博士学位論文

膵体尾部切除術後の糖尿病発症率とその危険因子
：長期観察研究

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近畿大学大学院
医学研究科医学系専攻

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Doctoral Dissertation

High incidence of diabetes mellitus after distal pancreatectomy and its predictors: A long-term follow-up study

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Major in Medical Sciences
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同　意　書

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また、標記論文を再び学位論文として使用しないことを誓約いたします。

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High Incidence of Diabetes Mellitus After Distal Pancreatectomy and Its Predictors: A Long-term Follow-up Study

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Abstract

Context: Glucose tolerance worsens after distal pancreatectomy (DP); however, the long-term incidence and factors affecting interindividual variation in this worsening are unclear.

Objective: To investigate the changes in diabetes-related traits before and after DP and to clarify the incidence of diabetes and its predictors.

Methods: Among 493 registered patients, 117 underwent DP. Among these, 56 patients without diabetes before surgery were included in the study. Glucose and endocrine function were prospectively assessed using a 75-g oral glucose tolerance test preoperatively, 1 month after DP, and every 6 months thereafter for up to 36 months. Pancreatic volumetry was performed using multidetector row computed tomography before and after surgery.

Results: Insulin secretion decreased and blood glucose levels worsened after DP. Residual pancreatic volume was significantly associated with the reserve capacity of insulin secretion but not with blood glucose levels or the development of diabetes. Among 56 patients, 33 developed diabetes mellitus. The cumulative incidence of diabetes at 36 months after DP was 74.1%. Multivariate Cox regression analysis showed that impaired glucose tolerance as a preoperative factor as well as a decreased insulinogenic index and impaired glucose tolerance at 1 month postoperatively were identified as risk factors for diabetes following DP.

Conclusion: Impaired glucose tolerance and reduced early-phase insulin response to glucose are involved in the development of new-onset diabetes after DP; the latter is an additional factor in the development of diabetes and becomes apparent when pancreatic beta cell mass is reduced after DP.

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

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; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment for insulin resistance; IGT, impaired glucose tolerance; ISI (comp), insulin sensitivity index composite; MDCT, multidetector row computed tomography; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PD, pancreaticoduodenectomy; ROC, receiver operating characteristic; RPV, residual pancreatic volume.

Pancreatic β-cell dysfunction is an important risk factor for the development of diabetes. Known molecular mechanisms of pancreatic β-cell dysfunction include oxidative stress in pancreatic cells (1) and dedifferentiation (2), decreasing functional β-cell mass. The etiology of type 1 diabetes is mainly the autoimmune-mediated absolute loss of β-cell mass due to the destruction of pancreatic β cells, while that of type 2 diabetes is due to insulin resistance, resulting in absolute and relative insulin deficiency, respectively (3). In both cases, an insufficient functional β-cell mass is involved in the pathogenesis of diabetes mellitus.

Pancreatectomy provides a unique opportunity for β-cell adaptation to decreased β-cell mass. Therefore, we focused on the insufficiency of pancreatic β-cell function and the development of diabetes after pancreatectomy (4-6). In a total pancreatectomy, pancreatic β cells (and α cells) are completely lost, resulting in insulin dependence requiring lifelong insulin therapy, as in type 1 diabetes (4). In partial pancreatectomy, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), approximately 50% of the pancreatic volume is removed (7-10). A decrease in pancreatic volume is expected to decrease β-cell mass and insulin secretory capacity, resulting in a worsening of glucose tolerance. However, our previous studies have shown that in the early postoperative period (1 month after surgery), there was a significant difference in postoperative glucose metabolism between PD and DP, with PD improving blood glucose levels and DP worsening them in many cases. Therefore, we speculated that in DP, blood glucose worsened purely due to

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a decrease in pancreatic β-cell volume, whereas in PD, blood glucose did not necessarily worsen due to resection and reconstruction of the digestive tract in addition to a decrease in β-cell volume (5). In PD, subsequent long-term follow-up has revealed that a decrease in the preoperative insulinogenic index is a risk factor for the development of postoperative diabetes (6). However, in DP, the incidence of postoperative diabetes and risk factors for the development of diabetes need to be evaluated. In DP, the association between purely decreased β-cell mass and impaired glucose tolerance (IGT) may be assessed more clearly than in PD. Various clinical indices, such as age, sex (female), body mass index (BMI), HbA1c, IGT, insulinogenic index, and homeostatic model assessment for insulin resistance (HOMA-IR), have been reported as risk factors for new-onset diabetes after DP (7, 10-12). However, few reports have examined insulin secretory capacity and glucose tolerance before and after DP in detail, with sufficient follow-up duration. In this study, we examined the incidence of new-onset diabetes mellitus after DP with a longitudinal evaluation of oral glucose tolerance test (OGTT) over 3 years and examined preoperative and postoperative factors associated with the development of diabetes mellitus, including insulin secretion capacity.

Materials and Methods

Participants

The Kindai Prospective Study on Metabolism and Endocrinology after Pancreatectomy (KIP-MEP) is a series of prospective studies measuring preoperative and postoperative glucose tolerance over time in patients scheduled for pancreatectomy. The KIP-MEP study is being conducted solely at the Kindai Hospital and has been ongoing since June 2015; this study analyzed 493 enrolled patients through November 2022. In the KIP-MEP study, only patients scheduled to undergo DP were included. Details of participant selection criteria and study protocol review have been described previously (6). Based on the exclusion criteria shown in Fig. 1, 56 patients were included in the study. According to the exclusion criteria, patients with diabetes mellitus before pancreatectomy were excluded to clarify the incidence and risk factors of new-onset diabetes after surgery. All patients provided written informed consent to participate in this study. This prospective, observational study protocol was reviewed and approved by the Institutional Ethics Committee of Kindai University Faculty of Medicine.

Surgical Techniques

DP with splenectomy was the standard procedure used in this study. In most cases, after treatment of the splenic vessels, the pancreas was cut at the level of the portal and superior mesenteric veins. Data on the underlying diseases that indicated DP in this study are presented elsewhere (Table S1 (13)).

Pancreatic Volumetry

The % residual pancreatic volume (%RPV) was determined retrospectively using multidetector row computed tomography (MDCT) images obtained 1 month before surgery. The contrast was administered intravenously before surgery; 0.5-mm slice

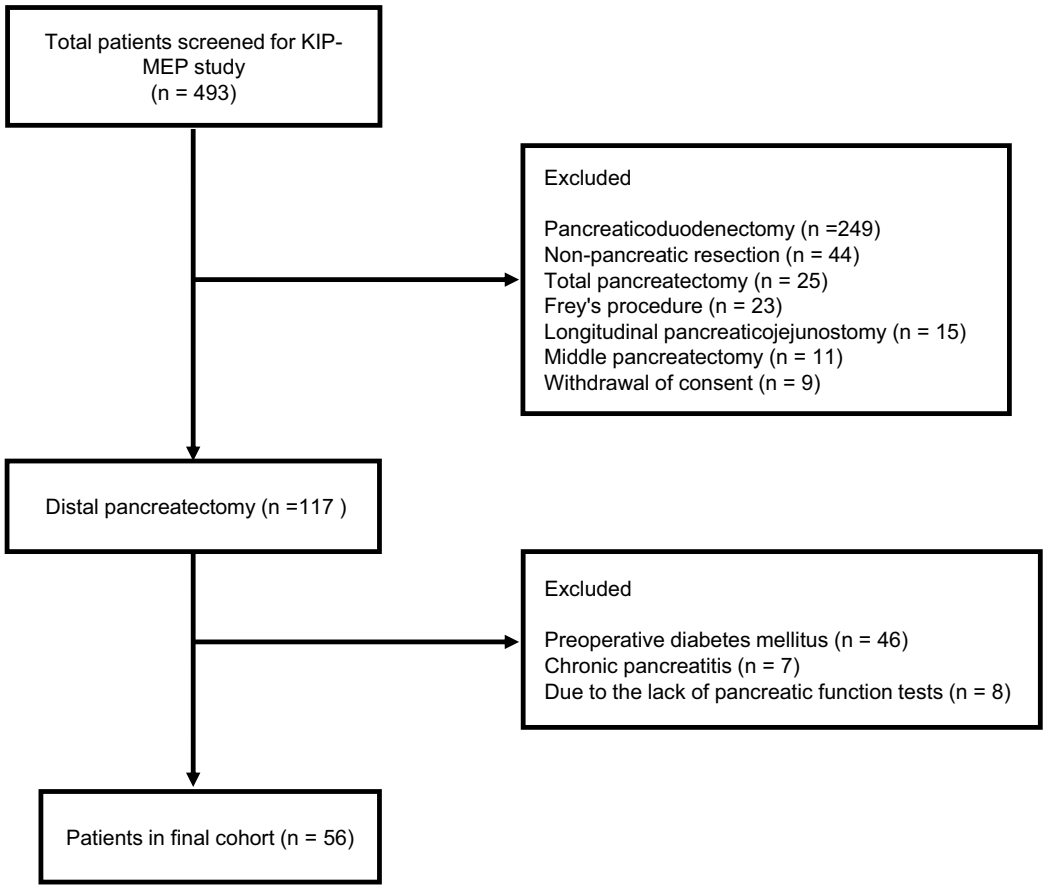

Figure 1. Flow diagram of patient enrollment. KIP-MEP, Kindai Prospective Study on Metabolism and Endocrinology after Pancreatectomy.

64-row serial MDCT images were acquired; MDCT data were transferred to a computer workstation (Synapse Vincent; Fujifilm Corporation, Japan), and the pancreatic volume was measured. As a specific step in the measurement method, first, in 1 slice of the preoperative CT, tumors, cystic lesions, pancreatic ducts, bile duct dilatations, and blood vessels were excluded; the boundaries of the pancreatic parenchyma were delineated, and the area of the preoperative total pancreatic parenchyma region was measured. Next, preoperative and postoperative CT scans were compared to delineate the actual pancreatic resection line. Subsequently, the boundaries of the pancreatic parenchyma and the resection line were delineated on preoperative CT, and the residual pancreatic area was measured based on the area surrounded by the boundaries and the resection line. The area of the pancreatic parenchymal region was calculated for each slice using the method described above, and the product of the pancreatic area (square mm) × slice thickness (mm) was used as the volume of pancreatic parenchyma per slice (mL). The total pancreatic parenchymal volume preoperatively and residual pancreatic volume postoperatively were calculated as the sum of the slice volumes. %RPV was calculated by the following equation: %RPV = RPV (mm)/total pancreatic parenchymal volume (mm) × 100. Finally, the %RPV was calculated for 54 of the 56 cases. Pancreatic volume measurements were performed by 1 person blinded to patient information such as diabetes onset or blood information but were familiar with the measurements.

Data Collection

The preoperative and postoperative examination schedules are shown elsewhere (Fig. S1 (13)). Preoperative and 1-month postoperative pancreatic endocrine and exocrine examinations and MDCT for pancreatic volumetry were performed during hospitalization. After discharge, a 75-g OGTT and measurement of glycemic control indices, including HbA1c, were performed every 6 months on an outpatient basis and monitored for up to 36 months. Details of data collection for the KIP-MEP study have been described previously (6). Briefly, pancreatic endocrine function was assessed mainly by the 75-g OGTT and glucagon stimulation test, and exocrine function was assessed by the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test; OGTTs were performed up to 180 minutes with sampling every 30 minutes. Based on the OGTT data, indices of various insulin secretory capacities and sensitivities were calculated. The insulinogenic index was calculated to evaluate early insulin response to glucose according to the following formula: (30 minutes – 0 minutes insulin [μIU/mL])/(30 minutes – 0 minutes glucose [mmol/L]). The insulin sensitivity index composite (ISI [comp]) was calculated to evaluate insulin sensitivity according to the following formula: 10 000/square root of (fasting glucose × fasting insulin × mean area under the curve (AUC) glucose × mean AUC insulin during OGTT with 120 minutes) (14). The adaptation and disposition indices, a measurement of insulin secretory capacity corrected for insulin resistance, were calculated from C-peptide, the insulinogenic index, and ISI (comp) using the 75-g OGTT (15, 16). C-peptide was determined using Elecsys C-Peptide kit (Catalog # 03184897, RRID:AB_2909476). Insulin was determined using Elecsys Insulin (Catalog # 07027559, RRID:AB_2909455).

Endpoints

The primary endpoint was new-onset diabetes mellitus. As secondary endpoints, factors associated with new-onset diabetes were evaluated using Cox regression analysis. The factors were classified into preoperative factors and factors at 1 month postoperatively. The definitions of new-onset diabetes used in this study are either (1) a postoperative HbA1c level ≥6.5% or (2) a fasting blood glucose (FBG) level ≥7.0 mmol/L, or 3) a blood glucose level ≥11.1 mmol/L after 2 hours on 75-g OGTT. These definitions were in accordance with the World Health Organization's criteria for the diagnosis of diabetes.

Statistics

Quantitative data are expressed as mean ± standard error of the mean (SEM). Categorical variables are expressed as frequencies (%) of patients. Categorical variables were compared using the chi-square test, and continuous variables were compared using paired or unpaired t-tests. Cumulative diabetes incidence was estimated from Kaplan–Meier survival curves and compared using the log-rank test. Risk factors for incident diabetes mellitus were assessed using Cox proportional hazards modeling, with the calculation of hazard ratios (HRs) and 95% CI. Variables included in the multivariate Cox regression analysis were selected from those previously reported as risk factors for new-onset diabetes (7, 10-12) and those that showed significant differences when progression to diabetes was compared with nonprogression in this study, and we also avoided duplication of variable categories. Receiver operating characteristic (ROC) curves were used to estimate the optimal cutoff values of the risk factors for predicting the occurrence of new-onset diabetes after surgery. All significance tests were 2-tailed. Statistical significance was defined as $P < .05$. All statistical analyses were performed using Bell Curve for Excel software (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Diabetes Development During Long-term Follow-up

To investigate the long-term incidence of diabetes, initially we prospectively followed up participants without diabetes for up to 36 months. In total, 33 patients developed diabetes during the 36-month follow-up. The cumulative incidence rates of new-onset diabetes after DP were 30.4% at 1 month, 52.7% at 6 months, 61.1% at 12 months, 63.9% at 18 and 24 months, 66.6% at 30 months, and 74.1% at 36 months (Fig. 2). Furthermore, when analyzing the incidence rate for each diagnostic index, it appears that 2 hours after the 75-g OGTT, HbA1c, and FBG play more significant roles in the development of new diabetes, in that order.

Changes in Various Clinical Parameters Before and 1 Month After DP: In Total Patients

Table 1 compares the changes in various clinical indices in 56 patients who underwent DP 1 month before and after surgery. Body weight and BMI were significantly lower 1 month postoperatively than preoperative conditions (body weight: $P < .05$, BMI: $P < .05$). FBG was significantly higher 1 month postoperatively (5.05 ± 0.07 vs 5.62 ± 0.10 mmol/L, $P < .001$). Fasting insulin and fasting C-peptide were significantly lower 1 month postoperatively (fasting insulin: 5.83 ± 0.40 vs 4.38 ± 0.30 μIU/mL, $P < .01$, fasting C-peptide: 0.56 ± 0.03 vs 0.46 ± 0.02 nmol/L, $P < .01$). A 75-g OGTT up to 180 minutes showed that the AUCs for glucose were

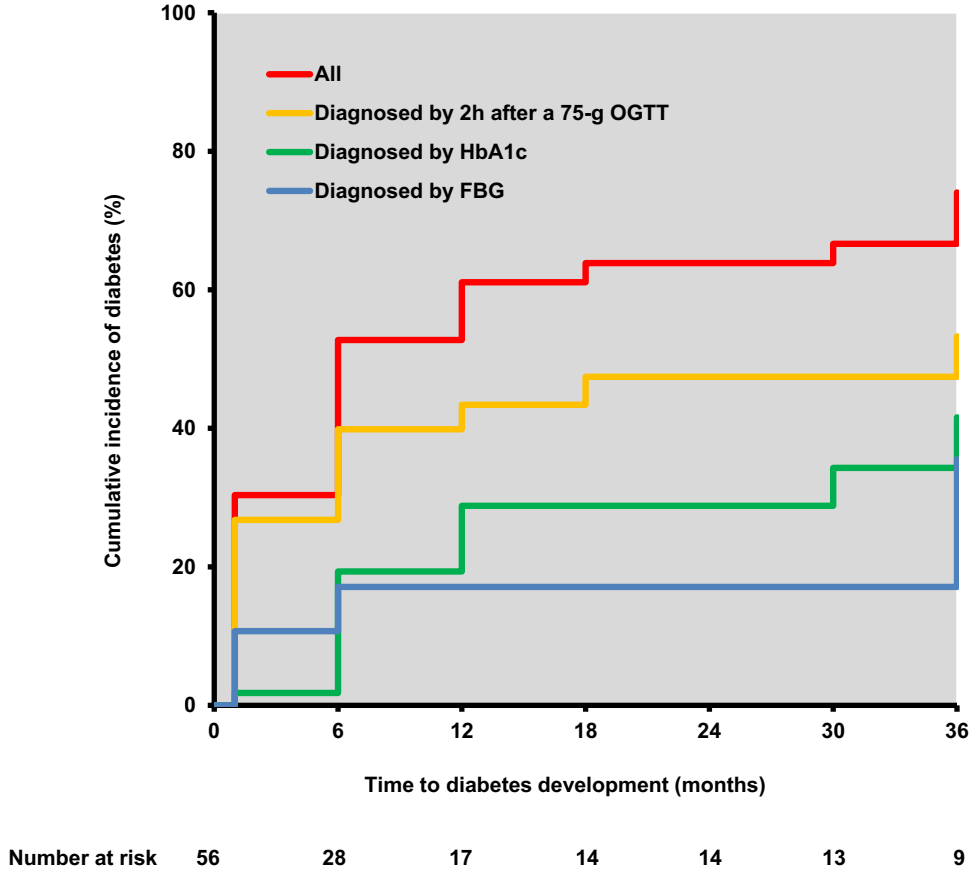

Figure 2. Cumulative incidence of new-onset diabetes after pancreaticoduodenectomy for all cases and by the diagnostic index. All cases include those that meet 1 of the diagnostic indicators or 2 simultaneously. 75g-OGTT, 75-g oral glucose tolerance test; FBG, fasting blood glucose.

significantly higher ($P < .001$), and AUCs for insulin and AUCs for C-peptide immunoreactivity (CPR) were significantly lower (AUCs for insulin: $P < .01$, AUCs for CPR: $P < .01$) at 1 month postoperatively. Regarding insulin secretion and sensitivity, the insulinogenic index and adaptation indices were significantly lower at 1 month postoperatively (insulinogenic index: 15.2 ± 1.8 vs 9.1 ± 0.9 mIU/mmol, $P < .01$, adaptation index: 44.5 ± 2.0 vs 31.8 ± 1.5, $P < .001$), but insulin sensitivity as assessed by ISI (comp) was not significantly different (8.3 ± 1.5 vs 10.4 ± 2.2, not significant [NS]). In the glucagon stimulation test, CPR at 0 minutes, CPR at 5 minutes, and ΔCPR were all significantly lower at 1 month postoperatively (CPR at 0 minutes: $P < .05$, CPR at 5 minutes: $P < .001$, ΔCPR: $P < .001$). The BT-PABA test for pancreatic exocrine function showed no significant differences before and after the surgery. No differences in HOMA-IR were observed before or after the surgery. Postoperative %RPV was 54.6% of the preoperative volume and was positively correlated with reserve capacity for insulin secretion, as assessed by insulin and C-peptide response during OGTT (1-month postoperative OGTT AUC insulin: $R = 0.454$, $P < .001$, 1-month postoperative OGTT AUC CPR: $R = 0.475$, $P < .001$) (Fig. 3).

Comparison Between Progressors and Nonprogressors to Diabetes: Participant Baseline Characteristics Before DP

To examine the risk factors for worsening glucose tolerance due to DP, we compared the preoperative clinical characteristics of 33 patients in the group that developed diabetes (progressors to diabetes) and 23 patients in the group that did not develop diabetes (nonprogressors to diabetes) during the above 36-month follow-up (Table 2). Regarding the classification of preoperative glucose tolerance, progressors had significantly more IGT cases than nonprogressors (22 [66.7%] vs 8 [34.8%], $P < .05$). HbA1c was significantly higher in the progressors than in nonprogressors ($P < .05$). The AUCs for glucose in the 75-g OGTT up to 180 minutes were significantly higher in the progressors than in the nonprogressors ($P < .001$). The AUCs for insulin in the 75-g OGTT up to 180 minutes were significantly higher in the progressors than in the nonprogressors ($P < .05$). The AUCs for CPR in the 75-g OGTT up to 180 minutes were significantly higher in the progressors than in the nonprogressors ($P < .05$). Figure 4 shows changes in blood glucose, insulin, and CPR levels after the glucose challenge. In progressors to diabetes, glucose levels were significantly higher from 30 to 120 minutes after the glucose challenge (Fig. 4A), insulin levels were significantly higher from 90 to 120 minutes (Fig. 4B), and CPR levels were significantly higher from 90 to 150 minutes (Fig. 4C). Insulin secretory capacity, as assessed by insulinogenic index and glucagon load, was not different between the 2 groups. Insulin resistance as assessed by ISI (comp) and HOMA-IR was not different between the groups either (ISI [comp]: 7.1 ± 1.4 vs 10.0 ± 3.1, NS, HOMA-IR: 1.38 ± 0.14 vs 1.24 ± 0.11, NS). There were also no differences in the BT-PABA test.

Table 1. Demographic, glycemic, endocrine, and exocrine parameters before and 1 month after distal pancreatectomy

	Preoperative (N = 56)	Postoperative (N = 56)	*P*
Age (years)	65.9 ± 1.5	—	
Males, n (%)	19 (33.9%)	—	
Height (cm)	157.0 ± 1.1	—	
Body weight (kg)	53.2 ± 1.2	49.7 ± 1.1	<.05
BMI (kg/m^2)	21.5 ± 0.4	20.0 ± 0.4	<.05
Glucose tolerance			
NGT, n (%)	26 (46.4%)	11 (19.6%)	
IGT, n (%)	30 (53.6%)	28 (50.0%)	
Diabetes, n (%)	0 (0%)	17 (30.4%)	
Histology of pancreas lesion			
Malignant, n (%)	31 (55.4%)	—	
Benign, n (%)	25 (44.6%)	—	
HbA1c (mmol/mol)	39.8 ± 0.50	39.2 ± 0.53	
HbA1c (%)	5.79 ± 0.05	5.74 ± 0.05	
Fasting blood glucose (mmol/L)	5.05 ± 0.07	5.62 ± 0.10	<.001
Fasting insulin (μIU/mL)	5.83 ± 0.40	4.38 ± 0.30	<.01
Fasting C-peptide (nmol/L)	0.56 ± 0.03	0.46 ± 0.02	<.01
OGTT			
Insulinogenic index (mIU/mmol)	15.2 ± 1.8	9.1 ± 0.9	<.01
ISI (comp)	8.3 ± 1.5	10.4 ± 2.2	
Adaptation index	44.5 ± 2.0	31.8 ± 1.5	<.001
Disposition index	84.4 ± 9.9	102.2 ± 28.3	
$AUC_{0\text{-}180}$ glucose (mmol/L·min)	1420.1 ± 34.0	1697.7 ± 44.6	<.001
$AUC_{0\text{-}180}$ insulin (μIU/mL·min)	9488.0 ± 795.0	6817.6 ± 602.8	<.01
$AUC_{0\text{-}180}$ CPR (nmol/L·min)	473.9 ± 24.8	381.3 ± 22.7	<.01
Glucagon stimulation test			
CPR at 0 minutes (nmol/L)	0.53 ± 0.02	0.46 ± 0.02	<.05
CPR at 5 minutes (nmol/L)	1.74 ± 0.09	1.18 ± 0.07	
ΔC-peptide (nmol/L)	1.21 ± 0.08	0.72 ± 0.05	<.001
HOMA-IR	1.32 ± 0.10	1.14 ± 0.09	
BT-PABA test (%)[a]	58.0 ± 1.4	54.0 ± 2.1	
%RPV[b]	—	54.6 ± 2.4	

Data are presented as mean ± standard error of the mean. Categorical variables were compared using the chi-square test, and continuous variables were compared using paired t-tests between preoperative and postoperative values. Statistical significance was defined as $P < .05$.
Abbreviations: AUC, area under the curve; BMI, body mass index; BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; CPR, C-peptide immunoreactivity; HOMA-IR, homeostatic model assessment of insulin resistance; IGT, impaired glucose tolerance; ISI (comp), insulin sensitivity index composite; NGT, normal glucose tolerance; OGTT, oral glucose tolerance tests; %RPV, % residual pancreatic volume.
[a]The BT-PABA test was performed in 52 patients preoperatively and in 49 patients postoperatively.
[b]The %RPV was measured postoperatively in 52 patients.

Preoperative Risk Factors for the Development of Diabetes

To evaluate the independent risk factors contributing to the development of diabetes after DP, we performed a multivariate Cox regression analysis, including preoperative factors with significant differences (Table 2) and risk factors identified in previous reports (age, sex, and BMI) (7, 10-12). Since several factors related to blood glucose and insulin were among the factors under consideration and their contents overlapped, the analysis was classified into Models 1 to 3. The presence of IGT before surgery (HR 2.650, 95% CI 1.216-5.772, $P < .05$) was detected as a significant factor in Model 1, and the AUCs for glucose in the 75-g OGTT up to 180 minutes (HR 1.002, 95% CI 1.001-1.004, $P < .05$) in Model 3 (Table 3). A similar analysis using the AUCs for glucose in the 75-OGTT up to 120 minutes after loading was also significant (Table S2 (13)). In addition, a comparison of the cumulative incidence of diabetes (Kaplan–Meier method) between IGT and normal glucose tolerance (NGT) showed that the incidence was significantly higher ($P < .05$) in IGT, at 86.9% at 36 months postoperatively (Fig. 5). For the AUCs of glucose in the 75-g OGTT up to 180 minutes, the cutoff values of blood glucose were calculated by ROC analysis at each loading point from 0 to 180 minutes, and the cumulative incidence of diabetes was calculated using high and low cutoff values. At 36 months postoperatively, values at 30, 90, and 120 minutes of loading were significantly higher (30 minutes: $P < .05$; 90 minutes: $P < .01$; 120 minutes: $P < .01$) in the groups above the cut-off values (Fig. S2 and S3 (13)).

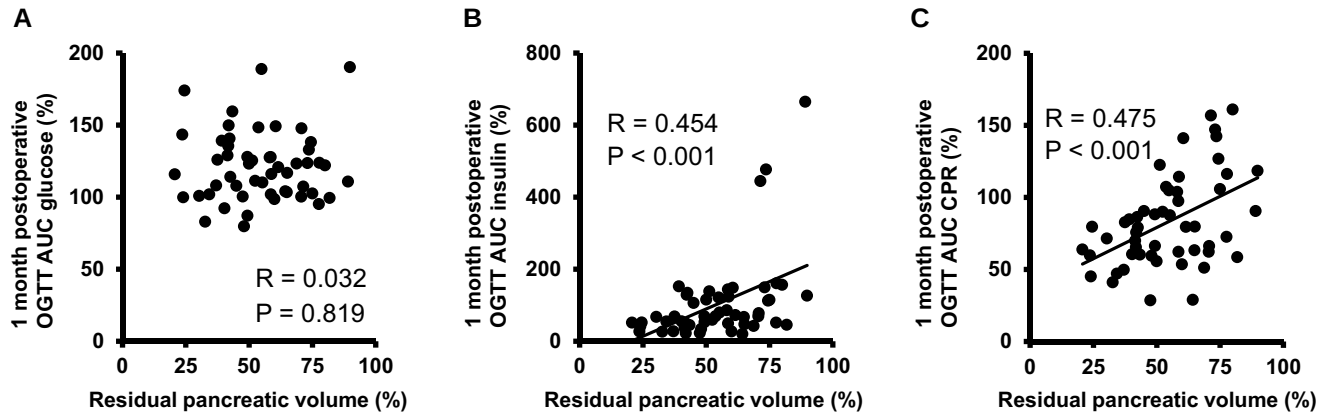

Figure 3. Correlation of residual pancreatic volume after distal pancreatectomy (DP) with AUC glucose (A), AUC insulin (B) and AUC CPR (C) during 75-g OGTT assessed 1 month after surgery. AUC, area under the curve; CPR, C-peptide immunoreactivity.

Table 2. Baseline clinical characteristics of diabetes progressors and nonprogressors before distal pancreatectomy

	Progressors to diabetes (N = 33)	Nonprogressors to diabetes (N = 23)	*P*
Age (years)	67.5 ± 2.0	63.7 ± 2.2	
Males, n (%)	12 (36.4%)	7 (30.4%)	
Height (cm)	157.2 ± 1.2	156.7 ± 2.2	
Body weight (kg)	53.5 ± 1.5	52.7 ± 2.2	
BMI (kg/m^2)	21.7 ± 0.56	21.3 ± 0.63	
Preoperative glucose tolerance			
NGT, n (%)	11 (33.3%)	15 (65.2%)	<.05
IGT, n (%)	22 (66.7%)	8 (34.8%)	<.05
Histology of pancreas lesion			
Malignant, n (%)	17 (51.5%)	14 (60.9%)	
Benign, n (%)	16 (48.5%)	9 (39.1%)	
HbA1c (mmol/mol)	40.7 ± 0.59	38.6 ± 0.82	<.05
HbA1c (%)	5.87 ± 0.05	5.68 ± 0.07	<.05
Fasting blood glucose (mmol/L)	5.15 ± 0.11	4.92 ± 0.10	
Fasting insulin (μIU/mL)	5.99 ± 0.61	5.59 ± 0.46	
Fasting C-peptide (nmol/L)	0.59 ± 0.04	0.52 ± 0.03	
OGTT			
Insulinogenic index (mIU/mmol)	12.9 ± 1.9	18.4 ± 3.5	
ISI (comp)	7.1 ± 1.4	10.0 ± 3.1	
Adaptation index	44.8 ± 2.4	45.7 ± 2.8	
Disposition index	67.9 ± 10.7	108.0 ± 17.6	
$AUC_{0\text{-}180}$ glucose (mmol/L·min)	1514.1 ± 39.5	1285.1 ± 48.8	<.01
$AUC_{0\text{-}180}$ insulin (μIU/mL·min)	10717.8 ± 1183.5	7723.6 ± 827.0	<.05
$AUC_{0\text{-}180}$ CPR (nmol/L·min)	514.3 ± 35.7	415.9 ± 28.6	<.05
Glucagon stimulation test			
CPR at 0 minutes (nmol/L)	0.56 ± 0.03	0.49 ± 0.03	
CPR at 5 minutes (nmol/L)	1.73 ± 0.13	1.76 ± 0.13	
ΔC-peptide (nmol/L)	1.17 ± 0.11	1.27 ± 0.12	
HOMA-IR	1.38 ± 0.14	1.24 ± 0.11	
BT-PABA test (%)[a]	56.6 ± 2.0	60.1 ± 2.0	

Data are presented as mean ± standard error of the mean (SEM). Categorical variables were compared using the chi-square test, and continuous variables were compared using unpaired t-tests between progressors and nonprogressors of diabetes. Statistical significance was defined as $P < .05$.
Abbreviations: AUC, area under the curve; BMI, body mass index; BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; CPR, C-peptide immunoreactivity; HOMA-IR, homeostatic model assessment of insulin resistance; IGT, impaired glucose tolerance; ISI (comp), insulin sensitivity index composite; NGT, normal glucose tolerance; OGTT, oral glucose tolerance tests.
[a]The BT-PABA test was performed on 52 patients (31 diabetes progressors and 21 nonprogressors).

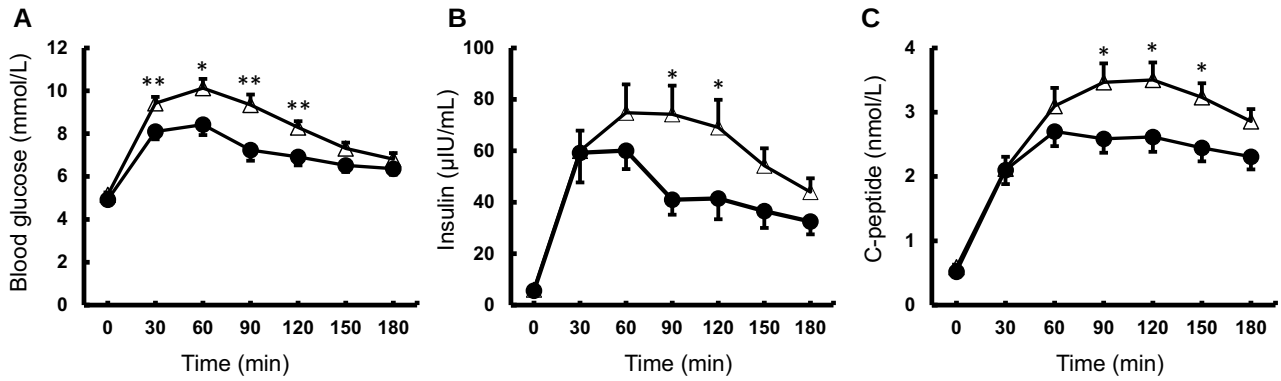

Figure 4. Graphs of 75-g oral glucose tolerance test obtained progressors (open triangle) and nonprogressors (closed circle) to diabetes at before distal pancreatectomy. (A) Changes in blood glucose levels. (B) Changes in insulin levels. (C) Changes in C-peptide levels. Data are expressed as mean ± SEM. *$P < .05$ and **$P < .01$ vs nonprogressors to diabetes.

Table 3. Multivariate Cox regression analysis of preoperative risk factors of postoperative new-onset diabetes mellitus

	Model 1		Model 2		Model 3	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.029 (0.998-1.062)	NS	1.015 (0.979-1.052)	NS	1.021 (0.989-1.055)	NS
Sex, females	1.533 (0.712-3.304)	NS	1.217 (0.571-2.593)	NS	1.588 (0.725-3.480)	NS
BMI (kg/m^2)	0.979 (0.858-1.117)	NS	1.002 (0.878-1.144)	NS	1.019 (0.888-1.169)	NS
Preoperative glucose intolerance, IGT	2.650 (1.216-5.772)	<.05				
HbA1c (mmol/mol)			1.126 (0.999-1.269)	NS		
OGTT						
$AUC_{0\text{-}180}$ glucose (mmol/L·min)					1.002 (1.001-1.004)	<.01
AUC CPR (nmol/L·min)	1.002 (1.000-1.004)	NS	1.009 (0.999-1.003)	NS	1.000 (0.999-1.002)	NS

Statistical significance was defined as $P < .05$.
Abbreviations: AUC, area under the curve; BMI, body mass index; CPR, C-peptide immunoreactivity; HR, hazard ratio; IGT, impaired glucose tolerance; NS, not significant; OGTT, oral glucose tolerance tests.

Comparison Between Progressors and Nonprogressors to Diabetes: Clinical Characteristics of the Participants 1 Month After DP

To examine the postoperative risk factors for worsening glucose tolerance due to DP, clinical characteristics at 1 month after DP for progressors and nonprogressors to diabetes were compared (Table 4). The HbA1c level was significantly higher in the progressors than in the nonprogressors (40.5 ± 0.69 [5.85 ± 0.06] vs 37.5 ± 0.68 mmol/mol [5.58 ± 0.06%]; $P < .01$). The FBG level was significantly higher in the progressors than in the nonprogressors ($P < .05$). The insulinogenic index, a measure of the early secretion of insulin in response to glucose, was significantly lower in the progressors than in the nonprogressors (7.20 ± 1.01 vs 11.7 ± 1.37 mIU/mmol, $P < .05$). When it was adjusted for %RPV, the difference was not significant. The disposition index, a measurement of insulin secretory capacity corrected for insulin resistance, was significantly lower in the progressors than in the nonprogressors (38.4 ± 4.8 vs 100.8 ± 15.3, $P < .001$). The AUCs for glucose in the 75-g OGTT up to 180 minutes were significantly higher in the progressors than in the nonprogressors ($P < .001$). The AUCs for CPR in the 75-g OGTT up to 180 minutes were significantly higher in the progressors than in the nonprogressors ($P < .05$) and remained significant even after adjustment for %RPV ($P < .05$).

Risk Factors for the Development of Diabetes in the First Postoperative Month

Multivariate Cox regression analysis was used to evaluate the risk factors contributing to the development of new-onset diabetes after DP using 1-month postoperative factors (Table 5). As in the analysis of preoperative factors, age, sex, BMI, and residual pancreatic volume, which have been previously reported as risk factors (7, 10-12), were also included in the factors considered. As shown in Table 4, there were significant differences in glycemia-related indices such as HbA1c, FBG, and the AUC for glucose in the 75-g OGTT up to 180 minutes; however, HbA1c was excluded from the analysis since it could be directly related to the development of diabetes. In addition, overlapping factors among the blood glucose- and insulin-related factors were analyzed separately in Models 1 to 5. The analysis showed that the insulinogenic index was an independent and significant risk factor for the development of new-onset diabetes in Model 3 (HR 0.929, 95% CI 0.872-0.991, $P < .05$), and the AUCs for glucose in the 75-g OGTT up to 180 minutes were significant risk factors (HR 1.003, 95% CI 1.001-1.004, $P < .001$) in Model 5 (Table 5). The cut-off value of the 1-month postoperative insulinogenic index for predicting new-onset diabetes was determined using ROC analysis. The allowed cut-off value of the insulinogenic index was 7.947 mIU/mmol ($AUC_{0.729}$) (Fig. 6A). The incidence rates of new-onset diabetes in patients

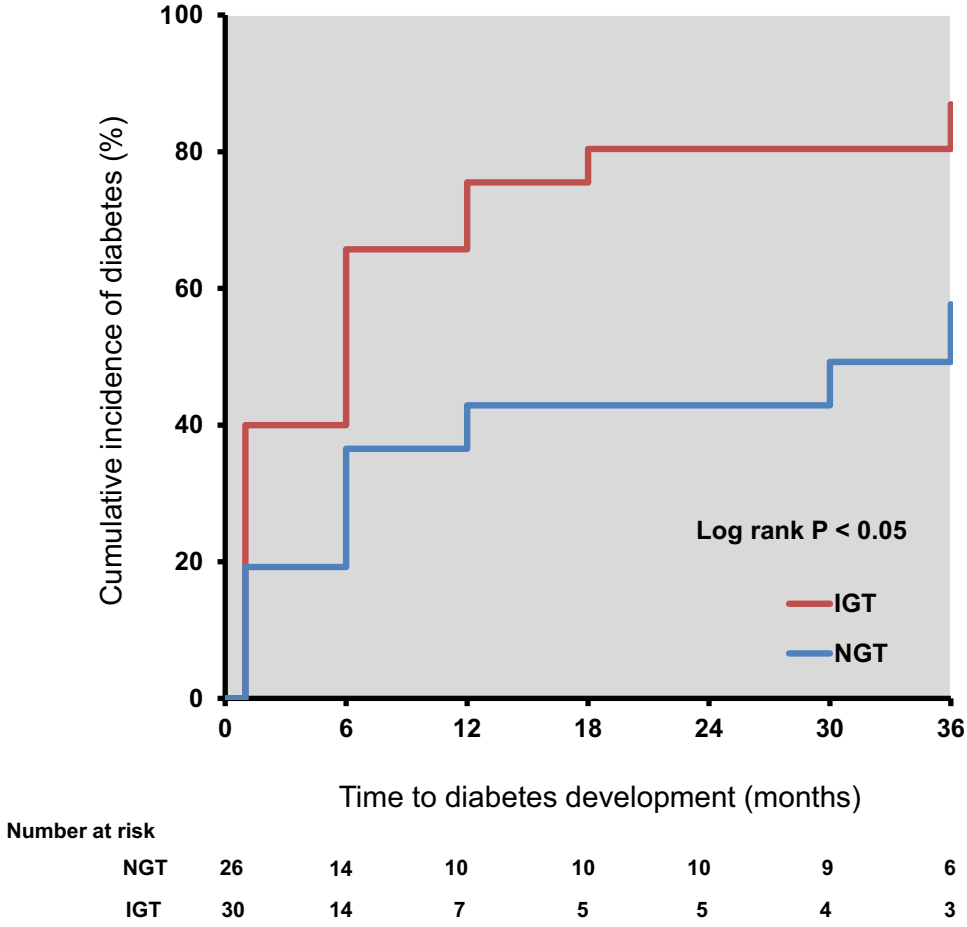

Figure 5. The cumulative incidence rates of new-onset diabetes after distal pancreatectomy between IGT group and NGT group were significantly different. IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

with an insulinogenic index value of less than 7.947 mIU/mmol and those with an insulinogenic index value >7.947 mIU/mmol were 100% and 50.6%, respectively, at 36 months after DP ($P < .01$) (Fig. 6B).

Discussion

The results of this study revealed that (1) the cumulative incidence of new-onset diabetes after DP is as high as 74.1% (Fig. 2), (2) insulin secretion, including initial and reserve capacity, is decreased, and blood glucose levels increased after DP (Table 1), (3) insulin secretion, but not blood glucose levels, was significantly associated with residual pancreatic volume, and (4) the risk factors for the development of diabetes after DP include the presence of impaired glucose tolerance as a preoperative factor (Table 3), the presence of impaired insulinogenic index, and impaired glucose tolerance as factors at 1 month postoperatively (Table 5).

There are many reports on the incidence of diabetes after DP, wherein the incidence ranges from 7.5% to 57.1% (7, 10-12, 17-19), which is very wide. This may be due to the different methods used to diagnose diabetes between the reports. The incidence of diabetes after DP tends to be higher in reports in which a 75-g OGTT was performed and tends to be lower when diabetes was diagnosed using HbA1c and FBG. Therefore, we examined all diagnostic methods (OGTT, HbA1c, and FBG) in the present study and compared the incidence of diabetes among different diagnostic methods, as well as between this study and previous studies using the same method. In reports assessing the incidence of diabetes using a 75-g OGTT in prospective observational studies similar to the present study, the incidence of diabetes after DP was approximately 40% (10, 12, 19). In this study, the cumulative incidences of diabetes after 1 month of DP was 30.4%, and after 6 months of DP it was 52.7% (Fig. 2), indicating a high rate of diabetes early after DP and a significant impact of DP on glucose tolerance. At 36 months, it was 74.1%, which was much higher than in previous studies in Caucasian populations (18), suggesting that the remaining β cells after partial pancreatectomy were more prone to deterioration in Japanese patients in the present study. The high incidence of new-onset diabetes in this study is in accordance with previous studies in the Japanese population (19), suggesting β-cell vulnerability in the Japanese population in the face of increased insulin demand due to reduced β cell mass in the DP (3).

In DP, digestion and absorption seem to be less inhibited since part of the pancreas is purely resected without reconstruction of the gastrointestinal tract. The pancreatic exocrine capacity examined by BT-PABA did not change before and after surgery in the present study (Table 1). Therefore, the pathophysiology of glucose intolerance in DP can be considered a pure change in the pancreatic endocrine capacity, independent of the gastrointestinal factors often found in PD. In addition, since the pancreatic tail is reported to have more β cells than the pancreatic head based on embryological studies

Table 4. Clinical characteristics of diabetes progressors and nonprogressors 1 month after distal pancreatectomy

	Progressors to diabetes (N = 33)	Nonprogressors to diabetes (N = 23)	*P*
Height (cm)	157.2 ± 1.2	156.9 ± 2.4	
Body weight (kg)	49.6 ± 1.4	49.9 ± 2.0	
BMI (kg/m^2)	20.0 ± 0.52	19.9 ± 0.56	
HbA1c (mmol/mol)	40.5 ± 0.69	37.5 ± 0.68	<.01
HbA1c (%)	5.85 ± 0.06	5.58 ± 0.06	<.01
Fasting blood glucose (mmol/L)	5.81 ± 0.14	5.35 ± 0.13	<.05
Fasting insulin (μIU/mL)	4.73 ± 0.40	3.88 ± 0.44	
Fasting C-peptide (nmol/L)	0.49 ± 0.03	0.41 ± 0.03	
OGTT			
Insulinogenic index (mIU/mmol)	7.20 ± 1.01	11.7 ± 1.37	<.05
Insulinogenic index/%RPV (mIU/mmol/%)	0.16 ± 0.03	0.26 ± 0.05	
ISI (comp)	7.5 ± 0.9	14.7 ± 5.1	
Adaptation index	32.0 ± 2.0	31.5 ± 2.4	
Disposition index	38.4 ± 4.8	100.8 ± 15.3	<.001
$AUC_{0\text{-}180}$ glucose (mmol/L·min)	1870.0 ± 51.5	1450.6 ± 43.2	<.001
$AUC_{0\text{-}180}$ insulin (μIU/mL·min)	7437.4 ± 868.7	5928.4 ± 758.9	
$AUC_{0\text{-}180}$ insulin/%RPV (mIU/mmol/%)	153.9 ± 19.0	110.9 ± 14.8	
$AUC_{0\text{-}180}$ CPR (nmol/L·min)	419.3 ± 30.2	326. 8 ± 31.8	<.05
$AUC_{0\text{-}180}$ CPR/%RPV (mIU/mmol/%)	8.58 ± 0.81	6.27 ± 0.67	<.05
Glucagon stimulation test			
CPR at 0 minutes (nmol/L)	0.49 ± 0.03	0.40 ± 0.03	
CPR at 5 minutes (nmol/L)	1.19 ± 0.10	1.15 ± 0.10	
ΔC-peptide (nmol/L)	0.70 ± 0.07	0.75 ± 0.08	
HOMA-IR	1.27 ± 0.13	0.97 ± 0.12	
BT-PABA test (%)[a]	55.1 ± 2.5	52.4 ± 3.6	
%RPV[b]	55.2 ± 3.1	53.7 ± 3.9	

Data are presented as mean ± standard error of the mean (SEM). Continuous variables were compared between diabetes progressors and nonprogressors using unpaired t-tests. Statistical significance was defined as $P < .05$.
Abbreviations: %RPV, % residual pancreatic volume; AUC, area under the curve; BMI, body mass index; BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid; CPR, C-peptide immunoreactivity; HOMA-IR, homeostatic model assessment of insulin resistance; IGT, impaired glucose tolerance; ISI (comp), insulin sensitivity index composite; OGTT, oral glucose tolerance tests.
[a]The BT-PABA test was performed in 49 patients (29 diabetes progressors and 20 nonprogressors).
[b]%RPV was measured in 52 patients (32 progressors to diabetes and 20 nonprogressors to diabetes).

(20-22), DP with resection of the pancreatic tail may substantially impact β-cell function. In fact, the insulin secretory capacity to different stimuli, oral glucose (OGTT), and intravenous glucagon (glucagon stimulation test), was significantly decreased, resulting in a postoperative increase in blood glucose levels (Table 1). Insulin resistance, as assessed by ISI (comp) during the OGTT and HOMA-IR, did not change after DP. Residual pancreatic volume evaluated by volumetry with MDCT was significantly correlated with residual insulin secretory capacity but not with blood glucose levels after DP (Fig. 3). These data indicate that decreased pancreatic volume after DP was directly reflected by decreased insulin secretory capacity; however, decreased insulin secretory capacity was not directly related to glucose intolerance and diabetes, suggesting the contribution of other factors, in addition to decreased insulin secretory capacity, to the development of diabetes after DP. To investigate these factors, we compared the patients who progressed to diabetes (progressors) with those who did not (nonprogressors) after DP.

We hypothesized that the lower the preoperative insulin secretory capacity, the greater the likelihood of developing diabetes after DP. However, the results were different. The AUCs of insulin and CPR in the preoperative 75-g OGTT up to 180 minutes were higher in those with progression to diabetes than in those without (Table 2). Cox regression analysis examining preoperative risk factors associated with the development of diabetes after DP identified IGT and glucose AUC in the 75-g OGTT up to 180 minutes, but not preoperative insulin secretory capacity, as significant factors (Table 3).

To further clarify the factors contributing to the development of glucose intolerance and diabetes after DP, we examined the predictors of diabetes 1 month postoperatively. This is because the volume of the pancreas resected by DP varies greatly depending on the localization and size of the tumor, and the degree of deterioration in glucose tolerance after surgery is influenced by the residual pancreatic volume. Contrary to expectations, however, there was no difference in %RPV between patients who progressed to diabetes and those who did not (Table 4), and %RPV was not a significant risk factor in the Cox regression analysis (Table 5). A significant risk factor was a high AUC of glucose in the 75-g OGTT up to 180 minutes, similar to the preoperative factor, indicating that the blood glucose level itself was strongly associated with the subsequent development of diabetes. In addition,

Table 5. Multivariate Cox regression analysis of 1-month postoperative risk factors for new-onset diabetes mellitus

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.032 (0.987-1.080)	NS	1.026 (0.983-1.071)	NS	1.021 (0.974-1.071)	NS	1.028 (0.983-1.074)	NS	1.039 (0.991-1.089)	NS
Sex, female	1.293 (0.598-2.797)	NS	1.303 (0.598-2.838)	NS	1.162 (0.530-2.547)	NS	1.355 (0.626-2.934)	NS	1.360 (0.614-3.013)	NS
BMI (kg/m^2)	1.018 (0.864-1.200)	NS	0.975 (0.813-1.170)	NS	1.081 (0.950-1.230)	NS	1.050 (0.907-1.215)	NS	0.981 (0.826-1.166)	NS
Fasting blood glucose (mmol/L)			1.664 (0.942-2.940)	NS						
OGTT										
Insulinogenic index (mIU/mmol)					0.929 (0.872-0.991)	<0.05				
Disposition index							0.999 (0.997-1.001)	NS		
$AUC_{0\text{-}180}$ glucose (mmol/L·min)									1.003 (1.001-1.004)	<.001
$AUC_{0\text{-}180}$ CPR (nmol/L·min)	1.002 (0.999-1.004)	NS	1.002 (1.000-1.004)	NS					1.000 (0.998-1.003)	NS
%RPV	0.987 (0.966-1.009)	NS	0.988 (0.966-1.010)	NS	0.990 (0.968-1.013)	NS	0.989 (0.968-1.011)	NS	0.989 (0.966-1.012)	NS

Statistical significance was defined as $P < .05$.
Abbreviations: CPR, C-peptide immunoreactivity; HR, hazard ratio; NS, not significant; RPV, residual pancreatic volume.

reduced early-phase insulin secretion, as assessed by the insulinogenic index, was found to be a significant risk factor, regardless of the residual pancreatic volume (Table 5). These data indicate that the early phase insulin response to glucose is an additional factor that contributes to the development of diabetes after DP. Altogether, the data suggest that reduced pancreatic volume after DP resulted in decreased insulin secretory capacity as a whole, and when this was combined with an impaired early-phase insulin response, as evaluated by the insulinogenic index, diabetes developed. Impaired early-phase insulin response has been reported to be a risk factor for diabetes in the natural history of type 2 diabetes (23-25) as well as PD (6).

In the present study, insulin secretory capacity at the preoperative time point, including the insulinogenic index, was not identified as a significant risk factor for the development of diabetes after DP. However, the pattern of blood glucose levels and insulin secretion in diabetes progressors in the 75-g OGTT up to 180 minutes at the preoperative time point (Fig. 4) was similar to that of typical IGT that progressed to type 2 diabetes; namely, they showed a lack of insulin response in the early phase and a delayed insulin secretory response in the later phase. Insufficient insulin response in the early phase appears to result in a late increase in insulin and C-peptide levels and increased AUCs for insulin and C-peptide (Table 2), which is often observed in patients with IGT and early diabetes (26). Thus, both post-DP diabetes progressors and those who progress from typical IGT to type 2 diabetes may share a common predisposition for diabetes progression. However, the onset of diabetes after DP occurs early in the postoperative period, unlike IGT, in which type 2 diabetes usually develops several years later (Fig. 2). This is probably because DP causes a large decrease in pancreatic cells (Fig. 3). To further clarify whether decreased insulin secretion or increased insulin resistance is responsible for the development of diabetes after DP, we compared the insulinogenic index and ISI (comp) after DP in patients with new-onset diabetes (Fig. S4 (13)). Our observation indicate that insulin secretion tended to be decrease consistently across various time points, while insulin resistance remained relatively stable. Although it is generally believed that the inability of pancreatic beta cells to compensate for insulin resistance by insulin secretion is important for glucose intolerance in type 2 diabetes, since the subjects in this study were not obese, it is possible that impaired insulin secretion after DP itself plays an important role in the development of diabetes.

In addition, the results of preoperative OGTTs for the PD reported previously (6) and for the DP reported here are shown elsewhere (Fig. S5 (13)). Both DP and PD showed a pattern often associated with IGT and early diabetes: an absence of insulin response in the early phase and a delayed insulin secretory response in the later phase. Notably, the major difference lies in the fact that in PD, only cases with a markedly reduced insulin response in the early phase progressed to diabetes. We attribute this distinction to the difference in surgical reconstruction of the gastrointestinal tract, as discussed in our previous paper (5), which makes blood glucose less likely to worsen in PD. Thus, it becomes evident that a substantially low insulin response in the early phase is a critical factor for the development of diabetes.

In our current study, we did not detect any discernible effect on the development of diabetes related to sex differences. One previous paper that conducted DP reported that glucose

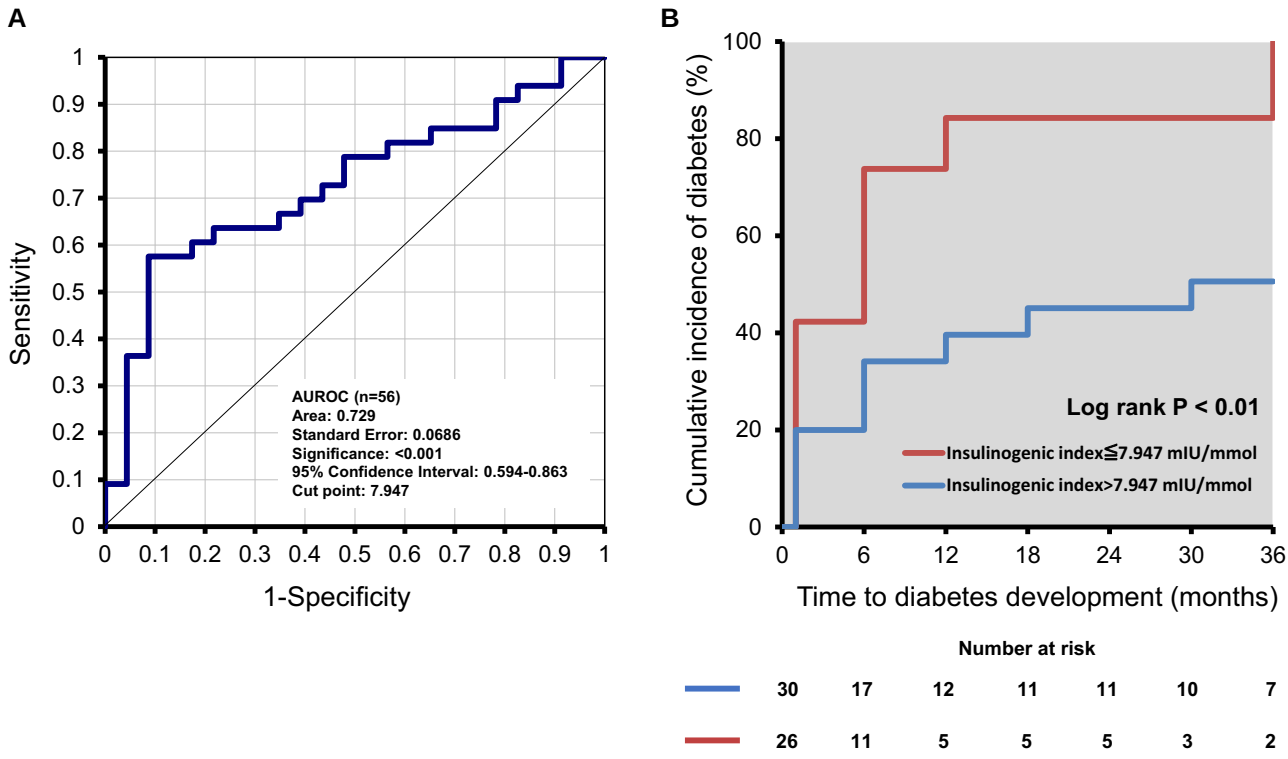

Figure 6. (A) Receiver operating characteristic (ROC) curve of the ability of the insulinogenic index to distinguish new-onset diabetes. (B) The cumulative incidence rates of new-onset diabetes after distal pancreatectomy between the 2 comparative groups divided by the insulinogenic index were significantly different. AUROC, area under the receiver operating characteristic curve.

tolerance is more likely to worsen in women (10), and although the reason for this is not clear, it has been speculated that some compensatory mechanism may be involved due to some hormonal difference between the sexes. However, it is usually known that type 2 diabetes is more common in men in Japan, and it was thought that the decrease in insulin secretory capacity due to pancreatectomy might significantly affect men, but such a result was not obtained in the present study.

This study had several limitations. Firstly, the subjects of this study were Japanese (ie, Asians), who are generally considered to have low insulin secretory capacity. Western Caucasians, who have high insulin secretory capacity, were not included in this study; therefore, it is unclear whether the accelerated effects on diabetes development would apply to non-Asians. Secondly, insulin was the only hormone included in this study; other hormones related to glucose tolerance such as glucagon, somatostatin, and pancreatic polypeptides were not included. This is an issue for future research.

In summary, many patients develop diabetes due to decreased insulin secretion after DP. Hyperglycemia, including IGT, was detected as a risk factor for the development of diabetes preoperatively, and hyperglycemia and low insulinogenic index were detected as risk factors for the development of diabetes 1 month postoperatively. The results of this study will be useful for the management of postoperative diabetes by allowing the prediction of future diabetes onset in patients with DP.

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Disclosures

The authors have nothing to disclose.

Data Availability

The primary datasets generated and analyzed in the current study are not publicly available but are available from the corresponding author upon reasonable request.

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