技スポーツへの参加を強く希望し，転倒の危険があっても制止を守らない[5]．感染症を合併したり，機敏な危険回避行動がとれずに事故にあったりする事例があるので，家族や学校は制止に苦慮する．労作制限で家族や学校のトラブルを軽減するために，ガイドラインとして提示した．制限を超えて活動する場合は本人に警告し，周囲に援助や安全配慮を依頼する．反対に，何 kg になったら何ができるという体重増加の治療動機に活用できる[6]．

栄養療法
－グレリンの臨床応用－

1．栄養療法の重要性

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 ヵ月摂取させる臨床試験（ミネソタ・スタディ）を行った[7]．長期間の飢餓は神経性食欲不振症に似た症状と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神経性食欲不振症のやせ願望以外の心理・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ので，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．また，やせると高度な知的作業である精神療法にますます導入しにくいという悪循環が生じ，慢性遷延化しやすい．

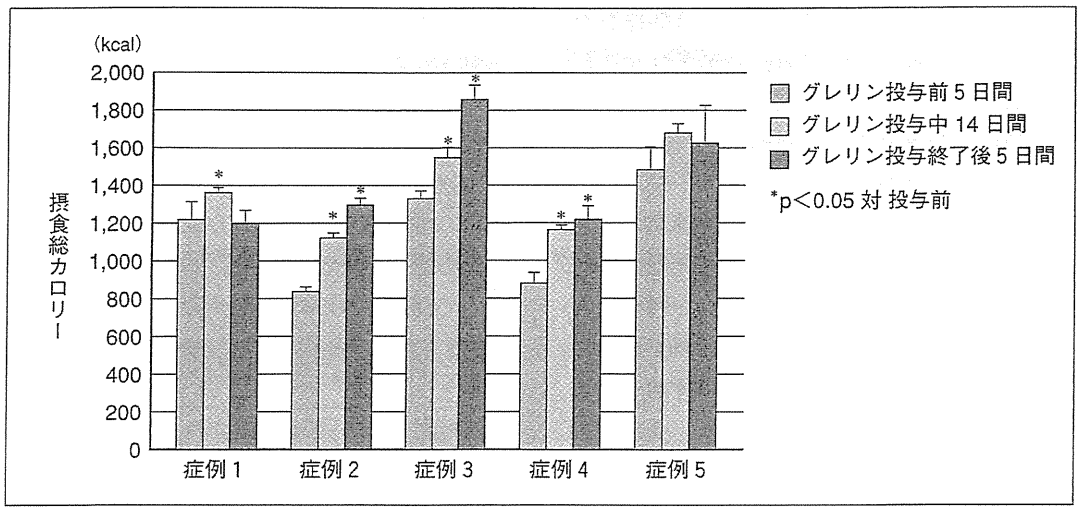
2．低栄養による消化器症状：栄養改善薬としてのグレリンの有用性

治療意欲を持った神経性食欲不振症患者でも，食後の胃のもたれや，少量でも満腹になると訴える．心理的なものではなく，胃排出能の低下，大腸運動の低下など客観的な機能障害が明らかになる．空腹時に胃から分泌されるグレリンは，成長ホルモン分泌促進や正のエネルギーバランスをもたらし，食欲低下を引き起こす心不全，慢性閉塞性肺疾患，がん，機能性胃腸症患者で食欲亢進作用が報告されている．筆者らは，神経性食欲不振症患者の摂食量に対するグレリンの効果と安全性について検討した．グレリンは有害事象なく食欲と摂食量を増加させ，本症の病態改善薬として利用できる可能性が示された（図1）[8]．

主たる後遺症である骨粗鬆症の予防と治療

神経性食欲不振症患者の 50% で，初診時の腰椎骨密度が同年齢の健常女性の平均値の－2 SD 以下に低下しており，25% は－2.5SD 以下で骨粗鬆症と診断される．本症では，低体重，低栄養，低インスリン様成長因子–I（IGF–I）血症，低エストロゲン血症[5]，高コルチゾール血症などの骨密度の低下を来しやすい多くの要因がある．骨芽細胞で合成される骨基質タンパク質であるオステオカルシン（OC）は，ビタミンK不足状態ではグルタミン酸残基（Glu）が γ–カルボキシグルタミン酸残基に変換（Gla 化）されないため，骨基質に取り込まれずに低カルボキシル化オステオカルシン（ucOC）として血中に放出される．ucOC は骨におけるビタミンK充足状態を反映する．神経性食欲不振症群の血清 ucOC は健常女性群に比べて有意に高値で，制限型で 44%，むちゃ食い/排出型で 50% がビタミンK不足と判断された（図2）．健常状態では，腸内細菌が産生するビタミンK量で必要量を充足できる．むちゃ食い/排出型では呕吐や下剤乱用により腸内細菌叢が変化し，ビタミンK合成能が低下している可能性が考えられた．健常日本人の半数は血中 25–水酸化ビタミンD（25OHD）が 20pg/m*l* 以下でビタミンD不足と判断されるが，本症患者の 58% で 25OHD が 20pg/m*l* 以下でビタミンD不足と判断された．

図1　制限型神経性食欲不振症患者におけるグレリンの摂食量への効果

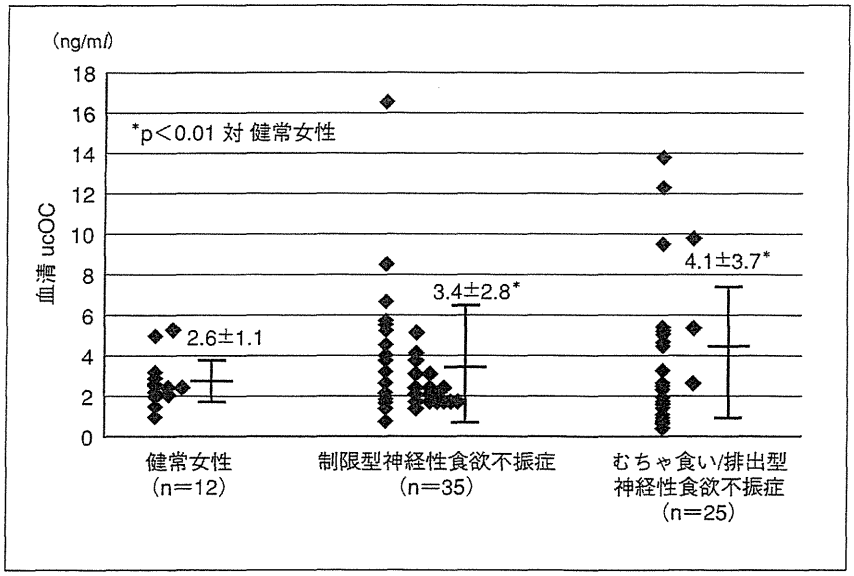


制限型神経性食欲不振症女性患者5例（年齢14～35歳，BMI 9.7～14.7kg/m^2，病悩期間1～15年，平均摂取エネルギー 1,145kcal）に，3μg/kg体重のグレリンを朝食と夕食の15分前に静脈内投与した．全例でグレリン投与後に胃蠕動運動の亢進と便秘の解消が認められ，visual analogue scales for appetiteによる空腹感が一過性に増加し，摂食量は12～36%増加し，三大栄養素すべてが有意に増加した．グレリン投与直後に熱感や発汗を認めたが，眠気や血圧低下，精神症状の悪化は認められなかった．投与終了後も3例で摂取カロリーの増加を認めた．カラムは1日の平均±SDの摂取カロリーを示す．

本症の骨代謝異常は，体重に依存した骨形成の低下と骨吸収の亢進である[9]．骨形成マーカーである血清OCや骨型ALPは低下し，骨吸収マーカーである尿中クロスラプス排泄量（I型コラーゲンのC端テロペプチド）やNTx（I型コラーゲンのN端テロペプチド）は増加している．血清OCは，骨形成因子で栄養状態の有用なパラメーターである血清IGF-Iと有意な正の相関を示し，経静脈性高カロリー栄養法で血清IGF-I値を正常化させると，body mass index（BMI）が変化しなくても血清OS値は増加する[9]．本症では，強力な骨吸収抑制因子である血清エストラジオール（E_2）は低下しており，BMIと有意な正の相関を有する．閉経後女性では非常に低濃度のE_2（3.6～5 pg/ml）でさえ骨吸収を部分的に抑制していることが明らかにされているが[9]，本症も血清E_2が骨吸収を促進していることが推測された．

骨密度の最大の危険因子は低体重期間であり，筆者らの検討では，本症の骨密度低下の予防と治療はBMIを16kg/m^{2}以上に増加させることである．しかし体重増加を受容しないのが本症の特徴である．そこで，骨密度の低下を最小限にする治療が必要である．エストロゲン（プレマリン®0.625mg/日）の補充療法は，理想体重の70%以下の患者の非補充群の骨密度は1年に－20.1%と著明に減少したが，エストロゲン投与群では4.0%増加し，エストロゲン補充療法は有効であった．一方，理想体重の70%以上の患者では，エストロゲン投与群と非投与群で差を認めなかった．筆者らは，活性型ビタミンD_3あるいはビタミンK_2の投与により骨密度の低下を有意に阻止できることを明らかにしている（表2）．神経性食欲不振症患者は一般に，薬によって体重を増加させられることをおそれて内服薬のコンプライアンスが悪いが，これらのビタミン剤に対しては抵抗が少ない．筆者は，慢性化した高年齢患者の骨粗鬆症を除いて，ビ

図2　神経性食欲不振症患者の血中低カルボキシル化オステオカルシン（ucOC）値



神経性食欲不振症患者では，血中低 ucOC 値が健常女性（年齢 28.6±3.1 歳，BMI 21.4±3.0kg/m^2）より高く，制限型（年齢 25.3±6.4歳，BMI 14.4±2.5kg/m^2）の 44%で，むちゃ食い/排出型（年齢 27.5±6.2 歳，BMI 15.7±2.6kg/m^2）の 50% がビタミンK不足を示すカットオフ値（4.5ng/ml）を超えていた．

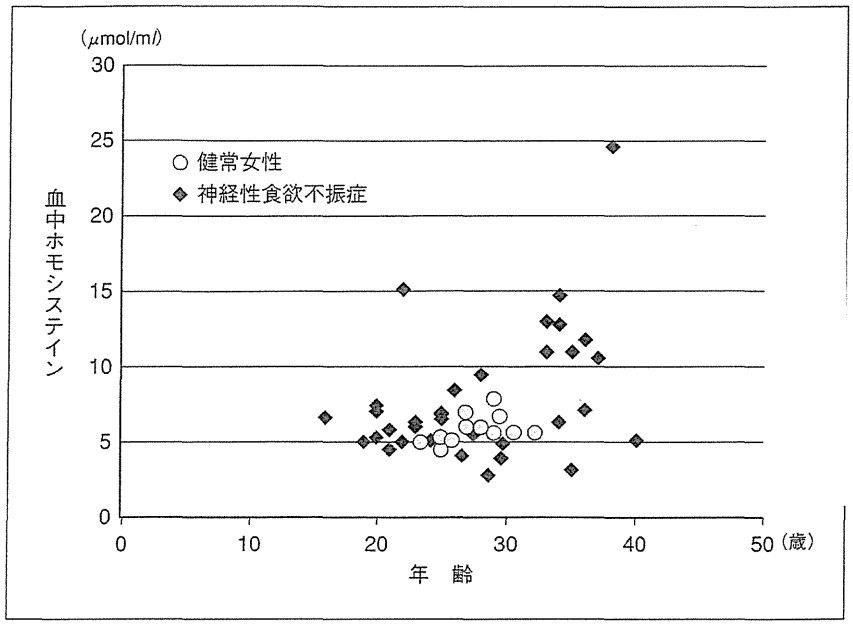
スホスホネートは骨軟化症などの副作用を考慮して使用しない方針である．

骨粗鬆症の骨折のリスクは，骨密度の低下と骨質の劣化で規定される．骨質とは，隣り合う骨コラーゲン分子同士の安定した架橋により規定される．秩序正しく分子を繋いで適度な弾力を保つ生理的架橋と，無秩序に分子を繋ぐ不良な非生理的架橋があり，ペントシジンは後者の代表である．ホモシステインは必須アミノ酸メチオニンの代謝産物である．ペントシジンなどのコラーゲンの不良架橋は，ホモシステイン高値，ビタミン B_6 不足，酸化ストレス，高血糖によって生じる．血中ペントシジン高値やホモシステイン高値は原発性骨粗鬆症や糖尿病における独立した骨折リスクマーカーになることが示されている．本症患者では，骨質マーカーである血中ホモシステインとペントシジンの平均値は年齢をマッチさせた健常女性と統計学的に有意差を認めなかった．しかし，患者群の中では，両マーカーは年齢と中等度の正の相関を有し，30歳以上では両マーカーは上昇しており骨質の劣化があると判断された（図3）．本症では，20 歳代から骨密度のみの判定で骨粗鬆症と診断されるが，骨質も併せて評価して治療方針を決定する必要があると考えられた．

家族支援

1980 年代後半から，家族は回復をサポートする資源と見なされている．米国精神医学会のガイドラインでも家族に対するサポートまたは家族療法が推奨されており，18 歳以下の患者に対する家族療法の有効性は確認されている．本邦では家族療法の専門家が少ないので広く行われていないが，筆者の把握する限りでは，精神保健福祉センターや NPO 法人や病院を基盤に 100ヵ所の家族心理教育や家族支援が行われている．

図3 神経性食欲不振症患者における年齢と血中ホモシステイン値



健常女性（n=12），神経性食欲不振症患者（n=34）の血中ホモシステイン値は，それぞれ 6.4±0.8μmol/ml と 7.6±4.8μmol/ml で統計学的に有意差はなかったが，患者群では 30 歳以上で上昇する傾向を示し，血中ホモシステイン値は年齢と中等度の正の相関（r = 0.478，p= 0.001）を有した．栄養マーカーや骨代謝マーカーとは相関を認めなかった．

家庭が安心して療養できる場になること，家庭内不和などの当面の大きなストレスがないことが早期回復の条件である．家族が病気に巻き込まれて疲弊せず，有効にサポートできるように，筆者らは家族を対象とした心理教育プログラムを実践し[10]，DVD も作成している（インターネットで購入可能 http://www3.grips.ac.jp/~eatfamily/）．

おわりに

慢性遷延化した神経性食欲不振症患者は，低栄養や重篤な合併症のために長期間，あるいは複数回の入院を繰り返さざるを得ない．欧米では 1980 年代から在宅中心静脈栄養法（home parenteral nutrition：HPN）が導入されている．2012 年の診療報酬改定に見られるように，日本の医療行政は地域での医療・介護システムと在宅医療の充実を強化する方針を打ち出した．筆者らは 8 例の HPN を経験している．訪問看護サービスや地域の医療機関と連携し，入院を回避でき，患者の QOL は改善しており，試みても良い方法と考えている．

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Medical Treatment for Eating Disorders: Prevention of Complications and Chronicity

Mari Suzuki-Hotta
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ORIGINAL RESEARCH PAPER

The outcome of Japanese anorexia nervosa patients treated with an inpatient therapy in an internal medicine unit

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ABSTRACT. OBJECTIVE: *To investigate the outcome of Japanese anorexia nervosa (AN) patients who were treated with the standard Japanese inpatient therapy.* METHOD: *Of the 88 female AN patients treated with our inpatient therapy between January 1997 and December 2002, 67 (76.1%) who agreed to cooperate in this study were assessed by the Global Clinical Score (GCS) at admission and follow-up, 6.3±1.8 years after discharge. Their clinical characteristics at admission and discharge were also examined.* RESULTS: *Four (6.0%) patients had died before follow-up. BMI was significantly increased during inpatient therapy. At follow-up, excellent, much improved, symptomatic, and poor outcomes on GCS were 57.1%, 14.3%, 14.3% and 14.3%, respectively. Younger age at admission and larger BMI at discharge were significantly associated with a better outcome.* DISCUSSION: *This study shows the potential for the use of this method for the treatment of AN patients in countries without specialized eating disorder units.*

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Key words:
Anorexia nervosa, eating disorder, inpatient therapy, outcome, follow-up.

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INTRODUCTION

Eating disorders, especially anorexia nervosa (AN) are a chronic, intractable and life-threatening disorders that are accompanied by characteristic pathological eating behaviors including restraint on food intake, binge-eating and purging, such as self-induced vomiting, as well as body image distortion manifested by intense fear of becoming fat (1). A recent review found that the outcome of AN has not improved even though many treatment strategies have been proposed over the second half of the 20th century (2). These findings suggest a need for developing new treatment strategies to improve the long-term outcome of eating disorders.

Regarding weight restoration, the efficacy of specialized, structured eating disorder units with bathroom locked has been shown (3), although no randomized controlled trials have been reported (4). A recent survival study showed the possibility that the introduction of even one eating disorder treatment center that includes inpatient treatment would improve the survival rate of eating disorder patients in some countries (5). However, such treatment is extremely expensive. Thus, it is necessary for inpatient treatment to be covered by medical insurance (6).

The situation of Japan is unique. There is only one payment policy for Japanese medical insurance, which is strictly controlled by the government, although there are also many public and private medical insurance plans. Patients can visit the treatment facility of their choice at the same cost (even at university hospitals). To the best of our knowledge, Japan is the only developed country that does not have an eating disorder treatment center. Payment is strictly regulated and hospitals can not hire highly trained specialists at an adequate salary. In this particular environment, inpatient treatment systems for eating disorders have had to be uniquely developed. Inpatient behavioral treatment is generally done in the general internal medicine unit without bathroom locked. With insufficient nursing staff and unstructured, non specific units, the policies related to behavioral treatment are generous rather than strict (7).

A Japanese manual to standardize the treatment of AN was developed by a research committee of the Ministry of Health and Welfare in 1991. The treatment manual is based on behavioral therapy and cognitive behavioral therapy which were the leading strategies for the treatment of AN at that time. We treat AN with a "cognitive behavioral approach with behavioral limitation" (8-10) that is based on improvements to the manual. In our experience, the outcome of this inpatient treatment for AN is similar to that of other developed countries.

There have been many studies reporting the outcome of AN in Europe and North America, but few in other areas (11). We feel that it is important to do research on the outcome of AN in these countries to determine possible racial and cultural differences in the outcome of AN. The current study is a retrospective outcome study of Japanese AN patients who were treated by the standard Japanese inpatient treatment. Their outcome was investigated to meet the six criteria for a good AN outcome study postulated by Hsu (12). The aim of this study is to show the favorable and comparative outcome of patients treated with this generous behavioral inpatient treatment for AN by assessing the medium term outcome by direct interview.

METHODS

Participants

The original sample consisted of 120 patients with AN who were admitted for inpatient treatment at the Department of Psychosomatic Medicine, Kyushu University Hospital. Of the original 120, 88 female patients were treated with the "cognitive behavioral approach with behavioral limitation". A diagnosis of AN was based on the section of the Structured Clinical Interview for DSM-IV Axis I Disorders concerning eating disorders (13). After a thorough description of the study, 67 (76.1%) agreed to participate and written informed consent was obtained. Nine patients could not be traced because they had relocated and twelve patients refused to participate for personal reasons or because of objections from their family.

This study was approved by the Kyushu University Research and Ethics Committee.

Inpatient therapy: The cognitive behavioral approach with behavioral limitation (8-10)

We treat AN patients with an inpatient therapy we call the "cognitive behavioral approach with behavioral limitation". Figure 1 is a diagram of the therapy protocols. This therapy follows the guidelines of the Japanese treatment manual and is based on operant behavioral therapy and cognitive behavioral therapy. Our patients receive counseling twice a week to learn to deal with problematic behaviors and cognitions. Group therapy and family counseling are also conducted. Through such combined therapy the patients realize and correct erroneous cognition about slenderness, eating, and personal relationships.

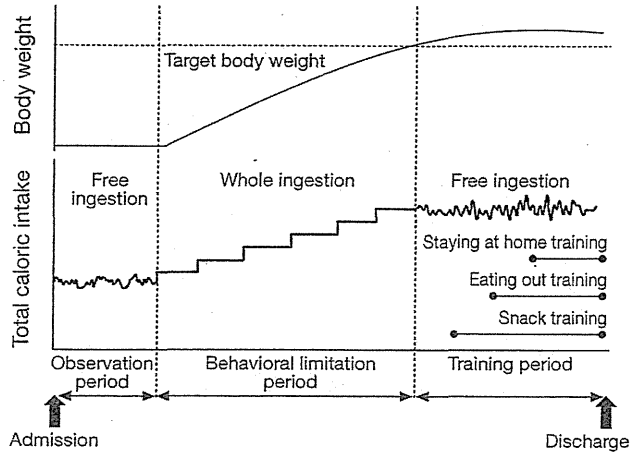

FIGURE 1
Treatment protocols.

This inpatient therapy is undertaken in our general medical unit. In this environment, it is impossible to completely monitor and control all the behaviors of the patients. In our inpatient therapy, a contract made with the patient voluntarily limits the patient's behaviors, which provides an invisible structure. Table 1 shows an example of the behavioral limitations and the schedule for lifting them. From the start of the "behavioral limitation" period until the patient reaches the target body weight, set at 85.0±5.0% of her recommended body weight for age and height, the behavioral limitations are lifted step by step as a token for every kg of weight gain. The patients make an agreement that they will eat all of the provided meals without purging and they will not eat other foods during the "behavioral limitation period". The initial amount of the meal is small enough that they can ingest it without too much difficulty. If a patient cannot ingest the minimum nourishment, about 35 kcal per 1 kg in body weight, nasogastric feeding is administrated, with consent, to make up for the lack of oral feeding. After the therapists confirm that a patient can eat the whole meal without difficulty, the amount of the meal is increased gradually by

TABLE 1
An example of behavioral limitation (for target body weight 45 kg).

BW (kg)	Behavior	Communication	Bathing	Others
32	Restricted to the room		Wiping with towel	
33				Permission to do handicrafts
34	Restricted to the ward		Showering once per week	
35		Permission to send letters		Permission to read books
36	Permission to go to the terrace			
37		Permission to receive letters	Showering twice per week	
38	Permission to go to the rooftop			Permission to listen to music
39		Permission to make telephone calls		
40	Free movement within the hospital		Showering three times per week	
41		Permission to receive telephone calls		
42	Free movement within the hospital grounds			Permission to use seasoning
43			Bathing	
44		Unlimited visits		
45	Permission to go outside the hospital grounds			

about 200 kcal, and nasogastric feeding is gradually reduced.

When a patient has reached the target body weight, the next stage of therapy, a "rehearsal of real life" period begins: 1) Free ingestion: Patients are expected to eat an appropriate amount of food from larger meals; 2) Snack training and eating out training: Patients have a snack between meals and eat the main meals outside the hospital; 3) Staying at home training: A rehearsal for the patients leaving the hospital in which they are protected by the structure of the therapy. The aim of this stage is to improve the patient's ability to control their behaviors and feelings and to prepare for life after discharge.

Follow-up procedure

During the period between May 2006 and August 2007, 88 patients were scheduled for follow-up examination. All patients and/or their parents were contacted, initially by letter, and were given information on the purpose and details of the study. At the same time, they received an explanation about the ethical considerations of the study. After informed consent was obtained, 67 patients (76.1%) were invited to participate. Forty-four had several assessments by face-to-face interview. Five were assessed by telephone interview, one answered a questionnaire, twelve were assessed by information from their parents (eight mothers, three fathers, one set of parents), and four had died, but relevant information on their status at death was obtained from their parents. The average period after onset of AN was 8.9±3.4 years (4.6-21.8 years), and the average period after discharge was 6.3±1.8 years (3.5-9.5 years).

Assessment

Assessment of AN severity was based on the Global Clinical Score (GCS) (14). GCS measures body weight, eating habits, menstrual state, social adjustment, and educational and/or vocational adjustment. Total scores of 0 to 3 were defined as "excellent", 4 to 7 were "much improved", 8 to 11 were "symptomatic", and above 11 were "poor". The standard body weight for calculating the percent of "average" weight for age and height on GCS was based on the Japanese "school health survey" (15) for participants under 19 years old of age and the "list to judge emaciation and obesity" (16) for others.

We obtained the following hospitalization data of the 67 participants from their medical records; age at onset, length of disease, age, subtype of AN, height, body weight, BMI, GCS at admission, body weight, BMI at discharge, and length of stay in hospital. The information to grade the participants based on GCS was obtained at follow-up. Forty-seven participants completed the Japanese version of the Zung Self-Rating Depression Scale (SDS) and the Eating Disorder Inventory (EDI).

TABLE 2
Clinical data of patients followed-up and not followed-up.

	Followed-up patients (N=67)		Not followed-up patients (N=21)		t value	df	p
Age at onset (years)	21.6	(8.1)	22.0	(9.0)	0.149	86	0.882[a]
Age at admission (years)	22.3	(8.4)	22.9	(9.0)	0.292	86	0.771[a]
Duration from onset to admission (months)	36.4	(62.8)	33.9	(32.7)	-0.176	86	0.861[a]
Subtype							0.210[b]
AN-R	29	(43.3%)	13	(61.9%)			
AN-BP	38	(56.7%)	8	(38.1%)			
BW at admission (kg)	22.3	(8.4)	22.9	(9.0)	-0.127	86	0.899[a]
BMI at admission	13.4	(1.9)	13.4	(1.9)	0.001	86	0.999[a]
SDS at admission[c]	51.0	(10.9)	51.5	(11.9)	0.146	80	0.885[a]
GCS at admission							0.198[b]
symptomatic	14	(20.9%)	4	(19.0%)			
poor	53	(79.1%)	17	(81.0%)			
BW at discharge (kg)	41.4	(6.1)	39.5	(5.6)	-1.271	86	0.207[a]
BMI at discharge	17.1	(2.2)	16.3	(2.0)	-1.331	86	0.187[a]
Increase in BW during inpatient treatment (kg)	8.8	(5.7)	7.1	(3.9)	-1.296	86	0.199[a]
Increase in BMI during inpatient treatment	3.7	(2.5)	2.9	(1.6)	-1.230	86	0.222[a]
Duration of hospital stay (days)	153.2	(94.9)	146.3	(64.5)	-0.374	86	0.710[a]
Timing of discharge							0.207[b]
Before achieving target body weight	24	(35.8%)	11	(52.4%)			
After achieving target body weight	43	(64.2%)	10	(47.6%)			

Values are expressed as mean (SD) or N. of patients (%). [a]Unpaired Student's t-test; [b]Fisher's exact test; [c]N=65/17 (Followed-up/Not followed-up). BW: body weight.

Data analysis

All analyses were performed using SPSS for Windows ver.12.0J. Categorical data were analyzed using Pearson's chi-square test or Fisher's exact test. When there was a statistical significant difference among groups, the data were further analyzed using residual analysis. Comparisons among groups were made using paired or unpaired t-test. The criterion used for statistical significance was $p<0.05$ in the tailed test. Stepwise multiple regression analysis was employed to determine the relationship between predictor variables with total score of GCS at follow-up as the dependent variable.

RESULTS

Differences between patients followed-up and not followed-up

No significant difference was found in the hospitalization data of the 67 patients followed-up and the 21 not followed-up (Table 2).

Mortality

At follow-up four participants (6.0%) had died. Of these, three died due to emaciation caused by AN and one due to cancer. According to the vital statistics of Japan in 2004, the expected age/gender specific mortality rate for our participants was 0.020. Thus, the standardized mortality ratio (SMR) was 198.5%, meaning the SMR for our participants was 1.99 times that of women of the same age.

Clinical features

Table 3 shows the clinical features of the 63 living participants at admission, discharge and follow-up. BMI at admission was very low. The BMI of 30 (47.6%) was under 13.0 at admission. During inpatient therapy, their BMI increased significantly (BMI at admission vs BMI at discharge; paired t-test t=-12.460, df=62, $p<0.001$). From discharge to follow-up BMI was also significantly increased (BMI at discharge vs BMI at follow-up; paired t-test t=-3.180, df=62, $p=0.002$). At admission, 49 participants (77.8%) were categorized as poor by GCS. At follow-

TABLE 3
Clinical features of patients at admission, discharge and follow-up (N=63).

	At admission	At discharge	At follow-up
Age at onset (years)	19.0 (5.9)	-	-
Age (years)	21.2 (6.9)	21.6 (6.9)	28.0 (6.8)
Duration after onset (months)	25.9 (38.6)	31.1 (37.7)	106.9 (41.6)
Subtype			
AN-R	29 (46.0%)	-	2 (3.2%)
AN-BP	34 (54.0%)	-	6 (9.5%)
BN	-	-	4 (6.3%)
EDnos	-	-	7 (11.1%)
BW (kg)	32.9 (5.9)	42.1 (5.5)	44.8 (5.8)
BMI	13.5 (2.0)	17.3 (2.0)	18.3 (2.2)
Increase in BW (kg) during inpatient treatment	-	9.2 (5.6)	-
Increase in BMI during inpatient treatment	-	3.8 (2.4)	-
GCS			
excellent	-	-	36 (57.1%)
much improved	-	-	9 (14.3%)
symptomatic	14 (22.2%)	-	9 (14.3%)
poor	49 (77.8%)	-	9 (14.3%)
Duration of hospital stay (days)	-	157.8 (95.0)	-
Duration after discharge (years)	-	-	6.3 (1.8)
Duration of treatment after discharge (months)	-	-	43.0 (29.1)
Number of rehospitalized patients	-	-	18 (28.6%)
EDI	-	-	45.4[c] (29.9)
SDS	50.3[a] (10.7)	40.5[b] (9.0)	43.9[c] (11.0)

Values are expressed as mean (SD) or number of patients (%). [a]N=66; [b]N=44; [c]N=47. BW: body weight.

up, 36 participants (57.1%) were categorized as excellent, with much improved, symptomatic, and poor 9 (14.3%) each. Nineteen participants (30.1%) still had an eating disorder according to DSM-IV criteria: two (3.2%) AN-R, six (9.5%) AN-BP, four (6.3%) BN, and seven (11.1%) EDnos. The duration of hospital stay was relatively long. After discharge, all participants had received outpatient treatment. The duration of medical treatment after discharge varied widely, and 18 participants (28.6%) were rehospitalized: nine once, six 2-6 times, and three more than 10 times.

Predictors for GCS at follow-up

Table 4 shows the result of stepwise multiple regression analysis for predicting total score of GCS at follow-up. The predictor variables selected were age, BMI, AN subtype, total score of GCS at admission, duration of illness, timing of discharge (before achieving target body weight, after achieving target body weight) and BMI at discharge; all correlated significantly with the total score of GCS at follow-up by Pearson's simple correlation test. To explore the relationship between total score of GCS at follow-up and these predictive variables, they were entered into a multiple regression analysis. The best fit model selected age at admission and BMI at discharge. The older age at admission and the lower BMI at discharge, the worse the outcome. No other variables were selected as significant predictors of outcome.

Comparison by achievement of target body weight

Table 5 shows a comparison of clinical features and outcome by whether or not the participant achieved their target body weight: "achieving group" and "not achieving group". At admission there was no significant difference in clinical features between the groups. The increase of body weight and BMI during hospitalization and the body weight and BMI at discharge of the "achieving group" were significantly larger than the "not achieving group". The duration of hospital stay was significantly longer for the "achieving group". At follow-up, the GCS outcome category tended to be different between the groups. According to residual analysis, more participants in the "not achieving group" were classified as poor.

DISCUSSION

In this study, the outcome of 67 female AN patients was evaluated 6.3±1.8 years (3.5-9.5 yrs) after discharge from our hospital. The primary findings of this study are: 1) patients who were treated with our inpatient therapy showed generally good outcome, 2) younger age at admission and larger BMI at discharge

TABLE 4
Multiple regression analysis for predicting GCS at follow-up.

Variables	β	Standardized β	t	p
Age at admission	0.290	0.365	3.162	0.002
BMI at discharge	-0.668	-0.244	-2.115	0.039

Backward elimination method (probability of t to remove >0.05). R=0.464; R^2=0.216; adjusted R^2=0.189; F-statistic=8.243; df=2; p=0.001. β: partial regression coefficient.

TABLE 5
Comparison of clinical features and prognosis by achievement of target body weight.

	Achieving (N=42)			Not Achieving (N=21)			t value	df	p
Age at admission (years)	20.9	(7.0)		21.7	(6.8)		0.399	61	0.692[a]
Duration from onset to admission (months)	21.5	(29.5)		34.7	(52.1)		1.077	61	0.291[a]
Subtype									0.063[b]
AN-R	23	(54.8%)		6	(28.6%)				
AN-BP	19	(45.2%)		15	(71.4%)				
BW at admission (kg)	33.1	(6.2)		32.5	(5.3)		-0.345	61	0.731[a]
BMI at admission	13.6	(2.1)		13.2	(1.6)		-0.856	61	0.396[a]
BW at discharge (kg)	44.2	(4.1)		37.8	(5.6)		-5.161	61	<0.001[a]
BMI at discharge	18.3	(1.3)		15.3	(1.7)		-7.834	61	<0.001[a]
Increase in BW during inpatient treatment (kg)	11.2	(5.3)		5.3	(3.8)		-4.488	61	<0.001[a]
Increase in BMI during inpatient treatment	4.7	(2.4)		2.2	(1.6)		-4.396	61	<0.001[a]
Duration of hospital stay (days)	197.0	(79.0)		79.5	(74.4)		-5.669	61	<0.001[a]
Age at follow-up (years)	28.1	(6.8)		27.6	(6.9)		-0.286	61	0.776[a]
Duration after discharge (years)	78.1	(21.1)		69.5	(22.2)		-1.501	61	0.138[a]
Duration of treatment after discharge (months)	41.3	(28.2)		46.5	(31.4)		0.666	61	0.508[a]
Number of rehospitalized patients	9	(21.4%)		9	(42.9%)				0.087[b]
BW at follow-up (kg)	44.7	(5.5)		45.0	(6.6)		0.191	61	0.849[a]
BMI at follow-up	18.4	(2.1)		18.3	(2.6)		-0.175	61	0.861[a]
Increase in BW after discharge (kg)	0.6	(5.0)		7.2	(6.5)		-4.512	61	<0.001[a]
Increase in BMI after discharge	0.1	(2.0)		2.9	(2.7)		-4.356	61	<0.001[a]
GCS at follow-up									0.058[c]
excellent	26	(61.9%)	[1.1][d]	10	(47.6%)				
much improved	5	(11.9%)	[-0.8][d]	4	(19.0%)	[-1.1][d]			
symptomatic	8	(19.0%)	[1.5][d]	1	(4.8%)	[0.8][d]			
poor	3	(7.1%)	[-2.3][d]	6	(28.6%)	[-1.5][d]			
Total score of GCS	4.1	(4.7)		6.6	(6.6)	[2.3][d]			

Values are expressed as mean (SD) or N. of patients (%). [a]Unpaired Student's t-test; [b]Fisher's exact test; [c]Chi-square test; [d]Residual analysis. BW: body weight.

were significantly associated with a better outcome.

In general, our patients were so severe that their mean BMI was in the lowest category used in previous follow-up studies. However, at discharge they showed a significant BMI gain (paired t-test; t=-12.460, p<0.001) and significant improvement of depression, evaluated by SDS (paired t-test; t=4.380, p<0.001). Moreover, at follow-up, 57.1% of the participants were categorized in GCS as excellent, 14.3% as much improved, 14.3% as symptomatic and 14.3% as poor. Steinhausen reviewed that in 45 outcome studies in which the patients were evaluated after 4-10 years, the same as our study, 47.0±15.7% of the participants recovered, 32.4±14.1% improved, and 19.7±10.6% remained chronically ill (2). Our results are similar to those of this review. SMR was about two times more likely than for women of the same age. This mortality result was better than the rate reported in previous studies (17).

A better outcome assessed by GCS at follow-up was associated with a younger age at admission and a larger BMI at discharge. These findings are consistent with the findings of previous studies (18-20). These results suggest that the following elements of our clinical approach may have a major influence on promoting a good prognosis: 1) Start proper inpatient treatment as soon as possible; 2) Promote the increase of body weight during the inpatient treatment. We recommended that the patients are hospitalized as soon as possible after their

first consultation. The age at admission is younger by not lengthening a duration from onset. A focus of our inpatient therapy is increasing the patients' BMI. Increased economic pressures for shorter hospital stays have made it difficult for AN patients to achieve a normal weight before discharge. Our results show that it is important to a good outcome by AN patients that they restore their weight early in their disease course. And we are able to confirm the validity of the two main tenets of our approach to inpatient therapy: early hospitalization and sufficient body weight gain.

In comparison of the "achieving group" with the "not achieving group", the body weight of the "achieving group" at discharge was greater than that of the "not achieving group", and the GCS outcome of the "achieving group" at follow-up was slightly better than that of the "not achieving group". One of the reasons for this difference is that the "achieving group" had extended treatment and may have profited more from the treatment than did the "not achieving group". Another reason is that the "not achieving group" may have initially had more difficulty than the "achieving group" in continuing the treatment regimen.

According to Crisp et al., the development and maintenance of AN conforms to an avoidance-learning paradigm. This theory is widely supported by clinicians and researchers. We confirmed this theory and consider that the essential mechanism of AN is "whole and thorough avoidance" (8) by which AN patients thoroughly avoid not only food and body weight but also other aspects of life, such as human relations and living a suitable lifestyle for their age. This avoidance seems to be a primary complicating factor for AN treatment. The "cognitive behavioral approach with behavioral limitation" is a therapy that powerfully and dexterously blocks avoidance. Such a behavioral therapeutic method that has a carefully structured period of behavioral limitation for the purpose of self-reflection is also seen in Morita therapy and Naikan therapy, Japanese psychotherapeutic methods known in the west (21).

There are some limitations to our study. First, we do not have a control group who did not have the inpatient therapy. Because the patients were in physically poor condition, including many with a potential risk of death, it was ethically impossible not to encourage them to have the inpatient therapy. It is very difficult to make a control group of such physically severe cases, so we are planning a study that compares our inpatient therapy with another therapy. Second, we did not take the influence of treatment after discharge into consideration, because it is difficult to distinguish the effects of treatment after discharge from the effects of the inpatient therapy. However, we consider that our inpatient therapy has a good influence on their process of the treatment after discharge, and has a certain impact on the outcome of our patients. Third, we obtained the hospitalization data from the medical records, which were not specifically adapted for this study. However, they were recorded accurately under the direction of our specialists in AN therapy. All the data necessary to this study was available.

The participants of this study were severe AN patients whose BMI was remarkably low at admission. However, they had significantly increased BMI by inpatient therapy, and their general outcome at follow-up was as good as that of previous studies. We have described detailed information on our inpatient therapy and considered its effect on the outcome of our participants. Considering that the treatment was undertaken in a general internal medicine unit, not in an eating disorder treatment center with a physical structure that would allow us to watch and control the behaviors of our patients completely, the good outcome is of great significance. This study shows a suitable method for the treatment of AN patients in countries without structured, specialized eating disorder units. Future prospective controlled study and a longer follow-up will be necessary to advance the findings of this study.

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シンポジウム：摂食障害の新たな展開

神経性食欲不振症のバイオマーカー

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抄録：神経性食欲不振症（AN）は遺伝，環境など多因子が関与して発症，持続する．多くの生物学的指標の変化は飢餓による二次的変動であるが，それらの変動は食欲や高次中枢機能に影響する．本稿ではANの症状に関連する遺伝子やその他の定量可能な生物学的指標（バイオマーカー）について述べる．

1）気分・不安などの精神症状：5-HT（セロトニン）活性の変動，5-HT受容体やBDNF（脳由来神経栄養因子）の遺伝子異常とANの関連の報告がある．

2）報酬系：カンナビノイド受容体やドーパミン関連蛋白の遺伝子異常，COMT（Catechol-O-methyltransferase）の遺伝的多型性などとANの関連が報告されている．

3）食欲制御：多くの摂食関連ペプチドの変動は低栄養に基づく．ただし，ANでは飢餓が慢性化しており，これらペプチドの影響は複雑である．われわれのデータでは，慢性化したANのBMI値は活性化グレリンではなくディスアシルグレリンや心理テストの成熟拒否と負の関連があった．また，栄養改善と摂食関連ペプチドの改善時期については差異が認められた．

4）代謝・体組成：体重減少を容易にする因子としてβ-アドレナリン受容体やUCP（脱共役蛋白質）の機能異常が注目されている．われわれは，BMI 13 kg/m^{2}までは，飢餓時のエネルギーの消費は脂肪分解に，それ以下では蛋白異化が中心となることやBMI値や除脂肪量が低下するほど身体的要因による緊急入院のリスクが増加することを報告している．さらに，BMIが12.5 kg/m^{2}以下のANの体重増加期は，基礎代謝が抑制され，除脂肪合成が優位であることを明らかにし，この時期は除脂肪組織の合成につながる身体管理の重要性を提言している．

Key words：神経性食欲不振症，バイオマーカー，グレリン，摂食関連ペプチド，基礎代謝，体組成

はじめに

神経性食欲不振症（anorexia nervosa：AN）は遺伝・生育歴・社会環境など多くの因子が関与して発症・持続すると考えられている[1]．これらのうち生物学的な因子の多くは，食行動異常に起因する飢餓症候群と関連があり，この生物学的な因子の変動は食欲や高次中枢に影響している[1]．

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バイオマーカーとは，尿や血清中に含まれる生体由来の物質で，生体内の生物学的変化を定量的に把握するための指標となるものである．本稿ではANのいくつかのバイオマーカーについて，①気分・不安などの精神症状，②報酬系，③食欲制御，④代謝・体組成に分類して，われわれの研究を含め報告したい．

気分・不安などの精神症状

現時点で検索した限りでもANとセロトニン（5-HT）受容体のpolymorphismの報告だけで42編の報告がある．気分に関与するモノアミン

Table 1　AN の気分に関するバイオマーカーの研究（血液・脳画像の研究）

	急性期 AN	回復期 AN
5-HIAA（セロトニン代謝産物）	⇩	⇧
$5HT_{1A}$ 受容体〈PET〉	⇧	⇧
$5HT_{2A}$ 受容体〈PET〉	⇩	⇩
血中 BDNF（脳由来神経栄養因子）	⇩	
線条体でのドーパミン受容体（DA2）〈PET〉		⇧

AN：anorexia nervosa
5HT：5-hydroxytryptamine
PET：positron emission tomography
BDNF：brain-derived neurotrophic factor

神経伝達物質であるセロトニン（5-HT）やドーパミン，さらに蛋白質である BDNF（brain-derived neurotrophic factor：脳由来神経栄養因子）と AN との関係について **Table 1** に概略をまとめた[1)2)]．一般に $5HT_1$受容体は神経抑制，睡眠，摂食亢進，体温調節，不安，脳血管収縮などに関連があり，$5HT_2$は神経興奮，平滑筋収縮，血管収縮・拡張，血小板凝集，胃収縮などに関連があるといわれている．各因子とも多彩な働きがあり一元的な評価は困難であるが，5-HT に関しては，急性期・回復期ともに中枢神経抑制系が優位に働いているのかもしれない．また，SSRI（selective serotonin reuptake inhibitors：選択的セロトニン再取り込み阻害薬）は臨床的に AN の治療に用いられているが，予後に関係するかは結論が出ていない[2)]．

実際に，イメージが食欲に及ぼす影響を検討する目的で，われわれは催眠下での摂食イメージが，満腹感・胃電図・摂食調節物質に与える影響を調査した（**Fig. 1a, 1b**）．健常女性 78 名中の特に被暗示性の高い 7 名（22.2±1.6 歳）を選出，胃電図を装着のうえ，催眠下で被験者に＜好きな食べ物を満腹になるまで食べる＞という暗示を与えた．その後，サンドイッチ（約 300 kcal）を 15 分以内に実際に食べてもらった．実験中，満腹感の測定，血液中のグレリン，レプチン，インスリン，グルコース，胃電図を測定した．その結果，催眠中の満腹感は有意に実食時と同様の変化を示し，胃電図は安静時と異なる傾向を認めた（**Fig. 1a**）．興味深いことに，催眠では実食時と異なり，摂食調節物質の変化は認められなかった（**Fig. 1b**）．暗示による満腹感の変化は，グレリンやレプチンなどの摂食調節因子を介さない pathway で引き起こされている可能性が示唆された（unpublished data）．

報酬系

AN では，統合失調症の病態との関連が示唆されているドーパミン受容体（DR-D2）の SNPs の報告，COMT（Catechol-O-methyltransferase）遺伝子は，ドーパミンの分解に必要な酵素であるが，val タイプをもつタイプは，AN になるオッズ比が 2.5 倍であるという報告，大麻に含まれる化学物質の受容体であるカンナビノイド受容体は，食欲・記憶・痛覚・脳内報酬系に働くといわれているが，AN において polymorphisms を認めるという報告などがある[2)]．食事に対する満足度が，AN では遺伝的に健常人と異なることが今後明らかになるかもしれない．

食欲制御

AN においては多くの摂食調整ペプチドの変動は低栄養に基づく．おそらく発病初期では，活性型であるアシル化グレリンやレプチンなどのやせた身体状態から求心性に視床下部に働く飢餓状態のシグナル（本能）は，健常人と同様に働き BMI 増加の方向へ何らかの影響を与えていると想像される．慢性期の AN の場合，飢餓状態に身体が順応しているためその評価は複雑になる．

われわれは，重回帰分析を用いて慢性期 AN 患者の BMI 値は，食事量と関連があるとされている活性化グレリン値やレプチン値と関連はなく，ディスアシルグレリン値や心理的因子である Eating Disorder Inventory の成熟拒否と負の

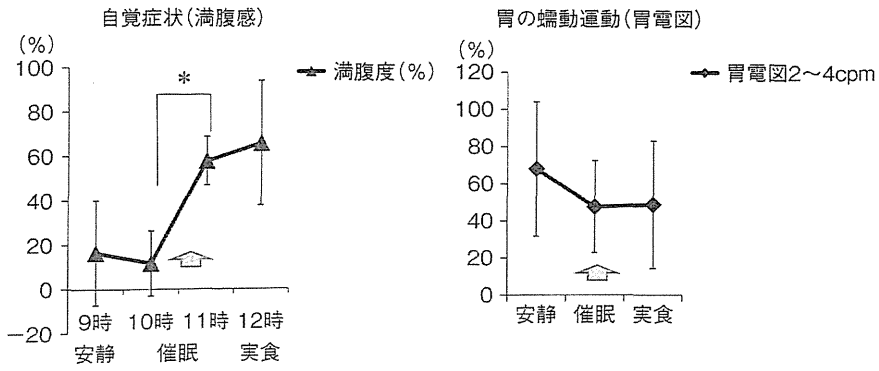

Fig. 1a 健常人：暗示が食欲に及ぼす影響の研究—満腹感および胃電図の検討—
＊p＝0.00029 Matsubara S, Kawai K et al. In preparation

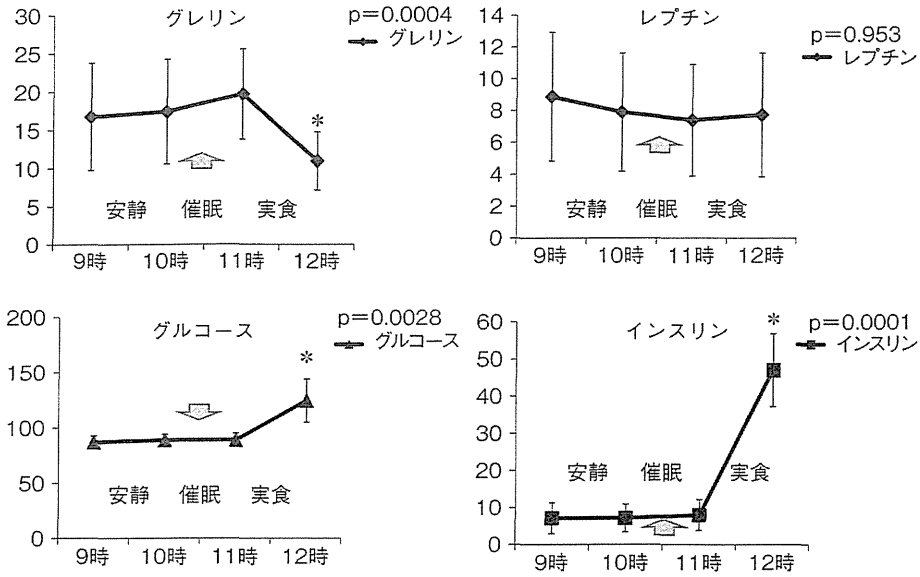

Fig. 1b 健常人：暗示が食欲に及ぼす影響の研究—摂食関連ペプチド—
Matsubara S, Kawai K et al. In preparation

関連があることを報告した（**Table 2**）[3]．さらに，AN 入院患者 16 名について，入院時，4 週間後，8 週間後にインピーダンス法（TANITA DC-320）で体重，体脂肪量の測定を行った．同日に血清レプチン値も測定した．各因子の経時的な変化は反復測定の分散分析を用いて検定を行った．摂取エネルギーや体脂肪量は，入院後徐々に増加した．入院 4 週間後の血清レプチン濃度は脂肪量の増加のパターンと異なり，入院時に比べ有意な増加はみられなかった（**Fig. 2** の上段）．8 週間後には血清レプチン濃度は有意に増加しはじめた．このレプチン値の変動の意義については明らかではないが，レプチンの上昇が抑制されていることは，摂取エネルギーの上昇に有利に働いている可能性がある．今後は，他の因子との関連も精査する必要がある．

代謝・体組成

体重減少を左右する因子として β-アドレナリン受容体や UCP（uncoupling protein：脱共役

Table 2　AN の BMI に影響を及ぼす身体的因子・心理的因子（重回帰分析）

Somatic factor	Psychological factor
Caloric intake（kcal）	SDS（Depression）
Age（yr）	STAI- I （State）, II （Trait）
Duration of AN（month）	EDI（8 subscales）
Glucose（mg/dl）	**Maturity fears*　β＝−0.375**
Insulin（μU/ml）	Hunger feeling（VAS）
Cortisol（μg/dl）	Fullness feeling（VAS）
Ccr（ml/min）	
Leptin（ng/ml）	
Active Ghrelin（fmol/ml）	
Desacyl Ghrelin（fmol/ml）*　β＝−0.486	

VAS：visual analog scale. Daily food intake was assessed by Total calories of the meal x intake ratio（%）（an average of three days）.　*p＜0.05
Kawai et al.：*Eating Weight Disord*　13, 198-204, 2008

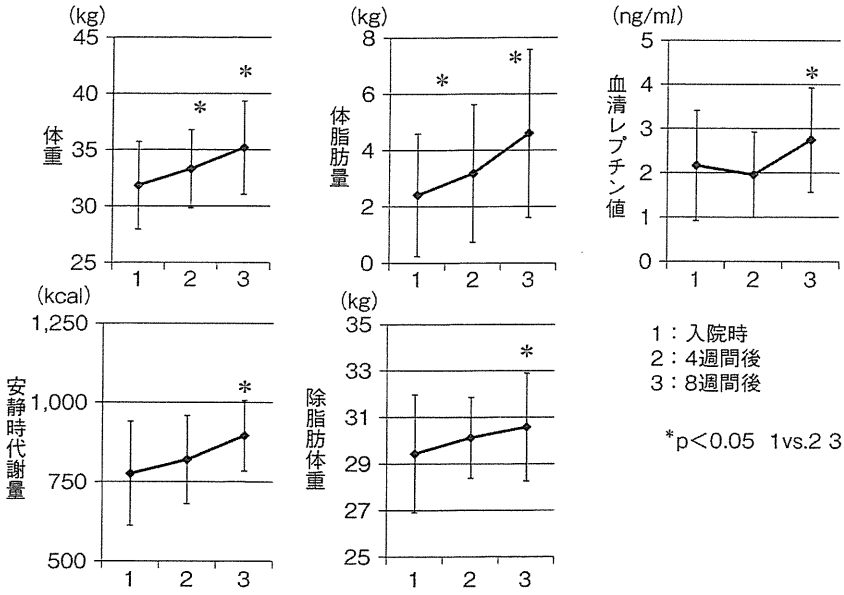

Fig. 2　入院後の体重・体組成・レプチン・安静時代謝の変化

蛋白質）の機能異常が注目されている．β3 アドレナリン受容体は心筋，平滑筋，褐色脂肪，白色脂肪細胞にも分布している．この肥満遺伝子の変異（日本人では約 1/3，アメリカ白人 10%）をもつ人は，内臓脂肪型の肥満になりやすく，基礎代謝量が標準タイプの人に比べて 1 日あたり 200 kcal 近く低下する[4]．また，UCP1 はミトコンドリア内に存在し，脂肪を代謝，熱を産生するときに働く．この肥満遺伝子の変異（日本人では約 24%）をもつと基礎代謝量が標準タイプの人に比べて 1 日あたり 100 kcal 近く低下するといわれている[4]．このように，個々人で体質が異なることも AN の発症に関与している可能性を理解しておく必要がある．

AN 患者 94 名の入院時の BMI 値と脂肪量および除脂肪量（筋肉・骨格・内臓・血液量など）を検討したわれわれの研究では，入院時 BMI 値と脂肪，除脂肪量の関連を検討してみると，それは非線形の関係にあり，その曲線は BMI 13 kg/m^{2}あたりを境に変化する傾向にあった[5]（**Fig. 3**）．入院時 BMI が 13 kg/m^{2}以上の症例群では BMI が減少するに伴って脂肪量が主に減

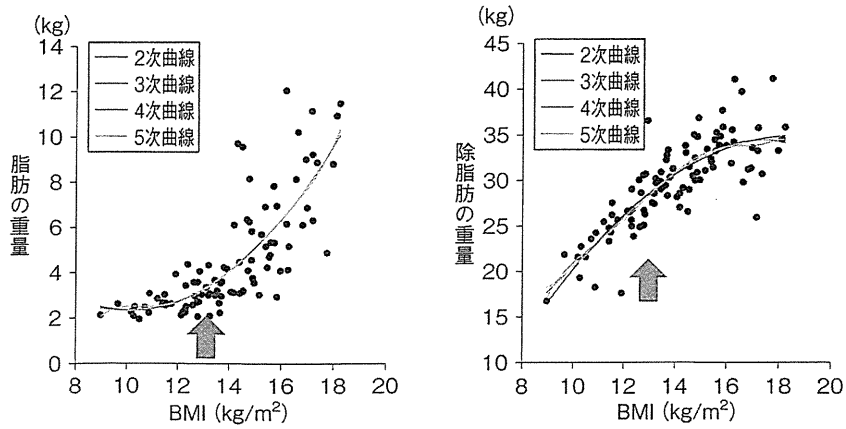

Fig. 3　入院時 AN の BMI と脂肪，除脂肪の関係
Yamashita S, Kawai K, et al：*Int J Eat Disord*　43：365-371, 2010

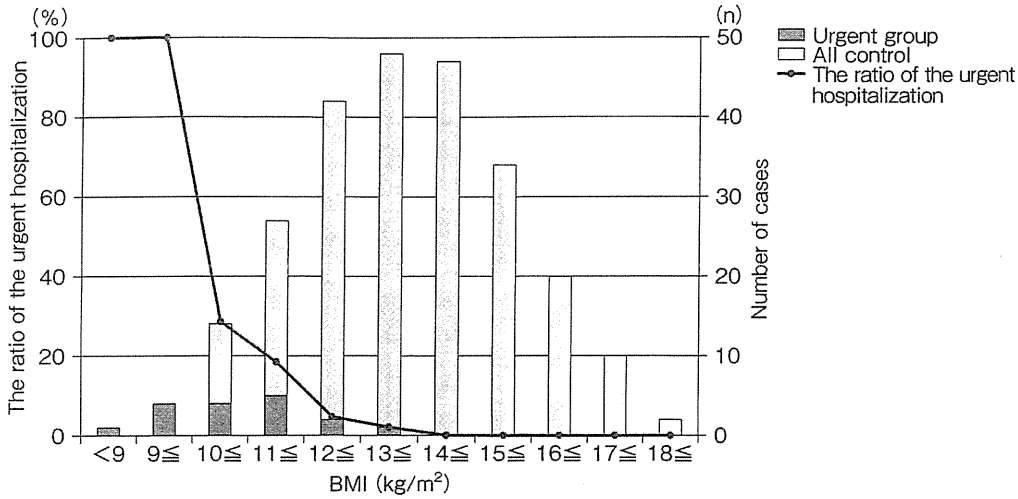

Fig. 4　初診時 BMI と緊急入院した AN の比率
$p<0.01$, exact Cochran-Armitage test for trend.
Kawai K, et al：*Biopsychosoc Med*　5：14, 2011

少し，入院時 BMI が 13 kg/m²以下の症例群では除脂肪量が主に減少していた．言い換えればBMI が 13 kg/m²以下になると，貯蔵エネルギーとして，使用される脂肪が枯渇し，筋肉などの異化によって主にエネルギーが消費されると考えられる．実際，外来受診した患者 249 名の BMI 値と意識障害・歩行困難で緊急入院した患者の割合を検討すると，緊急入院した AN の BMI が 13 kg/m²以下では身体的要因で緊急入院をきたすリスクが上昇していた（**Fig. 4**）[6]．この外来患者の中で入院した 92 名について体組成を調査したところ，筋肉・内臓組織・血液量などを表す除脂肪が減少すると緊急入院をきたすリスクが有意に上昇していた[6]（**Fig. 5**）．この時期は，治療において，除脂肪組織の合成につながる身体管理が重要であると考える．

次に，われわれは入院患者 16 名について，入院時，4 週間後，8 週間後にインピーダンス法（TANITA DC-320）で体組成や間接熱量計で安静時代謝量を測定した．さらに，その 16 名を BMI の中央値（BMI 12.5 kg/m²）で 2 群に分類し，低体重群に限定してさらに，経時的な変化

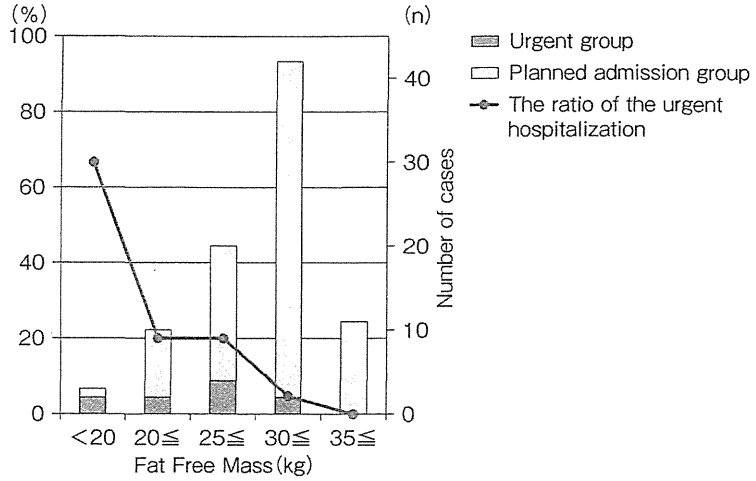

Fig. 5　入院時の除脂肪量と緊急入院した AN の比率
p＜0.01, exact Cochran-Armitage test for trend.
Kawai K, et al：*Biopsychosoc Med*　5：14, 2011

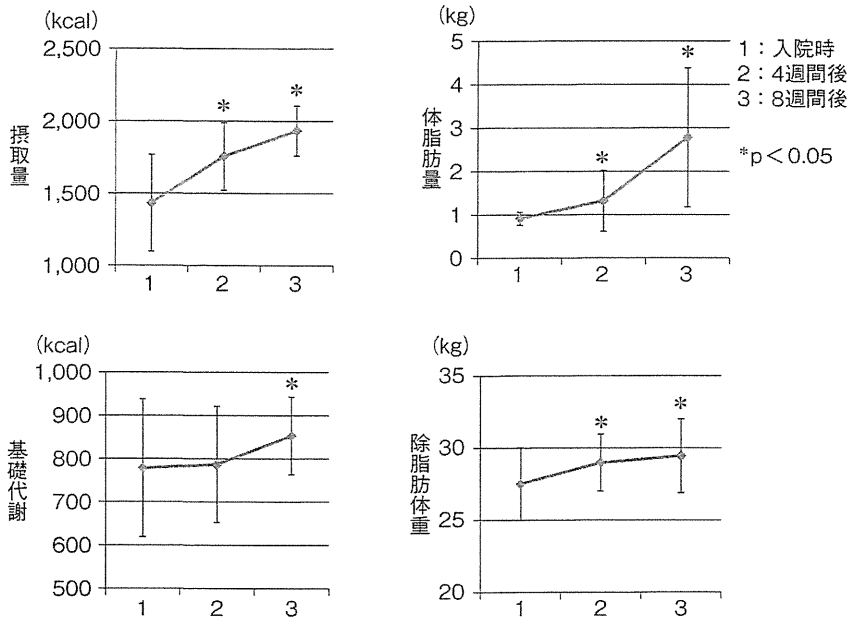

Fig. 6　BMI 値 12.5 kg/m²以下の AN における入院後の体重・体組成・安静時代謝の変化

の差を検討した．その結果，摂取エネルギー，体重，脂肪量は 4 週間後，8 週間後に有意に増加していたが，安静時代謝量や除脂肪の増加が有意になったのは 8 週間後であった（**Fig. 2** の下段）．BMI 12.5 kg/m²以下の群でも摂取量や体脂肪の増加が認められたが，基礎代謝は 8 週目まで有意に上昇しなかった（**Fig. 6**）．極度の低栄養状態では，入院 4 週間の期間は，生体での安静時代謝量が押さえられ，脂肪合成，蛋白同化作用が優先されている可能性がある．

これらの結果より，AN では体組成や安静時代謝量は血液中の摂食関連物質よりも，治療初期の栄養療法を考える指標として有用な印象がある．今後は，低栄養時の有効な栄養療法が必

要である．

結論

BMIが極度に低値の際は，除脂肪体重の増加が優先される．体組成や安静時代謝は，ANの入院治療上で有用な指標になりうる．

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