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Impaired gastrointestinal function affects symptoms and alimentary status in patients after gastrectomy.

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Abstract

Background

Postgastrectomy syndrome (PGS) remains a common complication after gastrectomy .

Aim

The aim was to investigate relationships between gastrointestinal (GI) function and various symptoms or alimentary status in postgastrectomy patients.

Methods

The subjects were 51 patients who had undergone total or distal gastrectomy replied to a questionnaire that asked presence of symptoms (esophageal reflux, nausea, abdominal pain, early satiation, diarrhea, early dumping general, early dumping abdominal and late dumping symptoms) and alimentary status (change in body weight, food intake per meal, frequency of meals per day). They also underwent assessment of GI function consisting of gastric emptying study by ^{13}C-acetate breath test (gastric retention rate at 5 minutes [RR5] a measure of as reservoir capacity, and half-emptying time [T1/2] measured as gastric emptying) and water load drink (WLD) test to evaluate tolerance to volume loading (TVL).

The relationships between GI function and each symptom or alimentary status were examined.

Results

The patients with nausea and early dumping general symptoms had significantly smaller reservoir capacity (p=0.030 Cohen's *d*=1.39, p=0.039 Cohen's *d*=0.79). The patients with diarrhea and early dumping general symptoms had significantly faster gastric emptying (p=0.031, Cohen's *d*=0.69 and p=0.038, Cohen's *d*=0.84, respectively). The patients with early satiation and early dumping abdominal symptoms had significantly impaired TVL (p<0.001, Cohen's *d*=1.30 and p=0.008, Cohen's *d*=0.81 each). Significant correlations were identified between TVL and body weight changes (*r*=-0.317 p=0.023) or food intake per meal (*r*=-0.467 p<0.001).

Conclusion

Impaired postoperative GI function was closely related to symptoms or worse alimentary status.

Abstract

Background

Postgastrectomy syndrome (PGS) remains a common complication after gastrectomy that affects patients' quality of life. Although impaired gastrointestinal function by gastrectomy procedures is thought to be the cause, the precise pathophysiology of PGS is yet to be clarified.

Aim

The aim of this study was to investigate relationships between gastrointestinal (GI) function and various symptoms or alimentary status in patients after gastrectomy.

Methods

Fifty-one patients who underwent total or distal gastrectomy at least one year previously were studied. All patients replied to a questionnaire that asked presence of symptoms (esophageal reflux, nausea, abdominal pain, early satiation, diarrhea, early dumping general, early dumping abdominal and late dumping symptoms) and alimentary status (change in body weight, food intake per meal, frequency of meals per day). They also underwent assessment of GI function consisting of gastric emptying study by ^{13}C-acetate breath test to examine reservoir capacity and half-emptying time, and water load drink (WLD) test to evaluate tolerance to volume loading (TVL). The

relationships between GI function and each symptom or alimentary status were examined.

Results

The patients with nausea and early dumping general symptoms had significantly smaller reservoir capacity*, the patients with diarrhea and early dumping general symptoms had significantly faster gastric emptying*, and the patients with early satiation and early dumping abdominal symptoms had significantly impaired TVL*. Significant correlations were identified between TVL and body weight changes* or food intake per meal* (* $p<0.05$).

Conclusion

Impaired postoperative GI function was closely related to symptoms or worse alimentary status.

Key words: postgastrectomy syndrome, gastrointestinal function, ^{13}C-breath test, water load drink test

Introduction

Postgastrectomy syndrome (PGS) impairs quality of life (QOL) in postgastrectomy patients [1]. With increase in early detection of gastric cancer, long-term survival rate has improved [2]. Therefore, postoperative QOL as well as curability of gastric cancer surgery has become an important issue [3, 4]. Impairment of gastrointestinal (GI) function after gastrectomy is considered to be responsible for symptoms or disturbance of alimentary status [5-7]. Nevertheless, there have hardly been any reports that investigated the relationship between them. This study was conducted to answer such a clinical question using ^{13}C breath test and water load drink (WLD) test.

Subjects and Methods

The subjects were 51 patients who had undergone gastrectomy for gastric cancer without recurrence for at least one year, consisting of total gastrectomy with Roux-en-Y reconstruction (TGRY) in 15, distal gastrectomy with Billroth-I reconstruction (DGBI) in 17, and distal gastrectomy with Roux-en-Y reconstruction (DGRY) in 19 patients. The mean age of the patients was 63.9 years. They consisted of 40 male and 11 female patients, and their mean postoperative follow-up period was 4 years and 6 months. All patients had been diagnosed with pathological stage Ⅰ (n=48) or stage II (n=3) gastric adenocarcinoma.

The subjects were asked to fill out a questionnaire concerning their symptoms and alimentary status, and underwent assessment of GI function consisting of gastric emptying by ^{13}C-acetate breath test and tolerance to volume loading (TVL) by WLD test.

Questionnaire on symptoms and alimentary status

The questionnaire included symptoms (esophageal reflux, nausea, abdominal pain, early satiation, diarrhea, early dumping general symptoms, early dumping abdominal symptoms and late dumping symptoms) and alimentary status (change in body weight, food intake per meal and frequency of meal per day).

Measurement of reservoir capacity and gastric emptying by ^{13}C-acetate breath test

^{13}C-acetate breath test was conducted according to the standardized procedure described by the Study Group of the Japan Society of Smooth Muscle Research [8)]. The test meal was a 200kcal/200 ml liquid meal (Racol, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) mixed with 100 mg of ^{13}C-acetate sodium salt. Expirates were sampled before and at 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes after meal, and $^{13}CO2/^{12}CO2$ ratio in the expirates was measured using UBiT-IR 300® (Otsuka Electronics Co., Ltd., Osaka, Japan). The data were subjected to a Wagner-Nelson analysis[9)], and gastric emptying rate at each time point was

quantitatively calculated. Reservoir capacity of the remnant stomach was measured by retention rate at 5 minutes (RR5) and gastric emptying was assessed by half-emptying time (T1/2) [10].

Measurement of TVL by WLD test

The subjects were asked to drink 10 ml/kg of room-temperature mineral water using a straw at a steady rate over 5 minutes and to score intensity of abdominal symptoms every 5 minutes until symptoms disappeared. The intensity of abdominal symptoms was scored as follows: 1 point for mild; 2 points for moderate; and 3 points for severe symptom, and duration of abdominal distension was also scored as follows: 1 point for <10 min; 2 points for 10 min to 20 min; 3 points for 20 to 30 min; and 4 points for equal to or over 30 min. WLD test total score was calculated by adding intensity score and duration score, and was used as an indicator of TVL [11]. WLD test total score ranged between 0 and 7 points.

Statistical analysis

T-test, χ^2-test, ANOVA followed by Turkey-Kramer multiple comparisons test and Pearson correlation analysis were used for data analyses. Cohen's *d* value was calculated as effect size when the inter-group *P*-value was less than 0.1. Effect size according to Cohen's *d* values was interpreted as follows: small; 0.20 to 0.49, medium;

0.50 to 0.79, and large; more than 0.80. Effect size according to Pearson product-moment correlation coefficients was interpreted as follows: small; 0.10 to 0.29, medium; 0.30 to 0.49, and large; more than 0.50.

This study was approval by the ethics committee of the Jikei University School of Medicine and was supported by a grant from MEXT (Ministry of Education, Culture, Sports, Science and Technology) and Supported Program for the Strategic Research Foundation at Private Universities (2011-2013) and carried out after obtaining written informed consent from each patient.

Results

Patients' characteristics, symptoms, alimentary status and GI function among gastrectomy procedures (Table 1)

The follow-up period of DGRY was significantly shorter than that of TGRY. There was no statistically significant difference in age or gender.

The differences in the incidence of early dumping general symptoms according to surgical procedures tended to be different ($p = 0.074$), and the incidence in TGRY and DGRY tended to be higher than that in DGBI ($p = 0.074$). There were no significant differences among surgical procedures in the incidences of any other symptoms.

Body weight change was the greatest in TGRY group, smaller in DGRY group, and the smallest in DGBI group, which however were not statistically significant (p=0.090). There was no statistical difference in food intake per meal. Frequency of meals per day was the highest in TGRY group, lower in DGBI group, and the lowest in DGRY group. The differences between TGRY group and DGRY group and between TGRY group and DGBI group were statistically significant (p=0.002, Cohen's d=1.23 and p=0.049, Cohen's d=0.85, respectively).

RR5 was the highest in DGBI, lower in DGRY, and the lowest in TGRY. RR5 of TGRY was significantly smaller than in DGBI (p=0.003, Cohen's *d*=1.21), and that of DGRY tended to be smaller than in DGBI (p=0.079, Cohen's *d*=0.66). T1/2 was the longest in DGBI, shorter in DGRY, and the shortest in TGRY, and significant acceleration of gastric emptying was observed in TGRY as compared with DGBI (p = 0.038, Cohen's *d* = 1.08). No significant difference in WLD test total score was observed among surgical procedures.

Comparison of GI function between patients with and without each symptom (Table2-4)

The patients with nausea and early dumping general symptoms had significantly smaller RR5 (p=0.030, Cohen's *d*=1.39; p=0.039, Cohen's *d*=0.79) and the patients with

diarrhea had smaller RR5 with marginal significance (p=0.059, Cohen's *d*=0.57) (Table 2). The patients with diarrhea and early dumping general symptoms had significantly faster T1/2 (p=0.031, Cohen's *d*=0.69 and p=0.038, Cohen's *d*=0.84, respectively) (Table 3). The patients with early satiation and early dumping abdominal symptoms had significantly impaired TVL (p<0.001, Cohen's *d*=1.30 and p=0.008, Cohen's *d*=0.81, respectively) (Table 4).

Correlation between GI function and alimentary status (Table 5)

Significant negative correlations were found between WLD test total score and body weight change (*r*=-0.317, p=0.023) as well as food intake per meal (*r*=-0.467, p<0.001). Tendency for a positive correlation was found between WLD test total score and frequency of meal per day (*r*=0.255, p=0.071). Tendency for a positive or negative correlation was found between T1/2 and food intake per meal (*r*=0.260, p=0.066) or frequency of meal per day (*r*=-0.265, p=0.060), respectively.

Discussion

Gastrectomy is the predominant treatment for gastric cancer to achieve cure, whereas PGS impairs patients' QOL. Although impairment of GI function caused by gastrectomy procedures has been considered as a cause of PGS, the information on this issue is limited. This study was conducted to prove the relationship between postoperative GI function and PGS, and demonstrated that reduced reservoir capacity, rapid gastric emptying and weakened TVL were associated with occurrence of symptoms or

worsened alimentary status. This is the first report to demonstrate a close association between objective degree of impairment of GI function and PGS.

The radioisotope method serves as a gold-standard to study gastric emptying directly and quantitatively [12, 13]. However, such a method requires special facilities, receives radiation exposure and is high-cost. On the contrary, ^{13}C-breath tests is an indirect method to study gastric emptying and is noninvasive, safe, reliable, easy to conduct and low-cost [8, 14, 15]. Sanaka *et al.* applied the Wagner-Nelson analysis to ^{13}C breath test and proved that gastric emptying rate obtained by this analysis was comparable to radioisotope method [9].

Recently, ^{13}C breath test has been applied to evaluate gastric emptying in patients after gastrectomy. Katsube *et al.*[15] reported that gastric emptying after distal gastrectomy (DG) was significantly faster, while one after pylorus-preserving gastrectomy (PPG) was significantly slower than the controls. Hayami *et al.* reported that the gastric emptying after PPG was significantly slower than those after DG, proximal gastrectomy or total gastrectomy (TG) [6]. Kawamura *et al*. reported that reservoir capacity and gastric emptying after gastric local resection (LR) were similar to those of healthy volunteers, and QOL of LR was well-maintained as compared to that of

DG [10]. Our results demonstrated that reservoir capacity was smaller and gastric emptying was faster after TG compared to DG.

Acceptance of food or liquid is also an important function of the GI tract. This acceptance capacity, TVL, is regulated by the stomach size, gastric accommodation, distribution and visceral perception of the gastrointestine. This acceptance capacity was measured by WLD test, which was developed to investigate pathophysiology of functional dyspepsia (FD) [16, 17]. A significant reduction of TVL has been reported in patients with FD [18]. Since conventional WLD test methods required patients to continue drinking until the maximum tolerated volume was reached, which force patients to experience painful distress [19]. In order to reduce such distress, we developed a modified WLD test in which water volume was set according to patient's body weight, and we reported the utility of our modified WLD test for studying pathophysiology of FD [11]. In this study, we for the first time applied our modified WLD test in the patients after gastrectomy. Although we could not find any difference in TVL among the types of gastrectomy, WLD test successfully revealed the relationship between TVL and symptoms or alimentary status which gastric emptying study could not detect.

Regarding the relationships between postgastrectomy GI function and symptoms, few studies have been reported. Hayami *et al.* [6] studied the association between gastric

emptying speed assessed by ^{13}C breath test and gastrointestinal symptoms measured by gastrointestinal symptom rating scale in patients after TGRY, DG with B-I or R-Y, proximal gastrectomy and PPG, and showed significant association between gastric emptying and scores of ‘indigestion’, ‘abdominal pain’ or ‘total score’, which indicated that faster gastric emptying speed is associated with worse symptom. Le Blanc-Louvry *et al.* [7] studied the association between the accommodation of the remnant stomach assessed by barostat and symptoms in patients after DG, and showed that patients with symptoms such as vomiting, early postmeal epigastric pain or epigastric fullness had significantly impaired accommodation as compared to asymptomatic patients.

In the present study, postoperative motor function such as gastric emptying speed and reservoir capacity were significantly different by the type of gastrectomy procedures. On the other hand, the type of gastrectomy procedures itself did not affect TVL. In TG and DG, as total or part or of stomach and pylorus is resected, most of drinking water is dumped into the small intestine. Therefore it is considered that TVL in TG and DG mainly demonstrates the function of small intestine. The acceptable capacity of small intestine is suspected to be variable among individuals and more important than the type of gastrectomy procedures in maintaining TVL. TVL is a newly proposed gastrointestinal function that has not paid attention so far. Investigating the

TVL after various types of gastrectomy including function-preserving gastrectomy may help to devise the gastrectomy procedures which maintain better TVL. At the present point, reducing burden of small intestine seems important. Preserving pylorus, preserving the larger size of the remnant stomach or reconstructing substitute stomach might be useful.

The results of the current study demonstrated a correlation between 1) decreased reservoir capacity and nausea, diarrhea or early dumping general symptoms, and 2) accelerated gastric emptying and diarrhea, early dumping general symptoms, smaller dietary intake or increased frequency of meal, and 3) impaired TVL and early satiation, early dumping abdominal symptoms, decreased body weight, smaller dietary intake or increased frequency of meal. These findings suggest that the development of gastrectomy procedures which maintain larger reservoir capacity, proper gastric emptying speed and better TVL could mitigate PGS.

Our study has some limitations. Firstly, there were significant heterogeneities with respect to time after operation and approach among gastrectomy procedures. Secondly, there were differences in the number of patients in each parameter evaluated. In order to overcome such limitations, well-designed large scale randomized controlled trials are needed.

Conclusion

Impaired postoperative GI function was closely related to symptoms or worse alimentary status in the patients after gastrectomy. Gastric emptying study and WLD test is useful to evaluate underlying pathophysiology of PGS.

Conflict of interest None.

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Table 1. Patients' Characteristics, symptoms, alimentary status and GI function among gastrectomy procedures

	TGRY （n=15）	DGBI (n=17)	DGRY (n=19)	*P* -value	
Sex (M/F)	10/5	13/4	17/2	0.268[a]	
Age * (years)	64.6±13.0	63.7±9.0	63.4±10.2	0.947[b]	
Time after operation* (months)	78.1±30.6	55.0±59.0	35.6±23.0	0.015[b]	TGRY vs. DGRY; p=0.011[c]
Approach (Open/Laparoscopic)	14/1	9/8	5/14	<0.001[a]	
Esophageal reflux	3/12 (20%)	4/13 (24%)	3/16 (16%)	0.842[a]	
Nausea	2/13 (13%)	2/15 (12%)	1/18 (5%)	0.695[a]	
Abdominal pain	2/13 (13%)	1/16 (6%)	3/16 (16%)	0.638[a]	
Early satiation	4/11 (27%)	8/9 (47%)	3/16 (16%)	0.116[a]	
Diarrhea	8/7 (53%)	4/13 (24%)	8/11 (42%)	0.215[a]	
Early dumping general symptoms	5/10 (33%)	1/16 (6%)	7/12 (37%)	0.074[a]	
Early dumping abdominal symptoms	5/10 (33%)	5/12 (29%)	8/11 (42%)	0.716[a]	
Late dumping symptoms	3/12 (20%)	3/14 (18%)	4/15 (21%)	0.967[a]	
Change in body weight* (%)	-14.6±11	-8.5±5.7	-9.0±7.9	0.090[b]	
Food intake per meal* (%)	56±26	64±18	71±16	0.121[b]	
Frequency of meals per day* (times)	4.9±1.2	4.0±0.9	3.6±0.9	0.002[b]	TGRY vs. DGRY, p=0.002[c], Cohen's *d* =1.23 TGRY vs. DGBI, p=0.049[c], Cohen's *d* =0.85
RR5* (%)	15.5±15.8	44.6±30.0	26.9±22.8	0.004[b]	TGRY vs. DGBI; p=0.003[c], Cohen's *d* =1.21 DGRY vs. DGBI; p=0.079[c], Cohen's *d* =0.66
T1/2* (minutes)	3.1±0.7	5.6±3.2	4.6±3.5	0.048[b]	TGRY vs. DGBI; p=0.038[c], Cohen's *d* =1.08
WLD test total score*	3.1±2.3	2.7±2.4	2.4±2.1	0.669[b]	

* Mean±SD

a; Chi-square test, b; ANOVA, c; Tukey-Kramer test

RR5 = retention rate at 5 minutes, T1/2 = half-emptying time, WLD = water load drink

Table 2. Comparison of reservoir capacity (RR5[%]) between patients with and without each symptom

	RR5 (%)			
	with symptom	without symptom	*P* -value	Cohen's *d*
Esophageal reflux*	30.8 ± 24.2	29.1 ± 26.9	0.859	-
Nausea*	5.5 ± 7.0	32.1 ± 26.2	0.030	1.39
Abdominal pain*	22.8 ± 22.9	30.3 ± 26.7	0.513	-
Early satiation*	30.7 ± 23.9	28.9 ± 27.3	0.827	-
Diarrhea*	20.9 ± 20.3	35.0 ± 28.2	0.059	0.57
Early dumping general symptoms*	16.6 ± 12.8	33.8 ± 28.2	0.039	0.79
Early dumping abdominal symptoms*	28.2 ± 28.0	30.1 ± 25.5	0.799	-
Late dumping symptoms*	26.2 ± 17.1	30.2 ± 28.0	0.670	-

* Mean±SD

RR5 = retention rate at 5 minutes

Table 3. Comparison of gastric emptying (T1/2) between patients with and without each symptom

	T1/2 (minutes)			
	with symptom	without symptom	*P* -value	Cohen's *d*
Esophageal reflux*	4.1 ± 1.9	4.6 ± 3.2	0.642	-
Nausea*	2.7 ± 0.2	4.7 ± 3.0	0.148	-
Abdominal pain*	3.5 ± 1.3	4.6 ± 3.1	0.396	-
Early satiation*	4.3 ± 2.3	4.6 ± 3.2	0.791	-
Diarrhea*	3.4 ± 1.1	5.2 ± 3.5	0.031	0.69
Early dumping general symptoms*	3.0 ± 0.4	5.0 ± 3.3	0.038	0.84
Early dumping abdominal symptoms	4.2 ± 2.4	4.6 ± 3.2	0.633	-
Late dumping symptoms*	4.5 ± 4.0	4.5 ± 2.7	0.952	-

* Mean±SD

T1/2 = half-emptying time

Table 4. Comparison of TVL (WLD test total score) between patients with and without each symptom

	WLD test total score			
	with symptom	without symptom	*P* -value	Cohen's *d*
Esophageal reflux*	3.1 ± 3.0	2.6 ± 2.1	0.565	-
Nausea*	3.6 ± 2.1	2.6 ± 2.3	0.368	-
Abdominal pain*	3.0 ± 2.1	2.7 ± 2.3	0.755	-
Early satiation*	4.5 ± 2.0	2.0 ± 1.9	<0.001	1.30
Diarrhea*	2.7 ± 2.3	2.8 ± 2.3	0.851	-
Early dumping general symptoms*	2.4 ± 2.1	2.8 ± 2.3	0.535	-
Early dumping abdominal symptoms	3.8 ± 2.1	2.1 ± 2.2	0.008	0.81
Late dumping symptoms*	1.9 ± 2.4	2.9 ± 2.2	0.201	-

* Mean±SD

WLD = water load drink

Table 5. Correlations between GI function and alimentary status

	RR5 (%)		T1/2 (minutes)		WLD test total score	
	r	*P* -value	*r*	*P* -value	*r*	*P* -value
Change in body weight (%)	0.095	0.505	0.125	0.383	-0.317	0.023
Food intake per meal (%)	0.186	0.192	0.260	0.066	-0.467	<0.001
Frequency of meal per day (times)	-0.198	0.164	-0.265	0.060	0.255	0.071

r ; Pearson product-moment correlation coefficient

RR5 = retention rate at 5 minutes, T1/2 = half-emptying time, WLD = water load drink