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NOTE

Ghrelin Increases Hunger and Food Intake in Patients with Restricting-type Anorexia Nervosa: A Pilot Study

MARI HOTTA*, **, RINA OHWADA**, TAKASHI AKAMIZU***, TAMOTSU SHIBASAKI#, KAZUE TAKANO** AND KENJI KANGAWA##

*Health Services Center, National Graduate Institute For Policy Studies, 106-8677 Tokyo, Japan
** Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical University, School of Medicine, 162-8666 Tokyo, Japan
***Ghrelin Research Project, Kyoto University School of Medicine, 606-8507 Kyoto, Japan
#Department of Physiology, Nippon Medical School, 113-8602 Tokyo, Japan
National Cardiovascular Center Research Institute, 565-8565 Osaka, Japan

Abstract. Ghrelin increases hunger sensation and food intake in various patients with appetite loss. Anorexia nervosa (AN) begins with psychological stress-induced anorexia and some patients cannot increase their food intake partly because of malnutrition-induced gastrointestinal dysfunction. The effects of ghrelin on appetite, food intake and nutritional parameters in anorexia nervosa (AN) patients were examined. Five female restricting-type AN patients (age: 14-35 y; body mass index: 10.2-14.6 kg/m^2) had persistently complained of gastrointestinal symptoms and failed to increase body weight. They were hospitalized for 26 days (6 days' pre-treatment, 14 days' ghrelin-treatment, and 6 days' post-treatment) and received an intravenous infusion of 3 μg/kg ghrelin twice a day. Ghrelin infusion improved epigastric discomfort or constipation in 4 patients, whose hunger scores evaluated by visual analogue scale questionnaires also increased significantly after ghrelin infusion. Daily energy intake during ghrelin infusion increased by 12-36 % compared with the pre-treatment period. Serum levels of total protein and triglyceride as nutritional parameters significantly increased after ghrelin treatment. There were no serious adverse effects including psychological symptoms. We found that ghrelin decreases gastrointestinal symptoms and increases hunger sensation and daily energy intake without serious adverse events in AN patients. Although the present study had major limitations of the lack of a randomized, placebo-controlled group, non-blindness of the investigators and the small number of patients recruited, it would contribute to further investigations for therapeutic potential of ghrelin in AN patients.

Key words: Ghrelin, Anorexia nervosa, Hunger, Food intake

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GHRELIN is mainly secreted by the stomach during starvation and it exerts a potent stimulatory effect on food intake and growth hormone (GH) secretion [1-3]. Endogenous ghrelin and its receptors are involved in the regulation of food intake, adiposity, and GH secretion [4]. Intravenous infusion of ghrelin is reported to increase food intake and body weight in healthy subjects [5-7] and to stimulate appetite and food intake in patients with congestive heart failure [8], chronic obstructive pulmonary disease [9], cancer [10], and functional dyspepsia [11].

Anorexia nervosa (AN) usually begins with psychological stress-induced anorexia and is characterized by fear of weight gain, starvation-induced abnormal behaviors, and a variety of biochemical and endocrinological abnormalities due to malnutrition. Chronic malnutrition induces both functional and organic changes in the gastrointestinal tract [12-14]. Most AN patients complain of chronic or recurrent upper abdominal discomfort and fullness, and chronic constipation. Laboratory examinations of the stomach reveal atrophy of the mucosa, alteration of peristalsis, and de-

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Correspondence to: Mari HOTTA, M.D., Ph.D., Health Services Center, National Graduate Institute For Policy Studies, 7-22-1 Roppongi, Minato-ku, Tokyo 106-8677 Japan.
E-mail: marihs@grips.ac.jp

Table 1. Clinical profile of AN patients in the present study

Case No	1	2	3	4	5
Age on entry (yrs)	27	31	25	35	14
Height (cm)	161	157	156	154	150
Weight before illness (kg) (BMI kg/m^2)	48 (18.5)	48 (19.5)	44.2 (18.2)	50 (21.1)	43 (19.1)
Age of onset (yrs)	16	24	17	20	13
Duration of illness (yrs)	12	6	8	15	1
The minimal weight (kg) (BMI kg/m^2)	29 (11.2)	30 (12.2)	32 (13.1)	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 (12.5)
The increment of daily energy intake (%)	12	36	16	33	14
Weight on the end of study (kg) (BMI kg/m^2)	36.4 (14.0)	31.5 (12.8)	35.7 (14.7)	26.6 (11.2)	28.4 (12.6)
Weight on 6 months after discharge (kg) (BMI kg/m^2)	43 (16.6)	38.5 (15.6)	38.2 (15.7)	28 8 (12.1)	34.5 (15.3)

layed emptying time [15]. Even after becoming fully motivated to gain body weight, AN patients often cannot increase their food intake because of malnutrition-induced gastrointestinal dysfunction, and this delays recovery. 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 AN patients.

To develop a possibly new medical treatment for AN, we investigated the effects of ghrelin on appetite, energy intake, and nutritional parameters in restricting-type AN patients without binge eating/purging as a pilot study.

Subjects and Methods

Subjects

Subjects in the present study comprised 5 Japanese female amenorrheic AN patients aged 26 ± 8 yr (mean ±SD) (range, 14-35 yr) and mean body mass index (BMI) of 13.0 ±1.8 kg/m^2 (range, 10.2-14.6 kg/m^2) (Table 1). Patients met the Diagnostic and Statistical Manual IV (DSM IV) criteria for AN [16], in addition to those of the Survey Committee for Eating Disorders of the Japanese Ministry of Health, Labor and Welfare [17]. All patients had restricting AN, and had never reported binge eating, vomiting or laxative/diuretic abuse. All subjects were tested to be negative for *Helicobacter (H) pylori*. None of the patients had started medication prior to the trial. Four patients except for case 5 had complained of such as epigastric discomfort, abdominal fullness or pain after eating and constipation for several years and had been treated with intensive pshychotherapy as well as supervision of dieticians. All patients had been admitted to undertake hyperalimentation therapy but then lost weight again. They had been motivated to gain weight, but could not increase their food intake, in part because of gastrointestinal discomfort. The study protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients provided written informed consent to participate in this study.

Methods

Study design

Due to ethical reasons, randomized controlled or blind methods were not applied for the present study. Subjects were hospitalized for 26 days (day -6 to day 20) in Tokyo Women's Medical University Hospital (Figure 1). Food intake and subjective hunger sensation were measured for 24 days (day -5 to day 19). The pre-treatment 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) [11]. After ghrelin infusion, subjects were monitored for the clinical efficacy and safety of ghrelin for 5 days (day 15 to day 19) as a post-treatment period. Since ghrelin at doses of 1 and 5 μg/kg tended to increase appetite dose-dependently and repeated administration of ghrelin at a dose of 3μg/kg increase food intake without severe adverse effects [6, 11], we chose 3μg/kg of ghrelin in the present study.

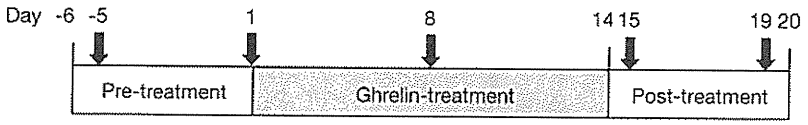

Fig. 1. The timeline of the present study
Subjects were hospitalized for 26 days (day −6 to day 20) and subjective hunger sensation was measured for 24 days (day −5 to day 19). The pre-treatment period was defined as the 5 days before ghrelin injection (day −5 to day −1). Subjects received an intravenous infusion of ghrelin 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 a post-treatment period. Blood and urine samples for biochemical and endocrinological parameters were taken in the morning after overnight fasting and psychological assessment was done on day −5, day 1, day 8, day 15, and day 19, respectively.

Ghrelin used in the present study

Human ghrelin was prepared as previously described [11]. Acylated peptide was dissolved in 3.75 % D-mannitol to yield a final concentration of 180 μg/mL. The solutions were filtered and stored at -20°C in sterile vials. Examination by the Japan Food Research Laboratories (Tokyo, Japan) did not find any traces of endotoxin in the ghrelin solutions. A pyrogen test based on the Pharmacopoeia of Japan was also negative.

Assessment of food intake and attitudes toward food

The primary endpoint of this study was energy intake. Patients were initially served with 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. Energy intake was calculated by dieticians as total energy, carbohydrate, fat, and protein intakes. When subjects ate all of the food served and wanted more, they were allowed to eat self-prepared foods yielding approximately 200 Kcal such as fruit or other snacks. Their attitudes toward food were evaluated by a questionnaire incorporating visual analogue scales (VAS) rating hunger, satiety, prospective consumption, fullness, desire for some meat or fish, desire of something salty, desire of something sweet and desire of something fatty. During pre- and post-treatment, AN patients answered VAS questionnaire at before and after every meal. During ghrelin treatment, they did at 15 min before ghrelin infusion and breakfast or dinner, 15 min after ghrelin infusion before breakfast or dinner, and after those meals. It is demonstrated that food intake correlates with perceptions of hunger and fullness as assessed by VAS in healthy volunteers [18].

Measurement of biochemical and endocrinological parameters

Blood and urine samples for biochemical and endocrinological parameters were taken in the morning after overnight fasting longer than 10 h on day -5, day 1, day 8, day 15, and day 19. Blood samples for ghrelin assay were collected in tubes with 1 mg/mL EDTA-2Na and 500 U/mL aprotinin. They were immediately centrifuged at 4°C, and plasma samples were then acidified with 1 normal HCl and stored at -80°C until assay.

Immunoradiometric assays were utilized to measure levels of plasma GH (Eiken Chemical Co. , Tokyo, Japan) and serum IGF-I (Daiichi Pharmaceutical Co., Tokyo, Japan). Plasma insulin measurements were performed using an ELISA kit (Eiken Chemical Co., Tokyo, Japan). Plasma levels of intact and desoctanoyl ghrelin were measured using Active Ghrelin and Desacyl-Ghrelin ELISA kits (Mitsubishi Kagaku Iatron, Tokyo, Japan), respectively.

Psychological assessment

Depression and anxiety levels were evaluated using the Japanese versions of the self-rating depression scale (SDS) [19] and state-trait anxiety inventory (STAI) [20] on day -5, day 1, day 8, day 15 and day 19, respectively. Eating behaviors, weight, and body image concerns were also assessed by eating disorder inventory (EDI) [21] on the same time as described.

Statistics

Data are expressed as mean ± SE. Two-way analysis of variance (ANOVA) was used for energy and nutrient intakes and for biochemical and endocrinologic data. Appetite scores were analyzed by a Wilcoxon

signed rank test comparing the changes in VAS. Statistical analyses were performed using the computer statistical package SPSS (version 13.0.; SPSS Inc., Chicago, IL). Levels of significance were determined at $p<0.05$.

Results

Gastrointestinal symptoms and hunger sensation

After ghrelin injection, all patients except for case 2 reported that they had sensations of stomach activity or that their upper abdominal fullness disappeared. Borborygmi were frequently audible just after each ghrelin infusion in all patients. During ghrelin treatment, no patients reported constipation. As case 5 complained of loose stools, the dose of ghrelin was reduced to 1.5 μg/body weight from day 7 to day 14 and this improved her symptoms.

Hunger sensation evaluated by VAS was higher just after ghrelin infusion than that before ghrelin infusion in all patients except for case 2 (Figure 2). The stimulatory effects of ghrelin on hunger sensation disappeared after eating and did not last until next meal. Only in case 1, hunger scores before breakfast or dinner during ghrelin treatment were lower than those during both the pre- and post-treatment periods.

Food intake and body weight

The mean daily intakes of energy, carbohydrate, fat and protein are presented in Figure 3. The daily energy intake of the 5 patients during the pre-treatment period ranged from 825 to 1426 Kcal. During ghrelin infusion, all patients except for case 5 showed a statistically significant increase in daily energy intake. The mean increase in daily energy intake during ghrelin infusion was 20 ± 4 % when compared with the pre-treatment period. The mean food intake during ghrelin treatment in case 2, who did not report an increase in hunger sensation after ghrelin injection, significantly increased compared to that of pre-treatment. Analysis of nutrients revealed significant increases in daily intakes of carbohydrate (in 3 patients; cases 2, 3, and 4), fat (in 1 patient; case 4) and protein (in all patients). During the post-treatment period, daily energy, carbohydrate and protein intakes remained higher than those in the pre-treatment period in 3 patients (cases 2, 3, and 4). The daily fat intake during post-treatment period also remained higher than that in the pre-treatment period in 4 patients (cases 2, 3, 4, and 5). The increments of body weight in 5 patients were ranged from -1.5 to 2.4 kg during the ghrelin study (Table 1). Case 4 increased water and fat components evaluated by dual X-ray absorptiometry (data not shown).

Biochemical and endocrinological changes

Complete blood count did not change significantly during this study. Serum total protein and triglyceride levels significantly increased after ghrelin treatment (Table 2). Other nutritional markers including serum levels of transferrin and glucose showed a tendency to increase during and after ghrelin treatment, but this did not reach statistical significance. With the exception of case 4, in whom elevated transaminase levels due to malnutrition were improved by ghrelin treatment, liver function was stable over the study period.

Mean plasma levels of insulin and leptin did not increase significantly during ghrelin treatment. Although the elevated plasma level of GH decreased and the suppressed serum level of IGF-I improved during the study in case 4, other patients did not show a significant change in those parameters. Mean plasma levels of PRL and ACTH measured in the morning before ghrelin injection did not change significantly during ghrelin treatment.

We previously reported mean levels of plasma active and desacyl ghrelin in healthy young women as 29.9 ± 3.1 and 94.1 ± 7.5 pmol/L, respectively [22]. In the present study, the plasma levels of active ghrelin in AN patients ranged from 13 to 73 pmol/L (mean, 42) before ghrelin treatment and then did not show a significant change. Plasma levels of desacyl ghrelin in AN patients ranged from 80 to 731 pmol/L (mean, 280) before treatment, and then showed a tendency to decrease during ghrelin treatment.

Adverse effects

No serious adverse events occurred in all cases during ghrelin treatment. We did not detect any changes in vital signs or biochemical and endocrinologic data after ghrelin treatment. The only exceptions were loose stools in case 5 and an occasional warm sensation in the trunk or mild sweating in 2 subjects. No patients developed somnolence during ghrelin treat-

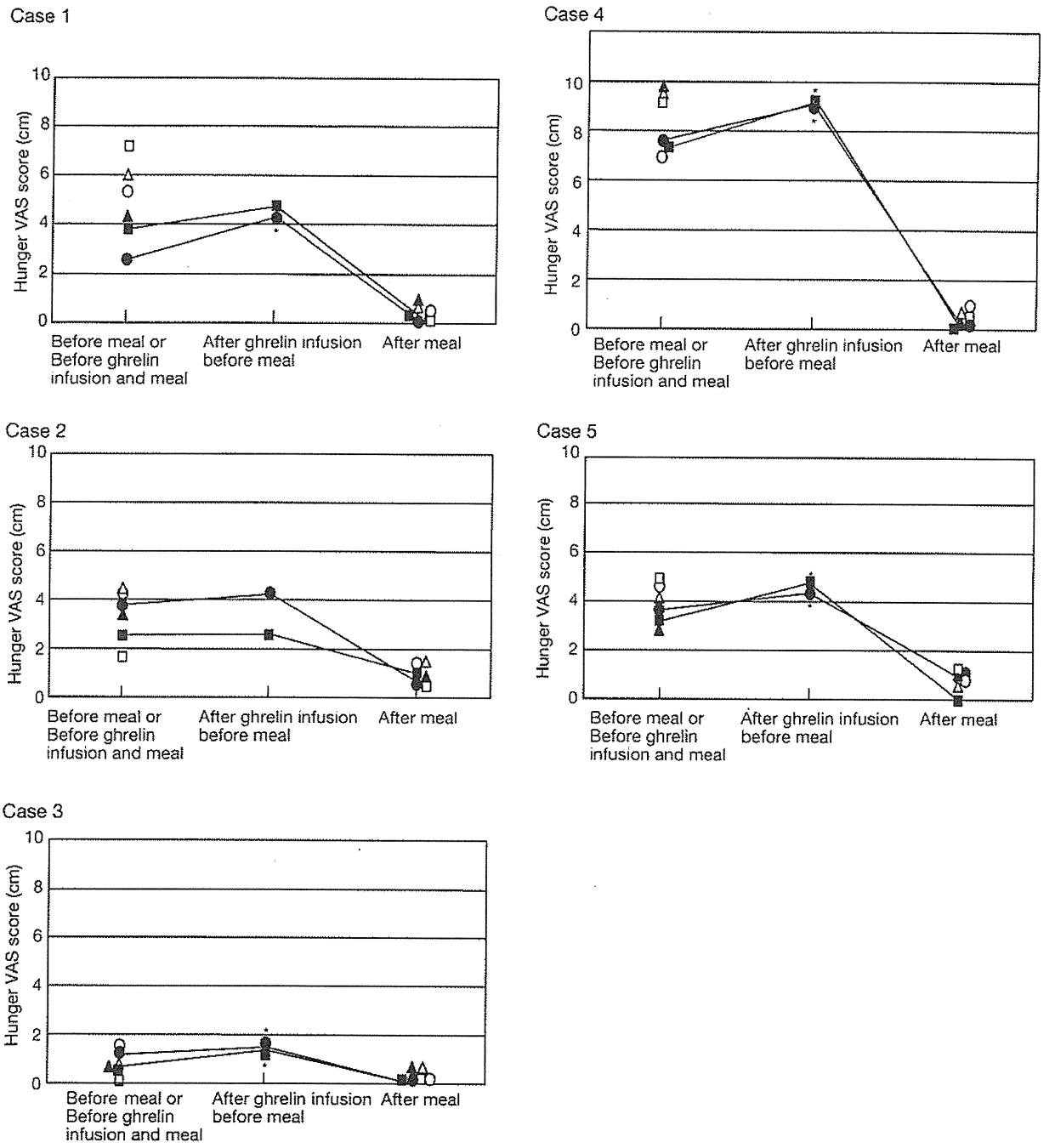

Fig. 2. Changes in hunger evaluated by VAS in AN patients

During pre- and post-treatment, AN patients answered VAS questionnaire at before and after every meal. During ghrelin treatment, they did at 15 min before ghrelin infusion, 15 min after ghrelin infusion before breakfast or dinner, and after those meals. Open circles (○), triangles (△) and squares (□) represent the mean of VAS hunger scores for breakfast, lunch, and dinner during pre and post-treatment periods, respectively. Closed circles (●), triangles (▲) and squares (■) represent the mean of VAS hunger scores for breakfast, lunch, and dinner during ghrelin treatment, respectively.

Data are expressed as mean. * $p<0.05$ *vs.* before ghrelin infusion

The mean of hunger scores before breakfast or dinner evaluated by VAS significantly increased after ghrelin infusion in all cases except for case 2.

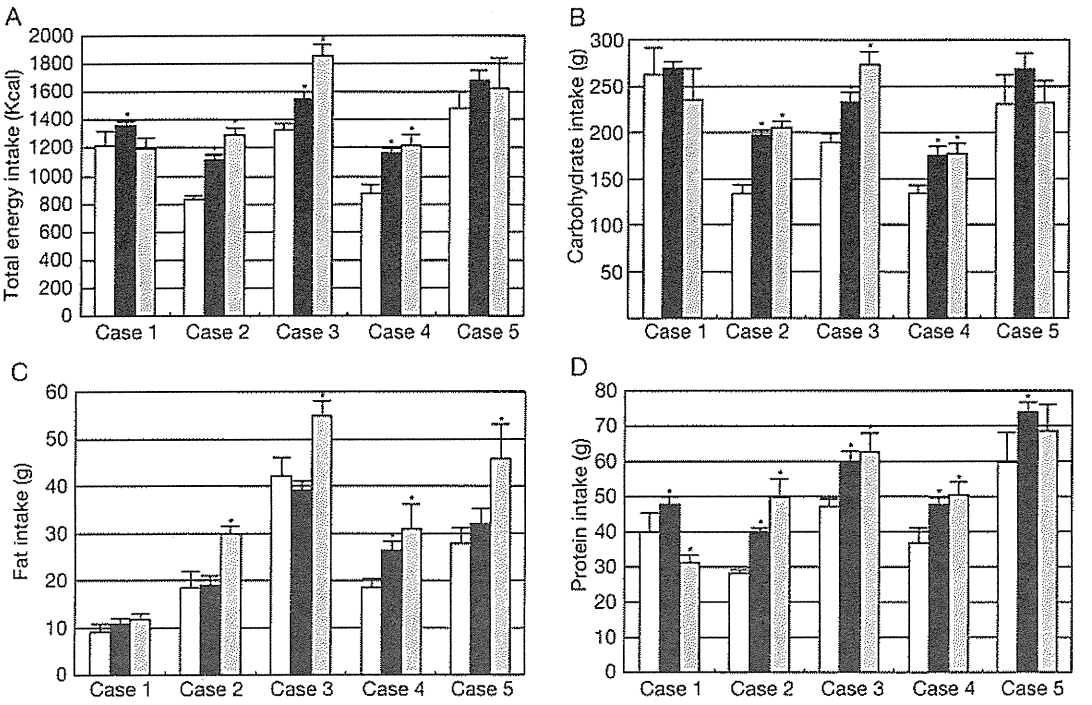

Fig. 3 Changes in the mean of total energy (panel A), carbohydrate (panel B), fat (panel C), and protein (panel D) intakes of AN patients.

Open (□), closed (■) and grey (▩) bars represent the mean of intake during pre-treatment, ghrelin treatment, and post-treatment periods, respectively. Data are expressed as mean ± SE. * $p<0.05$ *vs.* pre-treatment period.

Across the 5 patients, mean increase in daily energy intake during ghrelin infusion was 12-36%. Energy intake in the post-treatment period remained higher than that in the pre-treatment period in 3 patients.

Table 2. Changes in biochemical and endocrinological data in AN patients during the present study

	Day 1	Day 8	Day 15	Day 19
White blood cell (/μL)	3200±230	2820±331	2660±388	3240±614
Hemoglobin (g/dL)	12.7±0.8	13.0±1.2	12.7±1.1	13.0±0.9
Platelet (x10^4/μL)	15.8±2.4	16.0±2.4	15.6±1.9	16.4±1.8
Total protein (g/dL)	6.5±0.4	6.9±0.1	6.8±0.4	7.1±0.3*
Transferrin (mg/dL)	179±22	195±21	196±15	208±10
Retinol binding protein (mg/dL)	3.0±0.3	3.0±0.4	3.1±0.3	3.1±0.2
Blood sugar (mg/dL)	75±5	79±2	81±2	81±2
AST(U/L)	86±58	32±7	27±2	31±3
ALT(U/L)	164±139	60±35	37±11	38±10
Cholinesterase (U/L)	220±29	220±30	214±28	216±25
Triglyceride (mg/dL)	47±10	80±15*	72±9*	83±10*
Total cholesterol (mg/dL)	179±23	187±23	170±24	182±18
Immunoreactive insulin (U/mL)	2.00±0.29	1.57±0.46	2.21±0.46	2.39±0.27
Leptin (ng/mL)	1.4±0.3	1.2±0.2	1.3±0.1	1.3±0.1
GH (ng/mL)	16.6±14.6	11.2±10.3	8.7±7.0	3.6±1.9
IGF-I (ng/mL)	115±37	116±28	128±32	123±35
PRL (ng/mL)	10.8±2.0	8.2±1.3	9.9±1.5	9.3±1.5
ACTH (pg/mL)	28.3±7.4	19.1±4.3	22.9±2.6	25.1±3.5
Active ghrelin (pmol/L)	42±19	45±12	54±15	46±9
Desacyl ghrelin (pmol/L)	280±115	198±26	206±37	198±37

Data are expressed as mean ± SE. *$p<0.05$ compared to day 1.

ment. In terms of psychological tests, SDS and STAI showed no significant change during the study, and EDI did not show any increased fear of weight gain in these patients (data not shown).

Clinical course after discharge

All patients gained weight after discharge, as shown in Table 1. In case 3, menstruation resumed 6 months after discharge.

Discussion

The present study showed that ghrelin infusion (3 μg/kg twice a day) can decrease gastrointestinal symptoms and enhance hunger sensation and daily energy intake without serious adverse events in restricting-type AN patients. The major limitations of the present study relate to the lack of a randomized, placebo-controlled group and non-blindness of the investigators and the small number of patients recruited. A non-treated group is not possible due to ethical reasons. Although non-ghrelin infused subjects who receive intense counseling and supervision of dietitian might be considered as a control group, all subjects in the present study had already received those treatments as well as total parenteral nutrition during the previous admission but failed to increase body weight due to gastrointestinal symptoms. Since the daily energy intake of post-treatment period was still higher than that of pre-treatment period, we could not exclude a placebo effect of ghrelin. However, we insist that 4 patients who failed in gaining body weight for long periods but they could increase their food intake during and after ghrelin infusion. It is speculated as the patients told us that ghrelin triggered an improvement in gastrointestinal function, which ameliorated the fear of gastrointestinal discomfort after eating in these patients.

Ghrelin seems to improve gastrointestinal motility in AN patients in the present study. It is notable that borborygmi occurred immediately after ghrelin infusion and that abdominal fullness or constipation disappeared in all patients. Ghrelin plays a role in the regulation of gastrointestinal motility and acid secretion in rats [23-25] and increases the gastric emptying rate in normal-weight humans [26]. Although we did not investigate gastric emptying rate in AN patients after ghrelin injection, ghrelin improved epigastric discomfort. This was probably mediated partly through increased gastric peristalsis as shown in other diseases with gastrointestinal dysfunction [27-30].

Ghrelin infusion increased hunger scores evaluated by VAS questionnaires of AN patients in the present study. Although AN patients often report not to feel hunger or satiety sensation, hunger scores was higher just after ghrelin infusion than that before ghrelin infusion in 4 patients. Since the sensation of hunger is usually correlated with gastric emptying in humans [31], enhanced hunger sensation in AN patients may be caused in part by ghrelin-induced gastric motility. However, the stimulatory effects of ghrelin on hunger score did not last until the next meal. We considered that the short-term effect of ghrelin on hunger sensation is related to its rapid degradation. The plasma concentration of ghrelin reaches the peak at 15 min after injection and rapidly decreases [6]. Hunger scores before breakfast or dinner during ghrelin treatment were lower than those during both the pre- and post-treatment periods in case 1. It is likely that abdominal fullness induced by the increased amount of food eaten in the foregoing meal during ghrelin treatment probably disturbed the hunger sensation on the next meal.

In previous reports, continuous or repeated ghrelin infusion increased hunger sensation and food intake in healthy volunteers and various patients with appetite loss. Ghrelin infusion at a dose of 5 pmol/kg/min for 270 min increased food intake by 28 % in healthy young Caucasian volunteers [5] and by 31 % in middle-aged and elderly cancer patients [10]. Ghrelin infusion (2 μg/kg twice a day) for 3 weeks increased food intake and body weight by 0.8 kg in elderly patients with congestive heart failure [9], and by 1 kg in elderly patients with chronic obstructive pulmonary disease [8]. Moreover, in patients with functional dyspepsia, ghrelin infusion (3 μg/kg twice a day) for 2 weeks increased hunger sensation and food intake by 29 % without significant weight gain [11]. Since 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 case 4 gained 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 [32]. A decrease in body weight of 2 patients (cases 1 and 2) during ghrelin study might be attributable to a decrease in malnutrition-induced fluid

retention or improvement in bowel movements.

There were two reports about the effects of ghrelin on appetite in AN patients. 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 AN patients [33]. However, appetite was evaluated by VAS alone because the severely emaciated AN patients refused to eat in the study. Since it is well known that recognition of hunger and satiety in AN patients is generally impaired, appetite cannot be always analyzed correctly by VAS alone. Although 1 μg/kg ghrelin bolus infusion made AN patients feel hunger sensation in another study, their food intakes were not evaluated [34]. We therefore believe that studies aiming to investigate ghrelin as an appetite-stimulating substance should recruit only AN patients who are fully motivated to gain weight by psycho-educational therapy.

Adverse effects such as abdominal discomfort, diarrhea, transient flushing, truncal perspiration, and somnolence have been reported after ghrelin injection [6]. Two patients in the present study occasionally reported a warm sensation in the trunk and mild sweating. Since case 5 experienced mild abdominal pain and several episodes of loose stools per day, we reduced the dose of ghrelin to 1.5 μg/kg, which improved these symptoms. No other serious physical or biochemical deteriorations occurred. Moreover, malnutrition-related liver dysfunction and endocrinologic abnormalities in case 4 were improved after ghrelin treatment. Interestingly, ghrelin infusion increased somnolence in the study [33], however, none of the present 5 subjects reported increased sleepiness. We did not observe increased fear concerning weight gain, abnormal behavior, or unstable mental status owing to an increase in appetite during ghrelin treatment, and psychological tests did not demonstrate any significant change in mental state. The present patients who motivated to gain body weight felt happy to be able to eat after ghrelin infusion, and they were pleased to be free from uncomfortable gastrointestinal symptoms after this ghrelin study. It is notable that all patients gained weight after discharge.

In conclusion, we found that ghrelin decreases gastrointestinal symptoms and increases hunger sensation and daily energy intake without serious adverse events in AN patients. A double-blinded, randomized, and placebo-controlled study is indispensable for developing ghrelin as an effective appetite-stimulating therapy for AN patients. The present study would contribute to investigations for therapeutic potential of ghrelin in AN patients.

Acknowledgments

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FORUM

Trend Analysis of Research on Informed Consent in Clinical Trials : Comprehensive Retrieval via Electronic Databases

Taichi HATTA[*1], Toshinori MURAYAMA[*1,*2], Keiichi NARITA[*2], Eriko SUMI[*1,*2] and Masayuki YOKODE[*1,*2]

[*1] Department of Clinical Innovative Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
[*2] Translational Research Center, Kyoto University Hospital, Kyoto, Japan

Informed consent (IC) is an essential ethical requirement for conducting clinical trials. This study aimed to investigate changes in research on IC for clinical trials and compare the trend in Japan with that overseas.

In February 2010, the electronic databases, PubMed and Japana Centra Revuo Medicina were searched for studies on IC for clinical trials both in and outside Japan.

The literature search identified 89 Japanese studies and 401 overseas studies concerning IC for clinical trials. In Japan, these articles were first published in 1993, and the number increased remarkably from 2002. Many of these articles discussed the contribution of a clinical research coordinator or the understanding of the information by trial subjects. The overseas studies were first published in the early 1980s, and the number increased remarkably in the 1990s.

Since, the enforcement of the new Good Clinical Practice in 1998, observational studies on IC for clinical trials have been conducted in Japan. However, most of these studies applied a quantitative approach, and qualitative analysis is limited. In Japan, IC is not focused exclusively on the protection of trial subjects, but also serves as the basis for an important encounter to build the physician-patient relationship. Therefore, investigations of the IC process by qualitative and quantitative approaches are necessary.

Key words : informed consent, clinical trial, research ethics

1. Introduction

Informed consent (IC) is an essential ethical requirement for conducting clinical trials. Originating in the US, the concept of IC was introduced in Japan in the 1980s[1]. Initially, this concept failed to take full root because of its novelty, given the different medical and cultural backgrounds. In the 1990s, research suggested that the physician-patient relationship should be discussed in order to study the nature of the IC process in Japan[2]. However, before the social/cultural environment was fully matured, IC was legally required for the conduct of clinical trials according to the adoption of ICH-GCP in 1998[3]. In the modern era of increasing globalization, the historical and cultural backgrounds have to be reviewed so as to understand the problems surrounding IC in Japan. This will also inevitably lead to discussions about the methodology of observational study for IC.

The objectives of this study were to investigate the trends in investigations on IC for clinical trials, to review the studies on IC for clinical trials in Japan, and to compare the IC studies in Japanese clinical trials with those overseas.

2. Methods

1) Search of literature : Comprehensive retrieval via electronic databases

To examine the number of published papers on IC for clinical trials, we searched PubMed and Japana Centra Revuo Medicina (http://login.jamas.or.jp/enter.html), the latter being an electronic search engine for medical journals written in Japanese. Searches were originally conducted in December 2007, and repeated in February 2010.

To search for Japanese papers on IC for clinical trials, Japana Centra Revuo Medicina was searched using the retrieval terms "informed consent", "clinical trials" and "data collection", and PubMed was searched using "informed consent", "clinical trials", "data collection" and "Japan". Meanwhile, to search for overseas publications, PubMed was searched using the retrieval terms "in-

Address for correspondence : Murayama T. Translational Research Center, Kyoto University Hospital, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

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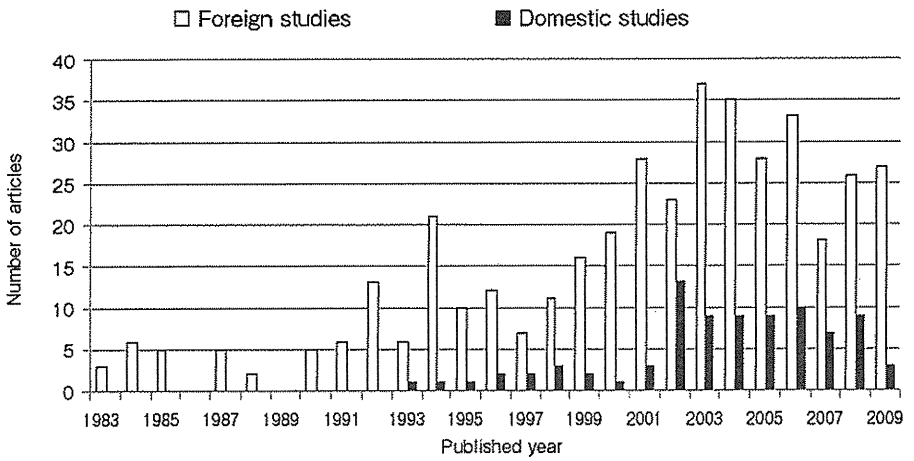

Fig. The number of IC studies for clinical trials

formed consent", "clinical trials" and "data collection", and those identified in the search of Japanese papers were excluded.

2) Extraction and investigation of observational studies on IC in Japan

Japanese studies with abstracts were checked to see whether they were observational studies on IC for participation in clinical trials, which used a questionnaire or an interview with patients, doctors or co-medicals. IC studies without abstracts were excluded because the contents could not be screened, and also most of them were conference proceedings or reviews. Moreover, studies related to decision making in general medicine or studies containing only discussion on the significance of IC for clinical research were also excluded. Then, the selected papers were classified according to the theme of the article and the method used in the study.

3. Results

1) Number of articles identified under each of the search conditions by year

Comprehensive retrieval via electronic databases identified 89 Japanese studies. There was no duplication of data between Japana Centra Revuo Medicina and PubMed. Four hundred and one overseas studies were identified. Figure shows the studies categorized by year of publication.

Japanese research was first reported in the 1990s, and the number increased greatly from 2002. On the other hand, overseas studies were first published in the early 1980s, and the number increased remarkably in the 1990s (Fig.).

2) Extraction and investigation of observational studies on IC in Japan

Thirty-two of 89 Japanese studies had abstracts. Among the 32 articles, 17 that reported observational studies on IC for participation in clinical trials using a questionnaire or an interview of patients, doctors or co-medicals were extracted[4-20]. Most of them dealt with IC for trials for new drug application (NDA).

Six of the 17 articles reported on 'the contribution of a clinical trials coordinator (CRC) in clinical trials'[4,6,11-13,16], 6 reported on IC assessment, such as 'the level of understanding of clinical trials'[7,9,10,14,15,20], and the others studied aspects of IC for clinical trials, such as preference of physicians to recruit participants[5,17], perception of pediatric nurses with regard to competency[8], use of videotape instruction for clinical trials[18] and communication training for CRC[19].

Articles on 'the contribution of a CRC in clinical trials' revealed the factors that participants and physicians recognized as merits in the clinical trials and their impressions of a CRC[4,6,11-13,16]. These articles reported that a CRC contributed mainly to communication with participants, such as drug administration guidance[4], care for participants[4,11] and help in decision-making processes[12,13]. Other articles described the role of a CRC or the expectations of physicians on a CRC[6,16].

Articles on 'the level of understanding of clinical trials' reported how well trial participants understood the clinical trials after receiving an explanation[7,9,10,14,15,20]. The responses suggested that most of the participants could understand the trials if they were given a full explanation. The aspects cited by the participants as difficult to

understand were 'the significance of a placebo' [10], 'double-blinded study' [10,14], 'randomized controlled study' [14] and 'main effect and side effects' [7,9,10,14,15,20].

When the 17 articles were categorized according to study method, the vast majority adopted a quantitative approach, while only one employed a qualitative approach[12]. Nakamura et al. took the verbatim record of IC communication between patients and CRCs, and conducted content analysis, which is a standard methodology in social sciences for studying the content of communication[12].

4. Discussion

1) Relation between domestic IC articles and Japanese social background

We included both articles and conference proceedings (with abstracts) on IC in the present analysis. Although the significance of each type of reference remains to be discussed, we considered them to be equal in this trend analysis. The rationale is that our purpose was to investigate the trends of research on IC for clinical trials, and if conference proceedings were excluded, the retrieved data might be too small to be analyzed properly and the trend might be biased.

In this study, a search of literature using electronic databases found that research on IC for clinical trials had been published in Japan since 1993, and the number increased remarkably from 2002. Many articles concerning IC for clinical trials discussed the contribution of a CRC or the understanding of information provided to trial subjects. These results might be related to the Japanese social background factors such as regulation and infrastructure regarding clinical trials. Specifically, it was a major task for institutions to train CRCs initially, and CRC developed rapidly as a new occupation to support clinical trials including IC.

Although IC started to be practiced substantially in Japan in the early 1980s[1], this study indicates that the focus on IC for clinical trials started later. One of the possible reasons for this delay is that the procedure of IC for general medical practice was different from that for clinical trials. It seems that IC was not regarded as a subject of observational study, but the discussion on IC mainly concerned the disclosure of diagnosis to cancer patient in the 1980s[2].

In the 1990s, some Japanese IC studies were retrieved by our research. With the adoption of ICH-GCP, the Pharmaceutical Affairs Law and the new GCP ordinance for NDA trials were fully enforced in 1988 and training courses for CRC organized by the Ministry of Welfare were started[3]. Since then, medical institutions that conduct NDA trials have set up clinical trial management centers and institutional review boards (IRBs)*, and organize systems that include personnel. There was probably an increased awareness of the importance of protecting the rights and well-being of trial subjects since the enforcement of ICH-GCP and the cooperation of CRC in clinical trials. However, it was probably not until written consent became a legal obligation for pharmaceutical developers and medical institutions that research on IC for clinical trials was started in full swing.

The Japanese articles began to increase in number greatly from 2002. In the 2000s, the Declaration of Helsinki was amended several times[21], and some Japanese guidelines on medical research were also revised by ministries, agencies and medical societies[22,23]. As mentioned in the Declaration of Helsinki, each potential subject should be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, as well as any other relevant aspects of the study[21]. During these changes surrounding clinical trials, several medical institutions built up their own infrastructures for clinical trials, and they accumulated and reported their experiences. Hence, the Japanese articles mainly focused on the contribution of CRC and the understanding of participants.

2) How should the quality of IC be evaluated?

From the viewpoint of IC quality, studies worldwide have mainly focused on participant understanding[25-27]. Our results also showed the same tendency in Japan[7,9,10,14,15,20]. This might have been influenced by the Declaration of Helsinki[21]. However, the extent of participant understanding is not always related to the process of IC or IC itself. The IC process is an individual issue and a subjective decision-making process, and contains psychosocial aspects such as medical culture and physician-patient relationship. Therefore it is difficult to identify all the factors associated with IC. In order to evaluate the process of IC in clinical trials, qualitative approaches would be useful, which include observation, interviews or verbal

*IRBs : To protect the rights of participants, IRBs have been set up in several hospitals in Japan since early in 1980s[24]. After adoption of ICH-GCP, the Pharmaceutical Affairs Law and the new GCP ordinance[3] empowered the function of IRBs.

interactions and focus on the meanings and interpretations of the participants[28]. To illustrate this approach, a representative article found by our comprehensive search is described below.

To reveal how CRC approached participants during IC, Nakamura et al.[12] took the verbatim records of IC communication between patients and CRCs. They conducted content analysis with the verbatim records, and categorized the approaches into 8 patterns including 'setting a good IC environment for participants and CRC,' 'providing information about the clinical trial' and 'estimating the stance of participants'. This is a pioneering IC study with a qualitative method in Japan.

The qualitative approach, which is not yet popular in IC evaluation, could reveal how gaps are formed between participants and medical professionals during the IC process. Therefore, to evaluate IC for clinical trials, we have to start to observe the process of IC in a multifaceted manner, namely, quantitatively and qualitatively.

3) Limitations of this study

Although we conducted a thorough search by comprehensive retrieval via electronic databases in order to identify articles on IC in clinical trials, our method has several limitations : 1) A database does not necessarily provide all the target articles that we would expect given the search conditions. Indeed, several articles dealing with IC for clinical trials in Japan were missed in our comprehensive retrieval[29-32]. 2) We excluded reports that did not contain abstracts. Therefore significant conference proceedings could have been overlooked.

5. Conclusion

After the enforcement of the new GCP, observational studies on IC for clinical trials have been conducted in Japan. However, most of them applied a quantitative research approach, and qualitative analysis of IC for clinical trials is limited. In Japan, IC is not aimed exclusively for the protection of trial subjects, and it is necessary to investigate the IC process by both qualitative and quantitative approaches.

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治験と臨床研究の統一は可能か
―― 臨床試験の科学性と倫理性の向上, 新たな制度と環境を求めて ――
《シンポジウム開催趣旨説明》

京都大学医学研究科薬剤疫学分野教授　川上　浩司

京都大学の川上でございます。本日は暑い中，多数のお運びをいただきまして，誠にありがとうございます。趣旨について，ご説明申し上げます。多分，これを聞かないと，「何でこういうことをやっているんだろう」ということが分からないかと思いますので，ぜひお聞きいただければと思います。

私自身は，今，京都大学の教授を仰せつかっておりますが，元々医師でございまして，FDAというところで，連邦政府の食品医薬品庁と言われますが，アメリカの医薬品行政の審査当局で行政審査官を拝命していました。特に，専門は先端医療の部分，癌ワクチン，遺伝子治療，再生医療などをどうやって世の中にデリバーするかということにかかる審査を担当していた次第でございます。

そもそも，医薬品行政，あるいは医薬品の審査というものは，当然のことながら，公的サービスの一環として国が実施するものであって，国民が，あるいは患者さんが安心して，安全に薬を使えるようにということで行われている訳でございます。

ところが，もう１つ，重要な意味を持っています。何かと言いますと，社会というのは，常に進化します。科学者はいて，大学もある。そうすると，常にspontaneousに発見が起こります。この発見が起きた場合，例えば新しい薬ができるかもしれない。ところが，このできた薬に対して，これを社会に適用しないというのは倫理的に問題があります。なぜならば，社会が研究の成果を享受できないことになるからでございます。ということで，フィルターとして，科学技術が進歩してしまう中で，それをどうやって国民が享受できるか，人間が享受できるかということにおいても，科学技術政策，あるいは基礎医学や薬学研究というものをどうやって社会に還元するかということも，実は審査が担う重要な役割と考えています。これは車の両輪みたいなものです（表１）。

これはよくお話し申し上げますが，医薬品や医療機器の開発は非常に重要であり，研究するのであれば，研究のための研究ではなくて，ぜひ社会に還元しようということを我々はずっと

表１　医薬品行政への期待

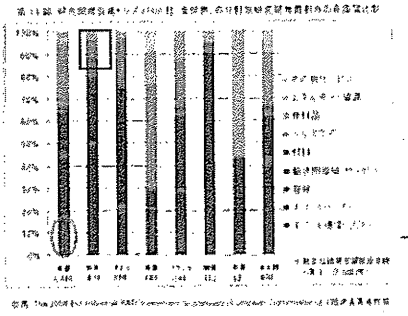
昨今，医薬品の安全性への懸念や対策，また科学技術政策上，基礎医学研究の応用による社会への成果還元という２つの観点から，医薬品審査の在り方が議論となっています。

考えてきている訳でございますが，残念ながら，日本の場合には，いわゆるイノベーションエコシステムの乖離と言われる現象がございまして，家電産業や自動車産業，あるいは米国の軍需産業や次世代牽引産業，これは宇宙開発事業などでございますが，こういった他の事業に関しては，しっかりと研究開発したものはバリューチェーンが繋がって産業化できている，回収できている。ところが，日本の医薬産業というのは，幾ら技術があっても，技術に投資をしても，回収できずに，バリューチェーンが繋がっている，ということが非常に大きな問題であるという認識がなされています（図１）。

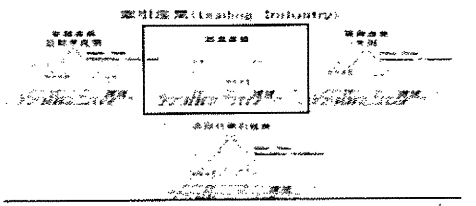
さて，では，臨床研究というものは何でしょうか。臨床研究というのは，研究者の分布からお話しさせていただくと，大きく分けて２つの領域を持っています。１つ目の領域は，いわゆるClinical epidemiology，臨床疫学研究と言われるようなものでして，これはいわゆるエビデンスに基づいた医療であるEBMを実践するためのエビデンスをつくるための研究です。アウトカムリサーチと言われたりもします。この説明はあまりしません。もう１つの車輪というのが，いわゆる臨床応用研究と言われるものでして，Translational Researchと言われるものになります。これは新しい薬などを開発していこうというものでございまして，臨床研究には２つの局面がある訳です（表２）。

臨床研究，Clinical researchというのは，過去の反省から人を対象とした研究，あるいは人から出てきたものを対象とした研究を行うに当たっては，科学的，倫理的妥当性を担保して行うということでヘルシンキ宣言というものが採択されまして，以降，いわゆるICH-E6，GCPというものが整って参りました。

医薬品・医療機器の開発は重要である。しかし，
研究開発投資はまったくバリューチェーンにつながっていない。



イノベーション・エコシステムが乖離している



出展：経済産業省産業構造審議会・
第３回基本問題小委員会（2009年２月２日）
第25回研究開発小委員会（2009年２月６日）

→システム研究と規制・制度改革は不可避である

図１

表２　臨床研究の両輪

- 臨床疫学研究
  Clinical epidemiology
- 開発型臨床研究
  Translational research

もう少し学術的にというか，分類的に臨床研究を捉えてみますと，臨床研究というのは２つの領域を持っています。１つが observational study，観察研究，もう１つが intervention，介入研究です。観察研究と介入研究は何が違うかと申しますと，観察研究というのは，通常のEBM として，プラクティスとして行われている医療行為というものをあるがままに捉えて研究を行うものです。例えば，医薬品においては，製造販売承認後の調査研究というものも入ってきます。

もう１つが介入研究でして，今，認められて行われているプラクティスを超えて，その超えている部分に対して評価することを介入研究と言います。この介入研究の中で最も端的に医療用品が入ってくる場合 —— 医療用品というのは医薬品，医療機器あるいは生物学的製剤を指します —— こういったものを評価しようということで行っているものが，特に clinical trial，臨床試験と言われるものでございます（図２）。

ところが，日本の臨床試験と言われるものはどういう仕組みを持っているかと申しますと，世界でも稀にみる制度を持っています。１つ目が，治験です。治験というのは，皆さんご案内のように，薬事法上の用語でございまして，薬事法というのは，製造販売業を取り締まるための法律です。繰り返して物をつくって販売して流通させるということ，これを薬事法というもので縛っているのでございますが，この薬事法上で行われている臨床試験を特に「治験」と呼んでいて，この「治験」というものが，皆さんご案内のように，医薬品医療機器総合機構（PMDA）で審査し，その後，厚生労働省の本省，薬食審というところでも審査をするということになっています（図３，図４）。

もう１つの道のりが，いわゆる未承認薬の「臨床研究」です。これは，製造販売業から漏れる場合 —— つまり薬事法に入らないような場合 —— 大学は製造施設を持っていませんし，販売して流通させるような仕組みを持っていませんから，薬事法では，範囲外になります。です

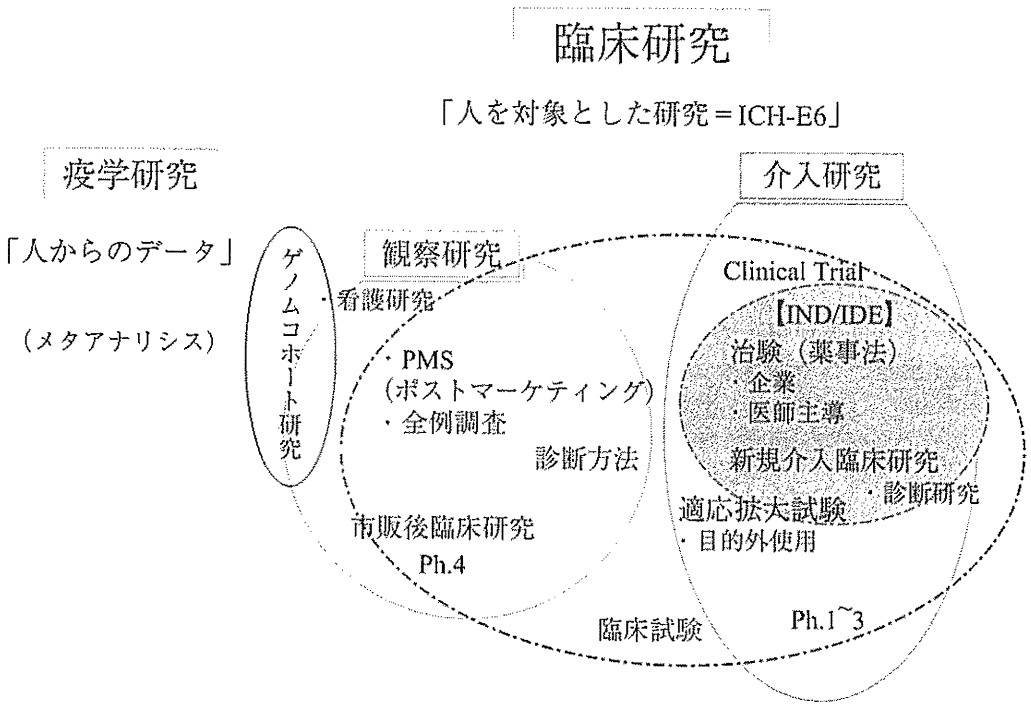


図２

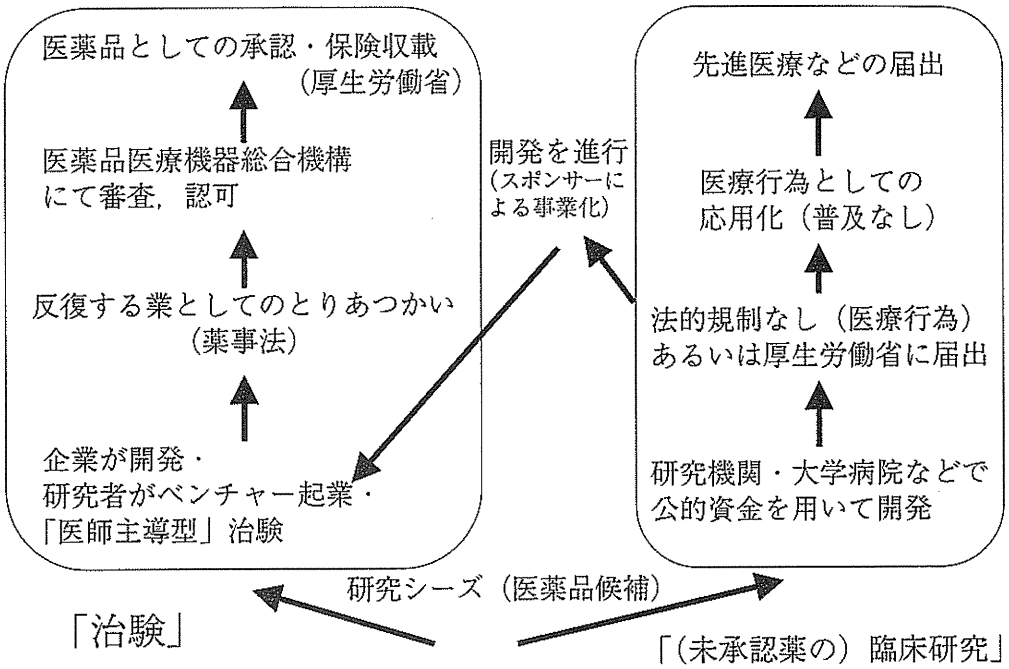


図3　我が国における臨床試験の現状

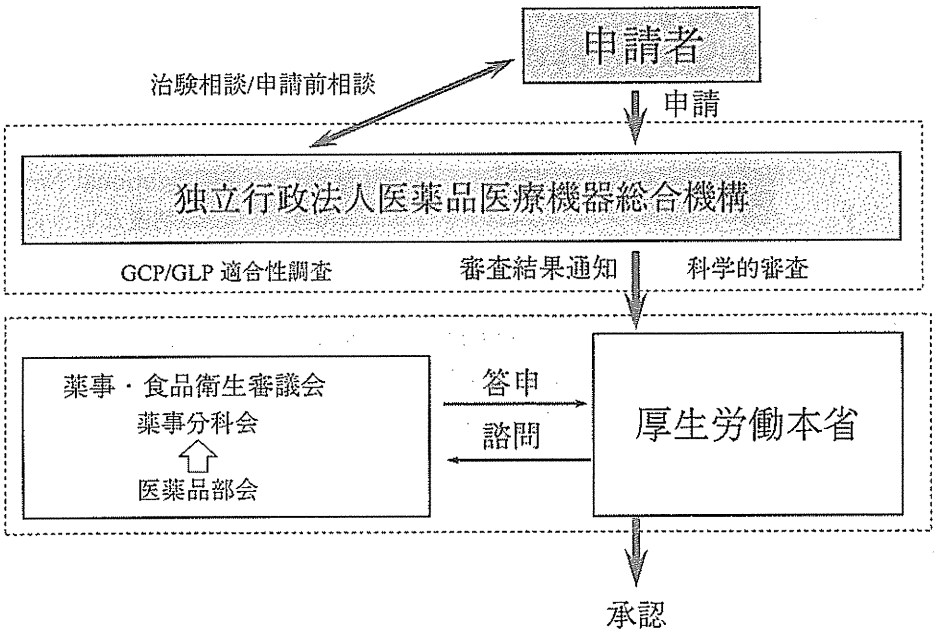


図4　日本における医薬品の承認審査

ので，公的資金を用いて行う場合には，「臨床研究倫理指針」によって「臨床研究」が行われる訳です。

この場合のゴールというのは，先進医療等々がある訳ですが，何が問題かと言うと，この「臨床研究」というものは，治験のように薬事法上のGCP省令で定められているものとは違いまして，GCPでは義務化されていません。ということで，ここでとられたデータというのは，