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REVIEW ARTICLE

Clinical application of ghrelin administration for gastric cancer patients undergoing gastrectomy

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Abstract Loss of body weight is a common (and the most serious) sequela after gastrectomy. It impairs quality of life, increases various diseases including infection, and may affect long-term survival. Ghrelin, an intrinsic ligand of the growth hormone secretagogue receptor, was discovered in the stomach in 1999. In addition to growth hormone secretion, ghrelin has pleiotropic functions including appetite stimulation, increasing bowel movement and absorption, and anti-inflammatory reactions. In consequence, ghrelin comprehensively leads positive energy balance and weight gain. The fundic gland of the stomach produces the majority of ghrelin, and plasma ghrelin declines to 10–30 % of the preoperative level after total gastrectomy and 50–70 % after distal gastrectomy. Although plasma ghrelin is never restored after total gastrectomy, it gradually recovers to the preoperative level within a few years after distal gastrectomy. Chronic gastritis due to *Helicobacter pylori* infection and vagotomy are additional factors that perturb the ghrelin secretion of gastric cancer patients after gastrectomy. A randomized clinical trial that revealed that recombinant ghrelin administration successfully increased both food intake and appetite, and ameliorated weight loss after total gastrectomy. Ghrelin administration could thus be a promising strategy to transiently improve the nutritional status of patients who who have undergone gastrectomy, but its effect in the long term remains unclear. Further studies are warranted to elucidate the mechanism of ghrelin and to create and evaluate the analogs that could be administered orally or subcutaneously.

Keywords Ghrelin · Gastrectomy · Gastric cancer · Weight loss

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Introduction

Loss of body weight is a common, serious outcome in patients with gastric cancer who have undergone gastrectomy. It correlates well with a decline in postoperative quality of life and is the most reliable indicator of malnutrition, which impairs immune function, infection susceptibility, and survival [1–3]. Although various mechanisms have been considered, such as the perturbation of absorption due to reduced pancreatic excretion [4, 5], a decrease in the gastric acid level [6], reflux esophagitis [7], intestinal floral alteration [8], and increased peristalsis and diarrhea [9], reduced food intake [10, 11] is the most conceivable explanation for weight loss after gastrectomy. To combat loss of appetite, surgeons dealing with gastric cancers have tried to increase food intake by producing a gastric substitute, such as a jejunal pouch, with limited success [12]. However, we frequently observe that patients do not exhibit significant weight loss after total gastrectomy when they resort to small but frequent meals. Another study indicated that the majority of patients with total gastrectomy were able to eat as much food as healthy subjects under a regulated program [13].

Taken together, we can conclude that (1) patients who have undergone gastrectomy have the ability to maintain body weight when food intake is adequately performed; (2) only loss of storage volume cannot account for reduced

food intake after gastrectomy; (3) there is a relatively large change in eating behavior after gastrectomy that is controlled by an unknown mechanism. In this review, we discuss ghrelin and research about its clinical applications.

The discovery of ghrelin and its features

Ghrelin is a peptide hormone that was discovered in 1999 as an endogenous ligand for the growth hormone (GH)-secretagogue receptor (GHS-R). The 28-amino-acid ghrelin peptide is the endogenous ligand for GHS-R1a, which stimulates GH release from the pituitary gland [14]. X/A-like cells of the oxyntic glands in the stomach produce the majority of ghrelin, and smaller amounts are secreted by other organs, such as the intestine, pancreas, kidney, and hypothalamus [15, 16]. Ghrelin has several physiological functions in addition to the secretion of GH, including the promotion of the appetite signal that antagonizes leptin in the hypothalamus [17], stimulation of gastrointestinal activity (e.g., peristalsis, gastric acid secretion, and pancreatic excretion through the vagal nerves) [18], and regulation of fat metabolism [19] (Table 1). Ghrelin also mitigates proinflammatory cytokine production and attenuates the stress signal [20]. Ghrelin exists as two major molecular forms: acyl ghrelin and des-acyl ghrelin. Ghrelin is octanoylated at Ser3, an unusual post-translational modification that is catalyzed by the enzyme ghrelin O-acyltransferase (GOAT) [21, 22]. Des-acyl ghrelin, which lacks the Ser3 residue octanoylation, is unable to release GH or bind to the classic GHS-R1a receptor [23]. These characteristics indicate that octanoic acid plays an important role in physiological activity via GHS-R1a, and des-acyl ghrelin has been considered an inactive form of ghrelin.

Ghrelin peptide is the only gastrointestinal hormone known to stimulate appetite. A randomized double-blind study of healthy volunteers demonstrated that ghrelin enhances appetite and increases food intake [24, 25]. Several clinical trials of patients with heart failure [26], pulmonary disease [27], cancer cachexia [28], or undergoing chemotherapy [29] concluded that ghrelin successfully improved their diseases along with increased oral food intake and body weight. In the field of surgical treatment for obesity, reduced ghrelin levels after sleeve gastrectomy are associated with successful weight loss and appetite suppression [30]. Taken together, the discovery of ghrelin allows the proposal of a new concept, body weight regulation by the stomach, which can be applied to various diseases with malnutrition.

Gastrectomy and ghrelin secretion

Fundic glands in the stomach produce the majority of ghrelin. Patients with resected gastric cancer experience low plasma ghrelin concentrations. Table 2 lists studies of the change in ghrelin concentration after gastrectomies [31–37]. In total gastrectomy patients, ghrelin concentrations were immediately reduced to 12–29 % of the preoperative concentration. In contrast, ghrelin concentrations decreased to 39–71 % of the preoperative concentration immediately after distal gastrectomy. These reductions in ghrelin concentration are a direct result of the fact that most ghrelin is produced by A-like cells in the fundic gland of the stomach. In fact, sleeve gastrectomy for bariatric surgery immediately results in a 67 % reduction in the concentration of ghrelin [38]. *H. pylori* infection also markedly reduces ghrelin-producing cells and plasma ghrelin.

Table 1 Physiological functions of ghrelin

Orexigenic effect via the hypothalamus [17, 58, 59]
Ghrelin, which increases c-fos expression in the arcuate nucleus, also activates hypothalamic neuropeptide Y (NPY)/Y1 receptors and agouti-related peptide (AgRP) pathways
Stimulation of GH secretion from the pituitary gland [17, 60–62]
Ghrelin is involved in GH release in a non-acute setting. GH regulates IGF-I levels, promotes anabolism, and increases muscle strength. Ghrelin enhances lipolysis via GH and stimulates protein synthesis, myoblast differentiation, and muscle growth via IGF-1
Antiinflammatory action [20, 63, 64]
Ghrelin inhibits the activation of NF-κB, a transcription factor known to control the production of multiple proinflammatory cytokines during inflammatory insults
Stimulation of gastrointestinal peristalsis [18]
Ghrelin acts on motor neurons in the myenteric plexus, activates a vago-vagal reflex, or may stimulate central pathways
Augmentation of cardiac output and reduction of blood pressure [26]
Ghrelin improves myocardial structure and function in chronic heart failure (CHF) via its GH-releasing effects
Inhibition of insulin secretion [65, 66]
Ghrelin has obesogenic/diabetogenic properties. These properties may be direct effects of ghrelin on pancreatic islet function and/or indirect effects through the modulation of GH secretion

Table 2 Representative reports of changes in ghrelin concentration in patients who have undergone gastrectomy

References	Procedure	Number of cases	Preoperative ghrelin level	% Postoperative decline of ghrelin concentration from baseline	
				Short term (%)	Long term (%)
Jeon et al. [32]	DG	24	Active 276 pg/ml (82.7 fmol/ml[a])	Day 1 51	
				Day 7 88	
Takachi et al. [35]	DG	38	Total 95 fmol/ml	Day 3 39	3 years 77
Wang et al. [36]	DG (B-I)	23	Active 468 pg/ml (138.8 fmol/ml[a])	Day 1 37	1 year 93
				Day 7 51	
Wang et al. [36]	DG (B-II)	19	Active 460 pg/ml (136.5 fmol/ml[a])	Day 1 36	1 year 82
				Day 7 51	
Kim et al. [34]	DG	45	Total 310 pg/ml (92 fmol/ml[a])	Day 2 71	3 months 81
Kamiji et al. [33]	DG	14	Active 993 pg/ml (294.2 fmol/ml[a])	–	6 years 77
Jeon et al. [31]	DG	18	Active 113 pg/ml (33.5 fmol/ml[a])	Day 1 50	1 year 57
				Day 7 85	
Zub-Pokrowieckae al. [37]	DG	10	Active 293 pg/ml (86.9 fmol/ml[a])	–	4–5 years 82
Jeon et al. [31]	TG	12	Active 390 pg/ml (115.7 fmol/ml[a])	Day 1 29	–
				Day 7 30	
Takachi et al. [35]	TG	26	Total 95 fmol/ml	Day 3 12	3 years 20
Kamiji et al. [33]	TG	7	Active 993 pg/ml (294 fmol/ml[a])	–	3–5 years 51
Zub-Pokrowiecka et al. [37]	TG	10	Active 293 pg/ml (86.9 fmol/ml[a])	–	4–5 years 46
Jeon et al. [32]	PG	4	Active 427 pg/ml(126.7 fmol/ml[a])	Day 1 25	–
				Day 7 48	

TG total gastrectomy, *DG* distal gastrectomy, *PG* proximal gastrectomy, *B-I* Billroth-I reconstruction, *B-II* Billroth-II reconstruction

[a] x pg/l was converted to x/3.3709 fmol/ml

Generally, patients with gastric cancer and atrophic gastritis have a low basal level of ghrelin. Therefore, the degree of decline caused by gastrectomy can be considered low. Ghrelin concentrations recover relatively soon after surgery; many studies have shown that at 7 days after surgery, the ghrelin concentrations of patients with distal gastrectomy were 51–88 % of preoperative levels. In the long term, postoperative plasma ghrelin levels sometimes approach preoperative levels in patients who have undergone distal gastrectomy. It has been reported that the number of ghrelin-producing cells does not increase after gastrectomy [39]. Persistent low body weight after gastrectomy might stimulate ghrelin secretion from individual ghrelin-producing cells in a negative feedback manner. In contrast, the plasma ghrelin concentrations of patients who have undergone total gastrectomy do not rebound to normal levels if the patients suffer from continuous malnutrition [35]. Although ghrelin is produced by organs other than the stomach, those sources cannot sufficiently compensate for the disappearance of ghrelin-producing cells in the stomach.

Vagotomy and ghrelin response

Both anterior and posterior vagal trunks were usually resected during gastrectomy for gastric cancer, especially in order to complete D2 lymph node dissection. Therefore, we should consider the influence of truncal vagotomy on ghrelin signals in both afferent and efferent pathways. In the rodent, vagotomy alone has led to the significant reduction of the baseline of fasting plasma ghrelin [40]. After radical esophagectomy for esophageal cancers (which includes truncal vagotomy and reconstruction of the whole gastric tube), ghrelin secretion in human patients was reduced by one-half compared to preoperative levels and gradually recovered within a few years [41, 42].

Vagotomy also perturbs the normal ghrelin secretion response (i.e., significant decline immediately after oral food intake). Pekic et al. [43] performed an oral glucose tolerance test (OGTT) in gastrectomized/vagotomized patients and BMI-matched control patients. Plasma ghrelin levels decreased significantly during the OGTT in control subjects, while no reduction was detected in gastrectomized-vagotomized patients. We frequently employ distal gastrectomy, which preserves the celiac branch of the vagal nerve. The downregulation of plasma ghrelin by food intake was significantly greater in patients with vagal nerve preservation than in patients with complete vagotomy (unpublished observation).

With respect to the efferent pathway, there is a report that the administration of exogenous ghrelin stimulated GH

secretion in vagotomized patients as much as in normal subjects [44]. Increases in appetite and amount of food intake after ghrelin administration are reportedly less significant in vagotomized patients than in control patients [45]. However, other studies in rats reported that ghrelin successfully stimulated food intake after vagotomy when administered intraperitoneally [46]. Moreover, in our previous study, intravenous administration of exogenous ghrelin successfully stimulated food intake and appetite immediately after total gastrectomy and esophagectomy [47, 48]. Our findings suggested that the administered ghrelin crossed the blood-brain barrier to the central nervous system, likely increasing the appetite signal through both the vagal pathway and the circulatory system.

As a whole, vagotomy definitely damages the normal control of ghrelin secretion. However, the relationship between ghrelin and vagotomy remains poorly defined in the output system of endogenous and exogenous ghrelin. Therefore, we cannot draw conclusions about the influence of vagotomy on the biological effects of ghrelin, although GH secretion and appetite stimulation may be differently involved with the vagal nerve. Further observation and experiments are required to clarify this issue.

Effects of ghrelin administration after total gastrectomy

Because the anabolic effect of ghrelin is apparent, the possible clinical applications of ghrelin in the context of various cachexic states (e.g., anorexia nervosa, heart failure, chronic obstructive pulmonary disease, and the terminal stage of unresectable cancers) should be considered. These studies have demonstrated increases of oral food intake and body weight in both humans and rats. The two species do differ with regard to body composition. For example, ghrelin administration tended to increase fat volume in the rat, while muscle weight and muscle power have been increased more than fat volume in humans.

There are two large differences in the rationale of ghrelin administration with respect to the cachexic states listed above and the post-gastrectomy state. By various means, cachexia has consistently exhibited high plasma ghrelin concentrations combined with weight loss as the result of negative feedback; the effect of exogenous ghrelin may be restricted if the ghrelin signals are already saturated by endogenous ghrelin. In contrast, the post-gastrectomy state is associated with low plasma ghrelin combined with significant weight loss. Therefore, in the latter context it appears reasonable to administer exogenous ghrelin to compensate for reduced endogenous ghrelin. In this respect, we can expect more significant ghrelin effects in gastrectomy patients than in cachexic patients. Another concern is the influence of vagotomy, which, as described in the previous section, might minimize the effect of ghrelin in gastrectomy patients.

There is a randomized, phase II study [47] in which 21 patients undergoing total gastrectomy were assigned to groups receiving ghrelin ($n = 11$) or a placebo ($n = 10$). In the 10 days after starting oral food intake (postoperative days 5–7), an intravenous drip infusion of synthetic human ghrelin (3 μg/kg) or placebo (pure saline) was administered twice daily (before breakfast and before dinner). The mean intake over the 10-day period represented a 32.7 % increase in the ghrelin group compared with the placebo group (13.8 vs. 10.4 kcal/kg/day). At the end of the study period, weight loss was 3.7 % for the placebo group compared with 1.4 % for the ghrelin group. They used dual-energy X-ray absorptiometry to measure body composition. Fat mass, lean body mass and basal metabolic rate decreased significantly in the placebo group; however, the reductions in lean body mass and basal metabolic rate were not significant in the ghrelin group, although the reduction of fat mass was significant. Therefore, exogenous ghrelin lessened weight loss, especially the loss of lean body mass. There were no significant side effects; however, one patient experienced grade 1 diaphoresis. Several months after the trial, there was no between-group difference in weight or appetite. The most critical drawback is that they are currently only able to administer ghrelin intravenously. For long-term administration, another delivery system (e.g., subcutaneous injection or inhalation) should be developed [49]. Oral ghrelin analog, which is already in clinical trials, is a possible ghrelin substitute.

As ghrelin is also a potent GH secretagogue, there are concerns about GH-mediated stimulation of tumor growth, especially regarding treatment of cancer patients. In vitro studies suggest that ghrelin may enhance the proliferation of prostate [50] and pancreatic [51] cancer cells, but not of a lung cancer cell line, where it induced dose-dependent inhibition of cell proliferation and increased apoptosis [52]. Some tumors from archival samples express ghrelin [53], whereas others (gastric cancer and esophageal cancer) do not [54]. According to a review that analyzed ghrelin administration studies, there was no report of anyone suffering from new cancer as an adverse event among 1,850 participants who were registered to 121 studies. [55–57].

Conclusion

Although our prospective randomized study had a limited number of patients and short-term observation periods, it revealed the beneficial effects of the administration of exogenous ghrelin on body weight and oral intake after total gastrectomy. Although there are issues that must be resolved before clinical application, including elucidation of the

duration of administration and adequate assessment of clinical benefits, surgeons dealing with gastric cancers should be encouraged by the availability of ghrelin. Although decline of ghrelin is certain to play a major role in appetite loss after gastrectomy, it cannot account for all causes that lead to body weight loss. Some patients continue to weigh less even after the amount of food intake has recovered, possibly because of vagotomy, defective fat absorption due to pancreatic insufficiency, bacterial overgrowth, and shortened small bowel transit time [13]. Although surgery is essentially non-physiological and highly invasive, it remains the most reliable therapeutic option to cure cancer. Therefore, it is our obligation to invent new procedures to minimize postoperative side effects.

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