participation in social activities and leads to increased medical expenses. Therefore, there is a pressing need for effective appetite-stimulating therapies for patients with AN.

Ghrelin is the only orexigenic hormone that can be given intravenously. Intravenous infusion of ghrelin is reported to increase food intake and body weight in healthy subjects as well as in patients with poor nutritional status. Here, we introduce the results of a pilot study that investigated the effects of ghrelin on appetite, energy intake, and nutritional parameters in five patients with restricting-type AN, who are fully motivated to gain body weight but could not increase their food intake because of malnutrition-induced gastrointestinal dysfunction.

1. INTRODUCTION

Since the 1960s, eating disorders, including anorexia nervosa (AN), began to be recognized as an important health problem among adolescent girls and young women in Western societies (Bruch, 1985). Although few Japanese patients with AN were recognized early on, according to the 2010 Survey Committee for Eating Disorders of the Japanese Ministry of Health, Labor and Welfare, the prevalence rate of AN in Japanese high-school girls is 0.25%.

AN is a psychosomatic disorder characterized by obsessive dieting in spite of thinness, fear of weight gain, abnormal eating attitudes, and starvation-induced psychological symptoms. Cultural, social, familial, psychological, and biological factors are involved in the pathogenesis of this disorder. There are two types of dieting in AN: restricting type, in which patients severely restrict food intake and binge eating/purging type, in which patients engage in self-induced vomiting or the misuse of laxatives after eating. Many patients with AN have a history of stressful events or traumatic experiences and develop AN as a way of coping with difficult circumstances, such as focusing on tallying calories or thinking about food, or binge eating and purging that distracts patients from their stress or emotional pain. In addition, patients may develop AN because they can control food and body weight but cannot manage other aspects of their life (Birmingham and Treasure, 2010).

AN is associated with extensive morbidity due to malnutrition as well as significant mortality (Neumarker, 1997). Some of the complications of this disorder remain even after recovery. Thus, nutritional support is of paramount importance to prevent impaired quality of life later on in patients with AN. Some patients with restricting-type AN who are fully motivated to gain body weight cannot increase their food intake because of

malnutrition-induced gastrointestinal dysfunction, which delays recovery. Chronicity of AN prevents patients from participating in social activities and increases medical expenses. It is reported that the cost of long-term disability for patients with AN is up to 30 times the yearly cost for care service and treatment (Su and Birmingham, 2003). Therefore, there is a pressing need for effective appetite-stimulating therapies for patients with AN.

Ghrelin is mainly secreted by the stomach during starvation and exerts a potent stimulatory effect on food intake and growth hormone (GH) secretion (Ariyasu et al., 2001; Kojima et al., 1999). Ghrelin is the only orexigenic hormone that can be given intravenously. Intravenous infusion of ghrelin is reported to increase food intake and body weight in healthy subjects (Wren et al., 2001) and to stimulate appetite and food intake in patients with congestive heart failure (Nagaya et al., 2004), chronic obstructive pulmonary disease (Nagaya et al., 2005), cancer (Neary et al., 2004), and functional dyspepsia (Akamizu et al., 2008).

2. PATHOPHYSIOLOGY OF AN

Patients with AN show diverse symptoms that affect multiple organ systems. Gains in body weight improve most of the medical complications and prevent deterioration of long-term sequelae.

2.1. Medical complications and sequelae due to malnutrition in AN

Routine laboratory examination reveals pancytopenia, decreased serum levels of total protein and albumin or rapid turnover of proteins, liver dysfunction, or serum cholesterol abnormalities. Hypoglycemic coma, dehydration-induced renal failure, rhabdomyolysis, pseudo-Bartter syndrome, and arrhythmia due to hypokalemia are serious complications and can cause death (Neumarker, 1997). Adolescence is a time of accelerated physical growth and maturity, which are affected by the nutritional status. Children with AN often show reduced height, and short stature is a sequelae of this disorder. AN is frequently accompanied by osteoporosis, which involves a reduction of bone formation and an increase in bone resorption (Hotta et al., 1998). We previously reported that duration of body mass index (BMI) < 16 kg/m^2 is a potent risk factor for bone loss because catabolic bone metabolism is improved in patients with BMI greater than 16 kg/m^2 with increased serum levels of insulin-like growth factor-I (IGF-I) as an osteogenic growth factor and estradiol as a strong inhibitor of bone resorption (Hotta et al., 2000). The recovery of spinal bone

mineral density also positively correlates with body weight. We find a variety of endocrinological abnormalities, including euthyroid sick syndrome, increased plasma levels of GH, hypogonadotropic hypogonadism, increased plasma levels of ACTH, and hypercortisolemia with the loss of diurnal rhythm in patients with AN (Hotta et al., 1986). Plasma levels of leptin, which positively correlate with body fat, are suppressed (Grinspoon et al., 1996), while plasma levels of adiponectin increase (Delporte et al., 2003) in patients with AN.

2.2. Gastrointestinal symptoms and complications

Chronic malnutrition induces both functional and organic changes in the gastrointestinal tract (Abell et al., 1987; Heather et al., 2002). Most patients with AN complain of early satiety, postprandial abdominal discomfort and fullness, and constipation, which are usually chronic or recurrent. Decreased and impaired motility of the stomach are common. Laboratory examinations of the stomach reveal atrophy of the mucosa, alteration of peristalsis, and delayed emptying time (Benini et al., 2004; Domstad et al., 1987; McCallum et al., 1985). Because acetaminophen is absorbed in the duodenum, plasma concentrations of acetaminophen can be used to measure gastric excretion (Fig. 24.1). Gastric excretion estimated by plasma acetaminophen concentrations in patients with AN were delayed (Heading et al., 1973), which can result in gastric stasis and early satiety and predispose patients to esophageal reflux. Currently prescribed appetite-stimulating drugs such as metoclopramide, cyproheptadine, and sulpiride are not always effective, and any increase in appetite may be minor. Therefore, there is a pressing need for effective appetite-stimulating therapies for patients with AN. In addition, even after becoming fully motivated to gain body weight, patients with AN may succumb to the fear of gastrointestinal discomfort and often cannot increase their food intake. Emaciation induces a vicious downward spiral of malnutrition and resistance to psychotherapy.

3. PLASMA GHRELIN IN AN

Intact ghrelin, which comprises 28 amino acid residues with an *n*-octanoyl ester at Ser^3, is unstable and rapidly degrades to inactive des-octanoyl form or smaller fragments (degraded ghrelin). Although it has been reported that plasma levels of total ghrelin (intact and degraded ghrelin) increase in patients with AN, we have to pay special attention to which form of ghrelin increases in patients with AN.

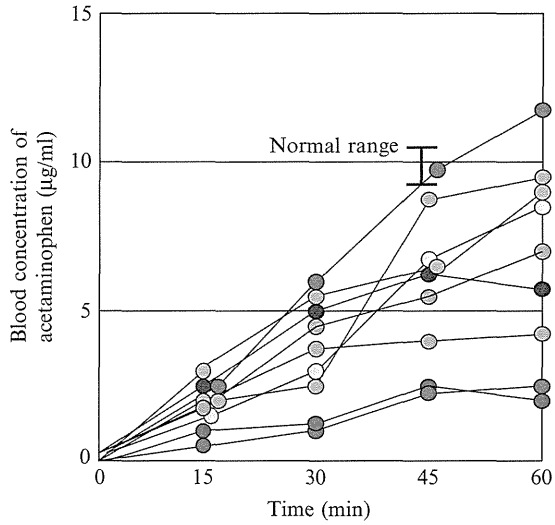

Figure 24.1 Plasma concentrations of acetaminophen in patients with AN. At 08:00 h after overnight fasting for longer than 12 h, blood samples were drawn from female patients with AN (age: 18.2–31.4 year, BMI: 11.48–17.08 kg/m^2) for the determination of plasma acetaminophen concentrations immediately before and every 15 min after the ingestion of 1.5 g acetaminophen and 200 kcal liquid diet for 60 min. The plasma level of acetaminophen in age-matched young women was 9.4 ± 0.5 μg/ml. Gastric excretion was delayed in 9 out of 10 patients with AN.

3.1. Plasma levels of intact and degraded ghrelin in patients with AN

It was previously reported that plasma levels of ghrelin negatively correlate with body fat and are higher in patients with AN than in healthy controls. However, the antibodies used for measuring plasma ghrelin levels in those studies were against C-terminus ghrelin (13–28) (Shiiya et al., 2002), ghrelin (1–11) (Nakai et al., 2003), or full-length ghrelin with or without octanoylation at Ser^3 (Otto et al., 2001; Tolle et al., 2003), all of which might detect intact as well as degraded ghrelin. Concentrations of intact ghrelin actually represent $<10\%$ of total circulating ghrelin levels (Yoshimoto et al., 2002). Because only intact ghrelin, not degraded ghrelin, has an orexigenic effect, plasma levels of intact ghrelin should be measured in patients with AN. Evaluation of plasma ghrelin levels depends on the specificity of the ghrelin antibody.

To determine differences in the profile of plasma levels of intact and degraded ghrelin between patients with AN and healthy women, plasma levels

Table 24.1 Five assays used to determine differences in the profile of plasma levels of intact and degraded ghrelin between female patients with AN and healthy women

Name of assay or kit	Ghrelin and its fragments against which antibodies are raised	
ICT-EIA	Cys^{12} ghrelin (1–11)	Cys^{29}ghrelin (1–28)
Active ghrelin ELISA	Ghrelin (1–10)	Ghrelin (13–28)
Des-acyl ghrelin ELISA	Des-octanoyl ghrelin (1–10)	Ghrelin (13–28)
Ghrelin active RIA	Ghrelin (1–10)	
Ghrelin total RIA		Ghrelin (14–28)

of intact, des-octanoyl-, N-terminus, and C-terminus ghrelin were measured using five assays (Table 24.1) (Hotta et al., 2004). The immunocomplex transfer-enzyme immunoassay (ICT-EIA) is designed to measure intact human ghrelin based on the principle of two-site sandwich enzyme-linked immunosorbent assay (ELISA) using two different polyclonal antibodies and specifically detects intact human ghrelin but does not detect shorter fragments or des-octanoyl ghrelin. The active ghrelin ELISA kit (Mitsubishi Kagaku Iatron, Tokyo, Japan) detects intact human or murine ghrelin specifically (Hosoda et al., 2000). Plasma levels of ghrelin from ICT-EIA were significantly correlated with values from the active ghrelin ELISA kit in healthy women ($r=0.876$, $p=0.0007$) and patients with AN ($r=0.796$, $p<0.0001$) (Hotta et al., 2004). Plasma levels of des-octanoyl ghrelin were measured using the des-acyl ghrelin ELISA kit (Mitsubishi Kagaku Iatron) (Hosoda et al., 2000). Plasma levels of N- and C-terminus ghrelin were measured using the ghrelin active RIA and the ghrelin total RIA kits (Linco Research, St. Charles, MO, USA), respectively. The antibody used in the ghrelin active RIA kit recognizes intact ghrelin and octanoyl ghrelin (1–10), but not des-octanoyl ghrelin, whereas the antibody used in the ghrelin total RIA kit recognizes intact and des-octanoyl ghrelin, and ghrelin (14–28). After an overnight fasting of longer than 12 h, blood was taken from subjects at 08:00 h and transferred into tubes with 1 mg/ml EDTA-2Na and 500 U/ml aprotinin. Blood samples were immediately centrifuged at 4 °C. Plasma samples were then acidified with 1 N HCl and stored at −80 °C until assay.

Mean plasma levels of intact ghrelin in 30 female patients with AN (BMI, 8.81–22.4 kg/m^2) obtained by ICT-EIA or the active ghrelin ELISA kit were lower than or similar to those of 16 age-matched healthy women, whereas levels of degraded forms of ghrelin, such as des-octanoyl ghrelin,

Table 24.2 Plasma levels of ghrelin in controls and patients with anorexia nervosa

Subject	Controls	AN
n	16	30
ICT-EIA (pmol/l)	65.0 ± 4.9	49.2 ± 2.9*
Active ghrelin ELISA (pmol/l)	29.9 ± 3.1	34.7 ± 3.2
Des-acyl ghrelin ELISA (pmol/l)	94.1 ± 7.5	223.5 ± 37.3*
Ratio of des-acyl to active ghrelin ELISA	3.34 ± 0.24	6.14 ± 0.44*
Ghrelin active RIA (pmol/l)	104.1 ± 9.5	136.7 ± 12.9*
Ghrelin total RIA (nmol/l)	1.85 ± 0.13	2.87 ± 0.25*
Ratio of ghrelin total to Active RIA	19.9 ± 2.1	21.9 ± 1.2

Data are expressed as mean ± SEM. *$p < 0.05$ compared to values of controls.

octanoyl N-terminus ghrelin, and C-terminus ghrelin, were significantly elevated in patients with AN compared with normal women (Table 24.2). Results also showed that no correlation existed between BMI and intact ghrelin in patients with AN. In contrast, plasma levels of degraded ghrelin or the ratio of des-octanoyl ghrelin to intact ghrelin correlated with BMI in patients and controls (Fig. 24.2) (Hotta et al., 2004).

Of note is the fact that plasma levels of intact ghrelin in patients with AN were not higher than in controls. Plasma ghrelin levels reportedly increase after cure of *Helicobacter pylori* infection (Nwokolo et al., 2003). In addition, the gastric banding procedure strongly suppresses plasma ghrelin levels despite a massive and permanent reduction in body weight (Leonetti et al., 2003), as gastric banding reduces plasma levels of motilin. These results indicate that injury to the gastric mucosa or impaired gastric peristalsis could decrease ghrelin secretion. Therefore, the reason patients with AN did not show higher plasma levels of intact ghrelin than controls seems likely due to a decrease in ghrelin secretion from gastric mucosa, induced by malnutrition.

Plasma levels of degraded ghrelin were much higher in patients with AN than in controls, which indicates that the profiles of intact and degraded forms of ghrelin in plasma of patients with AN differ from those of healthy women. Plasma levels of total ghrelin, but not intact ghrelin, are significantly correlated with renal function (Akamizu et al., 2004). The kidney represents an important site for the clearance and/or degradation of ghrelin. In patients with end-stage renal disease, plasma levels of C-terminus ghrelin are significantly correlated with serum creatinine levels (Yoshimoto et al., 2002).

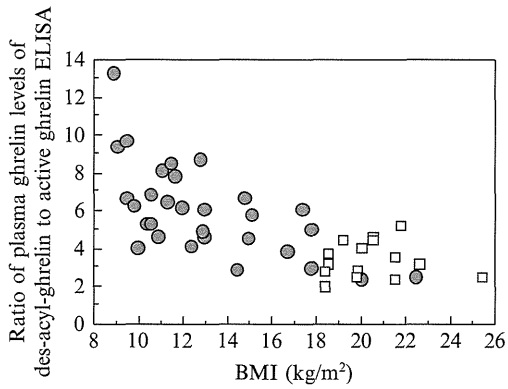

Figure 24.2 Relationship between BMI and the ratio of values from des-acyl ghrelin ELISA to those from Active Ghrelin ELISA. BMI significantly correlated with plasma ghrelin levels from degraded ghrelin and the ratio of values from des-acyl ghrelin ELISA to those from active ghrelin ELISA ($r = -0.737$, $p < 0.0001$). Open squares and closed circles represent healthy women and patients with AN, respectively.

Elevated plasma levels of C-terminus ghrelin have recently been demonstrated in hepatic cachexia (Tacke et al., 2003) with deterioration of the clinical status as determined by signs such as ascites or reduced renal clearance. AN is also usually complicated by dehydration, reduced glomerular filtration rate, and decreased creatinine clearance (Aperia et al., 1978). Elevation of plasma levels of degraded ghrelin in patients with AN may therefore result from decreased renal clearance related to decreased BMI.

3.2. Effects of glucose on plasma levels of intact and degraded ghrelin

Intravenous infusion of 50 g glucose or oral administration of 75 g glucose suppressed the secretion of C-terminus ghrelin in healthy subjects (Nakagawa et al., 2002; Shiiya et al., 2002), whereas meal-induced decrease in plasma ghrelin levels was not found in patients with AN (Nedvídkova et al., 2003). Since gastric excretion time is delayed in these patients, changes in plasma glucose levels and insulin secretion are extremely variable after oral glucose tolerance testing or after eating food in AN (Nozaki et al., 1994). We therefore used the 50-g glucose infusion test to investigate the effects of hyperglycemia on plasma ghrelin levels. When glucose was infused in six female patients with AN and six age-matched healthy women, plasma glucose levels increased significantly (controls: from 92.3 ± 2.3 to 182.0 ± 15.1 mg/dl, AN: from 68.7 ± 6.5 to

227.0 ± 29.7 mg/dl), and plasma levels of intact ghrelin promptly decreased significantly in both groups (controls: 58.8 ± 3.3% vs. AN: 63.2 ± 9.8% of the basal levels, $p = 0.206$). After glucose infusion in controls, plasma levels of degraded ghrelin significantly decreased. Conversely, plasma levels of degraded ghrelin displayed no significant changes after glucose infusion in patients with AN. These results may suggest that acute elevation of plasma glucose inhibits secretion of intact ghrelin from the stomach and that the substantial increase in fragments of degraded ghrelin in plasma would mask the response of degraded ghrelin.

4. CLINICAL APPLICATION OF GHRELIN IN PATIENTS WITH AN

There are two reports about the effects of ghrelin on appetite in patients with AN. In one study, 5 pmol/kg/min ghrelin infusion for 300 min had little effect on appetite in severely emaciated as well as weight-recovered patients with AN (Miljic et al., 2006). Since those patients with AN refused to eat, food intake was not investigated in the study. In another study, 1 μg/kg ghrelin infusion made patients with AN feel hunger sensations, although food intake was not evaluated (Broglio et al., 2004). We therefore believe that studies aiming to investigate ghrelin as an appetite-stimulating therapy should recruit only those patients with AN who are fully motivated by psychoeducational therapy to gain body weight.

4.1. Study design

Five Japanese female patients with restricting-type AN were included in the present study, who met the Diagnostic and Statistical Manual IV criteria for AN, in addition to those of the Survey Committee for Eating Disorders of the Japanese Ministry of Health, Labor and Welfare (Hotta et al., 1986) (Table 24.3). All subjects tested negative for *H. pylori*, and none of the patients had started medication prior to the trial. They had already taken intense counseling and supervision by a dietitian as well as total parenteral nutrition during a previous hospital admission but then had not been able to increase weight or lost weight again. All patients had been motivated to gain weight but could not increase their food intake for several years in four out of five in part because of gastrointestinal discomfort.

For ethical reasons, involving a nontreated group was not possible and a randomized controlled design or blinding methods were not applied to this study. The study protocol was approved by the Institutional Review Board

Table 24.3 Clinical profile of patients with anorexia nervosa in the present study

Case no.	1	2	3	4	5
Age on entry	27	31	25	35	14
Height (cm)	161	157	156.2	154	149.6
Weight before illness (kg) (BMI kg/m^2)	48 (18.5)	48 (19.5)	44.2 (18.1)	50 (21.0)	43 (19.2)
Age of onset (years)	16	24	17	20	13
Duration of illness (years)	12	6	8	15	1.25
The minimal weight (kg) (BMI kg/m^2)	29 (11.2)	30 (12.2)	32 (13.11)	23 (9.70)	27.4 (12.2)
Weight on entry (kg) (BMI kg/m^2)	37.9 (14.6)	32.5 (13.2)	35.0 (14.4)	24.2 (10.2)	28.2 (12.6)
The increment of total calorie (kcal)	12%	36%	16%	33%	14%
Weight at the end of study (kg) (BMI kg/m^2)	36.4 (14.0)	31.5 (12.8)	35.7 (14.6)	26.6 (11.2)	28.4 (12.7)
Weight at 6 months after discharge (kg) (BMI kg/m^2)	43 (16.6)	38.5 (15.6)	38.2 (15.7)	28 8 (11.8)	34.5 (15.4)

of Tokyo Women's Medical University. All patients provided written informed consent to participate in this study.

Patients were hospitalized for 26 days (day −6 to day 20) in Tokyo Women's Medical University Hospital. Food intake and subjective hunger sensation were measured for 24 days (day −5 to day 19). The pretreatment period was defined as the 5 days before ghrelin injection (day −5 to day −1). Patients received an intravenous infusion of ghrelin (3 μg/kg body weight) for 5 min twice a day (before breakfast and dinner) for 14 days (day 1 to day 14). After ghrelin infusion, subjects were monitored for clinical efficacy and safety of ghrelin for 5 days (day 15 to day 19) as the posttreatment period (Fig. 24.3). Since ghrelin at doses of 1 and 5 μg/kg tended to increase appetite dose dependently without severe adverse effects (Akamizu et al., 2004), we employed 3 μg/kg of ghrelin in the present study.

The ghrelin used in the study was an acylated peptide that was dissolved in 3.75% D-mannitol to yield a final concentration of 180 μg/ml, as described previously (Akamizu et al., 2008). The solutions were filtered and stored at −20 °C in sterile vials. Examination by the Japan Food Research

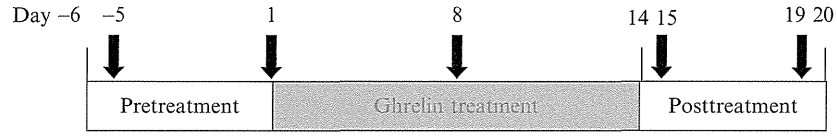

Figure 24.3 Timeline of ghrelin study. Subjects were hospitalized for 26 days (day −6 to day 20). The pretreatment period was defined as the 5 days before ghrelin injection (day −5 to day −1). Subjects received an intravenous infusion of ghrelin (3 μg/kg body weight) for 5 min twice a day (before breakfast and dinner) for 14 days (day 1 to day 14). After ghrelin infusion, subjects were monitored for the clinical efficacy and safety of ghrelin for 5 days (day 15 to day 19) as the posttreatment period.

Laboratories (Tokyo, Japan) did not find any traces of endotoxin in the ghrelin solutions. A pyrogen test based on the Pharmacopeia of Japan was also negative.

The primary end point of this study was energy intake. Since patients with AN lose appetite when too large an amount of food to eat is served, they were initially served an amount of food equivalent to their meals at home before hospitalization plus an additional 200 kcal.

Each dish was weighed before and after eating and was photographed by a digital camera. Energy intake was calculated by dieticians as the total energy, carbohydrate, fat, and protein intakes. When subjects ate all the food served and wanted more, they were allowed to eat self-prepared foods yielding approximately 200 kcal such as fruits or other snacks. Attitudes toward food were evaluated by a questionnaire incorporating visual analogue scales (VAS) rating hunger, satiety, prospective food consumption, fullness, desire for some meat or fish, desire for something salty, desire for something sweet, and desire for something fatty. It had been demonstrated that food intake correlated with perceptions of hunger and fullness as assessed by VAS in healthy volunteers (Parker et al., 2004). During ghrelin treatment, patients with AN answered the VAS questionnaire at 15 min before ghrelin infusion and breakfast or dinner, 15 min after ghrelin infusion before breakfast or dinner, and after those meals. They also answered the questionnaire before and after every meal without ghrelin treatment (Fig. 24.4).

Blood and urine samples for biochemical and endocrinological parameters, including complete blood count (CBC), total protein, albumin, rapid turnover proteins, liver function, lipid profile, immunoreactive insulin, leptin, GH, IGF-I, prolactin, ACTH, active ghrelin, and des-acyl ghrelin were taken in the morning after overnight fasting longer than 10 h on day −5, day 1, day 8, day 15, and day 19.

Psychological states were evaluated using the Japanese versions of the self-rating depression scale (Zung, 1965), state-trait anxiety inventory

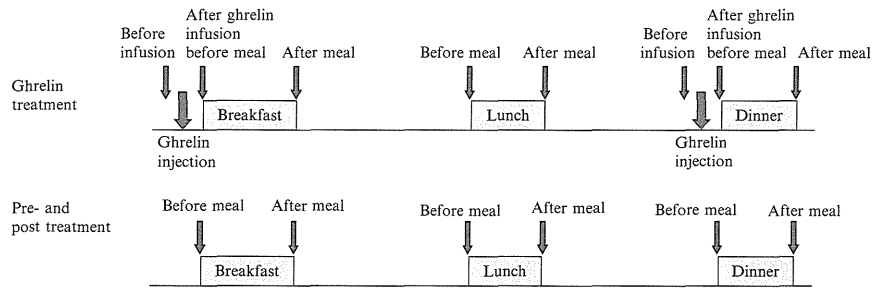

Figure 24.4 Schedule of visual analogue scales. Attitudes toward food were evaluated by a questionnaire incorporating visual analogue scales (VAS). During ghrelin treatment, patients with AN answered the VAS questionnaire at 15 min before ghrelin infusion and breakfast or dinner, 15 min after ghrelin infusion before breakfast or dinner, and after those meals. They answered the questionnaire also before and after every meal without ghrelin treatment.

(Iwata et al., 1998), and eating disorder inventory (Garner and Garfinkel, 1979) on day −5, day 1, day 8, day 15, and day 19.

Data were expressed as mean ± SE. Two-way analysis of variance was used for energy and nutrient intakes and for biochemical and endocrinologic data. Data were examined by Student's two-tailed paired *t*-test when appropriate. Appetite scores were analyzed by a paired *t*-test comparing the changes in VAS. Statistical analyses were performed using the computer statistical package SPSS (version 11.0.1; SPSS Inc., Chicago, IL). Levels of significance were determined at $p < 0.05$.

4.2. Effects of ghrelin infusion on hunger sensation and gastrointestinal symptoms

All patients reported that they had sensations of stomach activity or that their upper abdominal fullness disappeared 5 min after ghrelin injection, which continued for 30–60 min. Borborygmi were also audible within 30 min just after each ghrelin infusion, and no patient reported constipation during ghrelin treatment. Hunger sensation assessed by VAS was higher after ghrelin infusion than before ghrelin infusion in four patients. The stimulatory effects of ghrelin on hunger sensation disappeared after eating and did not last until the next meal.

The sensation of hunger is usually correlated with gastric emptying in humans (Sepple and Read, 1989). Ghrelin plays a role in the regulation of gastrointestinal motility and acid secretion in rats (Edholm et al., 2004; Masuda et al., 2000) and increases the gastric emptying rate in normal-weight

humans (Levin et al., 2006). Because recognition of hunger and satiety in patients with AN is generally impaired, appetite cannot be always analyzed correctly by VAS alone. However, hunger sensation was higher just after ghrelin infusion than before ghrelin infusion in four patients, and ghrelin improved epigastric discomfort in all patients. This was probably mediated through increased gastric peristalsis as shown in other diseases with gastrointestinal dysfunction (Binn et al., 2006; Murray et al., 2005; Strasser et al., 2008).

4.3. Effects of ghrelin infusion on food intake and body weight

The daily energy intake of the five patients during the pretreatment period ranged from 825 to 1426 kcal. During ghrelin infusion, four patients showed a statistically significant increase in daily energy intake (Fig. 24.5). Mean increase in daily energy intake during ghrelin infusion was 20 ± 4% when compared with the pretreatment period. Analysis of nutrients revealed significant increases in daily intakes of carbohydrate in three patients, fat in one

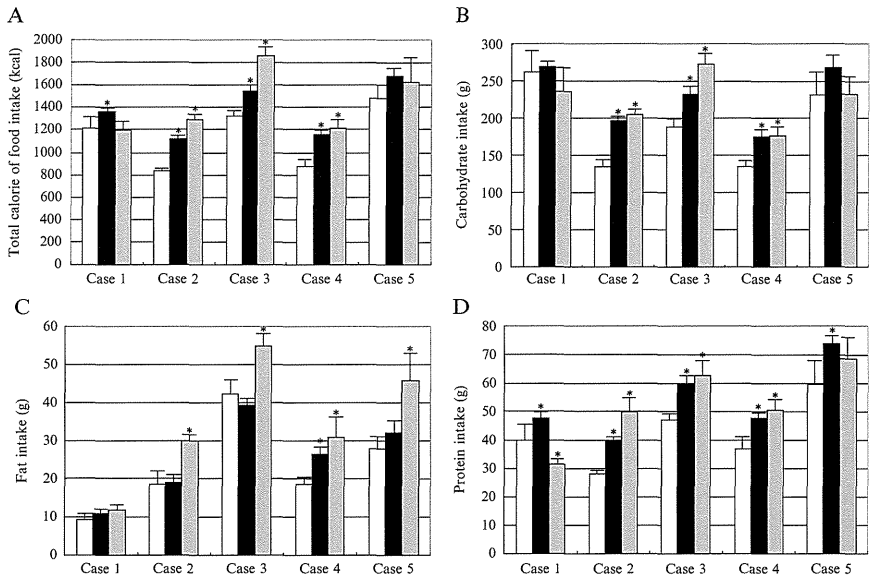

Figure 24.5 Changes in total energy (A), carbohydrate (B), fat (C), and protein (D) intakes of AN patients. During ghrelin infusion, four patients showed a statistically significant increase in daily energy intake. Mean increase in daily energy intake during ghrelin infusion was 20 ± 4% when compared with the pretreatment period. Open, closed, and gray bars represent intake during pretreatment, ghrelin treatment, and posttreatment periods, respectively. Data are expressed as mean ± SE. *$p < 0.05$ versus prescreening period.

patient, and protein in all patients (Hotta et al., 2009). Interestingly, daily energy intake during postscreening remained higher than in the prescreening period in three patients. Those residual effects continued for several days. The increments of body weight in five patients ranged from −1.5 to 2.4 kg during the study. Because a 1-kg weight gain requires 7000–8000 kcal, the increase in energy intake achieved for 14 days in this study was not enough to lead to any considerable weight gain. Although a patient was able to gain 2.4 kg and showed remarkable improvement in nutritional parameters and malnutrition-related liver dysfunction, we believe that water retention during the refeeding period contributed to this weight gain (Yucel et al., 2005). Although two patients lost body weight during the study, this effect was thought to be due to a decrease in malnutrition-induced fluid retention or improvement in bowel movements. The improvement effects of ghrelin on gastrointestinal symptom disappeared after the study ended. However, all patients gained weight after discharge and one resumed menstruation 6 months after discharge. As the patients told us that they were happy to eat free from uncomfortable gastrointestinal symptoms after ghrelin treatment, it is speculated that ghrelin triggered an improvement in gastrointestinal function, which ameliorated the fear of gastrointestinal discomfort after eating.

4.4. Effects of ghrelin infusion on biochemically nutritional markers

Serum total protein and triglyceride levels increased significantly between before and after ghrelin treatment. Other nutritional markers including serum levels of transferrin and glucose showed a tendency to increase after ghrelin infusion but did not reach statistical significance. Mean plasma levels of insulin and leptin did not increase significantly during ghrelin treatment. The mean level of serum IGF-I during ghrelin treatment did not significantly change. Mean plasma levels of prolactin, ACTH, and cortisol, which were measured early in the morning, before ghrelin injection, did not change significantly during ghrelin treatment.

4.5. Adverse effects of ghrelin infusion

No serious adverse events occurred during ghrelin treatment. We did not detect any changes in vital signs or biochemical and endocrinologic data after ghrelin treatment. Adverse effects such as abdominal discomfort, diarrhea, transient flushing, truncal perspiration (Akamizu et al., 2004), and somnolence have been reported after ghrelin injection (Miljic et al., 2006). The only noted

event was loose stools on day 6 in case 5, whose dose of ghrelin was reduced to 1.5 μg/body weight from day 7 to day 14, resulting in an improvement of symptoms. An occasionally warm sensation in the trunk or mild sweating was noted in two subjects. No patient developed somnolence during ghrelin treatment. Although we were concerned that the increase in appetite induced by ghrelin might aggravate mental status in patients with AN, we did not observe increased fear of weight gain, abnormal behavior, anxiety, or depression due to an increase in appetite during ghrelin treatment, and psychological tests did not demonstrate any significant changes.

5. CONCLUSIONS

We performed a pilot study of patients with restricting-type AN to investigate the effects of ghrelin on appetite, caloric intake, and nutritional parameters. Results indicated that ghrelin may have therapeutic potential in restricting-type AN patients who cannot gain weight because of gastrointestinal dysfunction. However, a major limitation of the present study relates to the lack of a randomized, placebo-controlled group and the small number of patients recruited.

Clinicians need to carefully consider whether patients may benefit from ghrelin therapy. Based on this study, appropriate patients for ghrelin therapy may include those with restricting-type AN who are fully motivated to gain weight through intense psychotherapy, but who cannot increase food intake because of persistent gastrointestinal discomfort. Clinicians also need to remember than even patients with AN who are motivated to gain weight may get scared when they feel hunger sensations after ghrelin therapy and may still refrain from eating even though they show an increase in borborygmi after each ghrelin infusion and experience increased hunger.

ACKNOWLEDGMENTS

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第6章

内科医の立場から

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はじめに：摂食障害(ED)の問題の本質をどのように考えるか

拒食や過食はボディランゲージ

摂食障害（eating disorder；ED）は，ストレスによって摂食中枢の障害をきたしやすい生物学的要因と，物事の完璧を期するあまり不安や恐怖を持ちやすい性格傾向を背景に，本人のコーピングスキルで対処できない問題に直面したときに発症する心身症である。青年期の心理的課題（人間関係や進路）や家庭・社会環境は発症と回復に影響する。拒食や過食は回避という誤ったストレス対処反応で，かつ，ボディランゲージである。

飢餓という生理的因子や精神科的併存症による修飾

神経性食欲不振症（anorexia nervosa；AN）では，食事制限や運動に没頭することで，達成感，優越感，周囲の関心，擬似安心感などの誤った代償を得て，かつ，現実逃避できるような心理になる。体重を増加させることは対処困難な問題に対峙させられる恐怖を感じるので，低体重を維持しようとする。単にやせて綺麗になる目的のダイエットが原因ではない。ところが，飢餓による心理・行動異常がANを複雑にしている。飢餓が重大な心理的な変化をもたらすことは意外にも周知されていない。健康人に行ったカロリー制限試験［Garner，1985］では深刻な精神的合併症が明らかになっている（図1）。対応は，叱責や説得による問題行動の矯正や閉鎖病棟への収容ではなく栄養療法である。体重と月経さえ回復すればANは治癒すると誤って理解されやすいが，本人のコーピングスキルが向上せずに体重だけの回復ほど恐怖心を持つことはないので，嘔吐や下剤の乱用，再発，引きこもり，自傷行為などが起こりうる。

神経性大食症（bulimia nervosa；BN）は，大食中は現実逃避できる気分になり，甘いものや油っこい食品が快感をもたらすという神経内分泌的エビデンスもある［Bello・Patinkin・Moran，2011］。一方で，体型や体重に病的なこだわりがあり，排出行為による飢餓や心理的ストレスが習慣化の要因である（図2）。

EDは広いスペクトラムの病態と重症度を有する。内科的治療を行う上で困難を感じるのは，気分障害，不安障害，パーソナリティ障害，その後，明らかになる統合失調症など精神科的併存症［鈴木，2012］や発達障害を合併している場合である。

心身とも健康な男性（兵隊）
24週間　　半飢餓食

25%の体重減少

食べ物への執着

レシピ，料理雑誌の収集
調理器具や食器の収集
コーヒー，スパイス，
チューインガム過剰使用
除隊後は料理人を志望

気分の不安定
抑うつ，不安，過敏性，怒り
不眠
強迫性
精神病的症状
人格の変化
自己評価の低下
認知の変化
集中力，判断力の低下，無気力

抑えられない過食　精神疾患の発病

図1：ヒトの半飢餓臨床試験　Minnesota study (Keys A et al. 1950)

飢餓が重大な心理的な変化をもたらすことは意外にも周知されていない。1940年代にKeysらが心身ともに強健な男性に徴兵免除の代わりに，約50%のカロリー制限食を6カ月摂取させる臨床試験（ミネソタ・スタディ）を行った。25%の体重減少が見られ，神経性食欲不振症に似て，食べ物に執着した言動が多くなり，レシピ，料理雑誌，調理器具食器の収集をし，調理人になりたいと言い出した。試験終了後は抑えられない過食が出現した。さらに，集中力や判断力など脳機能が低下し，抑うつ，不安，強迫性の増強，過敏性，怒り，気分不安定，不眠，自己評価の低下など深刻な精神的合併症を起こすことが明らかになった。治療者や家族が困惑するＡＮの心理・行動異常は飢餓によるもので，栄養状態を改善しない限り続く。対応は叱責や説得，閉鎖病棟への収容ではなく，適切な栄養療法である。飢餓症候群と格闘してエネルギーを浪費する医療者や家族が多いのは残念である。

他人の評価に過敏
八方美人
自信のなさ・自己否定

ストレス
不安
孤独
抑うつ
退屈

過食
甘い・脂肪

逃避，回避，快感

偏った認知
やせだけが
自分の価値

悪循環
習慣化・過激化

ダイエット
嘔吐・下剤
過剰な運動

浄化・爽快感

飢餓

図2：神経性大食症の過食と排出行為の悪循環