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Oral Food Intake Versus Fasting on Postoperative Pancreatic Fistula After Distal Pancreatectomy

A Multi-Institutional Randomized Controlled Trial

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Abstract: The usefulness of enteral nutrition via a nasointestinal tube for patients who develop postoperative pancreatic fistula (POPF) after miscellaneous pancreatectomy procedures has been reported. However, no clear evidence regarding whether oral intake is beneficial or harmful during management of POPF after distal pancreatectomy (DP) is currently available.

To investigate the effects of oral food intake on the healing process of POPF after DP.

Multi-institutional randomized controlled trial in Nagoya University Hospital and 4 affiliated hospitals.

Patients who developed POPF were randomly assigned to the dietary intake (DI) group ($n = 15$) or the fasted group (no dietary intake [NDI] group) ($n = 15$). The primary endpoint was the length of drain placement.

No significant differences were found in the length of drain placement between the DI and NDI groups (12 [6–58] and 12 [7–112] days, respectively; $P = 0.786$). POPF progressed to a clinically relevant status (grade B/C) in 5 patients in the DI group and 4 patients in the NDI group ($P = 0.690$). POPF-related intra-abdominal hemorrhage was found in 1 patient in the NDI group but in no patients in the DI group ($P = 0.309$). There were no significant differences in POPF-related intra-abdominal hemorrhage, the incidence of other complications, or the length of the postoperative hospital stay between the 2 groups.

Food intake did not aggravate POPF and did not prolong drain placement or hospital stay after DP. There may be no need to avoid oral DI in patients with POPF.

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Abbreviations: CT = computed tomography, DI = dietary intake, DP = distal pancreatectomy, ISGPF = International Study Group on Pancreatic Fistula, NDI = no dietary intake, POPF = postoperative pancreatic fistula, RCT = randomized controlled trial.

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INTRODUCTION

Distal pancreatectomy (DP) is a standard procedure for benign and malignant neoplasms of the distal pancreas. Despite recent advances in surgical techniques and perioperative management, the reported incidence of postoperative pancreatic fistula (POPF) after DP ranges from 10% to 40%.[1–4] The main reported risk factors for POPF are a high body mass index, history of diabetes, large-volume pancreatic remnant, extended lymphadenectomy, longer operative time, and a thick pancreatic stump after staple closure.[4–8] In an effort to avoid this intractable complication, numerous techniques and tools including staple closure, suture ligation with mattress stitches, pancreaticoenteric anastomosis, fibrin glue, and ultrasonic devices have been proposed and investigated.[3,4,9–16] However, there is currently no universally accepted effective technique.

Food intake releases gastrointestinal hormones such as secretin and cholecystokinin and promotes the secretion of digestive juices, including pancreatic juice.[17] Fasting is sometimes considered necessary to suppress the secretion of pancreatic juice in patients with POPF, and the necessity of ''nothing by mouth'' (nil per os, NPO) was also described in the International Study Group on Pancreatic Fistula (ISGPF) criteria.[18] However, fasting management requires total parenteral nutrition and leads to metabolic adverse events, including negative functional and morphological changes of the gastrointestinal mucosa and pancreas.[19] Klek et al[20] performed a randomized controlled trial (RCT) comparing fasting management and enteral nutrition via a nasointestinal tube in patients with POPF and reported that enteral nutrition was associated with significantly shorter times to POPF closure. In their cohort, however, miscellaneous operative procedures were performed, including pancreatoduodenectomy, DP, necrosectomy, and gastrectomy. Our recent RCT compared oral dietary intake (DI) and fasting in patients with POPF after pancreatoduodenectomy, showing that food intake did not aggravate POPF and did not prolong the length of drain placement or hospital stay.[21] However, no clear evidence regarding whether oral intake can be tolerated while POPF exists in patients undergoing DP is currently available.

In this study, we focused only on DP as the operative method. A multi-institutional RCT was conducted to investigate the effects of oral intake on the healing process by comparing the fasted group (no dietary intake [NDI] group) and the DI group during the management of POPF.

METHODS

Trial Design

This study was performed in Nagoya University Hospital and 4 affiliated hospitals, which performed at least 20 pancreatic resections per year. The study protocol was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000003940). A uniform protocol was submitted to and approved by the institutional review boards at each institution. The study was carried out in accordance with the international ethical recommendations described in the Declaration of Helsinki. Written informed consent was obtained from all patients. The coordinating center trained the research personnel at each institution before enrollment; therefore, operative procedures and intraoperative and postoperative management were unified in all institutions. All supporting data were collected from each institution using a secure electronic data capture system.

DP was performed in patients with disease of the pancreatic body and tail region from July 2010 to September 2012. The eligibility criteria were an age of $\geq$20 years and a diagnosis of POPF according to the ISGPF definition. The exclusion criteria were regular use of medication that might affect the healing process (eg, adrenal corticosteroids), current hemodialysis treatment, and past or current severe cardiovascular, pulmonary, renal, or liver dysfunction.

Surgical Technique

Operative procedures were identical throughout the study period, as previously reported.[22–25] In open DP cases, the pancreas was transected with a scalpel, and the main pancreatic duct on the cut surface was closed with 5–0 polypropylene in a continuous pattern. Bleeding from the pancreatic parenchyma was controlled with a combination of cautery and suture ligation. In laparoscopic DP cases, straight or rotated endoscopic linear staplers of various sizes (staple height, 3.5–4.2 mm) were used, depending on the thickness or hardness of the pancreas. A silastic flexible drain (Blake®; Ethicon, Inc., Somerville, NJ) was routinely placed adjacent to the pancreatic remnant and connected to a continuous-suction device (J-Vac Suction Reservoir; Johnson & Johnson, Tokyo, Japan).

Patient characteristics and perioperative and postoperative parameters were reviewed for the following clinical variables: age, sex, histologic diagnosis, comorbidities, preoperative body mass index,[26] preoperative serum albumin level, total lymphocyte count, hemoglobin concentration, platelet count, total bilirubin and cholinesterase levels, operative method, operative time, intraoperative blood loss, blood transfusion, drainage output volume and serum level of nutritional factors including albumin, prealbumin, transferrin, and retinol-binding protein as well as the total lymphocyte count on days 5, 12, and 21.[27] The estimated pancreatic parenchymal remnant volume was measured on transverse sections of preoperative multiphasic computed tomography (CT), as previously reported.[7,28] Briefly, serial transverse CT images were obtained at 2.0-mm intervals, the borders of the estimated pancreatic parenchymal remnant and the estimated transection line were outlined on every CT slice, and the corresponding volume was calculated as the product of the pancreatic parenchymal area times the slice thickness.

Randomization

The amylase level of the drainage fluid was measured on postoperative days 1, 3, and 5 and every other day thereafter until drain removal. POPF was defined according to the ISGPF criteria: that is, when the amylase level of the drainage fluid on postoperative day 5 was more than 3 times the upper limit of the normal serum level.[18] The amylase level of the drainage fluid was confirmed on postoperative day 5 for all patients, including patients without POPF on postoperative day 3. After diagnosis of POPF, patients were randomized in a 1:1 ratio to either the DI or NDI group on postoperative day 5. A computer-generated central randomization schema was implemented in an automated web system. No blocking or stratification was used.

Postoperative Management

After randomization, patients in the NDI group were fasted until drain removal. Parenteral nutrition was commenced after surgery via a central venous catheter. Unicaliq N (Terumo, Tokyo, Japan), a 1600-kcal all-in-one admixture containing vitamins, electrolytes, and trace elements, was administered continuously for 24 h/d. In the DI group, food intake was started on postoperative day 6. Rice porridge of 750 kcal (38 g protein, 30 g fat) was given for the first 3 days, soft rice of 1300 kcal (63 g protein, 40 g fat) was given for the next 4 days, and a solid diet of 1650 kcal (78 g protein, 45 g fat) was given thereafter. Actual oral caloric intake was measured at every meal. Parenteral nutrition was replenished daily depending on the DI of each individual patient, and the total calorie level was controlled to be equivalent to that of the NDI group. Patients in both groups were allowed to drink water. All patients received postoperative proton-pump inhibitors. No patients received postoperative somatostatin analogues or perioperative radiotherapy.

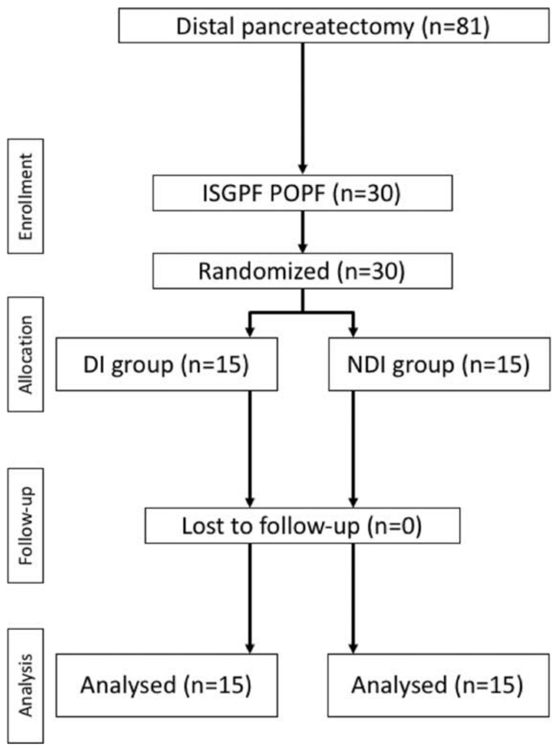

FIGURE 1. CONSORT diagram for the present trial.

TABLE 1. Clinical Characteristics of the Enrolled Patients and Perioperative Details

	DI Group (n = 15)	NDI Group (n = 15)	*P*
Age, y*	67.5 (56–82)	62 (43–78)	0.197
Sex, male/female	9/6	10/5	0.705
Disease			0.465
Pancreatic cancer	7	11	
IPMN	3	1	
Endocrine neoplasm	1	1	
Others	4	2	
Comorbidity			
Diabetes mellitus	2	5	0.195
Cardiovascular disease	1	2	0.543
Pulmonary disease	1	1	1.000
Hypertension	2	0	0.143
Peptic ulcer	2	0	0.143
Preoperative body mass index*	22.3 (16.3–33.6)	23.6 (16.7–26.3)	0.724
Preoperative chemotherapy	0	0	1.000
Preoperative blood test			
Albumin, g/dL†	4.1 ± 0.3	3.9 ± 0.4	0.196
Total lymphocyte count, per mm^3†	1770 ± 586	1640 ± 856	0.315
Hemoglobin, g/dL†	13.2 ± 1.6	13.1 ± 1.3	0.967
Platelet count, $\times 10^4/mm^3$†	19.7 ± 4.4	20.5 ± 3.9	0.647
Total bilirubin, mg/dL†	0.5 ± 0.2	0.7 ± 0.3	0.055
Cholinesterase, IU/L†	308 ± 60	291 ± 74	0.570
Operative method			0.543
Open DP with splenectomy	13	12	
Open spleen-preserving DP	1	2	
Laparoscopic DP with splenectomy	1	1	
Concomitant resection of other organs	1	2	0.543
Operative time, min*	205 (91–628)	285 (176–421)	0.236
Intraoperative blood loss, mL*	448 (50–1604)	558 (123–1377)	0.813
Intraoperative blood transfusion	2	2	1.000

DI = dietary intake, DP = distal pancreatectomy, IPMN = intraductal papillary mucinous neoplasm, NDI = no dietary intake.
* Values are median (range).
† Mean ± standard deviation.

Study Endpoints

The primary endpoint was the length of drain placement. The criteria for drain removal were a drain output volume of <20 mL/d, a drainage fluid amylase level of <3 times the upper limit of the normal serum level, clear drainage fluid, and no bacterial contamination.

One of the secondary endpoints was the incidence of clinically relevant POPF (ISGPF grade B/C). POPF was subclassified into grade A (requiring little change in clinical management or deviation from the normal clinical pathway), grade B (requiring a change in clinical management or adjustment of the clinical pathway), and grade C (requiring a major change in clinical management or deviation from the normal clinical pathway).[18] A POPF of grade B or C was considered clinically significant. The other secondary endpoints were the incidence of POPF-related intra-abdominal hemorrhage, postoperative mortality of any cause within 60 days after surgery, the length of the postoperative hospital stay, and the rates of postoperative complications other than POPF. POPF-related intra-abdominal hemorrhage and delayed gastric emptying were defined according to the criteria outlined by the International Study Group on Pancreatic Surgery.[29,30] The length of the postoperative hospital stay was defined as the number of days from the day of surgery through the day of hospital discharge.

Statistics

Two biostatisticians (KM and SM) were responsible for statistical analysis. Based on preliminary unpublished retrospective data from the authors' department, it was assumed that the length of drain placement in the NDI group was 10.0 ± 2.5 days (mean ± standard deviation) and that DI would prolong drain placement for 3 days in patients with POPF. Calculations using Wilcoxon test showed that 13 patients should be allocated to each of the 2 arms to achieve a power of 80% and significance level of 0.05 to evaluate the superiority of fasting. Allowing for an estimated dropout rate of approximately 10% in each group, enrollment of 30 patients was considered necessary to meet the primary endpoint of this study.

Differences in the numerical data between the 2 groups were examined using the chi-squared test or Fisher's exact test when $n < 5$. Differences in quantitative variables between the 2 groups were evaluated using Student *t* test or the Mann–Whitney *U* test if the distribution was abnormal. Risk factors for progression to clinically relevant POPF were evaluated using binomial logistic regression analysis. Statistical analysis was performed using

TABLE 2. Postoperative Complications

	DI Group (n = 15)	NDI Group (n = 15)	*P*
POPF			0.461
Grade A	10	11	
Grade B	5	3	
Grade C	0	1	
Clinically relevant POPF (grade B/C)	5	4	0.690
POPF-related hemorrhage	0	1	0.309
Length of drain placement, d*	12 (6–58)	12 (7–112)	0.786
Delayed gastric emptying	0	1	0.309
Intra-abdominal abscess	3	3	1.000
Biliary leakage	0	0	1.000
Ileus	0	1	0.309
Central venous catheter infection	1	4	0.142
Wound infection	1	1	1.000
Postoperative fasting period, d*	5 (5–5)	15 (7–46)	<0.001
Caloric intake from the diet (kcal/d, mean)			
POD 7	580	N/A	
POD 10	810	N/A	
POD 14	1060	N/A	
Drainage output volume, mL*			
POD 1	46 (5–120)	56 (14–250)	0.430
POD 3	10 (1–60)	10 (1–270)	0.181
POD 5	4 (1–60)	5 (1–50)	0.620
POD 7	5 (1–87)	5 (1–35)	0.836
Postoperative hospital stay, d*	24 (12–91)	26 (15–119)	0.418
Reoperation	0	0	1.000
Readmission	2	0	0.143
Mortality	0	0	1.000
Median total hospital cost, Japanese yen	1568,950	1529,100	0.901

DI = dietary intake, N/A = not applicable, NDI = no dietary intake, POD = postoperative day, POPF = postoperative pancreatic fistula.
* Values are median (range).

JMP® version 10 software (SAS Institute, Inc., Cary, NC). A *P* value of <0.05 was considered statistically significant.

RESULTS

In total, 81 patients underwent DP (Figure 1). Thirty patients with POPF after DP were randomized to the DI group (food intake from postoperative day 6) and the NDI group (no food intake until drain removal) from July 10, 2010 to September 30, 2012. No patient withdrew consent after randomization.

Patients' Characteristics and Perioperative Status

The patients' characteristics, preoperative status, and preoperative blood test results are summarized in Table 1. The primary disease for which surgery was performed was similar in the 2 groups. There were no significant differences in the other background data between the 2 groups. The operative time, blood loss, and the incidence of intraoperative blood transfusion were not significantly different between the 2 groups. The median postoperative fasting period was 15 days in the NDI group (Table 2). The mean actual caloric intake from the diet on postoperative days 7, 10, and 14 was 579, 813, and 1060 kcal, respectively.

Postoperative Changes in Serum Nutritional Indicators

The serum albumin level, total lymphocyte count, and levels of rapid-turnover proteins, including prealbumin, transferrin, and retinol-binding protein, were evaluated preoperatively and on postoperative days 5, 12, and 21. All parameters were lowest on postoperative day 5 in both groups and subsequently recovered; there were no significant differences between the 2 groups (Figure 2).

Amylase Level and Drainage Fluid Output Volume

Figure 3A and B shows the amylase level and peripancreatic drainage fluid output volume. The median postoperative amylase level of the drainage fluid was statistically similar between the DI and NDI groups (postoperative day 1, 6715 vs 7989 IU/L, $P = 0.513$; day 3, 1991.5 vs 2475.0 IU/L, $P = 0.396$; day 5, 451 vs 903 IU/L, $P = 0.295$; and day 7, 513 vs 750 IU/L, $P = 0.090$).

Comparison of Clinically Relevant POPF and Other Complications

Postoperative complications were compared between the 2 groups to clarify whether food intake influenced their incidence (Table 2). POPF progressed to a clinically relevant status (grade B/C) in 5 patients in the DI group and in 4 patients in the NDI group ($P = 0.690$). No significant differences were found in the length of drain placement between the DI and NDI groups (12 [6–58] vs 12 [7–112] days; $P = 0.786$); the cumulative incidence rates were also statistically equivalent between the 2 groups (Figure 3C). A drain was reinserted on the day after

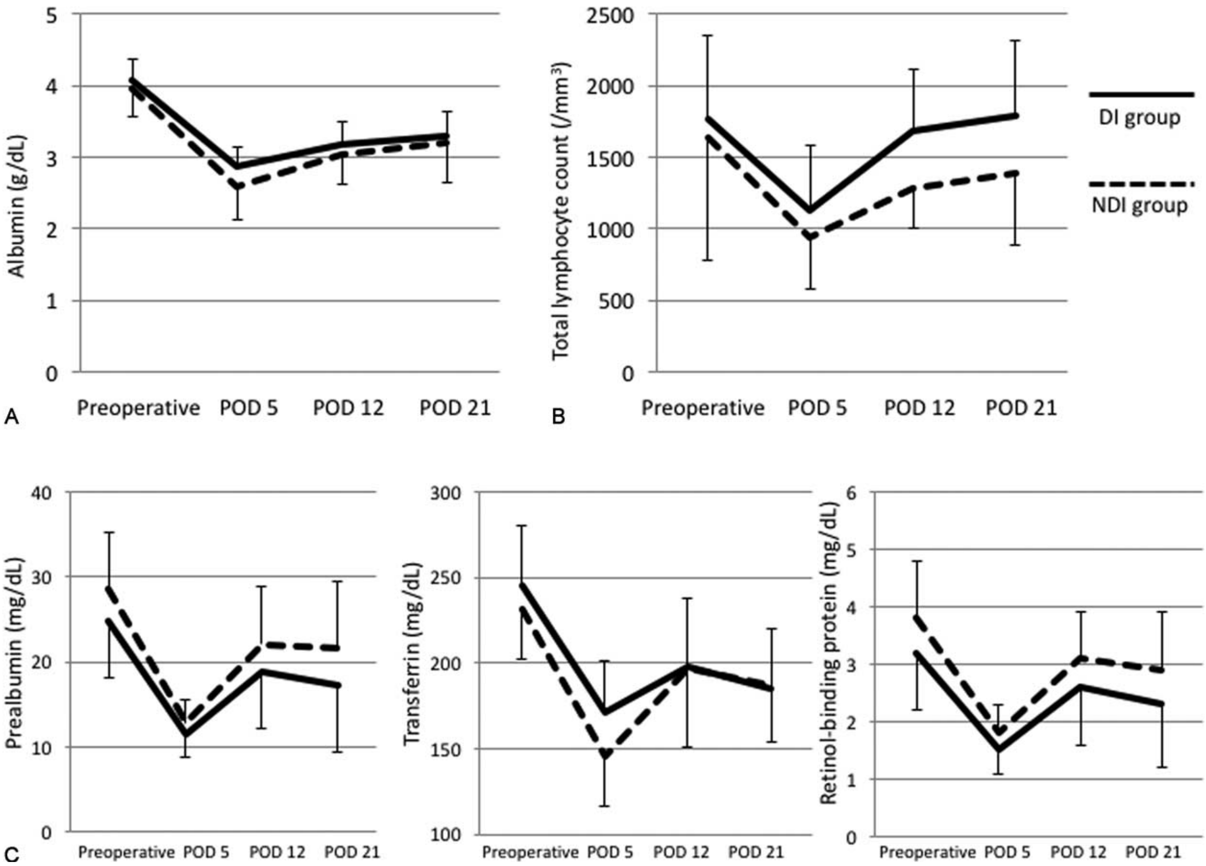

FIGURE 2. Preoperative and 5-, 12-, and 21-day postoperative (A) serum albumin level, (B) total lymphocyte count, and (C) levels of rapid-turnover proteins including prealbumin, transferrin, and retinol-binding protein. There were no significant differences between the DI and NDI groups at any time points. DI = dietary intake, NDI = no dietary intake.

the removal of the original drain in 1 case in the NDI group. In this case, the duration of drain placement was calculated from the insertion of the initial drain until the removal of the second drain. There were no significant differences in POPF-related intra-abdominal hemorrhage ($P = 0.309$), the incidence of other complications, or the length of the postoperative hospital stay ($P = 0.418$) between the 2 groups. The incidence of central venous catheter infection tended to be higher in the NDI group, although the difference between the 2 groups was not significant ($P = 0.142$). No patients in either group died of any cause within 60 days after surgery. No important harms or unintended effects were found in each group. The median total hospital costs were similar between the 2 groups (¥1568,950 in the DI group vs ¥1529,100 in the NDI group: $P = 0.901$; Table 2).

Predictive Factors for Progression to Clinically Relevant POPF

The factors predicting clinically relevant POPF (grade B/C) are shown in Table 3. Binomial logistic regression analysis showed that an estimated pancreatic parenchymal remnant volume was an independent predictive factor of clinically relevant POPF (odds ratio, 4.16; 95% confidence interval, 2.01–9.53; $P = 0.026$). DI after postoperative day 5 was not significantly associated with clinical progression of POPF.

DISCUSSION

Whether regular DI affects POPF and whether DI is possible when POPF occurs are issues of particular interest to clinicians. Klek et al[20] reported that enteral nutrition rather than parenteral nutrition with fasting was associated with significantly higher POPF closure rates and shorter times to POPF closure. In our recent study, oral food intake did not exacerbate POPF and did not prolong hospital stay in patients undergoing pancreatoduodenectomy.[21] However, no previous reports have fully addressed the impact of diet on POPF after DP.

In the present study, there was no significant difference in the prerandomization status between the DI and NDI groups, including the incidence of comorbidities, results of preoperative blood tests, preoperative body mass index, and output volume and amylase level of the peripancreatic drainage fluid. Both groups were sufficiently uniform to minimize potential bias related to the differences in baseline characteristics. After the initiation of food intake, no significant differences were found in the length of drain placement, incidence of clinically relevant POPF, or incidence of other postoperative complications, including ileus and POPF-related intra-abdominal hemorrhage (ISGPF grade C). Multivariate analysis showed that an estimated remnant pancreatic parenchymal volume was an independent predictive factor of progression to clinically relevant

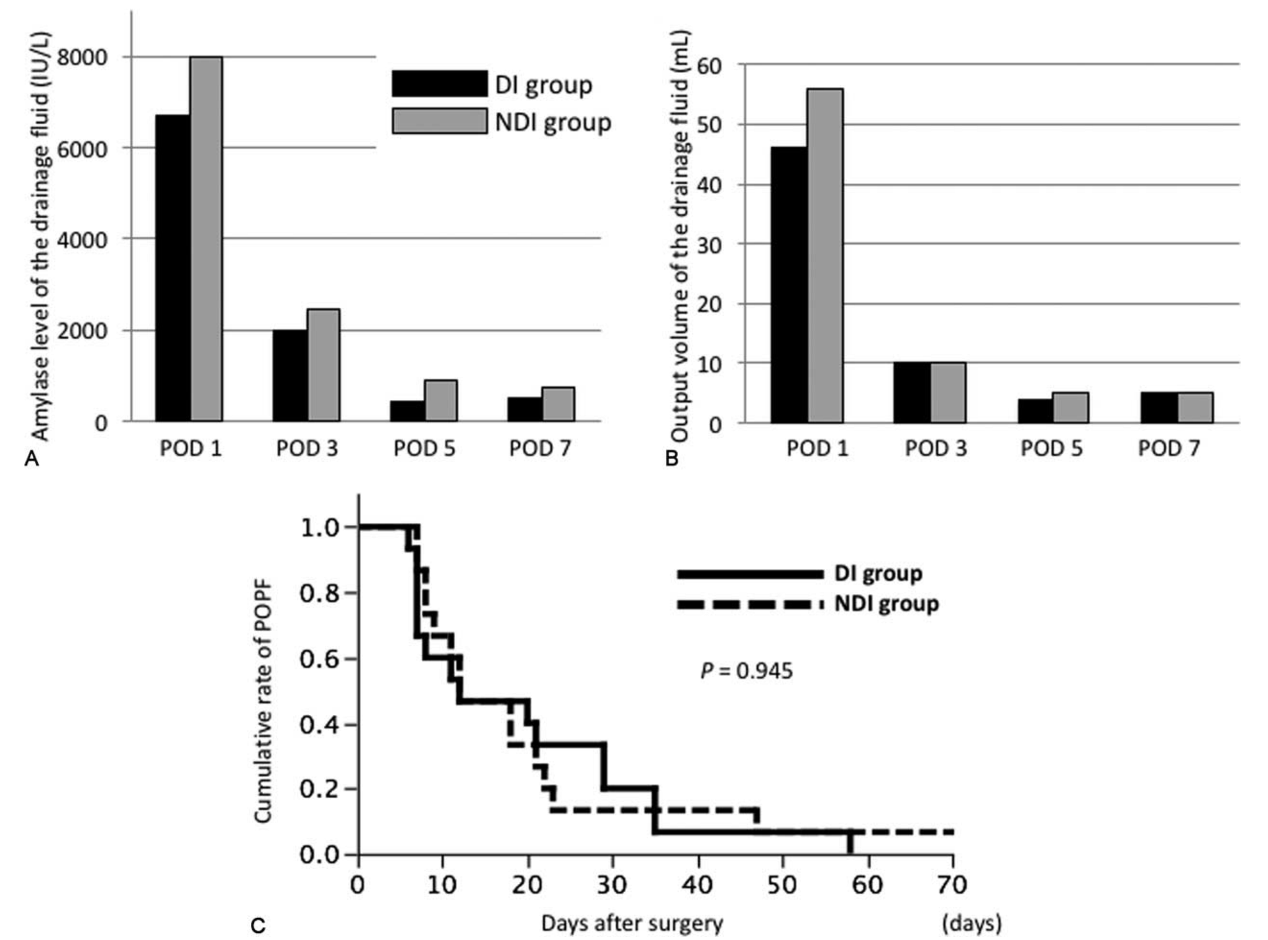

FIGURE 3. (A) Amylase level in the drainage fluid. No significant difference was found in the median amylase level on postoperative day 1, 3, 5, or 7 between the DI and NDI groups (6715 vs 7989 IU/L, 1991.5 vs 2475.0 IU/L, 451 vs 903 IU/L, and 513 vs 750 IU/L, respectively; $P = 0.513$, 0.396, 0.295, and 0.090). (B) Drainage fluid output volume. No significant difference was found on postoperative day 1, 3, 5, or 7 between the DI and NDI groups (46 vs 56 mL, 10 vs 10 mL, 4 vs 5 mL, and 5 vs 5 mL, respectively; $P = 0.704$, 0.181, 0.612, and 0.836). (C) Cumulative incidence rate of POPF after distal pancreatectomy. There was no significant difference between the 2 groups ($P = 0.945$, log-rank test). DI = dietary intake, NDI = no dietary intake, POPF = postoperative pancreatic fistula.

POPF. DI after postoperative day 5, however, was not significantly correlated with clinical progression of POPF.

Cholecystokinin is synthesized by I-cells in the mucosal epithelium of the jejunum and is secreted into the duodenum and upper jejunum.[31] Secretin is produced in the S-cells of the duodenum. The results of both of these gastrointestinal hormones is promoted by DI, resulting in the stimulation of pancreatic exocrine secretion; however, the control system of pancreatic exocrine secretion has still not been fully elucidated.[32] Enteral nutrition reportedly inhibits the exocrine pancreas by negative feedback involving a variety of hormones.[33] Secretion of pancreatic juice may not be significantly affected by conditions such as food volume and fat content of the diet. In the present study, patients who underwent DP were able to take only 65% to 75% of the meals that were provided, which might have minimized the influence of the diet on POPF. Enteral nutrition possibly has benefits in terms of compensating for the influence of increased pancreatic juice secretion, because there is a general agreement that enteral nutrition has more favorable impacts on the body, such as promotion of wound healing and minimization of exuberant granulation tissue, than does parenteral nutrition.[34] Previous RCTs and meta-analyses have also revealed that total enteral nutritional support is associated with lower mortality, fewer infectious complications, and decreased organ failure than is parenteral nutritional support in patients with acute pancreatitis.[35,36]

Klek et al reported that the median time to POPF closure was 37.5 and 43.5 days in the enteral and parenteral nutrition groups, respectively. These times to closure differed greatly from those in the present study (12 days in both groups). This difference may have occurred because Klek et al included patients undergoing various pancreatectomy procedures. Interestingly, no significant differences were found in nutritional status indicators after the initiation of food intake in the present study (eg, albumin level total lymphocyte count, and levels of rapid-turnover proteins including prealbumin, transferrin, and retinol-binding protein). In the DI group, the mean actual caloric intake from the diet on postoperative days 7, 10, and 14 was 580, 810, and 1060 kcal, respectively. Thus, the DI just after DP, an invasive surgical procedure, seemed to be insufficient for these adult patients. Additionally, the speed of POPF healing was similar between the DI and NDI groups in the

TABLE 3. Predictive Factors for Progression to Clinically Relevant Postoperative Pancreatic Fistula

	Univariate			Multivariate		
Variables	**Odds Ratio**	**95% CI**	***P* Value**	**Odds Ratio**	**95% CI**	***P* Value**
Age, y	0.96	0.87–1.06	0.464			
Sex, male	0.38	0.05–2.05	0.271			
Diseases other than pancreatic cancer	1.23	0.25–7.14	0.803			
Preoperative diabetes mellitus	0.47	0.08–2.96	0.407			
Comorbidity	1.07	0.21–5.21	0.936			
Preoperative body mass index, $\geq$25 kg/m^2	0.80	0.15–4.75	0.795			
Preoperative total lymphocyte count, per 10^2 mm^3	0.81	0.62–0.95	**0.006**	1.90	0.94–10.51	0.142
Preoperative serum albumin, g/dL	0.40	0.03–4.20	0.459			
Preoperative serum cholinesterase, per 10^2 IU/L	1.77	0.51–7.07	0.373			
Operative time, per 10^2 min	0.38	0.14–0.77	**0.005**	1.92	0.82–3.88	0.225
Intraoperative blood loss, per 10^2 mL	0.94	0.85–1.02	0.130			
Intraoperative blood transfusion	0.37	0.04–3.55	0.366			
Estimated remnant pancreatic volume, per 10 cm^3	4.73	1.55–15.19	**0.010**	4.16	2.01–9.53	**0.026**
Amylase level of the drainage fluid on POD 1, per 10^4 IU/L	0.93	0.68–1.29	0.604			
Amylase level of the drainage fluid on POD 3, per 10^4 IU/L	0.61	0.24–1.29	0.189			
Drainage output volume on POD 1, per 10 mL	1.09	0.93–1.42	0.343			
Drainage output volume on POD 3, per 10 mL	2.17	0.92–16.93	0.061			
DI group (dietary intake started on POD 6)	0.73	0.14–3.51	0.690			

CI = confidence interval, DI = dietary intake, POD = postoperative day.
Statistically significant results shown in bold.

present study; this differed from the results of the study by Klek et al, in which enteral nutrition was administered at 40 kcal/kg body weight.

The present study is not powered to show that oral food intake does not prolong time to POPF closure compared with fasting because the 2 groups exhibited no difference, although it was assumed that a difference of 3 days would be present. A type II error may exist, and this is the major limitation of the study. Statistically speaking, the results of this study only reject the hypothesis that oral food intake prolongs the duration of drain placement. Further investigation with an adequate sample size is necessary to confirm the noninferiority of management with oral food intake.

In conclusion, food intake did not aggravate POPF and did not prolong drain placement or hospital stay after DP. Although not confirmative, the present study implies that there is no need to avoid DI in patients with POPF. Considering also the study by Klek et al, fasting is deemed to be of little benefit.

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