Supplemental Procedures

Oral glucose tolerance test

The 75-g OGTT was initiated by venous blood sampling at baseline (0 min) followed by ingestion of an oral glucose load of 75-g glucose in 225 mL (Torelan G 75; Shimizu Pharmaceuticals, Shimizu, Japan). Additional venous blood samples were collected at 30, 60, and 120 min after ingesting the oral glucose load and centrifuged at 4 °C prior to measurement of glucose, insulin, GLP-1, and gastric inhibitory polypeptide (GIP) levels.

Area under the curve (AUC) calculations were performed using the trapezoidal rule. Insulin resistance was evaluated using the homeostatic model assessment of insulin resistance (HOMA–IR) and the Matsuda index, while β-cell function was evaluated using the homeostatic model assessment of β-cell function (HOMA–β) and insulinogenic index (II). HOMA–IR was calculated as fasting insulin (μU/mL) × fasting glucose/405 (mg/dL) (1). The Matsuda index was calculated as 10,000/square root of [fasting glucose (mg/dL) × fasting insulin (μU/mL) × mean glucose (mg/dL) × mean insulin (μU/mL) during OGTT] (2). HOMA–β was calculated as 360 × fasting insulin (μU/mL)/(fasting glucose (mg/dL) − 63) (1). The insulinogenic index was calculated as the increase in insulin levels from 0 to 30 min divided by the increase in glucose levels from 0 to 30 min during 75-g OGTT (3).

Clinical and laboratory data

Measurement of systolic and diastolic blood pressure, HbA1c, serum creatinine, and eGFR was performed as previously described (4). Plasma levels of active

GLP-1 and GIP were quantified using an enzyme-linked immunosorbent assay kit (GLP-1 Active Form Assay Kit-IBL and Human GIP Active form Assay kit-IBL; Immuno-Biological Laboratories, Fujioka, Japan) using a blood sampling tube containing an anticoagulant, protease inhibitor, and dipeptidyl peptidase-4 inhibitors. Performance status was calculated using the Zubrod scale (5).

Lipopolysaccharides (LPS) were analyzed using a high-sensitivity kinetic turbidimetric Limulus test with an ET-6500 Toxinometer (Wako Pure Chemical Industries, Ltd. Osaka, Japan) according to manufacturer's instructions, with the following modifications: samples were diluted 10-fold and preheated to 70 °C for 10 min prior to analysis to dissolve immune complexes. Samples obtained before surgery and 6 months after surgery were analyzed in the same run to minimize inter-assay and intra-assay variability. C-reactive protein (CRP) levels were measured using the latex agglutination method.

Resected volume estimation of the normal pancreatic region

To determine the resected volume of the normal pancreas by partial pancreatectomy, we used images obtained using multidetector-row computed tomography. The volume of the normal pancreas was calculated as the normal pancreatic region of a slice multiplied by the slice thickness (2–5 mm) using ImageJ/Fiji (NIH, Bethesda, MD; http://imagej.nih.gov/ij/). The percentage resected volume of the normal pancreas was determined as follows: (total volume of normal pancreas before surgery – total volume of normal pancreas after surgery)/total volume of normal pancreas before surgery × 100.

Microbiota analysis

After removing sequences consistent with data from the Genome Reference Consortium Human Build 38 (GRCh38) and phiX 174 reads from the raw Illumina paired-end reads, sequences were analyzed using QIIME2 version 2017.10 (https://qiime2.org/). Potential chimeric sequences were removed using DADA2 (6), followed by trimming 30 and 90 bases of the 3' region of the forward and reverse reads, respectively. Taxonomical classification was performed using the Naive Bayes classifier trained on Greengenes 13.8 with a 99% threshold of operational taxonomic unit full-length sequences. UniFrac distances and alpha diversities (Chao 1 and Shannon index) were calculated using QIIME2.

Measurement of fecal short chain fatty acids (SCFAs) and bile acids (BAs)

SCFAs were measured by suspending 50 mg of fecal sample in water (10%, w/v), followed by centrifugation. Next, 5-sulfosalicylic acid (2%, v/v) was added to the supernatant and incubated at 4 °C for 15 min. The samples were centrifuged, and 2-ethylbutyric acid was added to the supernatant to a final concentration of 100 μM as an internal standard, followed by hydrochloric acid (5%), and diethyl ether (200%). After mixing and centrifugation, the organic layer (containing SCFAs) was transferred to a vial. The remaining aqueous layer was re-extracted using diethyl ether, and the combined organic layer was analyzed using gas chromatography–mass spectrometry (GCMS-QP2010 Ultra; Shimadzu, Kyoto, Japan). The gas chromatograph was fitted with a capillary column VF-WAXms (30 m, 0.25 mm id, 0.36-μm film thickness; Agilent Technologies, Santa Clara,

CA). Full-scan mass spectra were recorded in the 40–90 *m/z* range. Quantification was performed by integrating the extracted ion chromatogram peaks for the following ion species: *m*/*z* = 60 for acetic acid at 9.7 min; *m/z* = 74 for propionic acid at 11.3 min; *m*/*z* = 60 for butyric acid at 12.5 min; *m*/*z* = 60 for valeric acid at 13.9 min; *m*/*z* = 73 for isobutyric acid at 11.9 min; *m*/*z* = 60 for isovaleric acid at 13.0 and *m/z* = 88 for 2-ethylbutyric acid at 14.2 min. The absolute levels of SCFAs were quantified using a calibration curve with prepared individual SCFAs and 2-ethylbutyric acid.

BAs were measured in lyophilized feces (approximately 10 mg). Samples were added to internal standards (d4-deoxycholic acid, d4-taurodeoxycholic acid, and d4-glycocholic acid; 200 ng/each) and mixed with 0.2 M NaOH (1 mL). The mixtures were then washed three times with hexane (1 mL), and the aqueous phases (0.7 mL) were applied to Oasis PRiME HLB 1 cc cartridges (Waters, Milford, MA) preconditioned with methanol (1 mL) followed by ultra-pure water (3 mL). The loaded cartridges were washed with ultra-pure water (0.5 mL), and the analytes were eluted with 1 mL of methanol:acetonitrile (1:1, v/v) for liquid chromatography–mass spectrometry analysis. BAs were analyzed using an ACQUITY UPLC system coupled to a Waters Xevo TQD MS. Separation was achieved using an ACQUITY UPLC BEH C18 column (2.1 × 150 mm, 1.7 μm; Waters) using an acetonitrile-isopropanol (9:1, v/v) gradient in water containing 0.1% acetic acid (25% to 95% acetonitrile:isopropanol in 12 min). Analytes were detected using multiple reaction monitoring in negative ion electrospray mode with source and desolvation temperatures set to 150 °C and 600 °C, respectively. The absolute levels of BAs were quantified using a calibration curve with prepared

internal standards and individual BA as follows: cholic acid, glycocholic acid, taurocholic acid, deoxycholic acid, chenodeoxycholic acid, hyodeoxycholic acid, ursodeoxycholic acid, taurodeoxycholic acid, taurohyodeoxycholic acid, tauroursodeoxycholic acid, taurochenodeoxy cholic acid, glycodeoxycholic acid, glycohyodeoxycholic acid, glycoursodeoxycholic acid, glycochenodeoxycholic acid, lithocholic acid, taurolithocholic acid, and taurolithocholic acid. BAs were purchased from Steraloids Inc. (Newport, RI) or Tokyo Chemical Industry Co. LTD. (Tokyo, Japan).

Immunohistochemistry and morphometry of the pancreas

Regarding pancreatic tissue processing, one block of formalin-fixed and paraffin-embedded pancreatic tissue was selected from each patient who underwent partial pancreatectomy. Samples were sectioned at a thickness of 4 μm. Immunohistochemistry was performed using a Leica BOND-III automated stainer (Leica Biosystems, Wetzlar, Germany). Immunohistochemistry was performed with anti-glucagon antibody (lot H1808; rabbit polyclonal; premixed; Nichirei Bioscience, Tokyo, Japan) and anti-insulin antibody (clone K36aC102; mouse monoclonal; premixed; Nichirei Bioscience). For glucagon analysis, deparaffinized sections were heated in an antigen retrieval buffer (pH 9.0; Nichirei Bioscience) at 98 °C for 20 min. For insulin analysis, sections were digested using proteinase type XXIV (0.3 mg/mL; Sigma-Aldrich, St Louis, MO) at 37 °C for 15 min. Islet cells expressing ALDH1A3 were analyzed using antibodies against insulin (Agilent Technologies) and ALDH1A3 (Novus, Centennial, CO). Fluorescein isothiocyanate or Cy3-conjugated secondary antibodies (Jackson

ImmunoResearch, West Grove, PA) were used for fluorescence microscopy.

To determine the percentage of ALDH1A3-expressing cells in the islets (ALDH1A3$^+$ cells/islet), two random sections were selected per patient and 10 islets were randomly selected and evaluated per section. Images were captured using a Keyence BZ-X710 microscope using BZ-X software (Keyence, Osaka, Japan). ALDH1A3$^+$ cells/islets were determined as the average value of ALDH1A3$^+$ cells/islets in observed islets using BZ-X software in a blinded fashion by two independent investigators (K.S. and K.T.).

Statistical analysis

The normality of distribution of the continuous variables was evaluated using the Shapiro–Wilk test. Data are presented as the mean ± standard deviation (SD) when variable distribution is normal, median with interquartile range when variable distribution is non normal, or the percentage. The χ^2 test or Fisher's exact test were used to analyze categorical variables. Differences were analyzed using Student's or paired *t*-tests, Mann–Whitney U-test, or Wilcoxon signed-rank test as appropriate for the data distribution. Analysis of similarities (ANOSIM) based on 1000 permutations was used to evaluate differences in microbial community composition between the PD and DP groups. The cumulative incidence of diabetes was estimated using the Kaplan–Meier method, and log-rank tests were used for comparisons between groups. Cox proportional hazard models were used to estimate hazard ratios with 95% CI of α-cell or β-cell area, α/β ratio, and ALDH1A3$^+$ cells/islet for PPDM in the DP group. Forward stepwise entry was used for the selection of covariates in the Cox proportional hazard model. *P* values

< 0.05 were considered statistically significant.

References

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Supplementary Table 1. The duration of follow-up and survival status of participants.

Surgery	Disease	Age (years)	Sex	Total observational period (years)	Follow-up period (years)	PPDM	Status at the end of last follow-up
PD	IPMN	71	male	5.16	1.68	1	Alive
PD	IPMN	44	female	3.05	3.05	0	Alive
PD	IPMN	55	female	3.24	3.24	0	Alive
PD	IPMN	65	male	3.72	3.72	0	Alive
PD	IPMN	68	male	4.87	4.87	0	Alive
PD	MCN	45	female	5.00	5.00	0	Alive
PD	NET	69	male	1.30	1.30	0	Dead (Interstitial Pneumonia)
PD	NET	55	male	5.41	3.01	1	Alive
PD	NET	65	female	3.59	3.59	0	Alive
PD	NET	56	female	3.79	3.79	0	Alive
PD	NET	57	male	3.89	3.89	0	Alive
PD	NET	69	male	4.13	4.13	0	Alive
PD	NET	74	female	4.14	4.14	0	Alive
PD	NET	47	female	4.18	4.18	0	Alive
PD	NET	73	female	4.46	4.46	0	Alive
PD	NET	55	female	4.47	4.47	0	Alive
PD	NET	65	female	4.71	4.71	0	Alive
PD	NET	63	male	4.91	4.91	0	Alive
PD	NET	67	male	5.42	5.42	0	Alive
PD	NET	57	male	5.54	5.54	0	Alive
DP	**SV**	40	male	1.23	0.61	1	Alive
DP	**SV**	64	female	4.35	4.35	0	Alive
DP	**IPMN**	79	female	5.47	0.03	1	Alive
DP	**IPMN**	49	male	5.77	0.10	1	Alive
DP	**IPMN**	56	female	5.28	2.50	1	Alive
DP	**IPMN**	68	female	5.27	2.97	1	Alive
DP	**IPMN**	62	female	5.15	5.15	0	Alive

DP	**MCN**	58	male	3.76	0.51	1	Alive
DP	**MCN**	63	female	4.58	2.49	1	Alive
DP	**MCN**	32	female	3.04	3.04	0	Alive
DP	**MCN**	42	female	3.99	3.99	0	Alive
DP	**MCN**	63	male	4.48	4.48	0	Alive
DP	**NET**	58	male	4.11	0.08	1	Alive
DP	**NET**	49	female	4.66	0.52	1	Alive
DP	**NET**	61	male	2.65	0.58	1	Alive
DP	**NET**	72	male	4.15	0.59	1	Alive
DP	**NET**	46	female	5.14	5.14	0	Alive
DP	**NET**	62	female	3.03	0.68	1	Alive
DP	**NET**	54	female	3.03	0.97	1	Alive
DP	**NET**	66	female	2.93	0.99	1	Alive
DP	**NET**	49	female	5.81	1.01	1	Alive
DP	**NET**	58	male	4.56	1.33	1	Alive
DP	**NET**	60	male	1.67	1.67	0	Alive
DP	**NET**	61	female	3.14	3.14	0	Alive
DP	**NET**	51	female	4.10	4.10	0	Alive
DP	**NET**	62	female	4.65	4.65	0	Alive
DP	**NET**	35	male	5.45	5.45	0	Alive
DP	**NET**	48	female	1.48	1.48	0	Dead (Cerebral hemorrhage)

Total observational period was defined as the time between the date of surgery and the date of last visit to our hospital.
Follow-up period was defined as the time between the date of surgery and the date of last visit to our hospital in patients who did not develop PPDM, or the time between the date of surgery and the date of diagnosis of diabetes in patients who developed PPDM.

Abbreviations: DP, distal pancreatectomy; PD, pancreatoduodenectomy; PPDM, post pancreatectomy diabetes; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumor; SV, splenic varices

Supplementary Table 2. Cox regression models for estimating the association between α-cell area, β-cell area, or α/β ratio and post-pancreatectomy diabetes in patients who underwent distal pancreatectomy.

	β-cell area			α-cell area			α/β ratio		
	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value
Univariate model									
β-cell area (%)	2.54	(1.07-5.98)	0.033	NA			NA		
α-cell area (%)	NA			4.28	(1.28-14.21)	0.018	NA		
α/β ratio	NA			NA			13.94	(0.75-256.46)	0.076
Multivariate model									
β-cell area	3.96	(1.26-10.79)	0.017	NA			NA		
α-cell area	NA			6.45	(1.62-25.66)	0.008	NA		
α/β ratio	NA			NA			17.08	(1.03-281.52)	0.048
γ-GTP (IU/l)	1.02	(1.01-1.04)	0.010	1.02	(1.00-1.04)	0.019	NA		
PG AUC (mg/dl･Hour)	1.03	(1.01-1.05)	<0.001	1.03	(1.01-1.05)	<0.001	1.03	(1.02-1.05)	<0.001
Total bilirubin (mg/dl)							18.09	(2.00-163.06)	0.010
Insulin resistance adjusted multivariate model									
β-cell area	3.68	(1.25-10.82)	0.018	NA			NA		
α-cell area	NA			6.46	(1.61-25.79)	0.008	NA		
α/β ratio	NA			NA			28.47	(1.40-664.40)	0.029
γ-GTP (IU/l)	1.02	(1.00-1.04)	0.020	1.02	(1.00-1.04)	0.034	NA		
PG AUC (mg/dl･Hour)	1.03	(1.01-1.05)	0.004	1.03	(1.01-1.05)	0.003	1.03	(1.01-1.05)	0.001
Matsuda index	0.99	(0.77-1.27)	0.940	1.00	(0.78-1.28)	0.993	1.00	(0.80-1.24)	0.946

AUC, area under the curve; HR, hazard ratio; CI, Confidence interval; GTP, glutamyl transpeptidase; PG, plasma glucose.

Supplementary Table 3. Baseline clinical characteristics of patients who underwent distal pancreatectomy and measurement of ALDH1A3-immunoreactivity

	Progressor	Non-progressor	P value
Number	6	10	
Age (years)	57.9 ± 6.8	50.0 ± 11.5	0.146
Gender (%male)	16.7	30	0.551
Body mass index (kg/m^2)	23.6 ± 2.7	23.0 ± 2.7	0.675
Current smoker (%)	0	0	1.000
HbA1c (%)	5.9 ± 0.3	5.8 ± 0.3	0.529
HbA1c (mmol/mol)	40.4 ± 3.4	39.3 ± 3.0	0.529
GA (%)	13.7 ± 1.9	14.1 ± 1.6	0.680
Triglycerides (mmol/L)	1.2 (1.0-2.3)	1.1 (0.7-1.4)	0.254
HDL cholesterol (mmol/L)	1.4 ± 0.2	1.6 ± 0.4	0.127
LDL cholesterol (mmol/L)	2.8 ± 0.8	2.8 ± 0.6	0.892
Total bilirubin (mg/dL)	0.9 ± 0.3	0.9 ± 0.3	0.622
AST (U/L)	21.5 (18.0-22.0)	17.5 (15.5-22.0)	0.703
ALT (U/L)	21.0 (17.5-23.0)	14.0 (10.3-17.3)	0.092
γ-GTP (U/L)	26.5 (16.5-31.3)	18.5 (17.2-29.0)	0.551
UA (μmol/L)	324.8 (256.7-388.6)	267.6 (257.2-290.0)	0.515
Amylase (U/L)	74.0 (69.0-85.0)	86.0 (69.5-92.0)	0.514
Lipase (U/L)	35.5 (29.0-40.5)	30.5 (29.3-32.0)	0.326
Creatinine (mg/dL)	0.6 ± 0.1	0.7 ± 0.2	0.117
eGFR ($mL/min/1.73m^2$)	84.6 ± 11.1	77.0 ± 20.3	0.425
75g OGTT			
Glucose (mg/dL)			
Fasting	91.8 ± 3.5	87.2 ± 4.8	0.068
30min	162.6 ± 38.1	134.4 ± 22.8	0.098
60min	179.3 ± 43.6	130.4 ± 28.6	0.022
120min	124.0 ± 13.7	118.9 ± 12.5	0.469
Insulin (μU/mL)			
Fasting	7.2 (6.9-8.6)	3.8 (3.0-4.5)	0.004
30min	39.3 (31.6-64.5)	27.2 (20.7-52.7)	0.313

60min	76.6 (41.9-91.2)	22.6 (18.8-39.6)	0.016
120min	73.6 (48.4-86.5)	25.6 (17.8-31.4)	0.005
Glucagon (pg/mL)			
Fasting	97.0 (86.0-114.0)	105.0 (106.0-112.5)	0.415
30min	107.0 (100.3-111.5)	105.5 (92.0-114.8)	0.832
60min	95.5 (84.8-104.0)	97.0 (88.2-105.2)	0.875
120min	99.5 (95.0-103.3)	98.5 (87.5-109.5)	0.587
GLP-1 (pmol/L)		(n=9)	
Fasting	1.6 (0.8-1.7)	1.8 (0.8-2.6)	0.413
30min	5.8 (5.6-7.0)	6.3 (3.5-7.5)	0.742
60min	4.4 (2.1-4.8)	4.5 (2.0-4.8)	0.871
120min	3.2 (2.8-4.6)	4.9 (4.1-5.4)	0.224
HOMA-IR	1.8 ± 0.6	0.8 ± 0.4	<0.001
Matsuda index	4.6 ± 1.0	9.9 ± 2.0	0.002
HOMA-β	96.6 ± 22.6	53.0 ± 14.4	0.003
Insulinogenic index	0.7 (0.5-0.9)	0.6 (0.4-0.8)	0.893
Urinary C-peptide (nmol/day)	16.9 (14.5-20.8)	1.2 (16.0-17.9)	0.875
β-cell area (%)	1.34 ± 0.37	1.01 ± 0.40	0.145
α-cell area (%)	0.62 ± 0.41	0.38 ± 0.29	0.093
α/β ratio	0.46 ± 0.12	0.34 ± 0.16	0.076
Primary disease (%)			
NET	5 (83%)	7 (67%)	0.551
MCN	1 (17%)	3 (33%)	0.551

Data are shown as mean ± SD or median (interquartile range).

ALT, alanine transaminase; AST, aspartate transaminase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration ratio; GA, glycoalbumin; GLP-1, glucagon-like peptide-1; GTP, glutamyl transpeptidase; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumor; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; UA, uric acid.

P value represents the difference among the four groups in percent (Chi-square test), mean (t-test), or median (Mann-Whitney U test)

Supplementary Table 4. Baseline clinical characteristics of patients who underwent pancreatoduodenectomy and measurement of ALDH1A3-immunoreactivity.

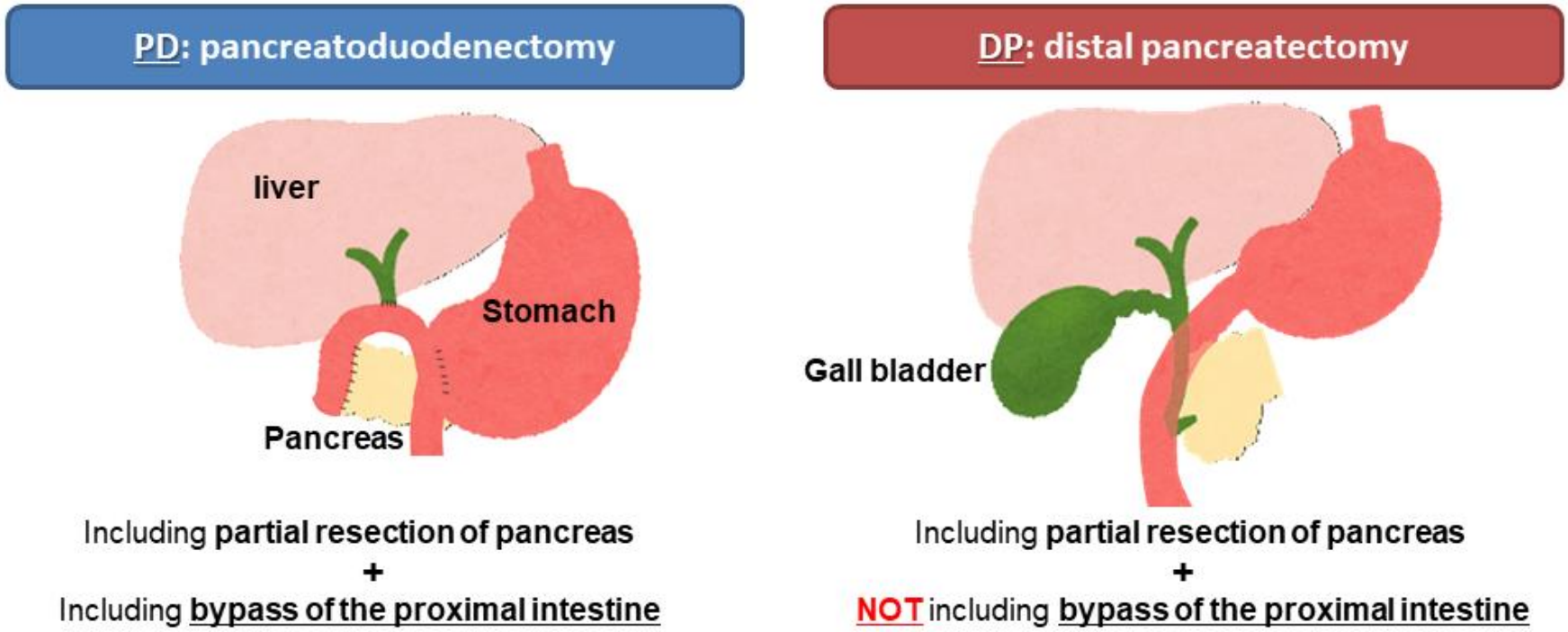
	Progressor	Non-progressor	P value
Number	5	6	
Age (years)	54.4 ± 12.9	58.8 ± 4.9	0.448
Gender (%male)	20.0	33.3	0.621
Body mass index (kg/m^2)	21.5 ± 3.2	22.5 ± 2.3	0.565
Current smoker (%)	0	0	1.000
HbA1c (%)	5.6 ± 0.3	5.7 ± 0.3	0.346
HbA1c (mmol/mol)	37.3 ± 3.6	39.1 ± 2.8	0.346
GA (%)	14.4 ± 1.5	14.0 ± 0.7	0.589
Triglycerides (mmol/L)	0.8 (0.6-1.4)	0.9 (0.8-1.1)	0.927
HDL cholesterol (mmol/L)	1.6 ± 0.2	1.5 ± 0.4	0.647
LDL cholesterol (mmol/L)	3.2 ± 0.8	3.2 ± 0.8	0.647
Total bilirubin (mg/dl)	1.2 ± 0.4	0.7 ± 0.3	0.082
AST (U/L)	14.0 (12.5-18.5)	15.5 (13.8-18.0)	0.781
ALT (U/L)	9.0 (6.5-13.5)	13.5 (10.8-20.2)	0.143
γ-GTP (U/L)	15.0 (10.5-32.5)	19.5 (13.8-64.5)	0.360
UA (μmol/L)	327.18 (202.2-374.7)	285.5 (165.1-346.5)	0.552
Amylase (U/L)	66.0 (58.0-75.5)	70.0 (55.5-82.3)	0.714
Lipase (U/L)	24.0 (20.0-29.5)	33.0 (26.8-44.2)	0.067
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.2	0.927
eGFR ($mL/min/1.73m^2$)	73.9 ± 23.1	71.1 ± 14.6	0.810
75g OGTT			
Glucose (mg/dl)			
Fasting	82.0 ± 2.4	87.0 ± 3.4	0.019
30min	135.4 ± 16.6	153.3 ± 16.6	0.108
60min	107.8 ± 34.5	144.7 ± 23.8	0.065
120min	120.2 ± 16.2	113.5 ± 24.0	0.610
Insulin (μU/mL)			
Fasting	5.2 (2.9-7.3)	4.9 (3.5-5.9)	0.931
30min	36.5 (17.4-100.3)	37.7 (33.8-86.3)	0.662

60min	24.4 (14.2-50.2)	27.3 (17.5-74.7)	0.792
120min	25.6 (17.8-42.5)	21.7 (13.6-30.1)	0.449
Glucagon (pg/mL)			
Fasting	105.0 (94.5-134.0)	97.0 (88.5-114.5)	0.360
30min	106.5 (83.3-123.5)	106.5 (83.3-123.5)	0.662
60min	100.0 (87.0-120.0)	96.5 (81.5-113.0)	0.792
120min	106.0 (89.5-124.5)	94.0 (81.5-108.8)	0.329
GLP-1 (pmol/L)			
Fasting	1.4 (1.1-2.6)	1.0 (0.8-3.9)	0.644
30min	8.4 (3.1-29.5)	6.4 (5.2-12.9)	0.931
60min	5.8 (2.5-15.5)	5.6 (3.2-8.9)	0.582
120min	5.2 (2.3-7.4)	3.1 (2.2-6.9)	0.662
HOMA-IR	1.0 ± 0.5	1.0 ± 0.3	0.159
Matsuda index	10.9 ± 5.6	9.1 ± 3.4	0.533
HOMA-β	95.4 ± 37.0	70.6 ± 13.5	0.159
Insulinogenic index	0.5 (0.4-1.5)	0.6 (0.4-1.2)	0.931
Urinary C-peptide (nmol/day)	11.2 (6.9-21.0)	15.1 (8.9-26.3)	0.662
β-cell area (%)	0.87 ± 0.25	0.80 ± 0.33	0.723
α-cell area (%)	0.26 ± 0.09	0.22 ± 0.21	0.429
α/β ratio	0.31 ± 0.09	0.25 ± 0.14	0.756
Primary disease (%)			
NET	3 (60%)	4 (66%)	0.819
IPMN	1 (20%)	2 (33%)	0.621
MCN	1 (20%)	0 (0%)	0.454

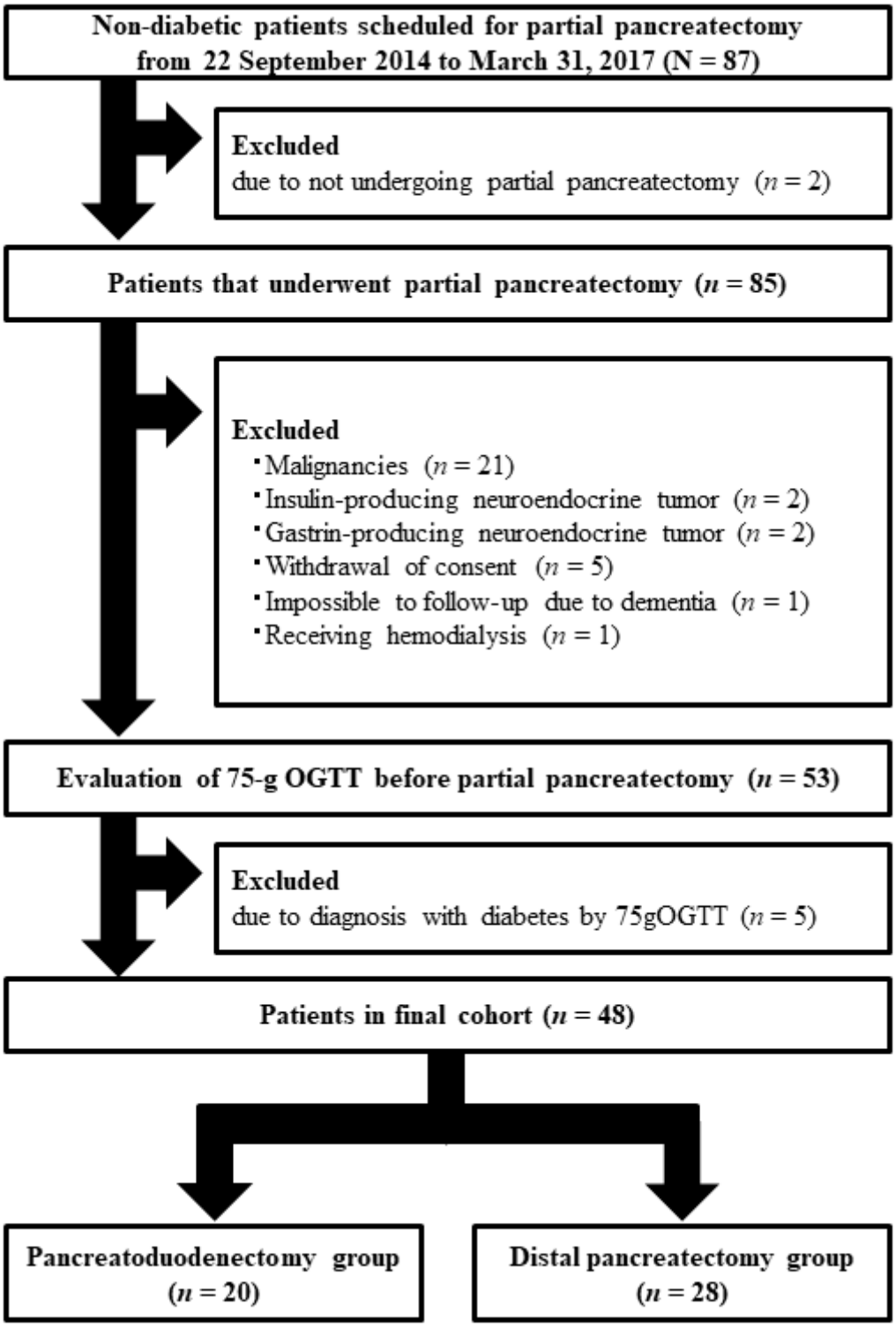
Data are mean ± SD or median (interquartile range).

ALT, alanine transaminase*;* AST, aspartate transaminase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration ratio; GA, glycoalbumin; GLP-1, glucagon-like peptide-1; GTP, glutamyl transpeptidase; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; IPMN, intraductal papillary; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumor; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; UA, uric acid.

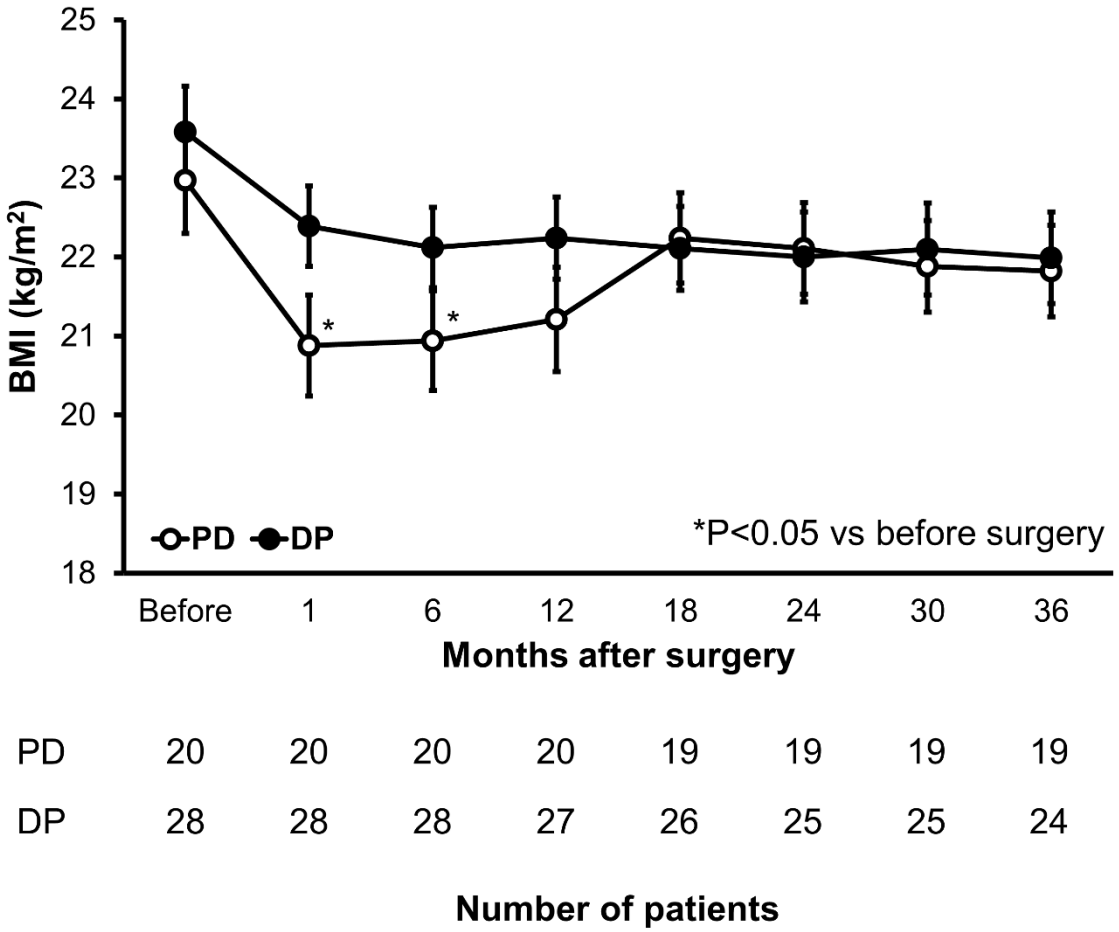
P value represents the difference among the four groups in percent (Chi-square test), mean (t-test), or median (Mann-Whitney U test)



Supplementary Figure 1. Diagram illustrating the surgical procedure of pancreatoduodenectomy (PD) and distal pancreatectomy (DP).

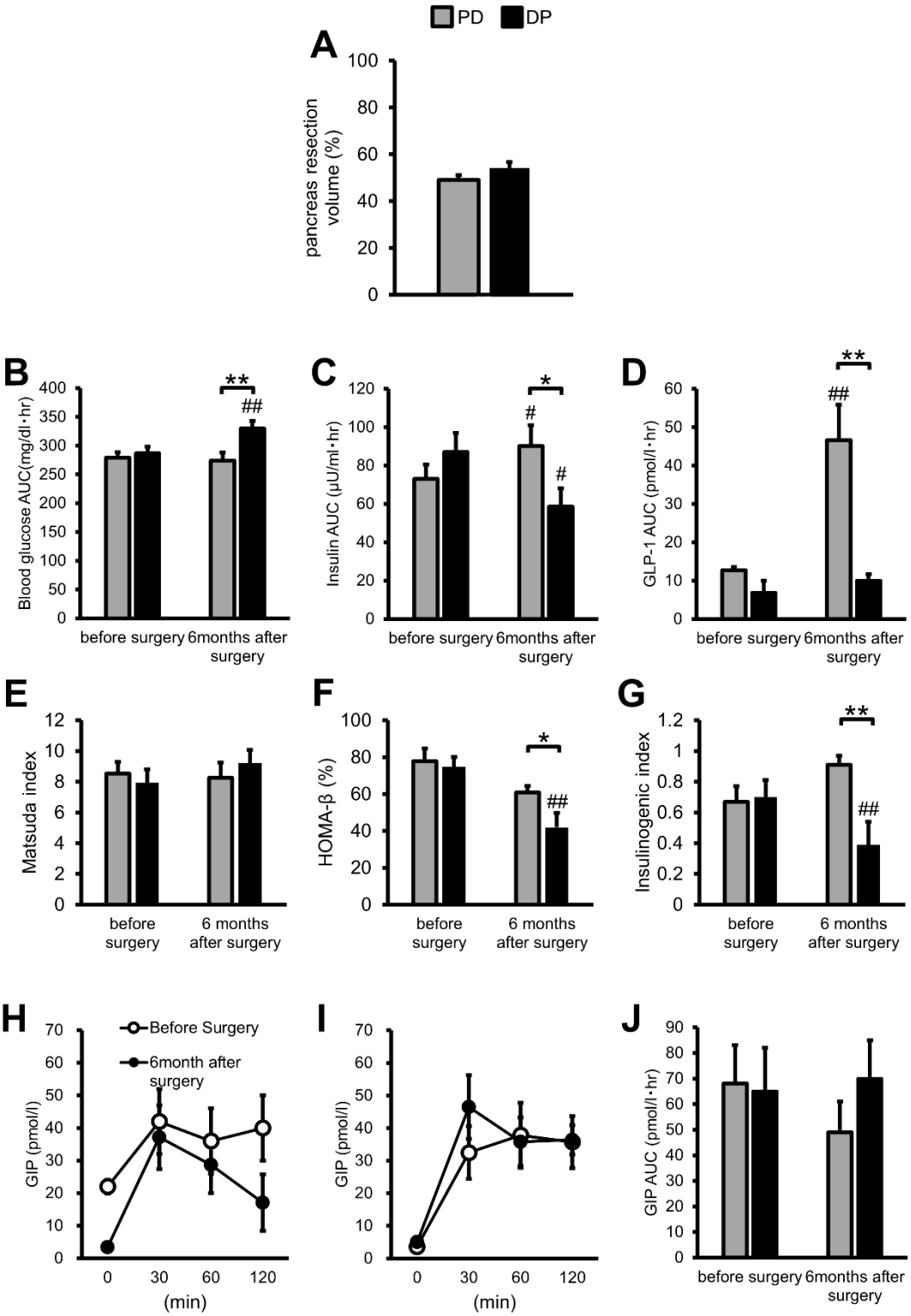


Supplementary Figure 2. Study flowchart



Supplementary Figure 3. Changes in BMI after partial pancreatectomy.

The number of patients who developed diabetes after surgery. Data are presented as mean ± SEM. PD, pancreatoduodenectomy; DP, distal pancreatectomy.


A
PD
DP
pancreas resection volume (%)
B
Blood glucose AUC(mg/dl・hr)
before surgery
6months after surgery
C
Insulin AUC (μU/ml・hr)
D
GLP-1 AUC (pmol/l・hr)
E
Matsuda index
before surgery
6 months after surgery
F
HOMA-β (%)
G
Insulinogenic index
H
Before Surgery
6month after surgery
GIP (pmol/l)
(min)
I
J
GIP AUC (pmol/l・hr)

Supplementary Figure 4. Additional data regarding changes in glucose metabolism, insulin, GLP-1, and GIP secretion before and after partial pancreatectomy.

A: Pancreas resection volume in the PD and DP group.

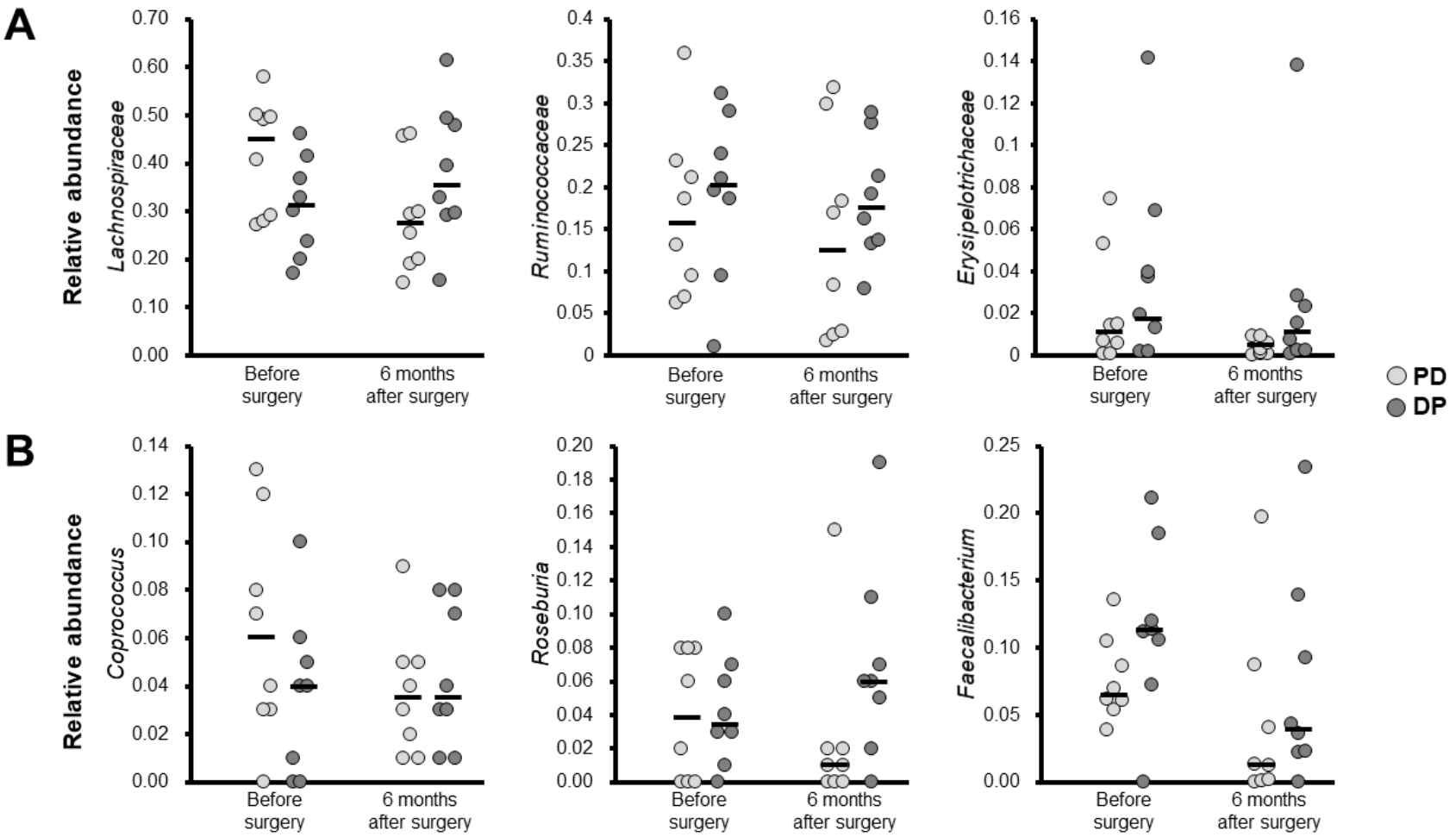
B–D: Area under the curve (AUC) during 75 g OGTT for glucose (*B*), insulin (*C*), and GLP-1(*D*) before and 6 months after surgery of patients who underwent PD ($n = 20$) and DP (before surgery, $n = 28$; 6 months after surgery, $n = 27$).

E–G: Matsuda index (*E*), HOMA-β (*F*), and II (*G*) before and 6 months after surgery of patients who underwent PD ($n = 20$) and DP (before surgery, $n = 28$; 6 months after surgery, $n = 27$).

H, *I*: GIP concentrations during 75 g oral glucose tolerance test performed before (open circles) and 6 months after (closed circles) surgery in patients who underwent PD (H; $n = 5$) or DP (I; $n = 8$).

J: AUC during 75 g OGTT of GIP before and 6 months after surgery in patients who underwent PD ($n = 5$) and DP ($n = 8$).

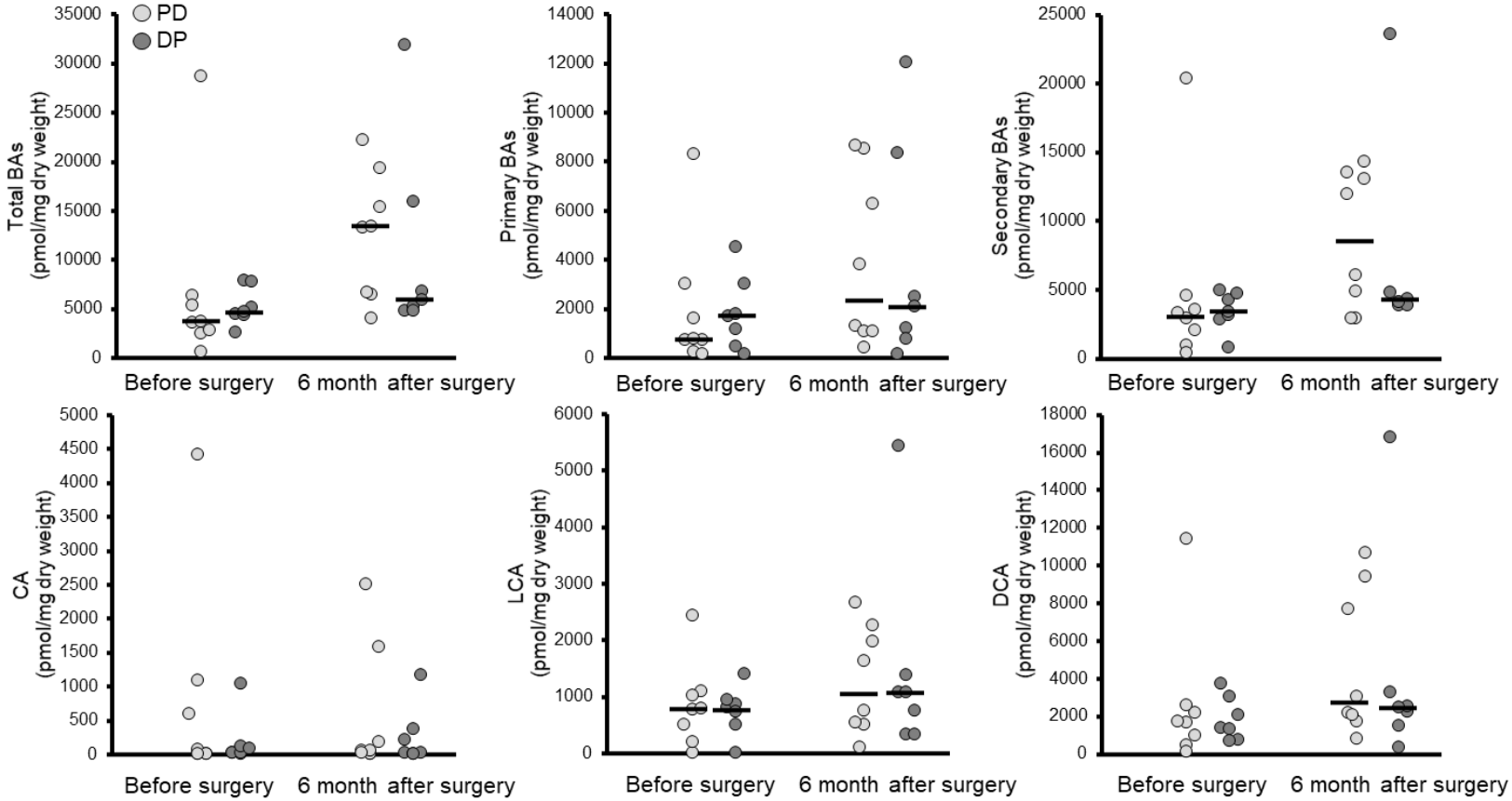
Data are presented as mean ± SEM. **P* < 0.05 ***P* < 0.01 at individual time points; #*P* < 0.01, ##*P* < 0.01 vs. before surgery.



Supplementary Figure 5. The relative abundance of gut microbiota species that produce butyrate.

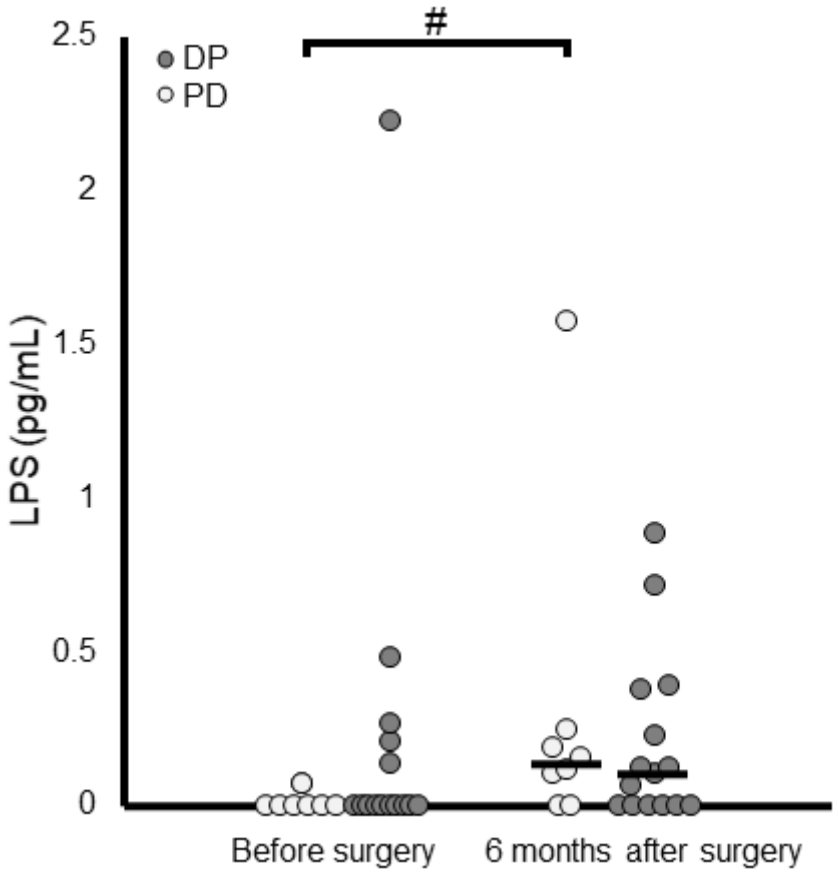
A: Relative abundance at the family level in patients who underwent PD (n = 8) and DP (n = 8).

B: Relative abundance at the genus level in patients who underwent PD (n = 8) and DP (n = 8). Black bars represent median values.



Supplementary Figure 6. Fecal concentrations of bile acids.

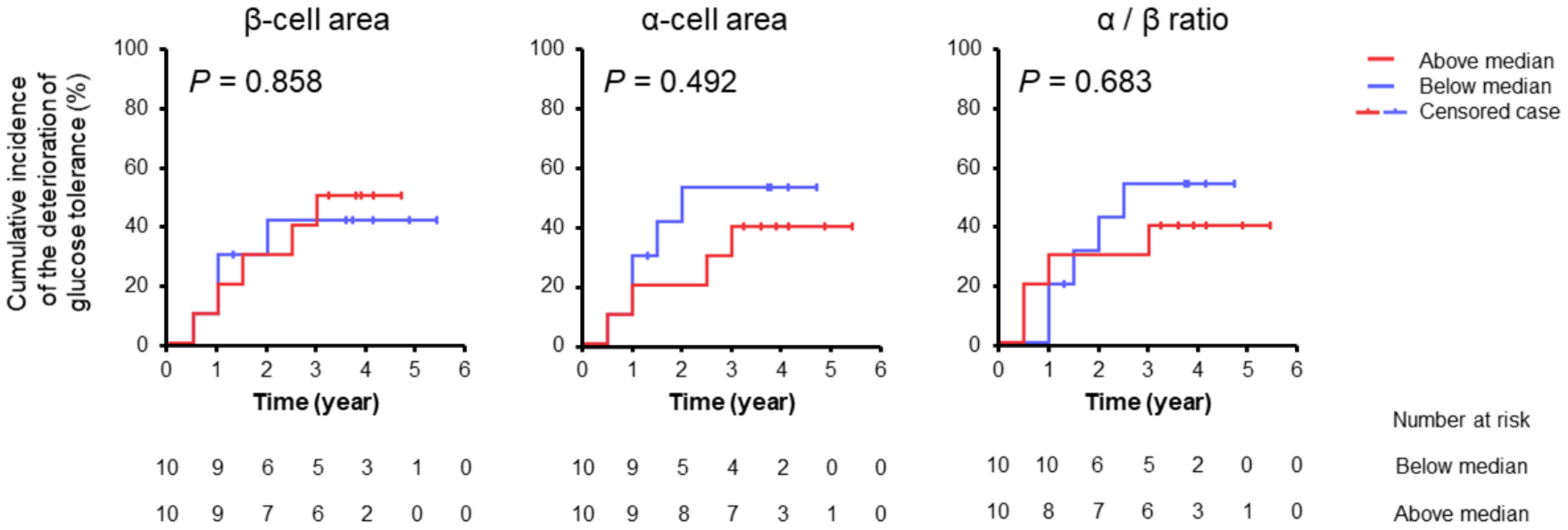
A: Bile acid (BA) levels in fecal samples before and 6 months after surgery in patients who underwent PD (n = 8) and DP (n = 8). Black bars represent median values. CA, cholic acid; DCA, deoxycholic acid; LCA, lithocholic acid. #P < 0.01, ##P < 0.01 vs. before surgery



Supplementary Figure 7. Serum levels of lipopolysaccharides (LPS).

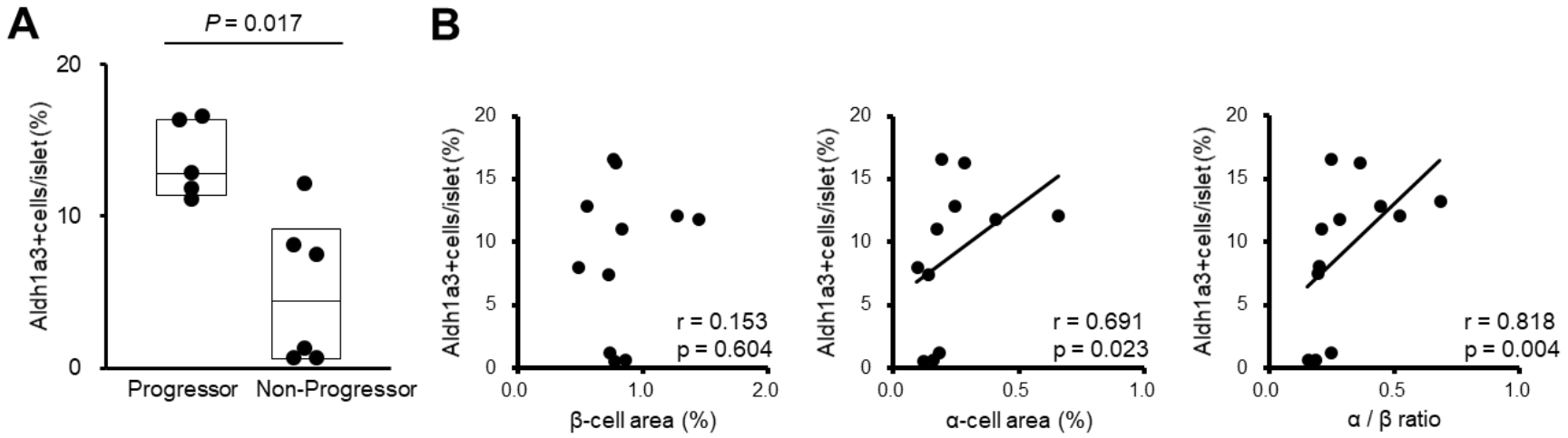
LPS levels were measured before and 6 months after surgery in patients who underwent PD (n = 8) and DP (n = 15).

#P < 0.01, ##P < 0.01 vs. before surgery



Supplementary Figure 8. The association between α-cell area, β-cell area, or α/β ratio, and the deterioration of glucose tolerance in patients who underwent pancreatoduodenectomy.

Kaplan-Meier curves for estimating the cumulative incidence of the deterioration of glucose tolerance after pancreatoduodenectomy, according to the median of β-cell area, α-cell area, or α/β ratio.



Supplementary Figure 9. ALDH1A3 expression in patients who underwent PD.

A: Quantitative analysis of ALDH1A3-positive cells per islet in resected pancreas of progressors (n = 5) and non-progressors (n = 6) who underwent PD. Box plot indicates the median and interquartile range.

B: Correlations between α-cell area, β-cell area, or α/β ratio and ALDH1A3-positive cells per islet in patients who underwent PD (n = 11).