Impact of Delayed Gastric Emptying After Pancreatoduodenectomy on Postoperative Nutritional Status: A Substudy of Prospective, Multicenter Randomized Study

Takuya Mizumoto
Kobe University Graduate School of Medicine
Hirochika Toyama (tymhr@me.com)
Kobe University Graduate School of Medicine
Ippei Matsumoto
Kindai University Faculty of Medicine
Sadaki Asari
Kobe University Graduate School of Medicine
Tadahiro Goto
Kobe University Graduate School of Medicine
Yoshihide Nanno
Kobe University Graduate School of Medicine
Jun Ishida
Kobe University Graduate School of Medicine
Shinichi So
Kobe University Graduate School of Medicine
Takeshi Urade
Kobe University Graduate School of Medicine
Kenji Fukushima
Kobe University Graduate School of Medicine
Hidetoshi Gon
Kobe University Graduate School of Medicine
Daisuke Tsugawa
Kobe University Graduate School of Medicine
Shohei Komatsu
Kobe University Graduate School of Medicine
Kaori Kuramitsu
Kobe University Graduate School of Medicine
Hiroaki Yanagimoto
Kobe University Graduate School of Medicine

Masahiro Kido
Kobe University Graduate School of Medicine
Tetsuo Ajiki
Kobe University Graduate School of Medicine
Takumi Fukumoto
Kobe University Graduate School of Medicine

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Abstract

Purpose

The aim of this study was to investigate the risk factors for delayed gastric emptying (DGE) and the impact of DGE on postoperative nutritional status after subtotal stomach-preserving pancreatoduodenectomy (SSPPD). The pathophysiology of DGE after SSPPD is still unknown, and the precise impact of DGE on various nutritional markers has been scarcely reported.

Methods

The risk factors for DGE were analyzed using a database created for a previously reported randomized controlled trial (UMIN000005827). To investigate the impact of DGE, data on patient nutrition were analyzed.

Results

Data from 196 patients were analyzed. DGE occurred in 30 patients (15.3%). Hand-sewn gastrojejunostomy was found to be significantly associated with DGE *(P =* 0.005). Serum levels of albumin (3.16 g/dL in patients with DGE versus 3.4 g/dL in patients without DGE) and total cholesterol (125.1 mg/dL in patients with DGE versus 147.2 mg/dL in patients without DGE) in DGE patients were lower at postoperative month (POM) one. There was no statistically significant difference in any of the nutritional parameters at POM three or later. On multivariate analysis, preoperative serum albumin < 3.5 mg/dL (Odds ratio, 3.27; *P* = 0.002) and DGE (Odds ratio, 2.68; *P* = 0.043) were significantly associated with decreased serum albumin level (< 3.5 mg/dL) at POM one.

Conclusion

DGE after SSPPD may be associated with hand-sewn gastrojejunostomy. DGE impairs patients' nutrition for the first postoperative month. However, its effect is limited to no more than three months.

Introduction

Pancreatoduodenectomy (PD) is the standard surgical procedure for periampullary tumors, including pancreatic adenocarcinoma (PDAC) [1]. Despite recent advances in preoperative imaging, perioperative management, and surgical procedures, PD remains one of the most challenging gastrointestinal procedures. Not only is the procedure technically demanding, but postoperative complications occur in up to 40% of PD patients [2–4]. Postoperative pancreatic fistula (POPF) and post-pancreatectomy hemorrhage (PPH), in particular, can lead to life-threatening conditions and postoperative mortality. Another unresolved postoperative complication after PD is delayed gastric emptying (DGE) [5]. Although

DGE is not life-threatening, it may impair patients' postoperative nutritional status and quality of life, compromising their compliance with postoperative anticancer treatment. DGE is self-resolving and recovers gradually over a period of weeks to months. However, the precise duration and severity of its impact on the nutritional status of patients remain unknown [6]. Furthermore, the mechanism underlying DGE after PD is not well understood. Several studies have been conducted in an attempt to reduce the incidence of DGE after PD [7–11]. However, no standardized approach has been developed that solely prevents the occurrence of DGE. Because the pathophysiology of DGE appears to be multifactorial, identifying its risk factors is crucial to developing strategies to reduce its occurrence.

This study was a substudy of a previously reported multicenter, randomized controlled trial (RCT) comparing retrocolic and antecolic gastroenteric reconstruction after PD [10]. Using a pre-built database for the RCT, analyses were conducted to determine the effect of DGE on postoperative nutritional status. Furthermore, DGE risk factors were also investigated. Although the RCT included both subtotal stomach-preserving PD (SSPPD) and pylorus-preserving PD (PPPD), the majority of patients underwent SSPPD. Because SSPPD is currently the standard procedure at our institution, only patients who underwent SSPPD were included in our study to minimize the heterogeneity of the dataset.

Material And Methods

Data collection

Patient information were obtained from the database created as part of a multicenter RCT (UMIN000005827) that compared the incidence of DGE after PD with retro- and antecolic alimentary tract reconstruction [11]. Kobe University Hospital and its affiliated hospitals were used to recruit patients. Only SSPPD patients ($n = 196$) were included in the study. This study was approved by the institutional review board of Kobe University Hospital and was performed in accordance with the ethical standards laid down in the 1964 Helsinki Declaration and its subsequent amendments.

Surgical procedures and postoperative management

Details have been reported previously [11]. In brief, the stomach was divided approximately 4 cm proximal to the pyloric ring. The modified Child method was used for reconstruction. Two-layered side-to-side gastroenterostomy was used to reconstruct the alimentary tract. Braun anastomosis was not performed. The number, types, and locations of the intra-abdominal drainage tubes were determined according to the surgeons' preferences. In principle, the nasogastric tube was removed on postoperative day (POD) one. Proton pump inhibitors or histamine H2-receptor antagonists were administered intravenously after surgery and converted to an oral dose. Prophylactic use of prokinetic drugs was not permitted.

Definitions of postoperative complications

DGE was defined and graded using the International Study Group of Pancreatic Surgery (ISGPS) consensus definition [12]. In this study, all DGE grades were positive for DGE. Primary and secondary

DGEs were not differentiated.

Based on the 2005 version of the International Study Group of Pancreatic Fistula (ISGPF) definition, POPF was defined and graded as A, B, or C [13]. Grade B/C in the present study was defined as clinically relevant POPF. The ISGPS consensus definition was also used to define PPH [14]. Surgical complications were graded using the Clavien–Dindo classification system [15].

Postoperative nutritional status

To investigate the impact of DGE on postoperative nutritional status, serial data on patients' nutrition (body mass index [BMI], serum total protein, serum albumin, total cholesterol, triglyceride, and cholinesterase) were analyzed on postoperative months (POM) one, three, and six. Data from POD 7 were added to the data used for the analyses of serum total protein and albumin.

Statistical analysis

The results were presented as the mean ± standard deviation (SD). Categorical variables were compared using the chi-square test or Fisher's exact test, and quantitative variables were compared using the Student's t-test. Only factors with a P-value < 0.10 on univariate analyses were included in the multivariate logistic regression model for the serum albumin level at POM one. The level of statistical significance was set at $P < 0.05$. JMP 12 software (SAS Institute Japan, Tokyo) was used for all statistical analyses.

Results

Risk factors of DGE

In total, 196 Japanese patients were included in the study. The results of the univariate and multivariate analyses on the incidence of DGE are shown in Table 1. DGE occurred in 30 patients (15.3%), with 6 patients (3.1%) having grade A, 17 patients (8.7%) having grade B, and 7 patients (3.6%) having grade C. On univariate analysis, hand-sewn gastrojejunostomy was significantly associated with DGE compared with stapled gastrojejunostomy ($P = 0.005$). Patients who had DGE had a significantly longer hospital stay (mean length of stay: 42.4 d) than in those who did not (mean length of stay: 26.8 d, $P < 0.001$).

Table 1
Preoperative and operative characteristics stratified by the incidence of delayed gastric emptying.

	Total *N* = 196	DGE – negative (*n* = 166)	DGE – positive (*n* = 30)	*P*-value
Preoperative variables				
Age, years, *n* (%)				0.878
< 70	102 (52.0)	86 (51.8)	16 (53.3)	
≥ 70	94 (48.0)	80 (48.2)	14 (46.7)	
Sex, *n* (%)				0.584
Female	74 (37.8)	64 (38.6)	10 (33.3)	
Male	122 (62.2)	102 (61.4)	20 (66.6)	
Body mass index, kg/m^2		21.7 ± 3.16	22.1 ± 3.03	0.462
Hemoglobin, g/dL		12.7 ± 1.69	12.5 ± 1.79	0.562
Serum total protein, g/mL		6.75 ± 0.60	6.70 ± 0.66	0.681
Serum albumin, g/mL		3.85 ± 0.57	3.66 ± 0.62	0.118
Hemoglobin A1c, %		6.38 ± 0.11	5.88 ± 0.25	0.070
Disease, *n* (%)				0.137
Pancreatic adenocarcinoma	83 (42.4)	74 (44.6)	9 (30.0)	
Others	113 (57.7)	92 (55.4)	21 (70.0)	
Diabetes Mellitus, *n* (%)				0.380
Absent	180 (93.3)	151 (92.6)	29 (96.7)	
Present	13 (6.74)	12 (7.4)	1 (3.3)	
Biliary drainage, *n* (%)				0.106
Absent	86 (44.8)	77 (47.2)	9 (31.0)	
Present	106 (55.2)	86 (52.8)	20 (69.0)	
Intraoperative variables				

POPF stands for postoperative pancreatic fistula; *PPH* stands for post-pancreatectomy hemorrhage; *AMY* stands for amylase; *POD* stands for postoperative day; *CRP* stands for C-reactive protein.

[a] According to the International Study Group of Pancreatic Fistula grading (2005)

*Statistically significant ($P < 0.05$)

	Total *N* = 196	DGE – negative (*n* = 166)	DGE – positive (*n* = 30)	*P*-value
Route of gastrojejunostomy, *n* (%)				0.501
Antecolic	96 (49.0)	83 (50.0)	13 (43.3)	
Retrocolic	100 (51.0)	83 (50.0)	17 (56.7)	
Method of gastrojejunostomy, *n* (%)				0.005*
Stapling	136 (69.4)	122 (73.5)	14 (46.7)	
Hand-sewn	60 (30.6)	44 (26.5)	16 (53.3)	
Duration of operation, min		550.7 ± 118.5	570.5 ± 175.0	0.439
Estimated blood loss, mL		693.5 ± 502.2	877.7 ± 707.5	0.086
Lymph node dissection, *n* (%)				0.815
Present	174 (88.8)	147 (88.6)	27 (90.0)	
Absent	22 (11.2)	19 (11.5)	3 (10.0)	
Texture of the pancreas, *n* (%)				0.101
Soft	104 (53.1)	84 (50.6)	20 (66.7)	
Hard	92 (46.9)	82 (49.4)	20 (33.3)	
Postoperative variables				
POPF[a], *n* (%)				0.952
Grade 0/A	156 (79.6)	132 (79.5)	24 (80.0)	
Grade B/C	40 (20.4)	34 (20.5)	6 (20.0)	
PPH, *n* (%)				0.446
Absent	183 (93.4)	156 (94.0)	27 (90.0)	
Present	13 (6.6)	10 (6.0)	3 (1.0)	
Bile leak, *n* (%)				0.776
Absent	191 (97.5)	162 (97.6)	29 (96.7)	

POPF stands for postoperative pancreatic fistula; *PPH* stands for post-pancreatectomy hemorrhage; *AMY* stands for amylase; *POD* stands for postoperative day; *CRP* stands for C-reactive protein.

[a] According to the International Study Group of Pancreatic Fistula grading (2005)

*Statistically significant ($P < 0.05$)

	Total *N* = 196	DGE – negative (*n* = 166)	DGE – positive (*n* = 30)	*P*-value
Present	5 (2.6)	4 (2.41)	1 (3.3)	
Intra-abdominal abscess, *n* (%)				0.900
Absent	152 (77.6))	129 (77.7))	23 (76.7)	
Present	44 (22.5)	37 (22.3)	7 (23.3)	
Drain fluid AMY on POD 3, U/L		10556 ± 50328	1159 ± 1649.8	0.308
Drain fluid AMY on POD 7, U/L		3891 ± 14606	7524 ± 18706	0.283
Serum CRP on POD 7, mg/dL		4.10 ± 4.03	4.90 ± 4.58	0.327
Length of hospital stay, days		26.8 ± 15.3	42.4 ± 27.1	< 0.001*
POPF stands for postoperative pancreatic fistula; *PPH* stands for post-pancreatectomy hemorrhage; *AMY* stands for amylase; *POD* stands for postoperative day; *CRP* stands for C-reactive protein.				
[a] According to the International Study Group of Pancreatic Fistula grading (2005)				
*Statistically significant (*P* < 0.05)				

Impact of DGE on postoperative nutritional status

Figure 1 depicts the serial of changes in the nutritional parameters due to the presence/absence of DGE. There were no statistically significant differences in BMI, serum total protein, and triglyceride levels at any of the time points. Serum albumin (DGE + : 3.16 ± 0.42 g/dL versus DGE - : 3.4 ± 0.5 g/dL) and total cholesterol (DGE + : 125.1 ± 39.3 mg/dL versus DGE - : 147.2 ± 29.6 mg/dL) were significantly lower in DGE patients at POM one; however, both parameters were equivalent between the groups at POM three. To determine the effect of DGE on serum albumin level at POM one, univariate and multivariate analyses were performed (Table 2). On univariate analysis, preoperative serum albumin (< 3.5 mg/dL), incidence of DGE, intraoperative blood loss > 500 mL, and hand-sewn gastrojejunostomy were all significantly associated with serum albumin < 3.5 mg/dL at POM one. DGE remained a significant risk factor for decreased serum albumin levels (< 3.5 mg/dL) at POM one after multivariate analysis.

Table 2
Factors influencing decreased serum albumin level one month after pancreatoduodenectomy.

	Total *N* = 186	Serum albumin level on POM1		*P*-value (Univariate)	*P*-value (Univariate)
		< 3.5 mg/dL (*n* = 98)	≥ 3.5 mg/dL (*n* = 88)		
Preoperative variables					
Age, years, *n* (%)				0.292	
< 70	96 (51.6)	47 (48.0)	49 (55.7)		
≥ 70	90 (48.4)	51 (52.0)	39 (44.3)		
Sex, *n* (%)				0.902	
Female	71 (38.2)	37 (37.8)	34 (38.6)		
Male	115 (61.8)	61 (62.2)	54 (61.4)		
Body mass index, kg/m^2, *n* (%)				0.053	0.066
< 25	157 (84.4)	78 (79.6)	79 (89.8)		
≥ 25	29 (15.6)	20 (20.4)	9 (10.2)		
Serum albumin, g/mL, *n* (%)				0.0004*	0.0015*
≥ 3.5	129 (69.4)	57 (58.2)	72 (81.8)		
< 3.5	57 (30.7)	41 (41.8)	16 (18.2)		
Disease, *n* (%)				0.841	
Pancreatic adenocarcinoma	81 (43.6)	42 (42.9)	39 (44.3)		

POPF stands for postoperative pancreatic fistula; *PPH* stands for post-pancreatectomy hemorrhage; *AMY* stands for amylase; *POD* stands for postoperative day; *CRP* stands for C-reactive protein.

[a] According to the International Study Group of Pancreatic Fistula grading (2005)

*Statistically significant ($P < 0.05$)

	Total *N* = 186	Serum albumin level on POM1		*P*-value (Univariate)	*P*-value (Univariate)
		< 3.5 mg/dL (*n* = 98)	≥ 3.5 mg/dL (*n* = 88)		
Others	105 (56.5)	56 (57.1)	49 (55.7)		
Diabetes Mellitus, *n* (%)				0.311	
Absent	174 (93.6)	90 (91.8)	84 (95.5)		
Present	12 (6.5)	8 (8.2)	4 (4.5)		
Biliary drainage, *n* (%)				0.209	
Absent	84 (45.2)	40 (40.8)	44 (50.0)		
Present	102 (54.8)	58 (59.2)	44 (50.0)		
Intraoperative variables					
Route of gastrojejunostomy, *n* (%)				0.654	
Antecolic	92 (49.5)	50 (51.0)	42 (47.7)		
Retrocolic	94 (50.5)	48 (49.0)	46 (52.3)		
Method of gastrojejunostomy, *n* (%)				0.002*	0.059
Stapling	130 (69.9)	59 (60.2)	71 (80.7)		
Hand-sewn	56 (30.1)	39 (39.8)	17 (19.3)		
Duration of operation, min, *n* (%)				0.453	

POPF stands for postoperative pancreatic fistula; *PPH* stands for post-pancreatectomy hemorrhage; *AMY* stands for amylase; *POD* stands for postoperative day; *CRP* stands for C-reactive protein.

[a] According to the International Study Group of Pancreatic Fistula grading (2005)

*Statistically significant ($P < 0.05$)

	Total *N* = 186	Serum albumin level on POM1		*P*-value (Univariate)	*P*-value (Univariate)
		< 3.5 mg/dL (*n* = 98)	≥ 3.5 mg/dL (*n* = 88)		
< 480	56 (30.3)	32 (32.7)	24 (27.6)		
≥ 480	129 (69.7)	66 (67.5)	63 (72.4)		
Estimated blood loss, mL, *n* (%)				0.011*	0.062
< 500	75 (40.3)	31 (31.6)	44 (50.0)		
≥ 500	111 (59.7)	67 (68.4)	44 (50.0)		
Texture of the pancreas, *n* (%)				0.246	
Soft	95 (51.1)	54 (55.1)	41 (46.6)		
Hard	91 (48.9)	44 (44.9)	47 (53.4)		
Postoperative variables					
Delayed gastric emptying, *n* (%)				0.005*	0.043*
Absent	157 (84.4)	76 (77.6)	81 (92.1)		
Present	29 (15.6)	22 (22.5)	38 (8.0)		
POPF[a], *n* (%)				0.059	0.123
Grade 0/A	150 (80.7)	74 (75.5)	76 (86.4)		
Grade B/C	36 (24.5)	24 (24.5)	12 (13.6)		

POPF stands for postoperative pancreatic fistula; *PPH* stands for post-pancreatectomy hemorrhage; *AMY* stands for amylase; *POD* stands for postoperative day; *CRP* stands for C-reactive protein.

[a] According to the International Study Group of Pancreatic Fistula grading (2005)

*Statistically significant ($P < 0.05$)

	Total *N* = 186	Serum albumin level on POM1		*P*-value (Univariate)	*P*-value (Univariate)
		< 3.5 mg/dL (*n* = 98)	≥ 3.5 mg/dL (*n* = 88)		
PPH, *n* (%)				0.685	
Absent	174 (93.6)	91 (92.9)	83 (94.3)		
Present	12 (6.5)	7 (7.1)	5 (5.7)		
Bile leak, *n* (%)				0.564	
Absent	181 (97.3)	96 (98.0)	85 (96.6)		
Present	5 (2.7)	2 (2.0)	3 (3.4)		
Intra-abdominal abscess, *n* (%)				0.076	0.693
Absent	146 (78.5)	72 (73.5)	74 (84.1)		
Present	40 (21.5)	26 (26.5)	14 (15.9)		
POPF stands for postoperative pancreatic fistula; *PPH* stands for post-pancreatectomy hemorrhage; *AMY* stands for amylase; *POD* stands for postoperative day; *CRP* stands for C-reactive protein.					
[a] According to the International Study Group of Pancreatic Fistula grading (2005)					
*Statistically significant ($P < 0.05$)					

Discussion

In this study, DGE independently impaired patients' nutritional status during the first postoperative period; however, this impact was only discernible before POM three. On POM three and POM six, all nutritional parameters were equivalent between the patients who had DGE and those who did not. DGE's influence on patients' nutritional status after SSPPD may be limited to no more than three months, and DGE may not have impaired their long-term condition. This is the first study to investigate the precise effect of DGE on the serial changes of various nutritional markers.

Adjuvant chemotherapy is initiated in patients with PDAC after adequate recovery from surgery [16, 17]. As a result, maintaining patients' nutritional condition after surgery is critical for initiating and tolerating adjuvant therapy. Matsumoto et al. previously reported that a low serum albumin level could be a predictor of incomplete adjuvant therapy [18]. Given that serum albumin levels at POM one were lower in

DGE patients in the current study, the presence of DGE may compromise adjuvant chemotherapy. In fact, a recent retrospective study reported by Futagawa et al. revealed the negative impact of DGE on long-term survival in patients with PDAC [19]. Preventing DGE may be important to improving the prognosis of patients with PDAC after PD. Because the precise effect of DGE on various nutritional markers has received little attention, the findings of our study may aid in further research into the pathophysiology of DGE and its clinical significance.

Kawai et al. reported that at POM 24, patients with DGE had lower serum albumin and prealbumin levels than those without DGE, implying that the impact of DGE on the patients' nutritional status of persists much longer than what our study revealed [20]. However, their analysis was limited to a single point in time, and data on serial changes in nutritional status were lacking. Furthermore, the study only included 11 DGE patients; hence, the small sample size may have compromised the study's findings. The disparity between our findings and those reported by Kawai et al. could also be due to differences in surgical procedures. While only the patients who underwent SSPPD were included in our study, the majority of patients who experienced DGE in the study by Kawai et al. underwent PPPD. As a result, preservation of the pylorus might have influenced the duration of DGE.

Several studies have attempted to elucidate the pathophysiology of DGE after PD [7–11]. Surgical procedure modifications such as pylorus resection, antecolic alimentary tract reconstruction, addition of Braun anastomosis, and Roux-en-Y reconstruction have been reported as possible solutions to reduce DGE, though the impact of these modifications on DGE is still controversial [8–11, 21, 22]. In the current study, it was discovered that stapled gastrojejunostomy was associated with less DGE than hand-sewn anastomosis. Several studies have shown that stapled anastomosis of gastro/duodenojejunostomy is superior to hand-sewn anastomosis in terms of DGE incidence after PD [23–25]. However, the majority of patients in previous studies underwent PPPD, and reports on SSPPD or conventional PD were scarce. The diameter of the anastomotic lumen, the stapling device (circular stapler or linear stapler), and the presence/absence of the pylorus ring were all significantly different between gastro/duodenojejunostomy within SSPPD and PPPD. Thus, mechanisms that may explain the superiority of stapled anastomosis over hand-sewn anastomosis may differ between the procedures. Murata et al. recently reported a retrospective study that demonstrated the superiority of stapled side-to-side gastrojejunostomy over conventional hand-sewn end-to-side gastrojejunostomy for DGE after SSPPD [25]. Avoidance of anastomotic edema and subsequent stricture formation was considered as a possible mechanism that reduces DGE after stapled anastomosis in this study. Because there have only been a few retrospective studies to date, the efficacy of stapling anastomosis in preventing DGE after SSPPD should be studied further in larger RCTs.

POPF has been linked to DGE in the literature [26, 27]. In the present study, however, POPF was not found to be associated with DGE. Furthermore, intra-abdominal abscess, drain fluid amylase on POD three and serum C-reactive protein on POD seven were not associated with the incidence of DGE, implying that intra-abdominal inflammation played little role in the development of DGE in our cohort. It is possible that

differences in patients' backgrounds played a role. However, we were unable to identify any mechanism that could adequately explain this disparity.

There were several limitations to this study. First, it was a non-randomized study using a pre-built database. Because of the nature of the study design, there could have been patient heterogeneity. However, because this was a sub-study of a larger multicenter RCT, the database used in the present study might have been reliable. Second, the POPF definition and grading were based on the ISGPF 2005 criteria, which were revised in 2010. However, because the definition of clinically relevant POPF was only slightly altered, the changes in the new criteria may not have had an effect on the results of this study. Finally, because of the retrospective nature of the present study, there were no criteria for selecting gastrojejunostomy methods (hand-sewn or stapled). Because each surgeon selected his or her own procedures, there may be biases in analyzing risk factors for DGE.

Conclusions

Hand-sewn gastrojejunostomy was associated with DGE after SSPPD. DGE impairs patients' nutrition in the short term; however, its impact is limited to no longer than three months.

Declarations

Competing Interests

The authors declare that they have no conflicts of interest related to this manuscript and that no funding was received for this study.

Authors' Contributions

TM and HT shared first authorship and contributed equally to this article.

Study conception and design: TM, HT, IM, HY, MK, TA, and TF.

Acquisation of data: TM, SA, TG, HY, YN, JI, SS, TU, KF, HG, DT, KK, SK, and HY.

Analysis and interpretation of data: TM, HT, HY, MK, TA, IM, and TF.

Drafting of manuscript:TM and HT.

Critical revision of manuscript:IM, HY, MK, TA, and TF.

All authors gave final approval of the publishable version of the manuscript.

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Figures

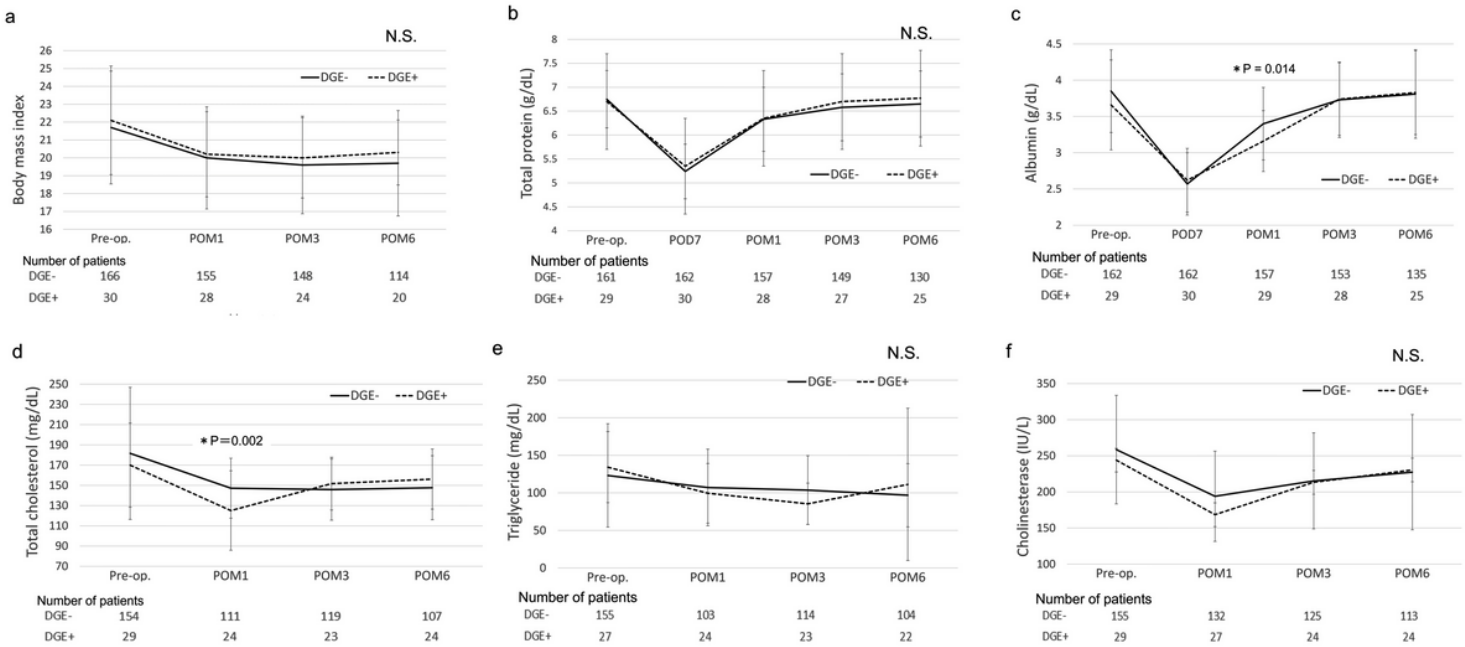

Figure 1

Serial changes in nutritional parameters according to the incidence of DGE.

a. Changes in body mass index

b. Changes in serum total protein level

c. Changes in serum albumin level

d. Changes in serum total cholesterol level.

e. Changes in serum triglyceride level.

f. Changes in cholinesterase.

DGE stands for delayed gastric emptying.