Rikkunshito increases serum intestinal polypeptide levels in patients after pylorus-preserving pancreatico-duodenectomy

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BACKGROUND: Animals treated with a Japanese herbal medicine Rikkunshito (Tj43) showed an enhancing effect on gastric emptying. The mechanism by which Tj43 alleviates the gastrointestinal disorders induced by anticancer agents was to increase serum ghrelin levels.

Aim: In this study, the effects of Tj43 on serum ghrelin and other intestinal polypeptide levels, and food intake were investigated after surgery.

METHODS: Forty-one patients who underwent pylorus-preserving pancreatico-duodenectomy (PpPD) due to pancreato-biliary malignant tumors at the University of Yamanashi Hospital between 2012 and 2015 were assigned to receive Tj43 just after surgery [Tj43 (+) patients, n = 21, 7.5 g daily dose starting the day after surgery], or 3 weeks after surgery [Tj43 (-) patients, n = 20]. One week after surgery, meals were starting. Oral calorie intake from carbohydrates and protein/fat were assessed in the two groups 2 weeks after starting meals. Blood samples were obtained before and after surgery for regular blood tests. Plasma acyl and desacyl ghrelin levels were assayed by ELISA, together with serum peptide YY (PYY), gastric inhibitory peptide (GIP), spexin, and cholecystokinin (CCK) levels.

RESULTS: There were no significant differences in clinical features between the two groups. Treatment of Tj43 did not show any complications. In Tj43 (-) patients, increases in active ghrelin were minimal. Levels of inactive ghrelin decreased in both groups after operation. However, in Tj43 (+) patients, the level of active ghrelin was significantly increased two weeks after treatment, and this increase was significantly greater than that of Tj43 (-) patients. Reflecting these results, oral calorie intake increased. The levels of spexin decreased after PpPD in both groups, while levels of PYY and CCK were not different before and after PpPD. However, these levels increased significantly in Tj43 (+) patients 2 weeks after treatment. GIP levels increased after surgery in all patients, but the increase was significantly greater in the Tj43 (+) patients compared with Tj43 (-) patients.

CONCLUSION: Tj43 treatment increased acyl ghrelin levels, leading to increased food intake. It also increased intestinal polypeptide hormones. Since the significance of this effect is still unknown, further investigation is needed.

Key Words: *Neurointestinal polypeptide; Japanese traditional herbal medicine*

Abbreviations: *PpPD: Pylorus-Preserving Pancreaticoduodenectomy; PYY: Peptide YY; GIP: Gastric Inhibitory Peptide; CCK: Cholecystokinin; DGE: Delayed Gastric Emptying; ELISA: Enzyme-Linked Immuno Sorbent Assay*

INTRODUCTION

The Japanese herbal medicine "Rikkunshito" (Tj43) is used to treat various gastrointestinal (GI) tract disorders [1]. Rats treated with Tj43 showed enhanced gastric emptying [2]. Recently, it was also reported that Tj43 administered in combination with an anti-emetic drug to patients with advanced breast cancer prevented the anorexia and vomiting that occur as adverse reactions to chemotherapy [3]. Thus, Tj43 prevents storage and enhances the discharge ability of the stomach.

Rikkunshito is used in the form of a powdered extract obtained by spray-drying a hot-water extract of a mixture of 8 crude drugs, i.e., *Atractylodis lanceae rhizoma*, *Ginseng radix*, Pinelliae tuber, Hoelen, *Zizyphi fructus*, *Aurantii nobilis pericarpium*, *Glycyrrhizae radix*, and *Zingiberis rhizoma*. Hesperetin, hesperidin, naringenin, 3, 3=, 4=, 5, 6, 7, 8-heptamethoxyflavone (HMF), nobiletin, tangeretin (*Aurantii nobilis pericarpium*), isoliquiritigenin, liquiritigenin, glycycoumarin (Glycyrrhizae radix), 8-shogaol, 10-shogaol, 10-dehydrogingerdin, 10-gingerdion, and 8-gingerol (*Zingiberis rhizoma*), which are typical components of Rikkunshito, were subjected to 5-HT-receptor binding assays. Rikkunshito and these ingredients were supplied by Tsumura & Co. (Tokyo, Japan). Delayed gastric emptying (DGE) is a common complication after pylorus-preserving pancreatico-duodenectomy (PpPD) against biliary-pancreatic disease, and is a serious event leading to abdominal discomfort, prolonged hospitalization and increased medical costs [4]. DGE is also associated with other major intra-abdominal complications including post-operative pancreatic fistula and intra-abdominal abscess [5]. Several technical factors including the type of resection, the method of reconstruction of intestinal drainage, and mechanical dilatation of the pylorus were shown to influence DGE [6-8]. Alternatively, an objective and exact comparison of previous studies is particularly difficult, due to the lack of a standard definition of DGE. A number of different definitions based on the period of nasogastric intubation and the ability to tolerate regular diets were proposed, and opinions about the incidence of DGE and its associated risk factors vary widely among clinical centers [9]. In 2007, the International Study Group of Pancreatic Surgery (ISGPS) proposed a consensus definition based on severity and clinical impact [5], which has been validated in a small number of reports [10,11].

It is known that ghrelin is an endogenous ligand of the growth hormone secretagogue receptor. It consists of 28 amino acids and is secreted mainly from the stomach [12]. Ghrelin has an intense appetite-enhancing effect in addition to a growth hormone secretion-promoting effect [12], and is the only hormone which exhibits an appetite-promoting effect following peripheral intravenous treatment [13]. In addition, ghrelin exhibits a variety of actions, including stimulation of secretion of growth hormone, gastric motility and mobility, gastric acid secretion [14], and induction of a positive energy balance [15]. The peripheral level of ghrelin is thought to be related to GI disorders, and treatment of ghrelin has been a novel therapy for patients with anorexia-related disorders [13]. However, the intravenous and repeated administration of ghrelin presents a considerable burden for patients.

Rikkunshito is used to treat various GI disorders including functional dyspepsia, gastroesophageal reflux, dyspeptic symptoms of post-GI surgery, and chemotherapy-induced nausea [1]. Takeda et al. reported that a flavonoid in Tj43 suppressed a cisplatin-induced decrease in plasma acylated ghrelin levels and increased food intake in rats, and was mediated by serotonin (5-HT2B and 5-HT2C) receptors [16]. Accordingly, the aim of this study was to investigate the effect of Tj43 on the secretion of active ghrelin, food intake and other intestinal polypeptides after PpPD.

MATERIALS AND METHODS

Patients and serum samples

Serum samples were obtained from 41 patients who underwent PpPD due to

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pancreato-biliary malignant tumors at the University of Yamanashi Hospital between 2012 and 2015 (Table 1). The histological diagnoses of the specimens were confirmed using the criteria of the uploaded World Health Organization classification. The stage was assessed according to the Union for International Cancer Control (UICC) classification, 7th edition [17]. This study was approved by the Ethics Committee of Yamanashi University (approved number: 1665) and was performed in accordance with the ethical standards laid down in Declaration of Helsinki and its later amendments. Survival was measured from the time of pancreatic resection until death or censor.

Patients were assigned to receive Tj43 after surgery [Tj43 (+) group; n = 21, 7.5 g daily starting the day after surgery via the enteral feeding catheter or oral intake, Tj43 (-) group; n = 20, 7.5 g daily starting 2 weeks after surgery via the enteral feeding catheter or oral intake] (Figure 1). Clinical features revealed no significant differences between the Tj43 (-) group and Tj43 (+). Rikkunshito, supplied by Tsumura & Co. (Tokyo, Japan), is a mixture of eight herbal plants, as shown in Table 2. Enteral nutrition (900 Kcal/day) was started at 1 post-operative day via the enteral feeding catheter. One week after surgery, the meal was started, and oral calorie intakes from diets (carbohydrates and protein/fat) were assessed in the two groups for 2 weeks after starting meals.

Blood samples

Blood samples were collected prior to surgery and 1, 2 and 3 weeks after surgery for regular blood tests. Serum and plasma samples were stored at -80°C until assayed.

Measurement of neurointestinal polypeptide hormones

Plasma acyl and desacyl ghrelin levels were assayed by enzyme-linked immuno sorbent assay (ELISA) kits (Iwai Chemicals Co., Tokyo, Japan). Serum peptide YY (PYY) (LifeSpan BioSciences, Seattle, WA), gastric inhibitory peptide (GIP) (Eagle Bioscience, Amherst, NH), spexin, and cholecystokinin (CCK) (LifeSpan BioSciences) levels were also assayed by ELISA.

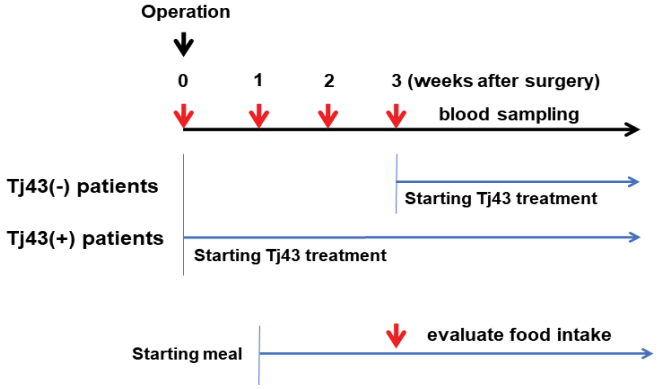
Statistical analysis

Data are expressed as the mean ± standard error of the mean (SEM). Comparisons between the two groups were assessed using the unpaired t-test. Associations between different categorical variables were assessed using the 2 test. Survival rates were calculated using the Kaplan-Meier method, and significant differences in survival were determined by the log-rank test. The Cox proportional hazards model served for uni- and multivariable survival

TABLE 1.

Clinical characteristics

		Control (n = 20)	Tj43 (n = 21)	P value
Age	**years**	**67±.7.0**	**66±.7.7**	**0.962**
Gender	Male Female	10 (50%) 10 (50%)	14 (67%) 7 (33%)	0.199
Disease	Pancreas ca (Ph) IPMC IPMA CBD Ca. Vater Ca. Panceas-NET GB ca.	7 (35%) 2 (10%) 2 (10%) 5 (25%) 3 (15%) 1 (5%) 0 (0%)	8 (38%) 2 (10%) 1 (5%) 5 (24%) 4 (19%) 0 (0%) 1 (5%)	
UICC Tumor stage (0 / I/ II / III /)	Pancreas ca (Ph) IPMC IPMA CBD Ca. Vater Ca. P-NET GB ca.	(0/0/1/0/6/0) (1/0/1/0/0/0) N/A (0/0/0/1/4/0) (0/0/1/2/0/0) N/A N/A	(0/0/0/3/5/0) (0/0/1/1/0/0) N/A (0/3/0/1/1/0) (0/0/2/1/1/0) N/A (0/0/0/0/1/0)	
Tumor differentiation (well/mod/poor)	Pancreas ca (Ph) IPMC IPMA CBD Ca. Vater Ca. P-NET GB ca.	(3/2/2) (0/2/0) N/A (0/5/0) (2/1/0) N/A N/A	(1/6/1) (1/0/1) N/A (2/2/1) (1/3/0) N/A (0/1/0)	
Time of operation	Minutes	500 ± 56	509 ±.72	0.299
Blood loss	ml	692 ±.54	959 ±.66	0.182
HbA1c	%	5.6 ± 2.2	5.7 ± 2.3	0.892
Tumor markers	CEA (ng/ml) CA19-9 (U/ml)	3.1 ± 1.3 455 ± 23	3.7 ± 1.1 451 ± 29	0.872



Note: *Tj43; Rikkunshito.*

Figure 1. *Study protocol.*

TABLE 2.

Composition of Rikkunsito (TJ-43)

JP Atractylodes Lancea Rhizome.	4.0 g
JP Ginseng	4.0 g
JP Pinellia Tuber	4.0 g
JP Poria Sclerotium .	4.0 g
JP Jujube	2.0 g
JP Citrus Unshiu Peel	2.0 g
JP Glycyrrhiza	1.0 g
JP Ginger	0.5g

(JP: The Japanese Pharmacopoeia)
7.5 g of TSUMURA Rikkunshito extract granules (TJ-43) contains 4.0 g of a dried extract of the following mixed crude drugs.

analysis. $p < 0.05$ was considered significant.

RESULTS

Treatment with Tj43

There were no significant differences in clinical features between the two groups (Table 1). The patients treated with Tj43 did not show any complications.

Plasma ghrelin levels

Desacyl (inactive form) and acyl (activate form) ghrelin was detected before surgery [acyl ghrelin: Tj43 (-) group; 13.6 ± 1.5 fmol/ml and Tj43 (+) group; 12.2 ± 1.9 fmol/ml, and desacyl ghrelin: Tj43 (-) group; 104.2 ± 7.5 fmol/ml and Tj43 (+) group; 103.4 ± 7.6 fmol/ml (mean ± SEM)]. The desacyl ghrelin levels were slightly decreased in both two groups after surgery [Tj43 (-) group; 97.8 ± 6.9 fmol/ml, and Tj43 (+) group; 98.4 ± 7.1 fmol/ml], as expected. Increases in acyl ghrelin were minimal in the Tj43 (-) group (14.3 ± 0.9 fmol/ml); however, they were significantly greater in the Tj43 (+) group compared with values before surgery (23.7 ± 1.9 fmol/ml) (Figure 2).

Consumption of meals

Reflecting the results of plasma ghrelin levels, total dietary calorie intake was greater in the Tj43 (+) group compared with Tj43 (-) group (Figure 3). In addition, calorie intake from carbohydrate was significantly greater in the Tj43 (+) patients compared with the Tj43 (+) patients. This was consistent with a previous report [18].

Levels of serum intestinal polypeptide hormones

Intestinal polypeptide hormones including GIP, PYY, spexin and CCK were detected in serum collected prior to surgery (Figures 4 and 5). The levels of spexin decreased after PpPD in both groups. Levels of PYY and CCK were not different before and after PpPD. However, these levels in the Tj43 (+) group significantly increased two weeks after Tj43 treatment. GIP levels increased slightly in patients after PpPD, and this increase was significantly greater in the Tj43 (+) group compared with the Tj43 (-) group

DISCUSSION

Effects of Tj43 on food intake after pancreatico-duodenectomy

Ghrelin and its receptor are produced and expressed in the hypothalamus arcuate nucleus neurons and the stomach, and administration of ghrelin to animals peripherally or intracerebrally enhances GI motility and increases food intake [19]. Furthermore, increases in the plasma ghrelin level were reported in functional dyspepsia [19], chronic gastritis, and gastric ulcer [20]. The association of ghrelin with GI diseases has thus been well-known. It was reported that Tj43 increases release of ghrelin from the intestine. Furthermore, Tj43 improved cisplatin-induced decreases in the plasma acylated-ghrelin level and food intake in rats. In the present study, Tj43 also increased plasma acylated-ghrelin levels (Figure 2A), confirming that Tj43 increases systemic activated ghrelin. This increase may improve food intake after surgery (Figure 3).

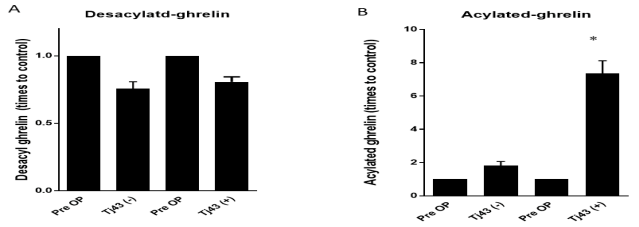
Post-operative DGE is the most common complication after PpPD. This serious complication can lead to epigastric discomfort, loss of appetite, prolonged hospitalization [4]. In the present study, Tj43 increased plasma acylated-ghrelin levels, as report previously [21]. Furthermore, the Tj43 patients showed increased meal intake compared with controls after PpPD, although the difference was not significant (Figure 2). Thus, Tj43 most likely improves DGE after PpPD by increase in active ghrelin levels.

Effects of Tj43 on gastrointestinal polypeptides

The GI hormones are polypeptides, produced from endocrine cells in the stomach, pancreas, and small intestine, and controlling various functions of the digestive organs [22]. These cells produce a variety of chemical transmitters that are involved in GI motility, secretion, absorption, growth, and development. The GI peptides are also found in the enteric nervous system and the central nervous system. Previous studies have shown that most of the gut peptides act as neurotransmitters and neuromodulators in the central and peripheral nervous systems [22]. In this study, the effects of Tj43 on serum levels of GI hormone including GIP, PYY, spexin and CCK were observed in patients following PpPD (Figures 4 and 5).

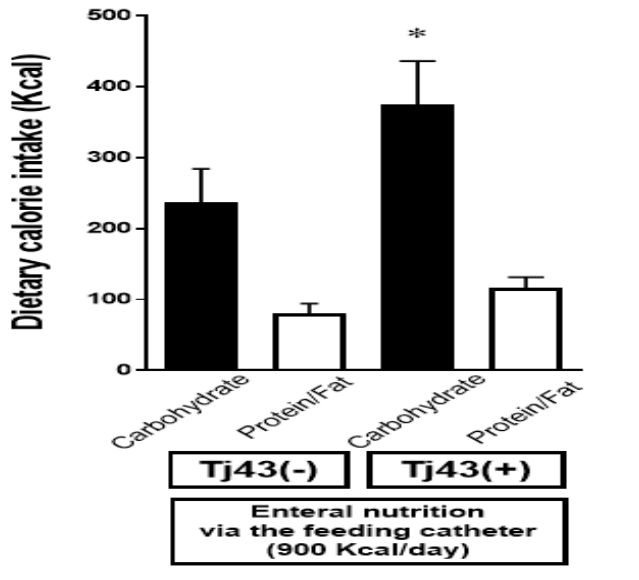
Peptide YY is found in the L cells of the GI mucosa, mainly in the ileum and colon. Small amounts of PYY (about 1-10%) are also found in the upper GI including the esophagus, the stomach, the duodenum and the jejunum [23]. Furthermore, PYY is produced by a discrete population of neurons in the brainstem, especially localized to the gigantocellular reticular nucleus of the medulla oblongata [24]. Moreover, Gustavsen et al. found that PYY-producing cells located in the islets of Langerhans in rat pancreas tissues [25]. They were observed either alone or co-localized with PP or glucagon [26].

The blood concentration of PYY increases after food intake and decreases by fasting [27], and has been shown to reduce appetite. It inhibits gastric motility and increases water and electrolyte absorption in the large intestine



Note: *Serum levels of (A) desacylated and (B) acylated ghrelin were measured by ELISA. Serum levels in the control groups were the acylated and desacylated ghrelin levels before operation. Tj43(-): patients without Tj43 treatment. Tj43(+): patients with Tj43 treatment. *, P <0.05 compared with the Tj43(-) group by ANOVA with Bonferroni's post-hoc test.*

Figure 2. *Serum acylated- and desacylated- ghrelin levels.*



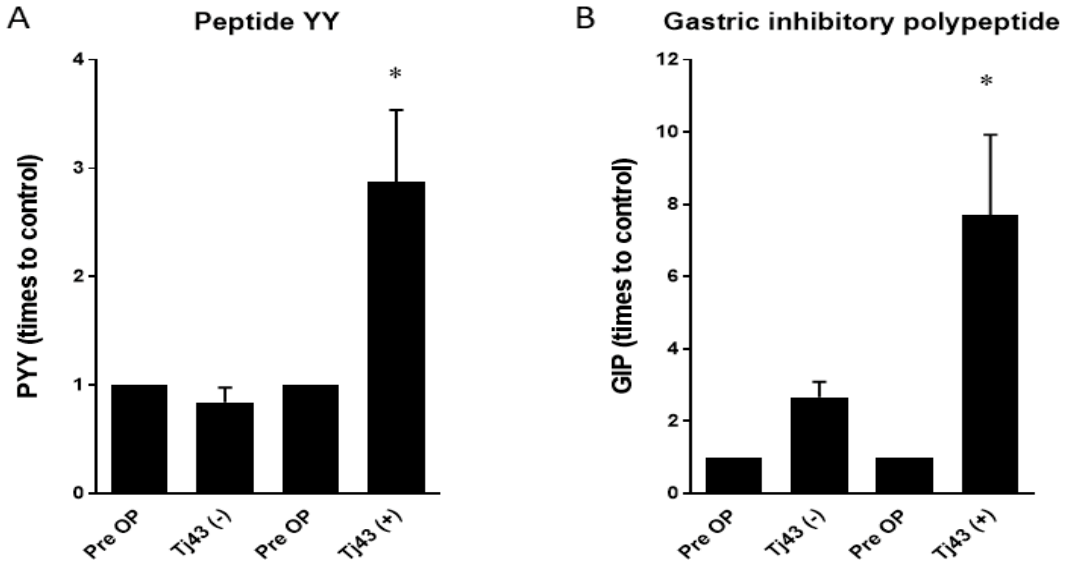
Note: *Two weeks after starting meals, the amount of food intake of each meal was observed and scored from 0 to 100% of the total meal served by nurses, and the average oral intake for five days was calculated and analyzed. Oral calorie intake from meal was assessed in the two groups. Tj43(-): patients without Tj43 treatment. Tj43(+): patients with Tj43 treatment. *, P <0.05 compared with the Tj43(-) group by ANOVA with Bonferroni's post-hoc test.*

Figure 3. *Food intake after operation.*

[28], and also suppress pancreatic secretion. In addition, PYY works by reducing the rate of gastric emptying, thereby increasing the efficiency of digestion and nutrient absorption after a meal. Thus, PYY has an opposing clinical effect to ghrelin. Comparing the effects of Tj43 on serum levels of active ghrelin and PYY (Figures 2 and 4), the increment of ghrelin was greater than that of PYY in the Tj43 group, suggesting that ghrelin may more strongly affected by Tj43 treatment. In animal studies, vasoactive intestinal polypeptide (VIP) stimulated PYY release [29], while gastrin inhibited basal and meal-stimulated PYY levels [30].

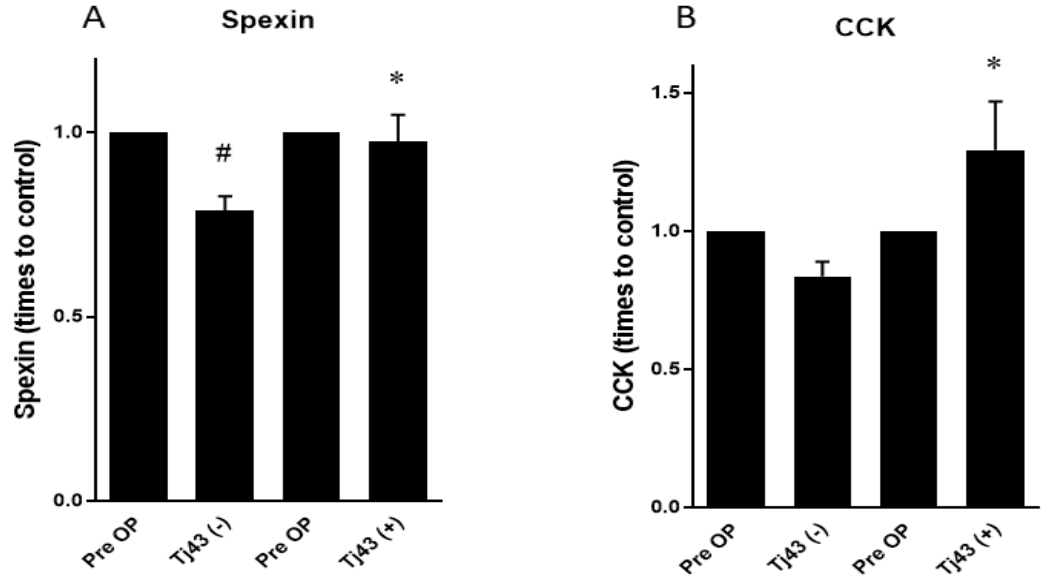
Cholecystokinin (CCK) which stimulates PYY release [31], is produced in the endocrine I cell of the mucosa of the duodenum and the jejunum [31]. Furthermore, it is also found in the central nervous system and peripheral nerves innervating the intestine like other GI hormones. In these locations, CCK probably functions as a neurotransmitter. In humans, the physiologic functions of CCK include the ability to stimulate gallbladder contraction, increase pancreatic enzyme and insulin secretion, and regulate food intake and GI motility [32]. In this study, CCK was also affected by Tj43 treatment after pancreatic surgery (Figure 5). Since CCK increases pancreatic enzyme and insulin secretion insulin secretion, Yj43 may be valuable after pancreatic resection.

The incretin hormones are intestinal peptides secreted after nutrient intake. Like hyperglycemia, they stimulate insulin secretion. Gastric inhibitory



Note: *Serum levels of (A) peptide YY and (B) acylated gastric inhibitory peptide were measured by ELISA. Serum levels in the control groups were the acylated and desacylated ghrelin levels before operation. Tj43(-): patients without Tj43 treatment. Tj43(+): patients with Tj43 treatment. *, P <0.05 compared with the Tj43(-) group by ANOVA with Bonferroni's post-hoc test.*

Figure 4. *Serum peptide YY and gastric inhibitory peptide levels.*



Note: *Serum levels of (A) spexin and (B) CCK were measured by ELISA. Tj43(-): patients without Tj43 treatment. Tj43(+): patients with Tj43 treatment. *, P <0.05 compared with the Tj43(-) group and #, P <0.05 compared with the control group by ANOVA with Bonferroni's post-hoc test. CCK: cholecystokinin.*

Figure 5. *Serum spexin and CCK levels.*

polypeptide (GIP; or glucose-dependent insulinotropic polypeptide) is an incretin hormone secreted from the upper intestine, including the duodenum and the jejunum (GIP, K cells). Gastric inhibitory polypeptide explains most of the incretin effect after oral glucose intake and promotes insulin secretion from the islet cells in a blood glucose-dependent manner. It inhibits gastric acid secretion, but has no effect on gastric emptying [33]. In the present study, plasma GIP levels were increased by Tj43 treatment in patients after PpPD (Figure 4). From this result, Tj43 may be advantageous for blood sugar control after pancreaticoduodenectomy.

Although Tj43 affected serum GI hormone levels in this study (Figures 4 and 5), the clinical significance of this effect remains unknown, and further investigation is needed for clarification on this issue.

CONCLUSION

Tj43 treatment increased acyl ghrelin levels, leading to increased food intake. It also increased intestinal polypeptide hormones. Since the significance of this effect is still unknown, further investigation is needed.

ACKNOWLEDGMENTS

These authors contributed equally to this work

CONFLICT OF INTEREST

None

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