Insulinogenic index at 15 min as a marker of nutritional rehabilitation in anorexia nervosa[1–3]

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ABSTRACT

Background: Insulin responses to the oral-glucose-tolerance test (OGTT) in anorexia nervosa (AN) are related to body weight and show various patterns. Although weight gain is a key indicator of a successful nutritional program, it is not a sufficiently accurate index for assessing nutritional status, especially in the periods of marked fear of obesity, because patients often manipulate body weight measurements.

Objective: The aim of this study was to determine the relation between insulin metabolism during the early phase of the OGTT and progress (weekly weight gain) during nutritional rehabilitation.

Design: Forty-eight inpatients with AN (25 AN restricting type and 23 AN bulimic type) underwent the OGTT, with additional blood sampling at 15 min, when energy intake reached 6694 kJ/d (1600 kcal/d). Thirteen healthy volunteers were also studied. To evaluate early-phase insulin metabolism, we calculated the insulinogenic index after 15 ($II_{15\,min}$) and 30 min. On the basis of weekly changes in body weight, the AN participants were divided into good (≥ 0.5 kg) and poor (< 0.5 kg) responders.

Results: Among the AN patients, 48% were poor responders. Analysis of variance showed significant differences in the $II_{15\,min}$ values ($P = 0.0005$) and showed that $II_{15\,min}$ values for good responders were significantly higher than those for the other groups.

Conclusions: These findings suggest that a lack of progress in weight gain is frequently observed in AN and that $II_{15\,min}$ values may be a useful marker with which to assess the weekly progress during nutritional rehabilitation. *Am J Clin Nutr* 2003;77:292–9.

KEY WORDS Anorexia nervosa, oral-glucose-tolerance test, insulin, glucose, insulinogenic index, nutritional rehabilitation, women

INTRODUCTION

Eating disorders, especially anorexia nervosa (AN), are characterized by severe emaciation, abnormal eating behavior, and various malnutritional complications (1). Metabolic changes in patients with AN, particularly those of glucose and insulin metabolism, have been documented (2–4). Recent studies of carbohydrate metabolism in AN have showed changes in insulin sensitivity (5–10), insulin resistance (11, 12), and various glucose and insulin responses to the oral-glucose-tolerance test (OGTT) (11, 13–15). Moreover, several studies suggest that carbohydrate metabolism and insulin secretion in eating disorders are closely related to nutritional status and eating behavior (13, 14, 16–18). Most of these changes normalize after a successful nutritional program restores normal body weight, so they appear to be closely related to chronic malnutrition.

Recent approaches to treating AN patients are multifaceted, involving psychotherapy, family therapy, and cognitive behavior therapy (19–21). Because the characteristic psychopathology in AN may closely relate to severe starvation, some therapists emphasize the need for a careful nutritional assessment and the formulation of a nutritional program before the other strategies are attempted (19–21). Thus, the restoration of body weight is one of the most important aspects of the beginning of the treatment program. Whereas weight gain is a key indicator of the nutritional program, the progress of nutritional status is not always accurately assessed because patients often manipulate body weight measurements, especially during periods of distinct fear of obesity (22).

In an attempt to define a more useful marker for assessing the weekly progress of nutritional rehabilitation, we proposed that patients with AN who gained sufficient weight during nutritional rehabilitation might show increased insulin secretion, especially during the early phase of the OGTT. Early-phase insulin secretion is influenced by an initial increase in blood glucose concentrations and gut hormones after the glucose load (23, 24). The aim of this study was to determine the relation between insulin metabolism during the early phase of the OGTT and progress (weekly weight gain) during nutritional rehabilitation in patients with AN.

SUBJECTS AND METHODS

Subjects

Sixty-three women participated in this study. Thirteen were healthy control subjects and 50 were consecutively enrolled patients with AN who were admitted to our department and similar departments of affiliated hospitals for inpatient treatment between January 1999 and July 2000. Written informed consent was obtained from all participants before starting the study, which proceeded in accordance with the principles of the Declaration of Helsinki.

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Of the 50 patients, 26 had AN restricting type (AN-R) and 24 had AN binge eating–purging type (AN-BP). Each clinical disorder was diagnosed on the basis of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV; 25), and patients were evaluated by trained interviewers using the structured interview method. None of the patients had diabetes mellitus or other metabolic diseases (26).

Thirteen age-matched female volunteers recruited by advertisement in a local community were paid for participation. They were assessed at clinical interviews and found to be mentally and physically fit to participate as control subjects. They ate normal diets, did not habitually use any medications, and had no personal or family history of diabetes mellitus or other metabolic diseases (26).

Our institutional treatment program

The treatment of AN in our department consists of behavior therapy involving operant techniques, nutritional rehabilitation, family therapy, and behavioral counseling in an inpatient setting (27). Our therapeutic program is based mainly on learning theory and consists of excluding reinforcing factors, positive reinforcement for reshaping desirable eating behavior, and negative reinforcement.

During the first 2 wk after admission, we observed the behavior of the patients, including that of eating. Each patient was served meals totaling 8370 kJ (2000 kcal)/d. No behavioral intervention or nutritional rehabilitation was applied during this period. Thereafter, we implemented the treatment program. Initially, all patients were confined to bed and all stimuli, including contact with family members, were controlled. The total energy of the daily diet started at ≤4184 kJ (1000 kcal), and energy intake was increased gradually by 837 kJ (200 kcal)/wk at the patient's request. To assess the weekly effects of nutritional rehabilitation, we weighed the patients at 0700 every Thursday. If a patient failed to gain weight when energy intake was increased, she was encouraged to remain in bed and start with the low-energy diet once again on Friday. Weight increases of >0.5 kg/wk were positively reinforced by releasing the patient from activity restrictions.

Procedure

On the 7th day after admission, we assessed baseline carbohydrate metabolism with the use of a standard OGTT (the 1st OGTT). The patients were questioned about their family history of diabetes mellitus, and the likelihood of alcohol abuse was evaluated by using the DSM-IV criteria (25). No alcohol consumption was permitted during hospitalization.

A standard OGTT (the 2nd OGTT) was also administered to each patient on the Thursday of the first week after energy intake reached 6694 kJ/d (1600 kcal/d). Serum potassium and serum aminotransferase concentrations (which affect glucose metabolism) were measured before glucose loading.

After the subjects had fasted overnight, blood samples were collected via a butterfly needle inserted into a forearm vein at 0700. The catheter was kept patent by a saline infusion with heparin as an anticoagulant. Subjects then drank a solution of 1.75 g glucose/kg body wt (Trelan G75; Shimizu Pharmaceutical Co, Ltd, Shizuoka, Japan) dissolved in 225 mL water over a period of 3 min. Blood samples were collected at conventional OGTT times (0, 30, 60, and 120 min) and also at 15 min after glucose loading. During testing, all patients remained recumbent, and no activity or eating was permitted.

Blood samples were collected and mixed in tubes containing an antiglycolysis agent (NaF method) and were then stored at 4 °C. Glucose concentrations were measured by using a glucose autoanalyzer (Hitachi 7170 Autoanalyzer; Hitachi Ltd, Tokyo). Plasma was separated by centrifugation (2000 × *g* for 5 min at room temperature) and was stored at −20 °C until insulin concentrations were measured by radioimmunoassay.

Evaluation of weekly progress during nutritional rehabilitation

We evaluated the weekly progress of the nutritional rehabilitation by measuring changes in body weight during the first week after energy intake reached 6694 kJ/d (1600 kcal/d). To accurately evaluate weight gain, we additionally weighed the patients at 0700 on the day after the 2nd OGTT (Friday) if we considered their weight gain to be questionable. We applied the lower value for measuring changes in body weight. Moreover, we excluded patients whose weight gain was due not to the effects of nutritional rehabilitation but to factors such as nutritional edema, heart failure during refeeding, or other metabolic diseases (1). When energy intake reached 6694 kJ/d (1600 kcal/d), patients were advised to gain >0.5 kg/wk and were divided on the basis of changes in body weight into good (≥0.5-kg change in body weight) and poor (<0.5-kg change in body weight) responders.

Evaluation of early-phase insulin secretion

Two types of insulin secretion occur (23): basal secretion, when a person is fasting, and additional secretion, when a person is eating. We evaluated basal glucose and insulin metabolism by measuring fasting serum insulin and fasting blood glucose concentrations. To evaluate the amount of additional insulin secretion, we calculated the insulinogenic index at 30 min ($II_{30\,min}$) during the OGTT as follows:

$$II_{30\,min} = 0.0077 \times [\text{insulin}_{30\,min}\,(\text{pmol/L}) - \text{insulin}_{0\,min}\,(\text{pmol/L})]/[\text{blood glucose}_{30\,min}\,(\text{mmol/L}) - \text{blood glucose}_{0\,min}\,(\text{mmol/L})] \quad (1)$$

This index can be used to evaluate the initial insulin secretion after glucose loading in patients with diabetes mellitus, and some researchers have reported that in patients with type 2 diabetes, $II_{30\,min}$ values decrease to 0.5 with a 100-g glucose load and to 0.4 with a 75-g load (28). Moreover, this index is derived from the OGTT, which is influenced by gastrointestinal factors, as opposed to the intravenous-glucose-tolerance test, which is not influenced by those factors. The index is also influenced by factors such as elevated blood glucose concentrations after loading, gut hormones, and gastrointestinal mobility (11, 28). Therefore, this marker might be superior to other methods of evaluating glucose homeostasis, including the minimal model analysis, in lean AN patients with abnormal eating behavior (10).

Insulin secretion after eating consists of early (<30 min after loading) and late phases that arise in response to increased and peak blood glucose concentrations, respectively (23, 24). Some studies indicate that gastrointestinal hormones play an important role in early-phase insulin secretion, especially 15 min after glucose loading (29). Therefore, to evaluate the response of early insulin secretion, we calculated the insulinogenic index at 15 min ($II_{15\,min}$) during the OGTT in addition to that at 30 min:

$$II_{15\,min} = 0.0077 \times [\text{insulin}_{15\,min}\,(\text{pmol/L}) - \text{insulin}_{0\,min}\,(\text{pmol/L})]/[\text{blood glucose}_{15\,min}\,(\text{mmol/L}) - \text{blood glucose}_{0\,min}\,(\text{mmol/L})] \quad (2)$$

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TABLE 1
Demographic and clinical characteristics of the patients at admission according to treatment response and of healthy control subjects[1]

	AN-R patients		AN-BP patients		
	Good responders (n = 14)	Poor responders (n = 11)	Good responders (n = 11)	Poor responders (n = 12)	Control subjects (n = 13)
Age (y)[2]	23.6 ± 4.6[3]	25.7 ± 5.2	24.5 ± 5.1	20.3 ± 3.9[4]	23.8 ± 1.8
Duration (y)[5]	4.5 ± 2.7	4.7 ± 2.5	6.4 ± 4.6	4.0 ± 3.4	
BMI (kg/m^2)[6]	12.7 ± 1.2[7]	13.3 ± 2.2[7]	13.7 ± 1.4[7]	14.5 ± 1.8[7]	20.9 ± 1.0
Alcohol[8]	1/14	0/11	3/11	0/12	0/13
Diabetes mellitus[9]	0/14	1/11	1/11	3/12	0/13

[1] AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge eating–purging type.
[2] Significant interaction between progress during treatment and AN subtype, $P < 0.05$ (two-factor ANOVA).
[3] $\bar{x}$ ± SD.
[4] Significantly different from poor responders with AN-R, $P < 0.005$ (one-factor ANOVA with Bonferroni correction).
[5] Duration of disease before admission.
[6] Significant main effect of AN subtype, $P < 0.05$ (two-factor ANOVA).
[7] Significantly different from control subjects, $P < 0.001$ (one-factor ANOVA with Bonferroni correction).
[8] History and present illness of alcohol abuse or alcoholic liver disease (yes/all). $P < 0.01$ by the chi-square test for all 5 subgroups.
[9] Family history of diabetes mellitus (yes/all).

Evaluation of other markers of glucose homeostasis

We evaluated glucose and insulin metabolism during the OGTT by measuring the ratio of fasting blood glucose to fasting serum insulin, the insulin area under the curve between 0 and 120 min, and the homeostasis model assessment for insulin resistance (HOMA-IR) (11, 30).

$$\text{HOMA-IR} = 0.403 \times [\text{blood glucose}_{0\,\text{min}}\ (\text{mmol/L}) \times \text{insulin}_{0\,\text{min}}\ (\text{pmol/L})/405] \quad (3)$$

Statistical analysis

Data are presented as means ± SEMs and were generated by using the STATVIEW software program (version 5.0; SAS Institute Inc, Cary, NC). To evaluate the main effects and interactions of AN subtype (AN-R compared with AN-BP) and progress during treatment (good compared with poor responders) with the demographic and clinical data, parametric data were analyzed by 2-factor analysis of variance (ANOVA). In addition, one-factor ANOVA was used to compare the AN and control subjects. Categorical data, such as alcohol abuse, diabetes mellitus, and liver dysfunction, were analyzed by use of the chi-square test. One-factor ANOVA followed by Bonferroni correction was used to compare the results of the $II_{15\,min}$, $II_{30\,min}$, and other markers of glucose homeostasis on the 1st and the 2nd OGTT to evaluate the relation between each variable and weekly progress during treatment. In addition, to evaluate the relations between before and during the therapeutic intervention for each variable, the change values between the 1st and 2nd OGTT were analyzed by 2-factor ANOVA. The main effects and interactions of the group (good responders, poor responders, and control subjects) and the time course for both blood glucose and serum insulin concentrations were evaluated between each AN subgroup and control subjects by 2-factor ANOVA. One-factor ANOVA followed by Bonferroni correction evaluated differences in blood glucose and insulin concentrations between group means at each time point on the OGTT. All results were considered significant at $P < 0.05$.

RESULTS

We excluded 2 patients (1 with AN-R and the other with AN-BP) from this study because of nutritional edema, resulting in a study population of 48 AN patients and 13 healthy control subjects. The 48 AN patients were subdivided into 4 groups according to body weight changes when energy intake reached 6694 kJ/d (1600 kcal/d): 14 and 11 with AN-R were good and poor responders, respectively, and 11 and 12 with AN-BP were good and poor responders, respectively.

Demographic and clinical data

As shown in **Table 1**, 23 of 48 patients (48%) were considered poor responders. Two-factor ANOVA showed a significant main effect of AN subtype on BMI and a significant interaction for age between progress during treatment and AN subgroup. No other main effects or interactions were significant.

The two-factor ANOVA results in **Table 2** show a significant main effect of AN subtype on BMI and a significant main effect of progress during treatment on change in body weight. As also shown in Table 2, there were significant differences in BMI and liver dysfunction between the AN subgroups and control subjects. No other variables exerted significant main effects or interactions.

Early-phase insulin metabolism

No significant differences in $II_{15\,min}$ values on the 1st OGTT between the AN patients and the control subjects were found by one-factor ANOVA followed by Bonferroni correction (**Figure 1**). On the 2nd OGTT, however, one-factor ANOVA showed significant differences among the subjects ($P = 0.0005$). The $II_{15\,min}$ values for good responders in both AN subtypes were significantly higher than those of the control subjects and the poor responders. Two-factor ANOVA showed a significant main effect of progress during treatment on the change values of the $II_{15\,min}$ between the 1st and 2nd OGTT, whereas there were no significant main effects of AN subgroup or interaction between progress during treatment and AN subgroup.

Response curves

Significant main effects of group and time course on both blood glucose and serum insulin concentrations in AN-R were found by two-factor repeated-measures ANOVA (**Figure 2**). Significant interactions between group and time course for both blood glucose and serum insulin concentrations were also detected.

As also shown in Figure 2, fasting blood glucose concentrations of poor responders with AN-R were significantly lower than those of control subjects by one-factor ANOVA followed by Bonferroni correction. Late-phase blood glucose concentrations (ie, 30 and

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TABLE 2
Clinical characteristics of the patients and control subjects at the time of the second oral-glucose-tolerance test (OGTT)[1]

	AN-R patients		AN-BP patients		
	Good responders (n = 14)	Poor responders (n = 11)	Good responders (n = 11)	Poor responders (n = 12)	Control subjects (n = 13)
BMI (kg/m^2)[2]	14.4 ± 1.8[3,4]	14.2 ± 1.7[4]	15.3 ± 1.6[4]	15.7 ± 1.7[4]	20.9 ± 1.0
Change in body weight (kg)[5]	0.9 ± 0.3	−0.02 ± 0.5	0.7 ± 0.2	−0.3 ± 0.6	—
Hospitalization (mo)[6]	2.8 ± 2.2	3.1 ± 1.0	3.2 ± 1.8	3.2 ± 2.2	—
Energy (kJ·d^{-1}·kg body wt^{-1})	195.0 ± 23.8	195.8 ± 41.4	184.1 ± 19.2	180.0 ± 18.8	—
Serum potassium (mmol/L)[7]	4.1 ± 0.4	3.9 ± 0.5	3.8 ± 0.5	3.9 ± 0.5	4.0 ± 0.1
Liver dysfunction[8]	9/14	5/11	4/11	2/12	0/13

[1]The second OGTT was performed when energy intake had reached 6694 kJ/d. AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge eating–purging type.
[2]Significant main effect of AN subtype, $P < 0.05$ (two-factor ANOVA).
[3]$\bar{x}$ ± SD.
[4]Significantly different from control subjects, $P < 0.0001$ (one-factor ANOVA with Bonferroni correction).
[5]Change in body weight during the week before the second OGTT. Significant main effect of progress during treatment, $P < 0.0001$ (two-factor ANOVA).
[6]Periods of hospitalization before the second OGTT.
[7]Normal range: 3.3–4.8 mmol/L.
[8]Serum aminotransferase shows abnormalities (yes/all). $P < 0.01$ by the chi-square test for all 5 groups.

60 min after the glucose load) of both good and poor responders with AN-R were significantly lower than those of control subjects. Serum insulin concentrations of good responders with AN-R 15 min after glucose administration were significantly higher than those of both control subjects and poor responders.

As shown in **Figure 3**, significant main effects of the time course for both blood glucose and serum insulin concentrations in AN-BP patients were detected by two-factor repeated-measures ANOVA, whereas significant main effects of the group or significant interactions between the group and the time course were not detected.

Other markers of glucose homeostasis

As shown in **Table 3**, whereas fasting serum insulin, the ratio of fasting blood glucose to fasting serum insulin, and HOMA-IR values differed significantly between good responders with AN-R and control subjects, glucose markers between good and poor responders among AN patients and control subjects were not significantly different on the 1st OGTT. On the 2nd OGTT, fasting serum insulin, the ratio of fasting blood glucose to fasting serum insulin, HOMA-IR, area under the curve, and $II_{30\,min}$ values did not differ significantly between good and poor responders. Two-factor ANOVA showed a significant main effect of AN subgroup on the change value of the $II_{30\,min}$ and a significant interaction for the change value of the area under the curve between progress during treatment and AN subgroup.

As also shown in Table 3, on the 1st OGTT, the fasting blood glucose values for good responders in both AN groups were significantly lower than those of the control subjects by one-factor ANOVA. Significant differences in the fasting blood glucose values between good and poor responders were not detected on the 2nd OGTT. Two-factor ANOVA showed a significant main effect of progress during treatment for the change values of fasting blood glucose, whereas there was no significant main effect of AN subgroup ($P = 0.32$) or interaction between progress during treatment and AN subgroup ($P = 0.15$).

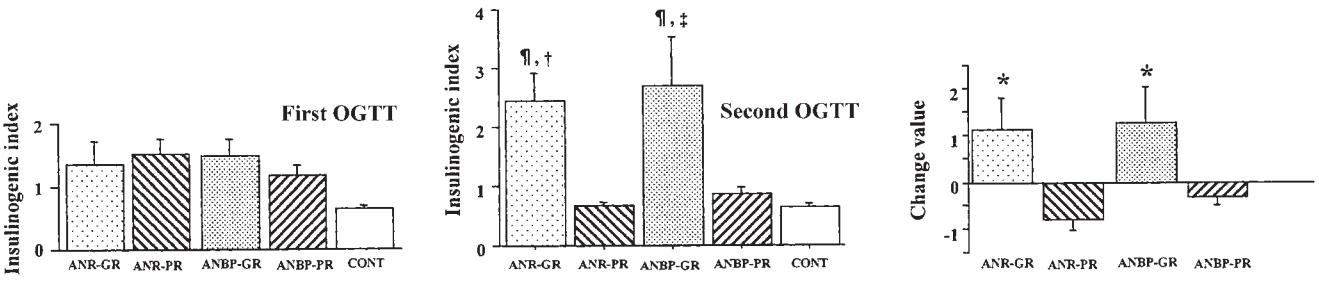

FIGURE 1. Mean (± SE) insulinogenic index after 15 min ($II_{15\,min}$) of the first and second oral-glucose-tolerance test (OGTT) in patients with anorexia nervosa restricting type who were good responders to treatment (ANR-GR; n = 14), patients with anorexia nervosa restricting type who were poor responders to treatment (ANR-PR; n = 11), patients with anorexia nervosa binge eating–purging type who were good responders to treatment (ANBP-GR; n = 11); patients with anorexia nervosa binge eating–purging type who were poor responders to treatment (ANBP-PR; n = 12), and control subjects (CONT; n = 13). The change value is the difference in the $II_{15\,min}$ value between the first and second test. There were no significant differences in the $II_{15\,min}$ value on the first test ($P = 0.092$), but there were significant differences on the second ($P = 0.0005$, one-factor ANOVA followed by Bonferroni correction). ¶Significantly different from control subjects, $P < 0.005$. †Significantly different from ANR-PR patients, $P < 0.005$. ‡Significantly different from ANBP-PR patients, $P < 0.005$. Two-factor ANOVA showed significant main effects of progress during treatment for the change values (*$P = 0.023$), but no significant main effects of AN subgroup ($P = 0.52$) and no progress during treatment–by–AN subgroup interactions ($P = 0.72$).

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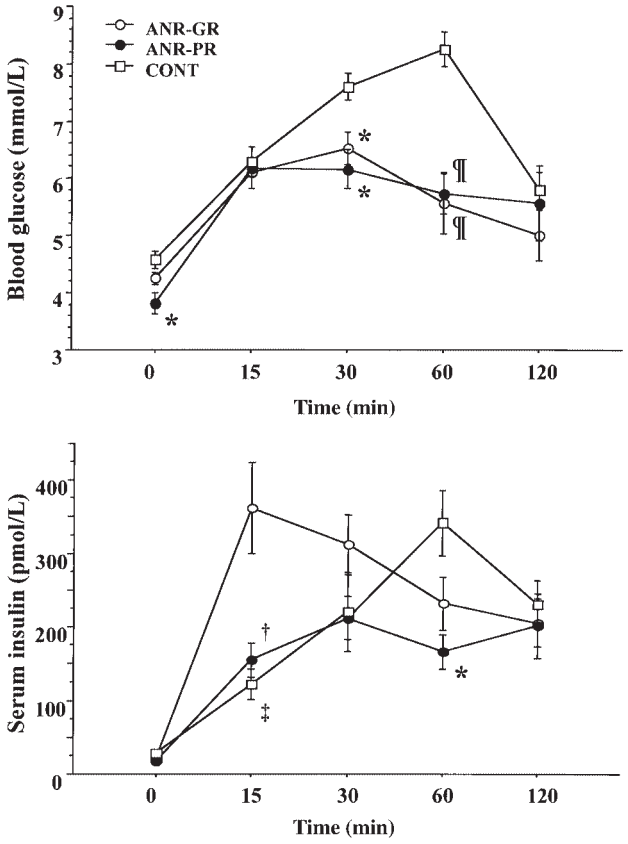

FIGURE 2. Mean (±SE) glucose and insulin response curves during an oral-glucose-tolerance test in patients with anorexia nervosa restricting type who were good responders to treatment (ANR-GR; $n = 14$), patients with anorexia nervosa restricting type who were poor responders to treatment (ANR-PR; $n = 11$), and control subjects (CONT; $n = 13$). There were significant main effects of group and time course on blood glucose concentrations ($P = 0.0068$ and $P < 0.0001$, respectively) and significant main effects of group and time course on serum insulin concentrations ($P = 0.033$ and $P < 0.0001$, respectively) by two-factor repeated-measures ANOVA. There were significant interactions between group and time course for both blood glucose and serum insulin concentrations ($P < 0.0001$ and $P < 0.0001$, respectively). Subgroup analysis was performed by one-factor ANOVA followed by Bonferroni correction. *¶Significantly different from control subjects: $^{*}P < 0.005$, $^{¶}P < 0.0001$. †,‡Significantly different from ANR-GR patients: $^{†}P < 0.005$, $^{‡}P < 0.001$.

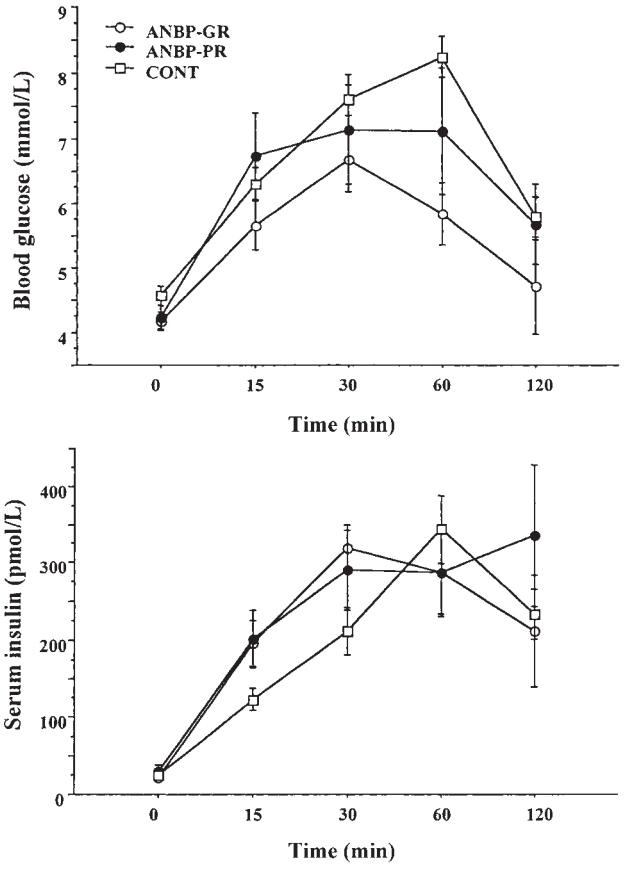

FIGURE 3. Mean (±SE) glucose and insulin response curves during an oral-glucose-tolerance test in patients with anorexia nervosa binge eating–purging type who were good responders to treatment (ANBP-GR; $n = 11$); patients with anorexia nervosa binge eating–purging type who were poor responders to treatment (ANBP-PR; $n = 12$), and control subjects (CONT; $n = 13$). There were significant main effects of time course for both blood glucose and serum insulin concentrations by two-factor repeated-measures ANOVA ($P < 0.0001$ and $P < 0.0001$, respectively). There were no significant main effects of group for both blood glucose and serum insulin concentrations ($P = 0.18$ and $P = 0.57$, respectively) and no significant group-by–time course interactions ($P = 0.10$ and $P = 0.17$, respectively).

DISCUSSION

The most important findings of this study were that the $II_{15\,min}$ values of good responders with AN were significantly higher than those of the other groups, suggesting that the response of early-phase insulin secretion increased in good responders, as $II_{30\,min}$ values were shown to do elsewhere (28). We found significant differences only in the $II_{15\,min}$ values during the 2nd OGTT between good and poor responders; other variables involving $II_{30\,min}$ values did not differ significantly. These findings suggest that the very early phase (15 min) of insulin metabolism, rather than that at 30 min, may play an important role in AN. This effect may relate to gastrointestinal hormones that reportedly activate early-phase insulin secretion (15 min) after a glucose load (29). Moreover, the fasting blood glucose values on the 2nd OGTT did not differ significantly between good and poor responders in either AN subgroups, whereas significant main effects of progress during treatment were detected in the change values of both the $II_{15\,min}$ and fasting blood glucose. These findings suggest that fasting blood glucose values during treatment (on the second OGTT) are an insufficient marker with which to evaluate the differences between good and poor responders.

Several studies have shown a significant difference between AN-R and AN-BP patients in the energy intake required to maintain a stable body weight after nutritional rehabilitation (31–33). Kaye et al (31) reported that AN-R patients required 30–50% more energy than did AN-BP patients. The present study found that basal blood glucose concentrations and those during the late phase of the OGTT were significantly lower only in AN-R patients compared with control subjects. These findings suggest that the normalization of blood

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TABLE 3
Other markers of glucose metabolism[1]

	AN-R patients		AN-BP patients		
	Good responders (n = 14)	Poor responders (n = 11)	Good responders (n = 11)	Poor responders (n = 12)	Control subjects (n = 13)
FBG (mmol/L)					
1st OGTT	3.96 ± 0.30[2]	4.13 ± 0.69	3.99 ± 0.37[2]	4.19 ± 0.43	4.58 ± 0.55
2nd OGTT	4.25 ± 0.39	3.82 ± 0.67[3]	4.19 ± 0.44	4.23 ± 0.65	4.58 ± 0.55
Change[4,5]	0.28 ± 0.50	−0.34 ± 0.63	0.20 ± 0.60	0.07 ± 0.63	—
FIRI (pmol/L)					
1st OGTT	16.84 ± 10.53[2]	21.43 ± 13.94	27.43 ± 17.06	28.71 ± 16.03	37.42 ± 14.43
2nd OGTT	30.10 ± 13.15	26.57 ± 15.90	30.79 ± 13.85	44.24 ± 40.48	37.42 ± 14.43
Change[4]	13.42 ± 19.08	4.68 ± 14.82	3.36 ± 19.90	16.74 ± 36.11	—
FBG:FIRI (mmol/pmol)					
1st OGTT	0.34 ± 0.20[2]	0.26 ± 0.16	0.20 ± 0.12	0.21 ± 0.14	0.14 ± 0.05
2nd OGTT	0.16 ± 0.06	0.21 ± 0.16	0.17 ± 0.10	0.17 ± 0.12	0.14 ± 0.05
Change[4]	−0.18 ± 0.21	−0.05 ± 0.15	−0.03 ± 0.09	−0.04 ± 0.08	—
HOMA-IR (mmol·pmol/L^2)					
1st OGTT	0.41 ± 0.25[2]	0.58 ± 0.48	0.67 ± 0.41	0.76 ± 0.46	1.07 ± 0.48
2nd OGTT	0.80 ± 0.38	0.64 ± 0.43	0.79 ± 0.39	1.18 ± 1.16	1.07 ± 0.48
Change[4]	0.39 ± 0.53	0.06 ± 0.40	0.12 ± 0.52	0.42 ± 1.00	—
AUC (pmol·h/L)					
1st OGTT	565.32 ± 228.94	674.16 ± 264.32	903.80 ± 636.71	685.66 ± 333.47	705.70 ± 282.98
2nd OGTT	634.73 ± 260.53	486.58 ± 181.47	704.32 ± 326.20	777.41 ± 515.13	705.70 ± 282.98
Change[4,6]	69.41 ± 229.08	−187.58 ± 378.44	−199.48 ± 704.57	91.75 ± 425.97	—
II_{30min}					
1st OGTT	1.82 ± 1.38	2.10 ± 1.41[3]	1.43 ± 1.30	1.19 ± 0.80	0.72 ± 0.45
2nd OGTT	1.68 ± 0.92	1.12 ± 0.84	2.27 ± 2.39	1.64 ± 1.36	0.72 ± 0.45
Change[4,7]	−0.13 ± 1.45	−0.96 ± 1.60	0.84 ± 2.89	0.45 ± 1.49	—

[1] $\bar{x}$ ± SD. FBG, fasting blood glucose concentration; OGTT, oral-glucose-tolerance test; FIRI, fasting serum insulin concentration; HOMA-IR, homeostasis model assessment for insulin resistance; AUC, insulin area under the curve; II_{30min}, insulinogenic index at 30 min. The first OGTT was performed on the seventh hospital day. The second OGTT was performed when energy intake had reached 6694 kJ/d.

[2,3] Significantly different from control subjects (one-factor ANOVA with Bonferroni correction): [2] $P < 0.001$, [3] $P < 0.005$.

[4] Each data point represents the change between the first and the second OGTT.

[5] Significant main effect of progress during treatment, $P < 0.05$ (two-factor ANOVA).

[6] Significant interaction between progress during treatment and AN subtype, $P < 0.05$ (two-factor ANOVA).

[7] Significant main effect of AN subtype, $P < 0.05$ (two-factor ANOVA).

glucose responses during the OGTT is significantly delayed only in AN-R groups. Therefore, we conclude that our findings are compatible with those of previous studies and that the $II_{15\,min}$ value is an important marker that can assess the progress of nutritional rehabilitation in both AN subtypes, despite significant differences between the subtypes in restoration of nutritional status.

Russell et al (17) administered the OGTT to 15 patients with bulimia nervosa and reported that patients with unstable weight who binged and vomited frequently had a blunted insulin response, that patients with stable weight who infrequently binged and vomited had exaggerated response patterns, and that responses were normal in patients after nutritional rehabilitation. Casper et al (34) administered the OGTT to 26 patients with AN and reported that the glucose and insulin responses of those who recovered normal body weight (n = 19) normalized, and that those patients who tended to be more diet-conscious developed elevated fasting free fatty acid (FFA) concentrations. Nonrecovered patients (n = 7) had abnormal eating attitudes, high fasting FFA concentrations, higher plasma glucose concentrations, and significant delays in serum insulin secretion during the OGTT. The authors implied that fasting FFA concentrations reflect eating attitudes. The results of these recent studies suggest that glucose and insulin secretion are closely affiliated with body weight and eating behavior, and that these responses are reversible during nutritional rehabilitation. Therefore, we believe that glucose metabolism is a good marker of nutritional rehabilitation in patients with AN. Although we also examined other markers of glucose homeostasis, only the $II_{15\,min}$ value closely correlated with nutritional rehabilitation.

In contrast, concentrations of several markers, such as FFAs, insulin-like growth factor 1, and gut hormones, change during nutritional rehabilitation in patients with AN (12, 35, 36). Caregaro et al (35) associated a significant increase in insulin-like growth factor 1 values with eating disorders during the early phase of a nutritional program. Otto et al (36) reported that fasting plasma ghrelin concentrations in patients with AN were significantly higher than those of controls and that therapeutic intervention caused a BMI increase of 14% as well as a 25% decrease in circulating ghrelin concentrations. These markers play an important role in the regulation of insulin metabolism; FFA counterregulates and gut hormones, especially incretin and ghrelin, activate

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insulin secretion (34, 36, 37). Further studies are needed to investigate the relation between these markers and the $II_{15\,min}$ value.

This study was limited by assessing the patients only when they were consuming 6694 kJ (1600 kcal). Although other investigators have found that the energy intake required to inhibit a decrease in body weight and to maintain it after nutritional rehabilitation is ≈5021 kJ (1200 kcal) and 7531 kJ (1800 kcal), respectively (22, 38); we considered 6694 kJ (1600 kcal) sufficient for weight gain. This was because we restricted activity during these periods of energy intake, allowing patients only to walk within the unit under staff observation. Moreover, many patients might have developed an intense fear of becoming fat during periods of high-energy intake and thus may have manipulated their body weight or overestimated their reports of daily intake (22, 27). We consider our reports of daily energy intake and the change in body weight to be reliable because these values were measured by the staff and not by the patients themselves. We weighed the patients twice if we considered their weight gain to be questionable and excluded patients whose weight gain was not due to nutritional rehabilitation but to other factors.

Another limitation of the present study is that we did not examine other factors that modify insulin secretion in patients with AN, including gastrointestinal function (39, 40); the entero-insular axis, including gastrointestinal hormones (37); and pancreatic b cell function (41). Because of this, we could not determine factors that caused the differences in the $II_{15\,min}$ values between good and poor responders. We observed that, whereas BMI did not differ either at the time of admission or during the second examination and energy intake was similar, changes in body weight significantly differed between good and poor responders in both AN subtypes. We deemed that the foregoing factors, especially gastrointestinal function and hormones, might be related to these findings, and further investigations are required to address these issues.

In summary, we found that $II_{15\,min}$ values closely correlated with progress during nutritional rehabilitation as measured by a weight gain of 0.5 kg/wk. This index may be a useful marker with which to assess the weekly progress of nutritional rehabilitation in patients with AN.

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