showed that ghrelin enhances appetite and increases food intake.[21,22] Thereafter, several clinical trials of patients with heart failure,[23] pulmonary disease,[24] and cancer cachexia[25] concluded that ghrelin successfully improved the diseases along with increased oral food intake and body weight. In the field of surgical treatment for obesity, reduction in ghrelin levels after sleeve gastrectomy is associated with successful body weight loss and appetite suppression.[26] Taken together, the discovery of ghrelin allows the proposal of a new concept, body weight regulation by the stomach, which could be applied to various diseases with malnutrition.

We reported previously that serum ghrelin levels decreased to 10% to 20% of the preoperative level immediately after total gastrectomy[27,28] and did not recover thereafter, accompanied by approximately 20% body weight loss.[10,12,27] These findings suggest that loss of ghrelin could be involved in body weight loss observed after total gastrectomy. The present prospective, randomized, placebo-controlled phase II study investigated the effects of exogenous ghrelin administration on postoperative body weight loss by improving appetite and oral food intake in patients with gastric cancer who had undergone total gastrectomy. We report here the successful results of the study, and further use of ghrelin for these patients is discussed.

Patients and Methods

Patients

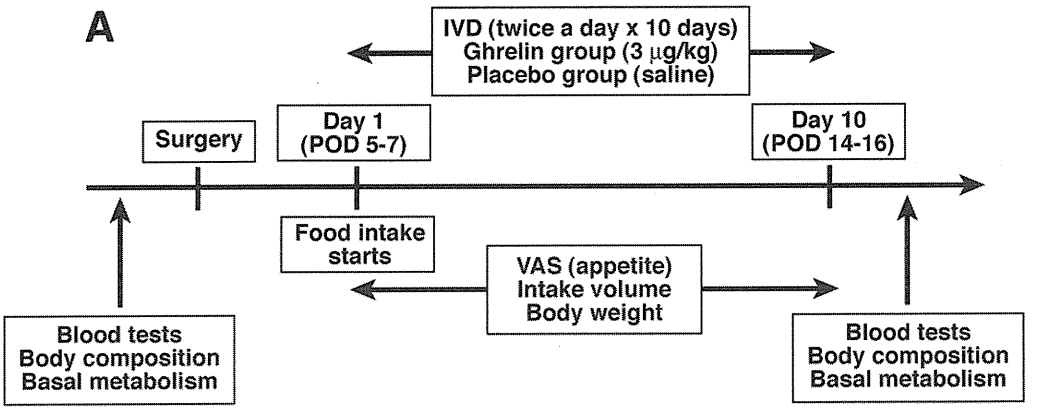
Twenty-one patients who underwent total gastrectomy at Osaka University Hospital between June 2006 and June 2008 were enrolled in the study. The inclusion criteria were as follows: (1) adenocarcinoma of the stomach confirmed by histopathologic examination, (2) preoperative clinical staging with less than stage II (International Union Against Cancer TNM stage classification), (3) curative surgical treatment (R0) (ie, total gastrectomy with D1 or D2 lymph node dissection), and (4) age between 20 and 80 years. The exclusion criteria were the presence of any of the following: (1) cardiopulmonary, liver, or renal dysfunction; (2) active dual malignancy; (3) pregnancy; (4) past history of gastrointestinal surgery; and (5) postoperative complications after total gastrectomy that could affect oral food intake, such as anastomotic leakage, pancreatitis, and mechanical ileus. Twenty-one patients were randomized by sealed envelope and divided into 2 study groups. The center office generated the allocation sequence and enrolled and assigned the patients to the 2 groups, and the random allocation sequence was concealed until interventions were assigned. Eleven patients received repeated administrations of ghrelin (ghrelin group), and 10 patients received repeated administrations of pure saline (placebo group). The study was approved by the Osaka University Ethics Committee, and all patients gave written informed consent before study entry in accordance with the Declaration of Helsinki. The study was registered at UMIN (http://www.umin.ac.jp; clinical trial no. UMIN000001925).

Preparation of Synthetic Human Ghrelin

Synthetic human ghrelin, which consists of 99.4% acyl ghrelin and 0.6% des-acyl ghrelin, based on analysis by high-performance liquid chromatography, was obtained from Peptide Institute Inc (Osaka, Japan). Endotoxin examinations and the pyrogen test for ghrelin solutions were conducted as described previously.[29] Synthetic human ghrelin was dissolved in distilled water with 3.75% D-mannitol and sterilized by passage through a filter. Ghrelin solution was stored in 2-mL volumes, each containing 210 μg. These solutions were stored at −20°C in sterile vials until preparation of ghrelin for administration.

End Points and Study Protocol

The primary end point of this study was an increase in orally ingested calories following ghrelin administration. The secondary end points included changes in body weight, appetite, body composition, basal metabolism, and blood tests. The study design is summarized in Figure 1*A*. The patient usually started oral food intake of rice porridge between postoperative day 5 and postoperative day 7. All patients were served standard postoperative meals, but they were always allowed to receive extra food when they desired. In the following 10 days after starting oral food intake, intravenous drip infusion of synthetic human ghrelin (3 μg/kg) or placebo was administered twice a day (before breakfast and before dinner). Ghrelin solution and placebo (pure saline) were added to a 50-mL saline bottle, which was intravenously infused over a 30-minute period. The same amount of ghrelin was administered through intravenous infusion during the 10-day treatment; the dose was calculated based on the body weight on the day before oral food intake. During the study period, the same protocol of intravenous infusion and the same menu of meals were provided for the 2 groups. The composition of the intravenous infusion fluid was 43.0 g glucose, 35 mEq Na, 20 mEq K, 35 mEq Cl, and 20 mEq lactate in 1000 mL. The protocol of intravenous infusion was 2000 mL/day from postoperative day 1 to postoperative day 7 and 1000 mL/day from postoperative day 8 to postoperative day 14. The study was performed in a single-blind manner; patients without knowledge of their treatment assessed the amount of food intake, appetite, and body weight every day during the treatment by themselves without any intervention by the hospital staff. Food intake calories based on the food weight measured by the patient, including standard meal and extra foods, were calculated by dietitians using a calorimeter. Preprandial appetite at every meal was scored by the visual analog scale (possible scales, 0–10 cm) recorded in the account sheet by each



POD; postoperative day, VAS; visual analogue scale; IVD; intravenous drip

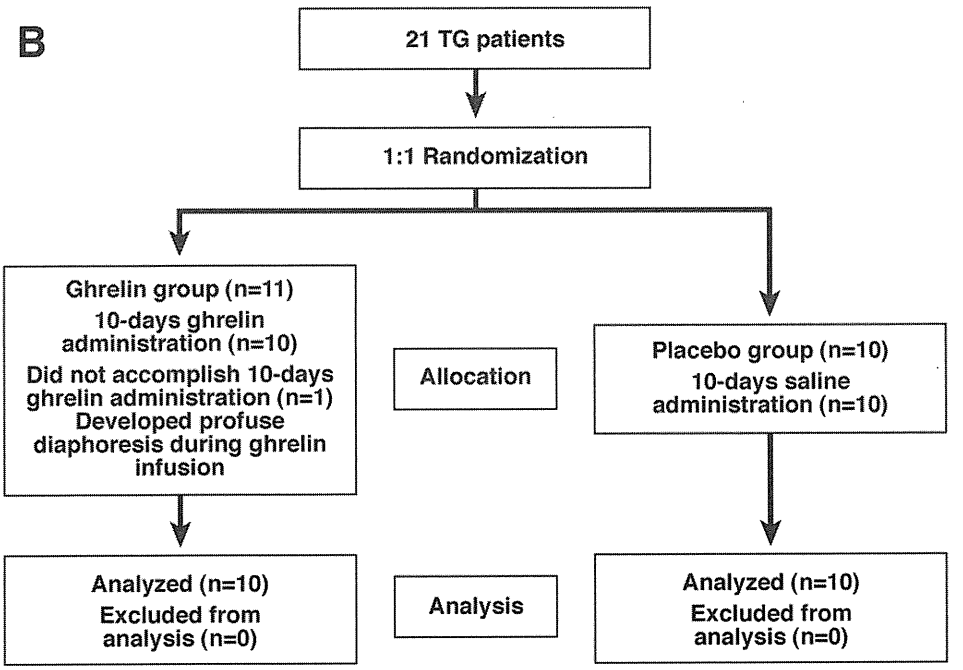


Figure 1. Study protocol and flow diagram.

patient. Body weight was measured with a beam scale to the nearest 0.1 kg, with patients standing barefoot and in light clothing.

Body composition was measured by using dual-energy x-ray absorptiometry (Hologic QDR-2000 instrument; Hologic Inc, Waltham, MA) to assess changes in lean body mass, fat mass, and bone mineral content before and after protocol treatment. The whole body was scanned in the single-beam mode, and the results were analyzed with body composition software. Basal metabolism was measured by using a metabolic analyzer (MedGem metabolic analyzer; HealtheTech, Golden, CO) to assess changes in basal metabolism before and after treatment. All subjects breathed through the MedGem using a disposable, scuba-type mouthpiece. During the measurement, oxygen consumption (VO_2) and body metabolic rate (BMR) were continuously and electronically recorded on a personal computer.

Blood Sampling and Assay

Blood samples were collected from patients before breakfast after an overnight fast, transferred into chilled tubes, stored on ice during collection, centrifuged, serum separated, and stored at −50°C until assay. Insulin-like growth factor (IGF)-I levels were measured by IGF-I IRMA "Daiichi" (TFB, Inc, Tokyo, Japan). Norepinephrine was measured using high-performance liquid chromatography (Tosoh Co, Tokyo, Japan). Cortisol and insulin were measured using the Cortisol Kit "TFB" (TFB, Inc, Tokyo, Japan) and chemiluminescent enzyme immunoassay (Fujirebio, Inc, Tokyo, Japan), respectively. Serum GH and leptin were

measured using GH Kit "Daiichi" (TFB, Inc, Tokyo, Japan) and Human Leptin RIA Kit (Linco Research Inc, St Charles, MO), respectively.

Sample Size Calculation and Statistical Analysis

We estimated that the difference in the effect of ghrelin or placebo on oral food intake calories should be at least 25% assuming 1200 and 1500 kcal/day in the placebo and ghrelin groups, respectively, with ±200 kcal for each SD. To analyze the difference in the effects in the ghrelin and placebo groups using Student *t* test, the study group should comprise at least 16 subjects, with a 5% α value and statistical power of 80%. Assuming that 20% of subjects in each group would not complete the study, the total number of subjects required in this study was estimated at 20.

Numerical values are expressed as mean ± SD unless otherwise indicated. Differences in parameters between the placebo and ghrelin groups were tested by Student *t* test or Mann–Whitney *U* test. Changes in parameters before and after total gastrectomy were tested statistically by the paired *t* test or Wilcoxon signed rank test. Changes in parameters between the 2 groups during the 10 days of follow-up were tested for significance by repeated-measures analysis of variance (ANOVA). A *P* value of $<.05$ was considered statistically significant. SAS for Windows software version 9 (SAS Institute, Inc, Cary, NC) was used to conduct repeated-measures ANOVA, whereas StatView version 5.0 (SAS Institute, Inc) was used for other tests.

Results

Patient Characteristics

The study flow diagram is summarized in Figure 1*B*. One of the 11 patients (9.1%) in the ghrelin group developed profuse diaphoresis during ghrelin infusion, equivalent to grade 1 by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Accordingly, we decided to stop ghrelin administration and the patient was excluded from further analysis. The 10-day course of ghrelin administration was well tolerated by the remaining 10 patients without any adverse events, although some reported transient periods of feeling warm and/or peristalsis during ghrelin infusion. Table 1 summarizes the clinical background of the 20 patients who completed the study. There was no significant difference in age, sex, body weight, body mass index, and clinical stage of gastric cancer between the 2 groups.

Table 1. Patient Characteristics

Parameter	Ghrelin group	Placebo group	*P* value
n	10	10	
Age (*y*)	64.8 ± 10.4	61.6 ± 8.4	.46
Sex (male/female)	7/3	4/6	.19
Body weight (*kg*)	62.2 ± 13.6	62.9 ± 11.5	.89
Body mass index (kg/m^2)	23.1 ± 3.1	24.5 ± 3.8	.36
Procedure (LATG/COTG)	8/2	9/1	.54
Clinical TMN stage			
T (T1/T2/T3/T4)	7/1/2/0	8/2/0/0	.49
N (N0/N1/N2)	9/1/0	9/1/0	1.00
Stage (I/II/III/IV)	8/2/0/0	10/0/0/0	.15

LATG, laparoscopic assisted total gastrectomy; COTG, conventional open total gastrectomy.

Effects of Ghrelin on Appetite, Food Intake, and Body Weight Loss

Appetite, oral food intake, and body weight were recorded by the patients throughout 10 days of ghrelin/saline administration. During this period, the patients in the 2 groups received the same amount (ie, volume and calories) of intravenous infusion. The mean appetite visual analog scale score was significantly higher in the ghrelin group than the placebo group during the 10-day period (Figure 2*A*; repeated-measures ANOVA, $P = .032$).

Food intake calories (kcal/kg/day) during the 10-day period were significantly higher in the ghrelin group than in the placebo group (Figure 2*B*; repeated-measures ANOVA, $P = .030$). Food intake gradually increased at an earlier period of food intake and was then unchanged thereafter; both groups showed a similar difference throughout the 10-day period. The mean intake calorie over the 10-day period was 13.8 and 10.4 kcal/kg/day for the ghrelin and placebo groups, and ghrelin administration accounted for about 32.7% of the increase.

Body weight loss was calculated in reference to the first day of oral food intake. During this period, body weight gradually decreased in both groups, although the loss was more evident in the placebo group. At the end of the intravenous drip protocol (Day 10), body weight loss was −3.7% for the placebo group but only −1.4% for the ghrelin group. For the 10-day period, body weight loss of the ghrelin group was less than that of the placebo group (Figure 2*C*; repeated-measures ANOVA, $P = .044$).

Effects of Ghrelin on Body Composition and Basal Metabolism

Consistent with the body weight changes, both lean body mass and fat mass decreased gradually during the study period. The mean change in fat mass was −8.8% (14,100 ± 5400 to 12,900 ± 5200 g) and −7.6% (19,000 ± 8400 to 17,700 ± 8300 g) for the ghrelin and placebo groups, respectively. The reduction was statistically significant for each group (Figure 3*A*; $P < .001$). The mean change in lean body mass in the placebo group was −7.8% (41,800 ± 6500 to 38,500 ± 5700 g), which was also significant (Figure 3*B*; $P < .001$); however, the change in the ghrelin group was only −2.9% (44,600 ± 10,500 to 43,200 ± 9600 g, Figure 3*B*; $P = .076$). Figure 3*C* shows the BMR values before and after total gastrectomy. BMR decreased significantly after total gastrectomy in the placebo group (21.8 ± 4.0 to 19.4 ± 3.4

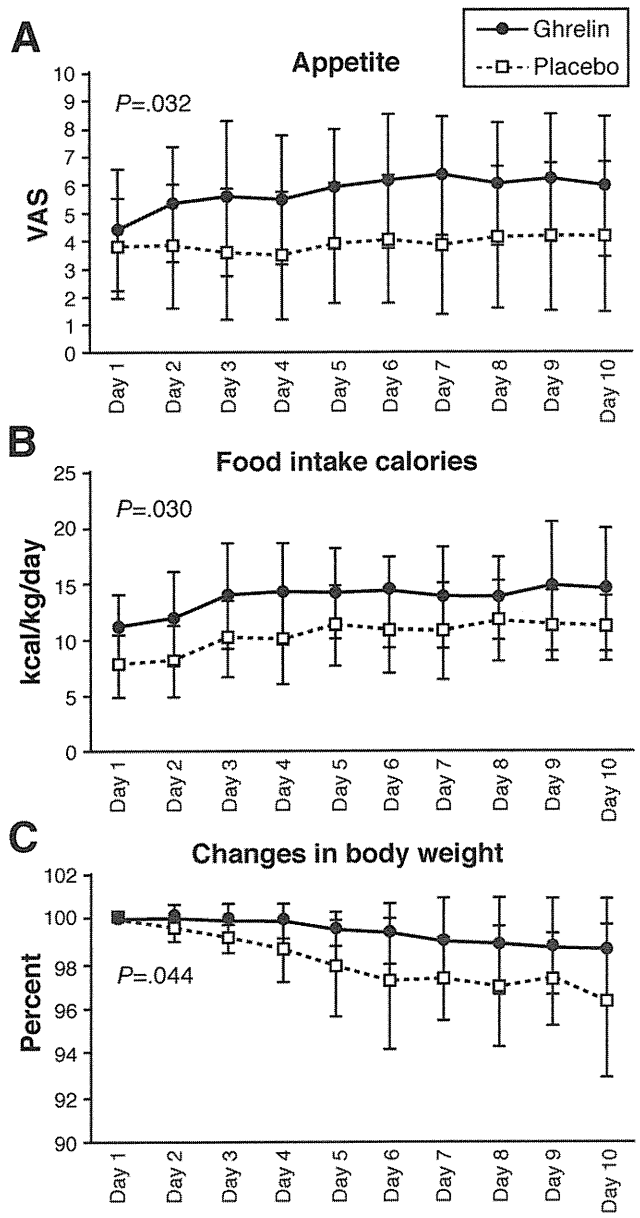


Figure 2. Serial changes in appetite, food intake, and body weight during the 10-day study in the ghrelin and placebo groups. Data are expressed as the mean ± SD of visual analog scale scores of (*A*) preprandial appetite at every meal, (*B*) daily total food intake calories per body weight (kcal/kg/day), and (*C*) percent body weight relative to the first day of oral intake in the ghrelin and placebo groups. The visual analog scale score throughout the study period, which was evaluated by repeated-measures ANOVA, was significantly higher in the ghrelin group than in the placebo group (5.7 vs 3.9 cm; $P = .032$). Likewise, food intake calories were significantly higher in the ghrelin group than in the placebo group (average, 13.8 vs 10.4 kcal/kg/day; repeated-measures ANOVA, $P = .030$). Body weight loss in the ghrelin group was significantly lower than in the placebo group (−1.4% vs −3.7%; repeated-measures ANOVA, $P = .044$).

kcal/kg; $P = .023$). In contrast, the reduction in BMR in the ghrelin group was smaller, and the difference between before and after treatment was not significant (22.6 ± 6.1 to 21.4 ± 6.0 kcal/kg; $P = .20$).

Blood Tests and Hormone Assays

Finally, we compared the results of certain blood tests that reflect the nutritional status and hormones (hemoglobin, total protein, albumin, total cholesterol, triglyceride, leptin, GH, cortisol, norepinephrine, insulin, and IGF-I) both before and after the 10-day period (Table 2). In the early recovery phase, the parameters associated with nutrition did not change in the placebo group but significantly improved in the ghrelin group. Leptin levels decreased significantly in both groups after total gastrectomy, consistent with the reduction in fat mass. On the other hand, there was no significant change in GH, cortisol, norepinephrine, insulin, and IGF-I levels after treatment in both groups.

Discussion

Body weight loss is a common finding in patients who undergo gastrectomy for gastric cancer, which not

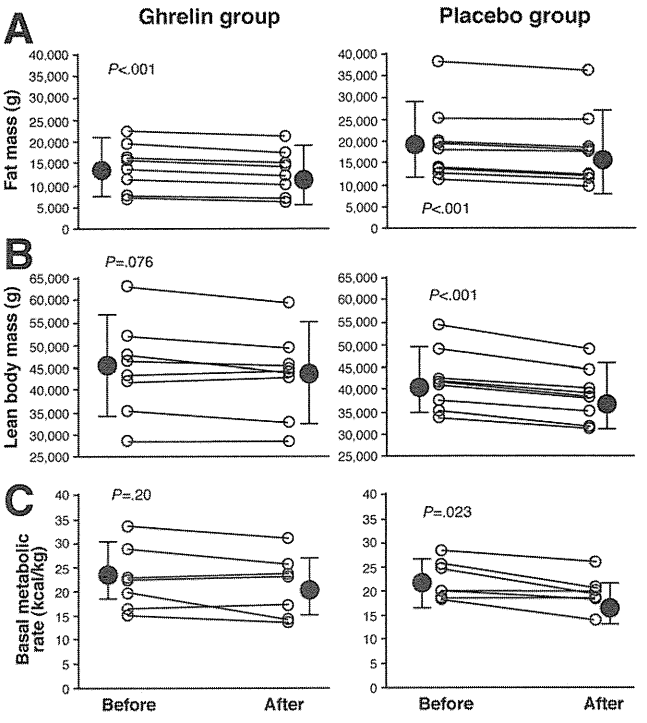


Figure 3. Body composition and basal metabolic rate before and after the study in the ghrelin and placebo groups. (*A*) Fat mass and (*B*) lean body mass measured by dual-energy x-ray absorptiometry and (*C*) basal metabolic rate were determined before and after the 10-day study. Changes for each patient (*open circles*) and the whole group (*closed circles*, ±SD) are shown for the ghrelin and placebo groups. The reductions in all 3 parameters were statistically significant in the placebo group by Student *t* test (fat mass, 19,000 ± 8400 to 17,700 ± 8300 g [$P < .001$]; lean body mass, 41,800 ± 6500 to 38,500 ± 5700 g [$P < .001$]; BMR, 21.4 ± 6.0 to 19.4 ± 3.4 kcal/kg [$P = .023$]). In the ghrelin group, the reduction of fat mass was significant while that of lean body mass and BMR was less than in the placebo group and not statistically significant (fat mass, 14,100 ± 5400 to 12,900 ± 5200 g [$P < .001$]; lean body mass, 44,600 ± 10,500 to 43,200 ± 9600 g [$P = .076$]; BMR, 22.6 ± 6.1 to 21.4 ± 6.0 kcal/kg [$P = .20$]).

Table 2. Results of Laboratory Tests

	Ghrelin group	Placebo group
Hemoglobin (*g/dL*)		
Before	12.2 ± 0.8	12.7 ± 2.4
After	11.8 ± 1.1	11.7 ± 1.4
Total protein (*g/dL*)		
Before	5.7 ± 0.3	6.0 ± 0.7
After	6.6 ± 0.4[a]	6.4 ± 0.3
Albumin (*g/dL*)		
Before	3.1 ± 0.2	3.4 ± 0.6
After	3.5 ± 0.4[a]	3.5 ± 0.2
Total cholesterol (*mg/dL*)		
Before	148 ± 43	176 ± 26
After	174 ± 37[a]	164 ± 32
Triglyceride (*mg/dL*)		
Before	82 ± 47	77 ± 29
After	113 ± 32[a]	99 ± 44
Leptin (*ng/mL*)		
Before	3.1 ± 1.4	7.9 ± 6.7
After	1.2 ± 0.4[b]	4.1 ± 4.0[b]
GH (*ng/mL*)		
Before	0.87 ± 1.5	0.62 ± 0.8
After	0.55 ± 0.7	1.65 ± 2.7
Cortisol (*μg/dL*)		
Before	18.6 ± 4.8	16.9 ± 4.6
After	17.0 ± 4.0	17.9 ± 6.7
Norepinephrine (*pg/mL*)		
Before	314 ± 132	294 ± 171
After	366 ± 122	269 ± 158
Insulin (*μIU/mL*)		
Before	6.1 ± 3.5	10.3 ± 5.5
After	5.1 ± 2.5	6.5 ± 6.0
IGF-I (*ng/mL*)		
Before	108 ± 33	92 ± 36
After	85 ± 53	76 ± 37

[a]$P < .05$, [b]$P < .01$ (paired *t* test; before vs after).

only associates with various pathologic conditions but also affects patients' social activity. Therefore, postoperative body weight loss needs to be investigated thoroughly, especially in Japan, where early gastric cancer accounts for more than 50% of the total incidence of gastric cancer,[30] and the 5-year survival rate of early gastric cancer is more than 90%.[31] Previous studies reported that body weight loss after total gastrectomy was approximately 15% to 20% of the preoperative weight.[10,12,27] Because the incidence of gastric cancer is associated with low body weight in not only Japan and Asian countries but also in the Western world, the estimated average body mass index after total gastrectomy is expected to be 18 to 20 kg/m^2, which is lower than the ideal body mass index. The correlation between low body weight and long-term survival rate has not been analyzed thoroughly even in healthy individuals. A large cohort study of healthy Japanese subjects surveyed over 10 years concluded that a body mass index less than 19 kg/m^2 was associated with high mortality risk at an odds ratio of 2.26 due to various diseases, including infectious, cardiovascular, and malignant diseases.[3] Although there are no concrete data for patients who undergo gastrectomy, these patients could be at risk for a higher mortality rate due to low body weight. Based on this background, the major purpose of this study was to minimize postoperative body weight loss by ghrelin administration through up-regulation of GH secretion and appetite.

At the end of the 10-day study period, ghrelin reduced more than half of postoperative body weight loss from −3.7% in the placebo group to −1.4% in the ghrelin group. Although this is a limited result in the early postoperative period, which is associated with the most profound body weight loss, to the best of our knowledge, ghrelin administration is the most effective procedure among various studies that were designed for the same purpose.[12,32]

After numerous experimental studies, clinical application of ghrelin commenced in healthy volunteers and then extended to patients with heart failure,[23] pulmonary disease,[24] and cancer cachexia.[25] The results of these studies confirmed the safety of ghrelin administration. In our study, the patients in the 2 groups showed no differences in postoperative complications (eg, infections, delayed wound healing, thromboembolism) and length of hospital stay. However, 1 of the 11 patients developed diaphoresis, corresponding to National Cancer Institute Common Terminology Criteria for Adverse Events grade 1. Although we stopped ghrelin administration following the study protocol, this symptom was consistently reported in previous trials although it was tolerated by patients.[23–25,29] The overall positive effects of ghrelin such as body weight gain and increase in food intake calories were observed consistently in all clinical trials, including the present study.[21–25] In addition, improvement of disease-specific status has been reported, including patients with chronic heart failure[23] and those with chronic obstructive pulmonary disease.[24]

To our knowledge, the present study is the first clinical trial in the field of gastroenterological surgery. Moreover, the present study differs in 2 aspects from previous studies.[23–25] The first difference related to the study subjects; the subjects enrolled in previous clinical studies were cachexic emaciated patients in whom the level of circulating ghrelin was predicted to rise. It has been considered that the efficacy of exogenous ghrelin is limited because of down-regulation by high endogenous ghrelin. In contrast, in the present study, in which circulating ghrelin levels were extremely low due to total gastrectomy, we replaced the low levels of endogenous ghrelin with an exogenous one; therefore, it seems more physiologically related to study the effect of ghrelin administration. Another point is that complete vagotomy at the esophagogastric junction was performed during total gastrectomy in our patients. Because the vagus nerve mediates both efferent and afferent ghrelin signals,[33–35] it was suspected that exogenous ghrelin would not adequately interact in the hypothalamus. In animal experiments, vagotomy or chemical blockade of the vagal

signal abolished the effects of intravenously administrated ghrelin.[36] In vagotomized patients, ghrelin administration did not increase food intake.[37] However, other studies reported that ghrelin administered intraperitoneally successfully stimulated food intake after vagotomy in rats[38] and that ghrelin administration in vagotomized patients enhanced GH secretion.[39] These animal experiments and clinical studies indicate that the effects of ghrelin administration are still controversial, at least in vagotomized patients. In the present study, intravenous administration of exogenous ghrelin successfully stimulated food intake and appetite immediately after total gastrectomy. Our results suggest that the administered ghrelin crossed the blood-brain barrier to the central nervous system, probably increasing the appetite signal through not only the vagal pathway but also the circulation. The relationship between ghrelin and vagotomy remains poorly defined, and further studies should be performed in the future.

BMR accounts for between 60% and 70% of the total energy expenditure in adults.[40] Furthermore, the fat-free mass is considered the best single predictor of energy expenditure, and 53% to 88% of the variation in BMR is accounted for by fat-free mass.[41] In the placebo group, the BMR decreased significantly after total gastrectomy, whereas it did not change in the ghrelin group. This result was consistent with the significant decrease in lean body mass, which was limited to the placebo group. In animal experiments, ghrelin enhances abdominal fat storage in white adipose tissue in rats,[19] whereas clinical studies, including the present study, have shown that ghrelin increases lean body mass relative to fat mass.[23,24] Differences in species and patient status may influence the effect of ghrelin administration on fat metabolism. Preservation of lean body mass against the postoperative catabolic metabolism might be caused by ghrelin-stimulated GH secretion from the pituitary gland. However, serum GH levels were stable in the 2 groups, probably due to the rapid turnover of GH. This phenomenon was already reported in a previous phase I study.[29] Baseline leptin levels tended to be lower in the ghrelin group, probably because this group included more men, who generally have lower leptin levels than women.[42,43] Leptin levels significantly decreased in parallel with the decrease in fat mass in both the ghrelin and placebo groups.

The influence of cancer proliferation is another issue of safety in ghrelin studies. Several in vitro studies reported the expression of ghrelin receptor in cancer cells and that ghrelin weakly enhanced their proliferation, for example, in prostate[44] and pancreatic[45] cancer cells. However, another study reported that ghrelin inhibited proliferation and increased apoptosis in a lung cancer cell line.[46] In a preliminary experiment in our laboratory using various gastric cancer cell lines, all cells examined were negative for ghrelin receptor and showed no growth response to exogenous ghrelin (unpublished observation, March 2005). In clinical studies of cancer cachexic patients, no adverse events concerning tumor growth stimulation have been reported.[25] With respect to the present clinical trial, this argument was partly evaded because patients who met the inclusion criteria accounted for more than 90% curability by surgery alone[31] and ghrelin was administered for only 10 days. However, care should be taken when administering ghrelin over longer periods.

Although we successfully demonstrated a short-term effect of ghrelin administration on food intake, appetite, body weight, and other parameters, its long-term effect and benefit still need to be evaluated before clinical application. Because ghrelin secretion does not recover even several years after total gastrectomy, long-term administration of ghrelin is probably required to maintain the short-term effects. For this purpose, ghrelin poses a practical problem in that it is an unstable short-acting peptide and needs to be administered intravenously. An easier administration route, such as subcutaneous injection and inhalation, should be investigated to allow outpatient and home use. GH secretagogues, which were discovered before ghrelin, are orally available and perhaps could be used as ghrelin substitutes. For example, RC-1291 is orally available, well tolerated, and effective in promoting body weight gain, as demonstrated in a phase I study in healthy volunteers.[47] Another issue worth further investigation is the clinical benefits of ghrelin therapy, because it is argued that increases in appetite and body weight are not sufficient reasons for medication. Thus, further studies are needed to evaluate other aspects of ghrelin administration, such as reduction of total medical cost and hospital admission, improvement of social activity and quality of life, and postoperative survival. For example, postoperative body weight loss is most progressive and rehabilitation is most important in the first 3 months after surgery. It is possible that ghrelin administration for at least 3 months would improve postoperative recovery.

In conclusion, this prospective randomized study in a limited number of patients provides convincing data for the beneficial effects of ghrelin on body weight and dietary activity after total gastrectomy. Although there are some issues to be resolved before clinical application, including drug delivery system, duration of administration, and adequate assessment of clinical benefits, surgeons dealing with gastric cancers and other gastroesophageal diseases should be encouraged by the availability of ghrelin. Because surgery is essentially not physiologic and highly invasive for the body but the most reliable therapeutic option to cure cancer, it is our obligation to invent novel procedures to minimize its side effects.

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Translational research of ghrelin

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Gastrointestinal peptides play important roles regulating feeding and energy homeostasis. Most gastrointestinal peptides including glucagon like peptide-1, peptide YY, amylin, and oxytomodulin are anorectic, and only ghrelin is an orexigenic peptide. Ghrelin increases appetite, modulates energy balance, suppresses inflammation, and enhances growth hormone secretion. Given its diversity of functions, ghrelin is expected be an effective therapy for lean patients with cachexia caused by chronic heart failure, chronic respiratory disease, anorexia nervosa, functional dyspepsia, and cancer. Clinical trials have demonstrated that ghrelin effectively increases lean body mass and activity in cachectic patients. Ghrelin interrupts the vicious cycle of the cachectic paradigm through its orexigenic, anabolic, and anti-inflammatory effects, and ghrelin administration may improve the quality of life of cachectic patients. We discuss the significant roles of ghrelin in the pathophysiology of cachectic diseases and the possible clinical applications of ghrelin.

Keywords: ghrelin; GHS-R; cachexia; growth hormone; obesity

Introduction

Feeding and energy homeostasis are controlled by the hypothalamus, limbic system, and peripheral organs, including the stomach, intestine, liver, adipose tissue, pancreas, and muscle. When food enters the gastrointestinal (GI) tract, stretch and macronutrients initiate the secretion of peptide hormones that transmit feeding signals via the afferent vagus nerve to the hypothalamus. Alternatively, some information is directly transmitted to the central nervous system through the blood–brain barrier. Nearly all GI peptides are anorectic and decrease feeding (e.g., cholecystokinin, glucagon like peptide-1, peptide YY, amylin, oxyntomodulin, and insulin), but only ghrelin is orexigenic. Recently, many questions regarding the role of GI peptides in regulating feeding and other functions have been clarified, and studies of the clinical utility of GI peptides as therapeutic agents are advancing. Our efforts have focused on ghrelin, and we previously identified roles for ghrelin in regulating cachexia, obesity, gastrointestinal diseases, and chronic obstructive pulmonary disease (COPD). In this review, we summarize the current status of translational research using the physiological functions of ghrelin, and we further discuss possible future directions for ghrelin research.

Biosynthesis of ghrelin

Ghrelin is a 28-amino acid peptide first isolated from the stomachs of humans and rats in 1999.[1] Acylation of its third residue, Ser-3, by the addition of middle-chain fatty acid, *n*-octanoic acid, is essential for its biological activity, including the binding and activation of the ghrelin receptor (formally known as the growth-hormone-secretagogue receptor (GHS-R)).[1] This acyl modification is performed by the polytopic membrane-bound enzyme ghrelin O-acyltransferase (GOAT).[2] Ghrelin mRNA is predominantly expressed in the stomach, but lower amounts are seen in the bowel, pituitary gland, kidney, lung, placenta, testis, pancreas, leukocytes, and hypothalamus. In addition, small amounts of ghrelin mRNA have been detected by real-time PCR in the adrenal gland, adipocytes, gall bladder, skeletal muscle, myocardium, skin, spleen, liver, ovary, and prostate.[3] Plasma ghrelin levels are higher in subjects with low body mass index (BMI) compared

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with normal- or high-BMI subjects,[4] and circulating ghrelin levels are elevated in underweight patients with COPD or those with anorexia nervosa.[5,6] Moreover, in patients with malignancy-associated cachexia, plasma ghrelin levels are increased by approximately 25% compared to normal subjects.[7] Finally, the high plasma ghrelin levels seen in the presence of an empty stomach rapidly decrease after feeding. These results suggest that ghrelin production is stimulated to maintain energy homeostasis and provide a defense against starvation.

Physiological functions of ghrelin

Ghrelin stimulates growth hormone (GH) secretion, food intake, and weight gain, but it has much broader physiologic functions, including roles in circulation, digestion, inflammation, and cell proliferation (Fig. 1).

Ghrelin stimulates GH secretion *in vitro* and *in vivo* in many species including humans.[1,8] Centrally or peripherally administered ghrelin strongly stimulates food intake in animals,[9] and intravenous administration of ghrelin to healthy humans increases energy intake from a buffet lunch by 28 ± 3.9%. Visual analogue scores for appetite are also increased under these conditions.[10] The orexigenic activity of ghrelin is independent of its stimulatory effects on GH secretion.[9] Continuous intracerebroventricular administration of ghrelin induces food intake and increased fat mass by selectively using carbohydrates, leading to weight gain.[11]

In addition to its ability to protect against cardiac dysfunction, ghrelin has other effects on the cardiovascular system. Intravenous infusion of ghrelin significantly decreases mean arterial pressure and increases cardiac output without affecting heart rate in healthy volunteers[12] and patients with chronic heart failure (CHF).[13] In addition, peripheral arterial infusion of ghrelin in normal subjects increases blood flow in a dose-dependent manner.

Ghrelin stimulates gastric acid secretion and gastric motility. These effects are lost following both vagotomy and administration of atropine, but a histamine H2-receptor antagonist has no effect on ghrelin-induced gastric functions. Thus, the effects of ghrelin on gastric function are transmitted via the vagus nerve.[14] Ghrelin also accelerates transit of a liquid meal through the small intestine in rats,[15] and it also ameliorates the delayed GI transit seen in alloxan-induced diabetic mice or streptozotocin-induced diabetic guinea pigs, suggesting that ghrelin

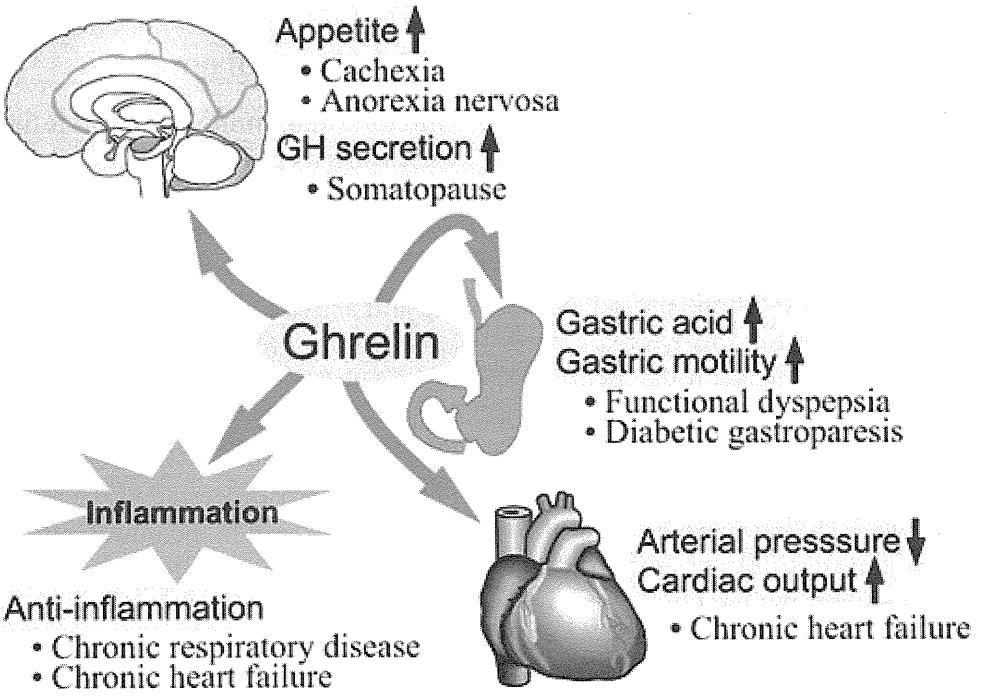

Figure 1. Physiological functions and potential for clinical applications of ghrelin. Ghrelin and ghrelin receptor agonists may have roles as novel therapeutics to affect multiple organ systems. Ghrelin-targeted therapy has been shown to be clinically beneficial in several diseases in humans.

may be a potential therapy for diabetic patients with gastroparesis.[16]

Ghrelin has anti-inflammatory activity and protects against endotoxin-induced shock by inhibiting the expression of proinflammatory cytokines by activated monocytes and endothelial cells.[17,18] Ghrelin attenuates sepsis-induced acute lung injury and reduces mortality by increasing pulmonary blood flow, downregulating proinflammatory cytokines, and inhibiting NF-kappaB activation in rats.[19] In addition to increasing appetite in cachectic patients with chronic respiratory infections, ghrelin's anti-inflammatory functions may protect against airway inflammation in patients with chronic pulmonary disease.

Translational research of ghrelin

Chronic heart failure. Plasma ghrelin levels are significantly higher in CHF patients with cachexia than in those without cachexia.[20] Chronic administration of ghrelin for 3 weeks improved left ventricular function and concomitantly increased plasma GH and insulin like growth factor-I (IGF-I) levels; it also attenuated left ventricular remodeling and cardiac cachexia in rats with CHF.[21] Moreover, treatment of CHF patients with ghrelin led to increased exercise capacity, food intake, and lean body mass.[20] Ghrelin also significantly decreased plasma norepinephrine in patients with CHF. In cachectic patients with CHF, ghrelin administration increased muscle strength and body weight but did not affect plasma levels of IL-6 or TNF-α,[22] despite the increased levels of proinflammatory cytokines seen in CHF patients with cardiac cachexia.[20] Taken together, these data suggest that treatment with ghrelin can ameliorate muscle wasting associated with CHF, but its anti-inflammatory properties in cardiac disease remain unclear.

Because both GH and IGF-1 are essential for myocardial growth and homeostasis,[23] beneficial effects of ghrelin in patients with cardiac cachexia may be partially explained by the ghrelin-induced GH and IGF-1 secretion. GH supplementation has beneficial effects on myocardial structure and function in CHF patients,[24] and both GH and IGF-1 lead to improved cardiac function through enhanced compensatory hypertrophy and decreased left ventricular wall stress in rats with CHF.[25] Hexarelin, a GHS-R agonist, prevents cardiac damage after ischemia-reperfusion in GH-independent mechanisms.[26] Ghrelin directly inhibits apoptosis of cardiomyocytes and endothelial cells through activation of extracellular signal-regulated kinase-1/2 and Akt serine kinases.[27] Thus, the benefits of ghrelin in cachectic patients with CHF are mediated by both GH-dependent and GH-independent mechanisms.

Gastrointestinal dysfunction. Disordered gastric emptying and dysregulation of gastroduodenal motility give rise to functional dyspepsia and gastroparesis,[28] and several studies have examined the safety and efficacy of ghrelin administration to patients affected by these disorders. Because ghrelin enhances gastric motility and secretion, it was hypothesized that treatment with ghrelin could lead to physiologic improvements in patients with gastroparesis. Indeed, a double-blind, placebo-controlled, crossover study showed that ghrelin increases gastric emptying in patients with diabetic gastroparesis,[29] and, in patients with idiopathic gastroparesis, ghrelin treatment enhances gastric emptying, and alleviates meal-related symptoms.[30] In addition, repeated intravenous infusions of ghrelin (3 μg/kg) twice a day for 2 weeks to patients with functional dyspepsia-related anorexia led to increased daily food intake compared to levels before and after ghrelin treatment. In this study, sensations of hunger were significantly elevated following ghrelin administration.[31]

Total gastrectomy can lead to significant weight loss and decreased appetite, with associated lower quality of life (QOL) after surgery. Plasma ghrelin levels fell to 10–20% of their preoperative levels immediately after total gastrectomy, and they remained significantly depressed for the entirety of the monitoring period.[32] Thus, ghrelin supplementation after gastrectomy may be an effective therapy to correct these defects, but further clinical studies are needed.

Chronic respiratory disease. Patients with late-stage chronic respiratory disease often have dramatically increased work-of-breathing requiring greater energy expenditure, and elevated levels of inflammatory cytokines are often seen in these patients. Together, these phenomena induce a relatively cachectic state in affected patients. A 3-week treatment with recombinant human ghrelin (2 μg/kg, intravenously, twice a day) improved the

exercise tolerance of patients with COPD, and ghrelin increased muscle strength and nutritional status of these patients.[33] Thus, even underweight patients with COPD may benefit from ghrelin treatment.

Chronic respiratory infections in patients can lead to a state of near constant inflammation characterized by a neutrophil-predominant airway infiltrate, and this can promote an end-stage cachectic state. The constant activation of neutrophils can cause substantial cytotoxicity to bronchial and alveolar epithelial cells, leading to impaired pulmonary function and requirements for excess energy expenditure with associated weight loss. We showed that treatment with ghrelin (2 μg/kg, intravenously, twice a day) for 3 weeks reduced both sputum volume as well as sputum neutrophil counts in patients with chronic respiratory infections.[34] In addition, treated patients demonstrated increased food intake, body weight, and walk tolerance. Decreased sputum concentrations of the inflammatory cytokines IL-6 and TNF-α were also seen.[34] Since neutrophil-induced cellular damage promotes further bacterial proliferation in the lungs, ghrelin may be able to interrupt this vicious cycle to promote healing in these patients. Further studies are needed to examine the possible therapeutic efficacy of ghrelin for refractory chronic respiratory disease.

Anorexia nervosa (AN). AN is a psychiatric illness and eating disorder characterized by disordered body image with an obsessive fear of gaining weight; it is often associated with extremely low body weight. The high plasma ghrelin levels seen in lean patients with AN reflects the negative energy balance of affected individuals.[4,35,36] No changes in appetite were reported following a single administration of ghrelin (300-min intravenous infusion, 5 pmol/kg) to patients with AN.[36] However, a bolus intravenous injection of 1 μg/kg ghrelin caused sensations of hunger in six of nine patients with AN, and this was similar to the effects seen in normal subjects (five of seven responders).[37] Recently, another study administered ghrelin (3 μg/kg twice a day) to five AN patients, and this led to decreased gastrointestinal symptoms and increased sensations of hunger and daily energy intake (12–36%) without serious adverse events.[38] Further clinical studies, including randomized controlled trials, are needed to further assess the use of ghrelin in the treatment of AN.

Cancer cachexia. Cancer, irrespective of the organ affected, often leads to a cachectic state. Cancer patients with cachexia survive for a shorter period of time and respond more poorly to anticancer therapies compared to those without cachexia.[39,40] Up to 50% of cancer patients show changes in eating at the time of diagnosis, and this likely contributes to weight loss.[39] Cachexia and anorexia are closely associated with decreased QOL in cancer patients. Ghrelin administration induced significant increases in body weight and food intake in rodent models of cancer cachexia.[41,42] Several randomized, double-blind placebo-controlled trials have examined the safety and efficacy of ghrelin or GHS-R agonist in patients with cancer-related cachexia. In these studies, food intake and sensation of hunger were significantly increased after ghrelin treatment.[43,44]

Ghrelin is a mitogen for hepatoma cells,[45] but it exhibits antiproliferative effects in lung carcinoma cells *in vitro*.[46] Thus, there are conflicting data about the possible role of ghrelin in oncogenesis, and studies are ongoing to further identify the function of ghrelin in carcinogenesis.[41,47–49] Large-scale long-term clinical trials are needed to determine whether ghrelin treatment promotes tumor growth.

Antiaging. GH secretion peaks during puberty and gradually decreases reaching 20–25% of peak levels by age of 60. The normal changes in GH hyposecretion state are referred to as somatopause, and this is thought to promote aging by reducing muscle mass, strength and bone mineral density, and increase fat mass.[50] GH supplement therapy improves muscle, bone, and fat mass, but its functional effects and long-term safety remain unclear.[51]

Administration of ghrelin to aged rodents stimulates GH secretion, food intake and weight gain, while maintaining low adiposity.[52,53] We confirmed the ability of ghrelin to increase soleus muscle mass in a disuse atrophy model in mice (unpublished data). A double-blind, crossover study using MK-677, a GHS-R agonist, recruited healthy men and women between 60 and 81 years, and the daily administration of MK-677 for 12 months significantly increased GH and IGF-I levels to those seen in healthy young adults. Treated subjects also had increased total lean body mass and intracellular

water (a biomarker of fat-free mass).[54] Total body fat, abdominal fat, muscle strength, and QOL did not change. This was a small-scale trial ($n = 65$), and further clinical studies are needed.

Chronic kidney disease. Malnutrition is a common and early feature of chronic kidney disease, and it is strongly associated with increased mortality in dialysis patients.[55,56] In a rat model of chronic renal disease, treatment with ghrelin increased food intake and lean body mass, and decreased circulating inflammatory cytokines.[57] A randomized double-blind crossover study showed that subcutaneous ghrelin administration (12 μg/kg) to malnourished dialysis patients for 1 week increased daily energy intake and decreased blood pressure.[58]

Diabetic neuropathy. Ghrelin has neuroprotective properties and prevents neuron apoptosis.[59] We recently reported that ghrelin, but not des-acyl ghrelin, reverses experimental diabetic peripheral neuropathy in mice,[60] suggesting that ghrelin may serve as a new therapeutic approach for diabetic neuropathy.

Conclusions and perspectives

The rates of obesity have been increasing worldwide, and obesity has become a major social and medical issue. Diet and exercise are important for the treatment of obesity, but these are difficult to implement and maintain for the duration of time needed to effect real weight change. To develop more effective pharmacologic treatments for obesity, the mechanisms regulating feeding and satiety must be fully understood, and GI peptides are becoming increasingly recognized for their contribution to energy homeostasis. Anorexigenic GI peptides, ghrelin receptor antagonists, and ghrelin neutralizing antibodies have been studied for their potential application as antiobesity drugs.[61,62] In addition, combination therapy with different GI peptides and leptin may also be effective for the treatment of obesity.[63] However, various adverse events, in particular nausea and vomiting, were often reported in clinical trials of GI peptides, and further research to determine the optimal administration route, dosage, and combination of drugs is needed.

Ghrelin has a number of different documented and putative physiologic functions, and it may be an effective therapy for multiple conditions (Fig. 1). Clinical trials examining the safety and efficacy of chronic ghrelin administration to patients after total gastrectomy, AN, diabetic gastroparesis, and disuse muscle atrophy are ongoing or in the planning stages. Although "acylated" ghrelin is the form currently in clinical use, the functions of des-acyl ghrelin should be examined in the future because important physiologic roles for des-acyl ghrelin have been reported.[27,64–66]

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Conflicts of interest

The authors declare no conflicts of interest.

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特集　高齢者の虚弱―評価と対策―

Topics

3．グレリンによるサルコペニアへの介入

米川　忠人　　越中　敬一　　中里　雅光

KEY WORD
- グレリン
- 加齢
- IGF-I

SUMMARY

本邦はまもなく人口の４人に１人が65歳以上という超高齢化社会に突入することから，抗加齢対策の研究が多くの基礎と臨床の施設で進行している．骨折は高齢者寝たきりの大きな誘因で，骨粗鬆症は易骨折性の原因であるが，骨格を保持する筋肉量の低下も転倒骨折の一因である．しかも，骨格筋の萎縮は廃用性，除神経，悪液質(癌や慢性感染症など)，栄養失調でも顕著に認められる．グレリンは摂食亢進に加えて成長ホルモン(GH)，インスリン様成長因子-Ⅰ(IGF-Ⅰ)を介する筋肉量の増大や抗炎症作用などの多くの生理作用を有し，サルコペニアによる筋肉量および筋力の低下に対しても有効な薬剤となる可能性がある．

グレリンとは

胃を主な産生源とするグレリン(ghrelin)は，28アミノ酸残基からなるペプチドで，３番目のセリン残基がn-オクタン酸によりアシル化されている．グレリンのアシル化修飾は容易に分解され，デスアシル体となり，その血中濃度はグレリンの約５倍に達する．グレリンはGH secretagogue受容体(GHSR1a)を介して生理作用を呈するが，n-オクタン酸の修飾が受容体結合に必須である[1]．グレリンの摂食亢進作用は迷走神経節の受容体を介して，延髄孤束核を通じて視床下部へ伝達され，エネルギー代謝調節に機能する[2]．しかしながら，GHSR1aを介さないデスアシル・グレリンによる作用も次々と明らかにされており，新規メカニズム解明の研究が進められている．

サルコペニアの病態

ヒトは30歳を過ぎると10年ごとに約５％前後の割合で筋量が減少し，60歳を超えるとその減少率は加速し，80歳までに通常約40％も筋量が減少する．加齢により上肢より下肢優位に筋肉量が減少し，寝たきりの原因となる下肢筋力の低下が著明となる．下肢筋力低下の判定基準として歩行速度が利用され，欧米では0.8 m/秒以下をサルコペニア診断アルゴリズムに用いている[3]．

筋線維には２種類あり，ミトコンドリアに富み，より酸素を利用して持続収縮可能な遅筋線維(type 1，赤筋)とミトコンドリアは比較的少なく瞬発収縮可能な速筋線維(type 2，白筋)に分けられる．速筋線維の中には，持続収縮に適しているtype 2aと，そうでないtype 2bと細分化される．サルコペニアでは速筋線維優位(特にtype 2b)に萎縮を示すのに対し，廃用性

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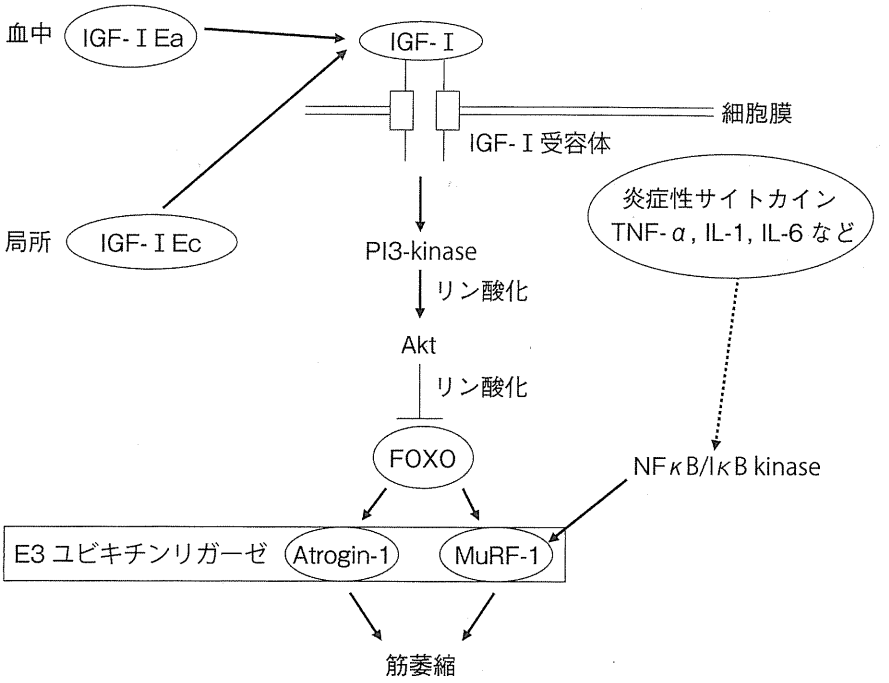

図1

骨格筋の IGF-Ⅰ受容体結合以降のシグナル伝達を示す．IGF-Ⅰが受容体結合以降，Akt リン酸化し，FOXO を核外へ移行する．Atrogin-1，MuRF-1 転写抑制からユビキチン・プロテオソーム抑制し，筋萎縮を回避する．炎症性サイトカインは NF-κB を介し，MuRF-1 を増加させ，筋萎縮に働く．

筋萎縮は遅筋線維優位に萎縮するのが特徴とされる．現在，廃用性筋萎縮をサルコペニアモデル動物として利用されているが，ヒトのサルコペニア病態とは一部に相違がある．

骨格筋は再生能力の高い組織であり，外傷後に損傷した筋線維を補うために，筋形質膜と基底膜の間に存在する筋衛星(サテライト)細胞が主たる筋再生の役割を果たす．老化筋組織において筋サテライト細胞の減少が確認されており，筋再生能力の低下と筋量の減少をもたらす．遺伝子レベルの相違においては，若年者と高齢者の筋芽細胞(myogenin 発現)の遺伝子発現量の違いが検討されている．高齢者において，①抗酸化遺伝子発現が低下しており，酸化ストレスでの変異の蓄積により再生能力が低下している，②筋細胞骨格に関する遺伝子と細胞外マトリックスの分解に関わる遺伝子変化により，分化最終段階での筋線維との融合が損なわれている，③フォークヘッド型転写因子(FOXO)の特異的活性化からユビキチン・プロテオソーム経路の活性化により筋萎縮に向かう．高齢者筋組織では，筋サテライト細胞数の減少に加え，筋芽細胞での遺伝子発現にも変化を来す．

ウイルスや細菌感染で増加する炎症反応のサイトカインの1つであるインターロイキン6(IL-6)血中濃度は，高齢者において血中 IGF-Ⅰ濃度と負の相関を示す．同時に骨格筋においても，炎症性サイトカインは NF-κB を介して，MuRF-1 を増加させ筋萎縮に移行する(後述)．

グレリン投与による GH/IGF-Ⅰを介する骨格筋への作用

骨格筋には GHSR1a が少量発現しているが，グレリンによる骨格筋への直接作用は不明であり，摂食量増加による栄養状態改善による作用と GH/IGF-Ⅰ増加による間接作用が主体となる．ヒトにおいて骨格筋で作用する IGF-Ⅰは，肝臓で産生される IGF-ⅠEa と運動負荷により局所で産生される IGF-ⅠEc である．IGF-Ⅰの受容体結合以降のシグナル伝達を**図1**に示す．PI3/Akt リン酸化による活性化後，FOXO は核外へ移行し，筋関連 F-box 蛋白(Atrogin-1)，筋

特異的フィンガーリング蛋白1(MuRF-1)の転写を抑制するため，内在するE3ユビキチンリガーゼ活性も低下する．最終的にミオシン重鎖やサルコメア構成蛋白の分解抑制から筋萎縮を回避する[4]．IGF-Iは運動ニューロンに対しても，酸化ストレスに対してアポトーシスを回避し，軸索の損傷に対しても修復増進作用がある．当科では，後肢懸垂による廃用性筋萎縮モデルマウスを用いてグレリン投与を試みた．懸垂開始後すぐに骨格筋のリン酸化Akt量とIGF-IのmRNAは減少し，Atrogin-1は増加したが，グレリンの長期投与にて後肢懸垂による筋萎縮を防ぐことが可能であった(投稿準備中)．グレリンは長期臥床による高齢者の廃用性筋萎縮を予防できる可能性がある．

デスアシル・グレリンとグレリンの骨格筋以外への生理作用

グレリンの生理作用は上記GH/IGF-Iを介する作用以外にも多岐にわたる．デスアシル・グレリンは，胎児脊髄神経に対して神経新生を促進し，血管内皮に対してKチャネルを介し血管内皮依存性に血管拡張を来す．骨格筋損傷時に対し，神経筋接合部の再生や局所血流の増加に作用する可能性がある．

血管内皮ではGHSR1aを介して，TNF-αに誘導されるNF-κBの活性を抑制し，抗炎症作用を示す．交感神経節前ニューロンからノルアドレナリンの遊離も抑制することが判明している．骨格筋に対する直接作用は不明だが，グレリンによる抗炎症作用やノルアドレナリン低下による交感神経抑制作用も考えられ，サルコペニアに関わる増悪因子の改善に作用する可能性がある．

グレリン投与による筋萎縮患者への治療効果

60歳以上の正常高齢者に対して，非ペプチド性のGHS受容体アゴニスト(MK-677)を経口投与し，GHとIGF-Iを若年者と同程度まで分泌量を増加させると，歩行速度や筋力増強は認めなかったものの内臓脂肪は減少し，加齢に伴う除脂肪体重の低下予防を示した[5]．しかし高齢者において，若年者と同程度に血中GHとIGF-Iを過剰に上昇させるのは，水分貯留による心負荷や血中IGF-I上昇に伴う潜在癌増大の可能性が残る．

慢性閉塞性肺疾患(COPD)に対して，グレリンを投与すると摂食量が増大し，最大吸気筋力が18%，最大呼気筋力が20%改善し，6分間歩行距離の延長が確認された．同時に血中ノルアドレナリンの低下ならびに喀痰中の好中球数と炎症性サイトカインの減少を認め，グレリンには筋力の増強のみならず，交感神経活性の抑制と抗炎症作用を有する[6]ことが明らかにされている．

サルコペニアは筋肉の蛋白異化が亢進している状態であり，必須アミノ酸を積極的に加えた食事で筋力と筋肉量の増加が望めるが，COPD患者にオクタン酸豊富な食事を摂取させると血中グレリン濃度の上昇を認めた[7]．摂食量が減少したサルコペニア患者には栄養成分も考慮する必要があろう．

結　論

サルコペニア患者に対してのグレリン投与は摂食亢進と筋肉量増加をもたらすだけでなく，抗炎症作用や交感神経抑制作用など多面的作用を併せもつ治療薬となる可能性がある．

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