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ORIGINAL ARTICLE

Application of an early oral feeding protocol after pylorus-preserving pancreaticoduodenectomy

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Abstract

Purpose This study evaluates the effect of an enhanced recovery after surgery (ERAS)-based nutrition support protocol on oral intake and weight change in patients who underwent pylorus-preserving pancreaticoduodenectomy (PPPD).

Methods A 14-day postoperative nutrition support protocol was developed to initiate oral intake after 1 week of enteral tube feeding and parenteral nutrition (early oral feeding, EOF). Forty-eight patients who underwent PPPD participated in the study (non-EOF, $n = 23$; EOF, $n = 25$). General information, nutrition supply route and amount, blood chemistry, and weight changes were tracked.

Results The enteral tube feeding duration was 2.7 days shorter in the EOF group than in the non-EOF group. Furthermore, the EOF group started oral liquid and soft diets 1.1 and 2.5 days earlier than the non-EOF group, respectively. Compared with the non-EOF group, the EOF group reported a higher energy intake (22.1%; $p = 0.001$) and protein intake (17.4%; $p = 0.000$) via oral route. Although cumulative energy and protein intakes were similar in both groups, weight reduction in the EOF group (3.6 ± 0.1%, 2.2 ± 0.7 kg) was significantly less than the non-EOF group (8.2 ± 0.9%, 5.2 ± 0.5 kg). The blood levels of total protein and transferrin increased and prealbumin decreased, regardless of the EOF application. Serum albumin increased significantly only in the EOF group.

Conclusion The EOF protocol developed for post-PPPD patients enables the early initiation and increase in the amount of oral intake while significantly alleviating weight loss.

Keywords Pylorus-preserving pancreaticoduodenectomy · Early oral feeding · Nutrition support protocol · Oral diet intake · Enteral tube feeding · Weight change

Introduction

Most patients who undergo pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD) experience a deterioration in nutritional status caused by a reduced dietary intake and weight loss, endocrine and exocrine disorders, and a poor quality of life [1]. Postoperative problems, such as pancreatic and gastrointestinal tract dyskinesia, digestive enzyme secretion disorders, nutrition absorption disorders, diarrhea [2], and steatorrhea can cause continued weight loss, which was observed in 39% of patients who underwent PPPD despite pancreatic enzyme therapy [3]. Almost all patients reported at least one of the following postoperative dietary obstacles: appetite loss, abdominal inflation, early satiety, bloating, belching, nausea, diarrhea, flatulence, and indigestion [4]. The conditions associated with delayed gastric emptying (DGE) limit postoperative meal initiation [5]. A deteriorated nutritional status correlates with an increased re-admission rate within 30 days of discharge among patients who have undergone pancreatic surgery [6]. Patients with a body mass index (BMI) of < 18.5 kg/m^2 have an elevated risk of postoperative death within 90 days [7]. Therefore, PPPD patients require adequate nutrition to maintain body weight.

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The invasive effect of pancreatic surgery on the endocrine and exocrine glands and the challenges associated with sufficient postoperative oral food intake highlight the importance of postoperative artificial nutrition support [8]. Nutritional support after PD, particularly immuno-enhancing enteral nutrition (EN), reduces postoperative complications, DGE, and hospital stay length [8]. Enhanced recovery after surgery (ERAS) strives to achieve better preoperative and postoperative patient care outcomes by promoting early recovery, reducing re-admission rate, and alleviating complications [9]. The ERAS guidelines recommend the initiation of a normal diet and a careful increase in oral intake according to tolerance during 3–4 postoperative days [9]. Patients should receive enteral tube feeding only under special indications, and routine parenteral nutrition (PN) should be avoided [9]. However, one study expressed concerns regarding the practical application of ERAS, as > 50% of the patients struggled to achieve oral intake immediately after surgery [10]. Other studies reported that additional time is necessary before initiating oral intake after PPPD [11, 12]. Furthermore, many researchers who recommend using the ERAS protocol also suggest combining PN and EN [13–17].

Modification of the ERAS guidelines, including early postoperative oral intake, may benefit PPPD patients. Hwang et al. reported that early postoperative oral intake (i.e., commencement of oral feeding within 48 h) increased total energy and protein intakes, and thereby reduced the hospital stay length and re-surgery rate among PPPD patients, but weight change was not mentioned [18].

This study aimed to develop an early postoperative oral feeding protocol based on a modified version of the ERAS guidelines for Korean patients undergoing PPPD and to clarify the impact of an increased early feeding intake amount on weight maintenance or alleviation of weight loss.

Materials and methods

Study subjects

This study was approved by the Institutional Review Board (IRB) of the Yonsei University College of Medicine (project number: 3-2016-0017). The early oral feeding (EOF) group included 25 patients who underwent PPPD in the Hepato-Biliary-Pancreatic Department of the Gangnam Severance Hospital between March and September 2016. Patients with a history of major surgery or radiation in the abdomen or pelvis, palliative surgery (i.e., metastatic disease), preoperative nutritional support, and prescription of immunosuppressants including steroid were excluded. Data including sex, age, illness, length of admission, meal starting day, amount of nutrient supply, blood chemistry variables, and body weight were collected.

Historic control

The non-EOF group ($n = 23$) was selected based on the criteria of PPPD patients who began enteral tube feeding on postoperative day (POD) 1–4. Eighteen patients in our non-EOF group were the same patients used for our previous study [19] who underwent PPPD between May 2007 and November 2008, received EN from POD 1, and were not subjected to the EOF protocol. The remaining five patients were additionally selected from the clinical records, under the conditions that they received the identical type of surgery during the same surgical period, began EN from POD 3 or 4 in addition to PN from POD 1, and were not subjected to our EOF protocol. Exclusion criteria were the same as those applied to the EOF group.

The PPPD early oral feeding (EOF) protocol

The nutrition support team and the Hepato-Biliary-Pancreatic Surgery Department at Gangnam Severance hospital devised a 2-week postoperative nutrition protocol for PPPD patients. This protocol aimed to initiate an EN or oral nutrition as early as possible and was carefully applied considering the patient's progress. The nutritional intervention for the EOF and non-EOF groups and the target energy and protein supplies per postoperative day are outlined in Table 1. The protocol included tube feeding and PN prior to oral feeding in accordance with studies that indicated the challenges of immediate postoperative EN [13–17]. Decisions regarding the oral feeding start time were based on a report from the European Society for Clinical Nutrition and Metabolism (ESPEN), which suggested the application of EN when a patient fails to maintain > 60% of the via oral intake for > 10 days [20]. Therefore, we decided to initiate oral intake after approximately 1 week of PN and EN.

PN was provided according to each patient's progress and physician's decision. Oral intake was subsequently initiated. The oral intake transitioned from liquid to soft diet and finally to normal diet (three dietary stages). This transition was based upon previous research that specified an oral diet start time and feeding types during the transition from EN to an oral diet [15, 17]. The liquid diet was given for 1 day, and the soft diet was maintained for 2 days. Subsequently, we also provided a normal diet according to previous studies that implemented solid and regular diets [15, 17]. A three-step post-pancreatic surgery diet (low volume, low fat, high protein) was applied (Table 1).

For the EOF group, the final energy intake goal was estimated as 1500 kcal/day, using the average weight of the subjects (62 kg) and the resting energy expenditure (25.4 kcal/kg) as defined by Sasaki [21]. The protein intake goal was set at 70 g/day with reference to the protein requirement measured via indirect calorimetry in a study of 886 critical patients and

Table 1 Post-pancreatic surgery diet (non-EOF) and PPPD nutrition support EOF protocol per postoperative day

	Non-EOF	EOF
POD 1	Dextrin solution[†]	Dextrin solution[†]
POD 2	Enteral tube feeding[††]	Enteral tube feeding[††]
POD 3		
POD 4		
POD 5		
POD 6	Step 1: full liquid diet × 3 times/day 500 kcal, protein 20 g/day	Step 1: full liquid diet × 3 times/day 600 kcal, protein 30 g/day
POD 7	Step 2: soft diet × 3 meals/day	Step 2: soft diet × 3 meals/day
POD 8	1400 kcal, protein 50 g/day	Snack × 3 times/day 1200 kcal, protein 60 g/day
POD 9		Step 3: normal diet × 3 meals/day
POD 10		Snack × 3 times/day 1500 kcal, protein 70 g/day

EOF early oral feeding, *POD* postoperative day

[†] Dextrin solution, a mixture of dextrose and free water (dextrose 5 g/100 mL), was provided through nasojejunal tube by manual injection using syringe to check gastrointestinal tract availability and to prepare for enteral nutrition

[††] Enteral nutrition formula, composed of carbohydrates, proteins, fats, fiber, and vitamins and minerals, was delivered through nasojejunal tube by a continuous enteral infusion pump for 18 h/day with 6 h of a rest period. The formula density was 1 mL/1 kcal and rate of infusion per hour was progressively increased

the standard recommendation outlined in the American Society for Parenteral and Enteral Nutrition (ASPEN) post-surgery nutrition support guidelines (1.2 g/kg) [22, 23]. The initiation days of enteral tube feeding, oral liquid diet, and oral soft diet were determined from medical documents and dietary records.

General characteristics and anthropometry

The subjects' sex, age, height (cm), weight (kg), weight change, diagnosis, surgery duration (minutes), and intake route data were recorded. The average weight (1–3 months before surgery) was determined via patient interviews, and their preoperative weights were measured on the day of surgery. The diagnosis and underlying disease (diabetes, high blood pressure) were determined from the medical records. The surgery duration and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were obtained from operative notes and intensive care unit (ICU) records.

Nutritional intake, blood level, and weight change analysis

The patients' oral intakes were evaluated via interviews of the patients and their guardians. EN and PN intakes were analyzed based on the respective nutritional contents. The energy and protein contents of meals were analyzed using CAN Pro 4.0 (The Korean Nutrition Society, Seoul, Korea). The levels of albumin (g/dL), total protein (g/dL), and serum transferrin (g/L), which correlate with the nutritional status [24–26], were collected from medical records. Data were collected 1 day before surgery, on the day of surgery, and 14 days post-surgery. Body weights during the hospital stay were obtained from medical records recorded on POD 0, 7, and 14 and were used to calculate BMI [body weight (kg)/height (m^2)] [27]. The weight and BMI values on the surgery day were compared with those on 7 and 14 days after surgery to calculate the reduction (Δ, kg) and reduction rate (%), respectively.

Statistical analysis

For the general characteristics and survey results, non-continuous variables are presented as n values and percentages, whereas continuous variables are presented as averages and means ± standard errors. Following a cross-analysis, the chi-square test and Fisher's exact test were used to confirm the statistical significance of non-continuous variables. A paired t test was used to compare pre- and post-treatment continuous variables, whereas the independent t test was used for comparisons between two groups. ANCOVA, which accounts for covariates, was used to adjust the baseline of each subject. All data were analyzed using IBM SPSS version 21 (Armonk, NY, USA), and a p value < 0.05 was considered statistically significant.

Results

General characteristics and anthropometry

The subjects had an average age, BMI, and APACHE II score of 62.9 ± 1.7 years, 23.8 ± 0.4 and 12.7 ± 0.8, respectively. None of the subjects experienced surgical side effects serious enough to warrant exclusion from the study. There were no significant differences in the average age, sex ratio, BMI, history of diabetes and high blood pressure, pathologic origin, average surgery duration, or APACHE II score between the non-EOF and EOF groups (Table 2).

Comparison of the nutrition supply route between the non-EOF and EOF groups

The EOF protocol was applied to the EOF group for 14 days. The average EN initiation days did not significantly differ between the non-EOF (POD 3.0 ± 0.2) and EOF groups (POD 2.6 ± 0.2). However, the EN duration was significantly shorter in the EOF group (4.0 ± 0.3 days) than in the non-EOF group (6.7 ± 0.6 days) by an average of 2.7 days ($p = 0.000$). The oral liquid diet was initiated 1.1 days earlier in the EOF group (POD 6.8 ± 0.3) than in the non-EOF group (POD 7.9 ± 0.4), a significant difference ($p = 0.049$). Similarly, the oral soft diet was initiated significantly earlier ($p = 0.001$) in the EOF group (POD 8.1 ± 0.4) than in the non-EOF group (POD 10.6 ± 0.5).

Comparison of the energy and protein supplies between the non-EOF and EOF groups

The non-EOF and EOF groups received energy and protein via PN immediately after the surgery, and then switched from EN to an oral diet, although such transition occurred earlier in the EOF than in the non-EOF (Tables 3 and 4). In the EOF group, the oral caloric and protein intakes gradually increased to 1313.8 kcal/day and 53.1 g/day, respectively, on POD 14. However, the non-EOF group consumed only 600 kcal/day and 23.3 g/day protein on POD 14. Over time, the EOF group received significantly higher total energy and protein supplies via oral intake, compared with the non-EOF ($p = 0.001$ and 0.002, respectively) (Tables 3 and 4). Compared with the non-EOF group, the oral intakes of energy and protein were 2573.5 kcal and 100.0 g higher, respectively, in the EOF group. The non-EOF group received an additional 2396.3 kcal of energy from PN, compared to the EOF group ($p = 0.033$). However, the total amounts of

Table 2 General characteristics of non-EOF and EOF groups

	Total ($n = 48$)	Non-EOF ($n = 23$)	EOF ($n = 25$)	p value
Age (year)	62.9 ± 1.7	61.9 ± 1.1	63.8 ± 2.5	0.564[a]
Height (cm)	161.9 ± 1.0	162.6 ± 1.6	161.3 ± 1.4	0.554[a]
BMI (kg/m^2)	23.8 ± 0.4	23.7 ± 0.6	24.0 ± 0.5	0.896[a]
Sex (n (%))				0.552[b]
Male	30 (62.5)	13 (56.5)	17 (68.0)	
Female	18 (37.5)	10 (43.5)	8 (32.0)	
Diabetes mellitus (n (%))				0.368[b]
Yes	16 (33.3)	6 (26.1)	10 (40.0)	
No	32 (66.7)	17 (73.9)	15 (60.0)	
Hypertension (n (%))				0.349[b]
Yes	14 (29.2)	5 (21.7)	9 (36.0)	
No	34 (70.8)	18 (78.3)	16 (64.0)	
Pathologic origin (n (%))				0.593[b]
Pancreas region	19 (39.6)	9 (39.1)	10 (40.0)	
Non-pancreas region	29 (60.4)	14 (60.9)	15 (60.0)	
Operation time (min)	431.1 ± 15.1	422.3 ± 22.0	439.2 ± 21.1	0.581[a]
APACHE II (score)	12.7 ± 0.8	11.6 ± 1.1	13.7 ± 1.1	0.168[a]

Values are mean ± SE

APACHE II Acute Physiology and Chronic Health Evaluation II

[a] p values were calculated by independent t test

[b] p values were calculated by Fisher's exact test

Table 3 Comparison of changes in oral, enteral, parenteral energy intake between the non-EOF and EOF groups during 14 postoperative days

	Oral energy intake (kcal/day)		Enteral energy intake (kcal/day)		Parenteral energy intake (kcal/day)		Total energy intake (kcal)	
	Non-EOF ($n = 23$)	EOF ($n = 25$)	Non-EOF ($n = 23$)	EOF ($n = 25$)	Non-EOF ($n = 23$)	EOF ($n = 25$)	Non-EOF ($n = 23$)	EOF ($n = 25$)
POD 1	0.0	0.0	0.0	33.3	651.7	102.3	622.8	129.4
POD 2	0.0	0.0	119.9	85.1	935.1	517.2	1049.5	577.3
POD 3	0.0	0.0	214.6	258.6	944.0	546.3	1141.7	781.9
POD 4	41.8	25.5	340.5	399.5	857.7	664.3	1234.0	1067.0
POD 5	49.0	42.1	429.0	531.9	798.6	528.2	1292.3	1093.1
POD 6	75.5	157.1	443.9	609.0	798.4	393.2	1346.0	1156.9
POD 7	380.7	261.2	478.4	365.2	592.8	382.1	1434.0	976.5
POD 8	294.2	467.2	218.9	155.2	342.1	394.1	896.6	987.4
POD 9	560.0	692.7	89.6	83.8	306.9	400.6	965.1	1149.1
POD 10	481.0	907.0	60.9	0.0	172.4	290.5	711.7	1153.2
POD 11	576.7	1020.3	33.6	0.0	142.2	147.6	807.0	1142.1
POD 12	583.5	1088.2	0.0	0.0	191.3	152.9	778.8	1231.3
POD 13	635.2	1211.6	0.0	0.0	127.8	144.4	746.3	1333.1
POD 14	600.5	1313.8	0.0	0.0	106.1	151.0	737.5	1398.3
Cumulative intake[a]	4124.9	6698.4	2429.2	2795.5	7018.5	4622.2	13,572.4	13,378.3
p value[b]	0.001		0.939		0.033		0.861	

Values are mean

POD postoperative day

[a] Cumulative energy intake during postoperative 14 days

[b] Cumulative intake *p* values were calculated by independent *t* test

energy and protein supplied via tube feeding did not significantly differ between the two groups. Additionally, the groups did not differ significantly in the cumulative intakes of energy and protein. However, the non-EOF group received 31.7 ± 3.9% of the total energy via oral diet, versus 53.8 ± 5.2% in the EOF group, and this difference was significant (Fig. 1a). Furthermore, the two groups respectively received 52.1 ± 3.9 and 34.7 ± 5.2% of the total protein intakes via the oral diet ($p = 0.010$) (Fig. 1b).

Changes in body weight between the two groups

Both the non-EOF and EOF groups exhibited decreases in body weight between 7 and 14 days after surgery ($p < 0.001$) (Fig. 1c), although the BMI values remained unchanged in both groups (Fig. 1d). However, on POD 14, the EOF group had a higher body weight (Fig. 1c) and had a smaller body weight loss from baseline (Fig. 1e), compared to the non-EOF group ($p = 0.003$ and 0.002, respectively). Regarding the weight loss percentages, the non-EOF and EOF groups had values of 8.2 ± 0.9 and 3.6 ± 1.0%, respectively (Fig. 1f).

Changes in blood chemistry between the non-EOF and EOF groups

On POD 14, the total blood protein concentrations increased significantly in both the non-EOF and EOF groups relative to the values on day of surgery, whereas the serum transferrin and prealbumin concentrations decreased significantly in both groups (Fig. 2a–c). Meanwhile, the serum albumin concentration increased significantly only in the EOF group (Fig. 2d). However, there were no significant differences between the groups in these blood parameters.

Discussion

In this study, we developed a nutrition support protocol (i.e., EOF protocol) for PPPD patients based on a modification of the principles of ERAS to include the use of EN and PN in combination with an oral diet, as well as the application of a normal oral diet as early as possible after surgery. Our data suggest that the EOF protocol increased oral energy intake, oral protein intake, and serum albumin levels, and alleviated postoperative weight loss compared with the non-EOF group.

Table 4 Comparison of changes in oral, enteral, parenteral protein intake between the non-EOF and EOF groups during postoperative 14 days

	Oral protein intake (g/day)		Enteral protein intake (g/day)		Parenteral protein intake (g/day)		Total protein intake (g/day)	
	Non-EOF ($n = 23$)	EOF ($n = 25$)	Non-EOF ($n = 23$)	EOF ($n = 25$)	Non-EOF ($n = 23$)	EOF ($n = 25$)	Non-EOF ($n = 23$)	EOF ($n = 25$)
POD 1	0.0	0.0	0.0	0.1	15.9	1.6	16.5	1.7
POD 2	0.0	0.0	6.6	2.4	27.7	22.3	36.7	24.7
POD 3	0.0	0.0	12.1	10.5	32.9	24.8	44.8	35.2
POD 4	2.4	1.0	17.6	16.6	30.6	30.9	50.8	48.6
POD 5	2.5	2.3	19.0	22.2	29.6	24.3	51.9	48.9
POD 6	2.8	7.0	19.6	24.0	27.3	17.8	51.7	48.8
POD 7	12.1	9.9	20.3	10.4	20.9	17.4	55.1	37.8
POD 8	10.9	18.0	8.8	6.2	6.3	17.1	27.0	41.3
POD 9	16.6	26.1	4.0	3.4	3.8	18.3	24.2	47.7
POD 10	18.1	34.7	2.6	0.0	3.8	13.6	22.9	48.3
POD 11	25.6	39.3	1.3	0.0	3.5	6.8	31.0	46.1
POD 12	22.4	41.4	0.0	0.0	5.2	9.0	27.3	50.4
POD 13	23.3	43.4	0.0	0.0	7.3	6.7	30.4	50.1
POD 14	23.3	53.1	0.0	0.0	2.6	6.0	27.2	59.1
Cumulative intake[a]	157.6	257.6	111.8	125.6	220.3	234.6	489.7	540.6
p value[b]	0.002		0.488		0.654		0.309	

Values are mean

POD postoperative day

[a] Cumulative energy intake during postoperative 14 days

[b] Cumulative intake *p* values were calculated by independent *t* test

According to the ERAS guidelines for postoperative nutrition in PPPD patients, an immediate oral diet intake is recommended [9]. However, this is not easily applicable to real-life situations. Braga et al. claimed that oral liquid diet was possible in only 55% of ERAS patients, and only 53% could consume solid food [10]. In a study of 210 patients undergoing

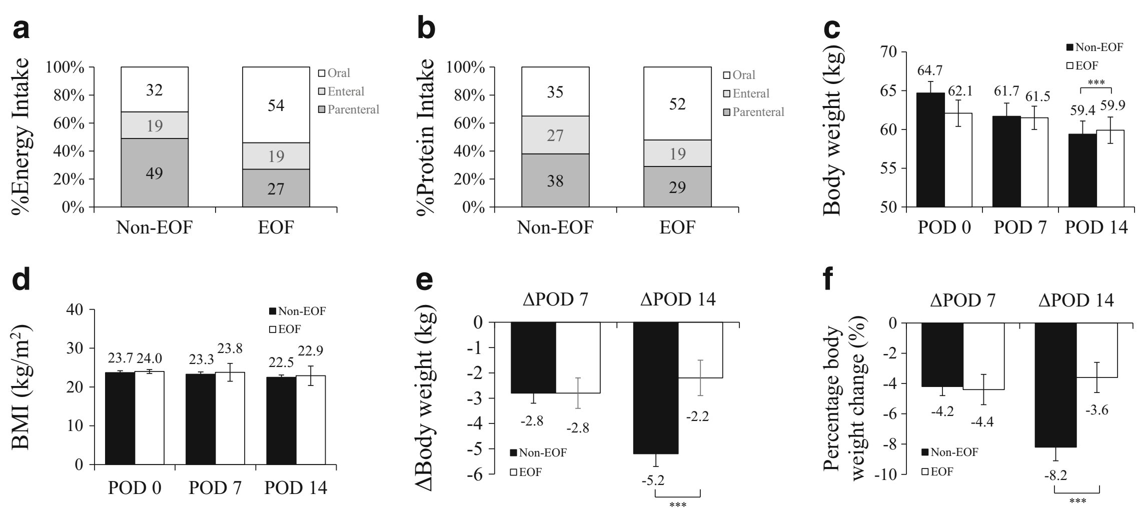

Fig. 1 The cumulative intake according to feeding routes and comparison of body weight, BMI and weight change between non-EOF and EOF groups. **a**–**b** *p* value of percentage of cumulative oral energy intake were calculated by independent *t* test ($p < 0.01$). Values are mean. **c**–**f** *p* values at POD 7 and POD 14 were calculated by ANCOVA for body weight and BMI. There was no baseline body weight and BMI difference (independent *t* test, $p = 0.264$, $p = 0.625$). Δ values were calculated as the difference from the baseline (POD 0). Values are mean ± SE. *POD*, postoperative day; *BMI*, body mass index

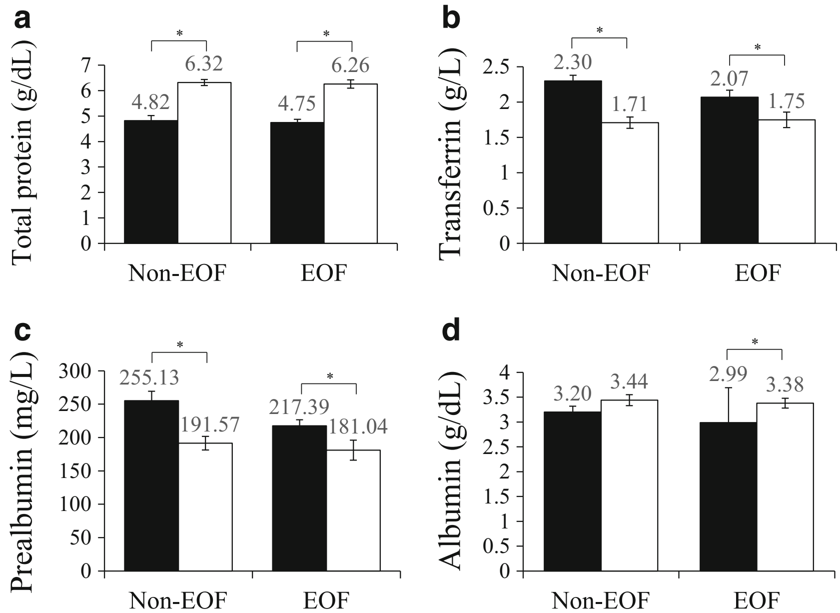

Fig. 2 Comparison of biochemical data between the groups at baseline (POD 0, ■) and after intervention (POD 14, □) *p* values of change values were calculated by independent *t* test. Values are mean ± SE. *POD*, postoperative day

PD and PPPD, the start day of oral water intake was POD 7.9 for PD patients and POD 7.8 for PPPD patients [11]. Another study of 398 patients undergoing pancreatic surgery found that oral intake began after the half-point of the total hospital stay (POD 11.6 for PD patients and POD 12.1 for PPPD patients during 24.7 days of hospitalization) [12]. Therefore, to overcome the limitations of ERAS, we included EN and PN in our EOF protocol for PPPD patients as transitional feeding phases prior to oral intake. Our EOF protocol allowed PN on POD 1 and EN on POD 2–5, in accordance with other studies that used a modified ERAS program [13–17]. Liu et al. provided 50% of the total energy requirement via EN on POD 1 and continued total parental nutrition until POD 7, with the initiation of an oral liquid diet [13]. Nagata et al. began tube feeding on POD 2 and gradually increased the formula volume to meet the maximum total caloric intake value by POD 4 with peripheral PN, and started an oral intake on POD 7 [14]. Our EOF protocol started an oral liquid diet on POD 6, oral soft diet on POD 7–8, and oral normal diet on POD 9. Grizas et al. also reported that oral liquid and solid diets were possible on POD 6 and 9, respectively [15]. Martignoni et al. reported that patients began a thin liquid diet on POD 3, oral soft diet on POD 4, and normal diet as early as POD 6, depending on each patient's condition [17]. In the present study, EN duration of the EOF group (4.0 days) was 2.7 days shorter than that of the non-EOF group, and the former group began an oral liquid diet 1.1 days earlier (POD 6.8). Furthermore, our EOF patients began an oral soft diet on POD 8.1, much earlier than the results reported by a different study (POD 13.2 ± 8.7) [28].

Patients in our EOF and non-EOF groups did not differ in terms of total intakes of energy and protein. However, a previous study reported that EOF increased the daily total calorie and protein intakes [18]. The oral intakes of energy and protein were significantly increased in the EOF group without affecting the total intakes. Kang et al. reported similar results in a study of 31 patients who underwent pancreatectomy and began an oral liquid diet between POD 5–7, followed by an oral soft diet on POD 6–13 [4].

Our EOF protocol significantly inhibited weight loss compared with the non-EOF protocol. As weight loss is associated with negative prognosis among pancreatic cancer patients [1, 29], our findings suggest that the EOF may successfully enhance the patient's nutritional status relative to the non-EOF. In a study by Pausch et al., 73.9% of 408 PD patients experienced an unintentional weight loss of 10% within 6 months before surgery with abnormal serum albumin levels and higher rates of overall complications, in-hospital mortality, and 90-day mortality than those without severe weight loss [7]. Another study of 849 patients who received gastric surgery found a correlation of reduced weight loss with higher postoperative survival rates [4]. Our EOF group experienced a weight loss of only 3.6% within 14 postoperative days, whereas the non-EOF group had a loss of 8.2%, suggesting that the EOF protocol may improve the patients' prognosis by preventing weight loss.

The weight loss suppressive effect observed in the EOF group may be attributable to higher oral energy and protein intakes relative to those in the non-EOF group, given the lack of difference in total energy intake between the two groups. This could imply that orally supplied nutrition is more bioavailable than nutrition provided via PN and EN. Previous studies have shown that gastrointestinal feeding increases glucose utilization [30–32]. McIntyre et al. observed higher blood glucose and plasma insulin levels in response to jejunal feeding relative to PN with the same amount of glucose was provided at the same speed [30]. This suggests that insulin secretion is affected not only by the blood glucose level and pancreatic β-cell response, but also by intestinal wall secretions stimulated by gastrointestinal feeding [30]. Besides hormonal secretion, gastrointestinal nutrition increases vagal activity, which can increase insulin reactions and intracellular glucose levels [31]. DeFronzo et al. discovered that oral energy intake leads to a sixfold greater glucose uptake by the liver compared with PN [32]. Cellular glucose can then be converted into glycogen via glycogenesis or stored in fat via lipogenesis [33], which can lead to body fat deposition [34]. Therefore, the increased oral energy intake in the EOF group relative to the non-EOF group might have led to the activation of gastrointestinal tract and insulin responses and, subsequently, to a decrease in body weight loss.

Additionally, intravenous nutrition was shown to increase protein turnover in cancer patients [35]. Under total parenteral amino acid supplementation, protein synthesis was found to decrease significantly by 21% ($p = 0.005$) relative to the pre-nutritional support status in malnourished cancer patients [35]. Bone marrow transplant recipients receiving low PN had higher serum albumin concentrations than did those receiving high PN, suggesting that a reduction in intravenous nutrition improves body protein synthesis [36]. In our study, therefore, an increase in oral feeding and reduction in PN may have improved the protein supply and/or synthesis and might thus have contributed to the alleviation of weight loss in the EOF group. In the non-EOF group, increased protein intake via PN might have caused inefficient protein utilization, thus contributing to higher weight loss.

There was no difference between the groups in blood levels of total protein, transferrin, and prealbumin on POD 14. However, only EOF led to a significant increase in the serum albumin level. The serum level of albumin, which has a half-life of 20 days [37], decreases in cases of cancer [38], injury, and surgery [39]. Hypoalbuminemia is as an independent factor for post-PPPD complications [40] and has been strongly associated with increased mortality from cancer and other serious diseases [41]. However, patients in the EOF and non-EOF groups exhibited similar decreases in prealbumin levels. ASPEN suggested that the serum albumin and prealbumin levels are not satisfactory indicators of malnutrition in critical patients because the energy requirements vary greatly among individuals and the serum levels are not affected by changes in nutrient intake [23]. Although the EOF protocol elicited higher blood albumin levels, a 14-day blood chemistry monitoring period might not accurately reflect changes in the nutritional statuses of PPPD patients.

Limitations of this study include the use of a historic control group. Improvement in the surgeons' surgical experience and management resources over time could influence the study results. However, surgery processes and techniques as well as comprehensive patient care plan applied to PPPD patients in both groups have not changed during the period of the current study using the historic non-EOF group and EOF groups. Secondly, lack of evaluation of postoperative edema might influence the body weight measurement. Nevertheless, in a study on the reconstruction of the aorta, extracellular fluid volume, which could be used as an index of edema, returned to that of preoperative days by POD 7 [42]. Postoperative edema has been known to greatly decrease after POD 5 by the application of a minimally invasive laparoscopic surgery [43]. The use of laparoscopic surgery and the measurements of body weight on POD 7 and POD 14 may have reduced the influence of postoperative edema on the group difference in body weight change in our study.

In conclusion, we have demonstrated that our EOF protocol is beneficial for patients who have undergone PPPD, as it alleviates the postoperative body weight loss without requiring an increase in the total energy intake, and thus may have a positive impact on early recovery and/or survival. Our results indicate the effect of an early postoperative introduction of oral feeding on increased oral energy and protein intakes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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