejunum, portion of the stomach, and gallbladder are removed, the function of the digestive tract is profoundly affected. PD in our study was performed by SSPPD, which is accompanied by pylorus resection and pancreaticogastrostomy; therefore, the
food stagnation time might be short. Careful consideration is desirable when our results were translated into other variants of the Whipple procedure, pylorus preserving, or pancreaticojejunostomy, which are associated with long retaining of food stagnation.

Whereas Elliott et al reported that approximately 20% of the patients without diabetes who received PD or DP developed diabetes within 1 week after pancreatectomy, in our study, however, only 4% of the patients (1 patient with PD and 3 patients with DP) developed diabetes. This inconsistency may be attributed, among other reasons, to differences in the survey period (1998-2010 vs 2015-2018), and consequent improvements in the surgical procedures and treatments. The presence of comorbidities may have also influenced this difference. The comorbidity index observed in the present study was significantly lower than that noted in the study by Elliott et al (see Supplementary Table 2 [17]), suggesting that the presence of comorbidities contributed to differences in the incidence of diabetes between the 2 studies, and also confirming that comorbidities are important factors associated with the development of diabetes after pancreatectomy. In our study, no significant difference was observed in the comorbidity index between the improvement and deterioration groups, and the comorbidity index did not remain a significant factor in the multiple regression analysis of the AUCs for blood glucose in all patients (see Table 4).

In this study, an important factor to be considered is the variation in the degree of change in the AUCs for blood glucose within each group. Whereas the AUCs significantly decreased after PD and increased after DP, the AUC for blood glucose after PD does not always improve and that of after DP does not always deteriorate for each patient (see Fig. 3 and Supplementary Figure [17]), suggesting that individualization is necessary for the application of our results in clinical practice. To clarify the factors contributing to the deterioration of glucose tolerance after pancreatectomy, we evaluated the differences between the patients with a deteriorated status and those with improvements. Multiple-regression analysis of the AUCs for blood glucose revealed that resection type and preoperative HOMA-IR were independent factors, in that DP and smaller preoperative HOMA-IR values were associated with deteriorations in the degree of glucose tolerance after pancreatectomy (see Table 4). Patients with a high preoperative HOMA-IR value were expected to experience greater benefits, in terms of improved insulin resistance rates after pancreatectomy, resulting in a lower degree of glucose tolerance deterioration. Whether the preoperative HOMA-IR value is high or low is influenced by body composition. Accordingly, a study examining patients' body composition before and after pancreatectomy is currently under way.

A limitation of our study is that we investigated the changes in patients' glucose tolerance and pancreatic function for a relatively short duration (less than a month) after pancreatectomy. However, the results obtained in the nondiabetic population after the short-term partial pancreatectomy provides basic information for applied conditions such as diabetes, leading to successful treatment in the short term under various pathophysiologies. In addition, our major concerns are whether these short-term changes after surgery consequently lead to long-term problematic issues such as the development of diabetes mellitus and malnutrition. An increase in the number of people with endocrine and exocrine insufficiency was previously reported with an increasing follow-up period after pancreatectomy (43). In our short-term study, although the glucose tolerance did not always deteriorate in PD, the result does not necessarily reflect long-term efficacy and problems in glucose metabolism including diabetes and reactive hypoglycemia, as well as nutritional status including body weight and body composition. In particular, late onset of reactive hypoglycemia will be problematic, and sometimes severe in PD, accompanied with pylorus resection, as in our case. The follow-up study of these patients will provide important information on long-term effects and problematic issues relative to the short-term changes described in the present study. We are currently in the process of the prospective follow-up of various clinical indicators of metabolism and pancreatic endocrine and exocrine function, including 75gOGTTs, every 6 months after pancreatectomy at our institute.

In conclusion, our study demonstrated that the changes in the rate of glucose metabolism are markedly different between PD and DP, with significant improvements observed after PD and deteriorations after DP, despite similarities in the resection volume, insulin secretion rate, and insulin sensitivity rate. Multiple-regression analysis further confirmed that resection type was an independent factor affecting glucose tolerance–related outcomes postoperatively. The differences observed between PD and DP as well as the variations within each group suggest the importance of individualization in the management of metabolism and nutrition after partial pancreatectomy. Finally, the apparent improvement of glucose tolerance in the short term after PD does not necessarily reflect its long-term benefits. In the PD group, malnutrition, malabsorption, and postprandial hypoglycemia have greater chances of occurrence in the long term. In addition, the risk of diabetes increases as patients gain weight, gastric motility changes, and exocrine insufficiency are treated; therefore, long-term follow-up with careful evaluation is necessary after partial pancreatectomy.
Acknowledgments
We thank Ms Shie Hayase and Ms Mariko Shiota for their skilful technical assistance.

Financial Support: This work was supported in part by the Promotion and Mutual Aid Corporation for Private Schools of Japan (grant to E.N.).

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Disclosures: The authors have nothing to disclose.

Data Availability: Primary data sets generated and analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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