Intravenous Glucose Tolerance Test–Derived Glucose Effectiveness in Bulimia Nervosa

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The aim of the present study was to estimate insulin secretion, insulin sensitivity (SI), and glucose effectiveness at basal insulin (SG) in subjects with bulimia nervosa. Eight bulimic patients and eight age-, body mass index–, and sex-matched healthy control subjects without a family history of diabetes were studied. The subjects all had normal glucose tolerance. They underwent a modified frequently sampled intravenous glucose tolerance test; glucose (300 mg/kg body weight) was administered, and insulin (4 mU/kg body weight/min) was infused from 20 to 25 minutes after administration of glucose. SI and SG were estimated by Bergman's minimal model method. Basal insulin (27 ± 3 *v* 45 ± 3 pmol/L) was significantly lower in bulimic patients than in normal controls ($P < .05$), but basal glucose was similar between the two groups (4.5 ± 0.1 *v* 4.9 ± 0.1 mmol/L, $P > .05$). The glucose disappearance rate (KG) and acute insulin response to glucose estimated by the intravenous glucose tolerance test ($AIR_{glucose}$) were similar between the two groups (KG, 1.35 ± 0.29 *v* 2.20 ± 0.21 min^{-1}, $P > .05$; $AIR_{glucose}$, 2,920 ± 547 *v* 2,368 ± 367 pmol/L · min, $P > .05$). No significant difference was observed in SI between the two groups (1.34 ± 0.18 *v* 1.25 ± 0.20 × 10^{-4} · min^{-1} · pmol/ L^{-1}, $P > .05$). On the other hand, glucose effectiveness at basal (SG) and zero (GEZI) insulin was significantly diminished in comparison to normal controls (SG, 0.011 ± 0.002 *v* 0.024 ± 0.002 min^{-1}, $P < .01$; GEZI, 0.008 ± 0.002 *v* 0.017 ± 0.003 min^{-1}, $P < .01$). Thus, bulimic patients with normal glucose tolerance without a family history of diabetes were characterized by normal insulin secretion, normal SI, and reduced SG and GEZI.

BULIMIA NERVOSA is a syndrome characterized by recurrent episodes of binge eating, an inability to stop eating voluntarily, and self-induced vomiting. In contrast, anorexia nervosa is a syndrome accompanied by extreme weight loss and rigid caloric deprivation. Thus, both are considered the extreme of eating disorders, but bulimic behavior is sometimes present in patients with anorexia nervosa and both bulimia and anorexia occur at different times in the same patients,[1-3] suggesting that common psychoneuroendocrinological findings may exist in both disorders. This idea is supported by the similarity in the secretion of anterior pituitary hormone such as corticotropin and thyrotropin.[4] On the other hand, there is a possibility that these two distinct eating disorders per se alter carbohydrate metabolism, since it is considered that undernutrition or protein energy malnutrition causes glucose intolerance in humans.[5]

There are some reports on carbohydrate metabolism in patients with eating disorders. In anorectic patients, plasma glucose and insulin levels are frequently low and an abnormal insulin response to glucose is reported.[6-8] The peripheral effects of insulin have been shown to be increased[9,10] or normal.[11] We previously reported anorectic patients (dietary restricters) who had diminished glucose effectiveness.[10] Glucose effectiveness is defined as the ability of glucose to normalize its own concentration at basal insulin. However, to the best of our knowledge, little is known about carbohydrate metabolism in patients with bulimia nervosa. Insulin secretion, insulin sensitivity, and glucose effectiveness can be measured simultaneously by the minimal model as shown by Bergman.[12] To this end, we used the minimal model approach in eight patients with bulimia nervosa, and the results were compared with data from eight sex-, age-, and body mass index–matched normal controls. All subjects had normal glucose tolerance based on the 1985 World Health Organization criteria[13] and had no family history of diabetes.

SUBJECTS AND METHODS

Eight bulimic and eight normal women matched for age and body mass index were studied (Table 1). The patients were outpatients and were diagnosed according to DSM-III-R criteria.[14] All subjects had normal glucose tolerance based on the 1985 World Health Organization criteria[13] and were free of neurologic, renal, cardiovascular, hepatic, or other internal disease. They were studied in the follicular phase of the menstrual cycle. For at least 3 days before the test, their body weight was stable and they did not perform heavy exercise. Moreover, they did not take any medications known to alter carbohydrate metabolism. Before participation, the nature, purpose, and risks of the study were explained to all subjects and informed written consent was obtained.

After an overnight fast, a butterfly needle was inserted into the antecubital vein and maintained by a slow drip of physiological saline. Subjects were allowed to rest quietly for at least 15 minutes before blood sampling was begun. Baseline samples for glucose and insulin assays were obtained at −20, −10, and −3 minutes. Glucose (300 mg/kg body weight) was administered intravenously within 2 minutes, and subsequent samples were obtained from the contralateral antecubital vein at frequent intervals until 180 minutes as previously described.[15,16] Plasma was frozen and stored at −20°C for subsequent analysis. Insulin (20 mU/kg over 5 minutes) was infused into the antecubital vein from 20 to 25 minutes after administration of glucose.[15,16]

Plasma glucose level was measured in duplicate with an automatic analyzer (Kyoto-Daiichi-Kagaku, Kyoto, Japan) by the glucose oxidase

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Table 1. Clinical Characteristics and Minimal Model Analysis of the Study Group (mean ± SEM)

Group	Age (yr)	BMI (kg/m²)	Fasting Glucose (mmol/L)	Fasting Insulin (pmol/L)	$AIR_{glucose}$ (pmol/L · min)	SI ($\times 10^4 \cdot min^{-1} \cdot pmol/L^{-1}$)	KG (min^{-1})	SG (min^{-1})	GEZI (min^{-1})	BIE (min^{-1})
Bulimia	21.4 ± 1.3	18.8 ± 1.3	4.5 ± 0.1	27 ± 3*	2,920 ± 547	1.34 ± 0.18	1.35 ± 0.29	0.011 ± 0.002*	0.008 ± 0.002†	0.003 ± 0.004
Normal	21.5 ± 0.4	20.6 ± 0.5	4.9 ± 0.1	45 ± 3	2,368 ± 367	1.25 ± 0.20	2.20 ± 0.21	0.024 ± 0.002	0.017 ± 0.003	0.006 ± 0.001

Abbreviation: BMI, body mass index.
*$P < .01$ *v* normal.
†$P < .05$ *v* normal.

method. Immunoreactive insulin was assayed in duplicate using a Phadeseph insulin RIA kit (Shionogi, Osaka, Japan). Coefficients of variation were 4% for insulin levels greater than 180 pmol/L and 7% for insulin levels less than 180 pmol/L, respectively.

The glucose disappearance rate (KG) was calculated as the slope of the least-square regression line relating the natural logarithm of glucose concentration to time from more than four samples drawn between 10 and 19 minutes.

Insulin sensitivity and glucose effectiveness were estimated by the minimal model approach.[12] In this analysis, fluctuations in circulating glucose levels over time are described by the differential equations, $dG(t) = -p1\ [G(t) - Gb] - X(t)G(t)$ and $dX(t) = -p2\ X(t) + p3\ [I(t) - Ib]$, where G(t) is the plasma glucose concentration, I(t) is the plasma insulin concentration, and Gb and Ib are baseline concentrations. X(t) represents the time course of the peripheral insulin effect. Parameter p1 represents the effect of glucose at basal insulin to normalize its own concentration in plasma independently of increased insulin. This parameter is known as glucose effectiveness (SG) and has been verified through comparison to studies in which the insulin secretory response was suppressed.[17] The ratio between p3 and p2 defines the insulin sensitivity index (SI), which represents the insulin-dependent increase in the net KG. Index SI has been validated by comparison to a direct measure of insulin sensitivity from glucose clamp experiments in humans.[18,19] The basal insulin effect (BIE) can be calculated as the product of basal insulin (Ib) and SI: $BIE = Ib \times SI$. Glucose effectiveness at zero insulin (GEZI) is the difference between SG and BIE: $GEZI = SG - (Ib \times SI)$. This measure is analogous to tissue glucose sensitivity.[20,21]

The minimal model program was written in Pascal (Borland International, Scotts Valley, CA) on a Macintosh IIcx computer (Apple Computer, Cupertino, CA) as described previously.[15,16] The precision of parameter estimates was evaluated using a covariance matrix as described previously[15,16] and expressed as the fractional standard deviation. The mean ± SEM of the fractional standard deviation for p1, p2, and p3 in 16 subjects was comparable to published results.[15,16]

Endogenous plasma insulin responses were expressed as the area under the insulin curve between 0 and 10 minutes after administration of glucose. The integrated area of plasma insulin above the basal level was calculated using the trapezoidal method.[22]

The data are expressed as the mean ± SEM. To evaluate differences between bulimic patients and normal subjects, data were analyzed by the Mann-Whitney *U* test, with *P* less than .05 being significant.[23]

RESULTS

The age of the bulimic patients was similar to that of the normal controls. Body mass index and fasting glucose level were lower in bulimic patients than in normal controls, but were not statistically significant. On the other hand, fasting insulin was significantly lower in bulimic patients than in normal controls (Table 1).

Metabolic parameters in bulimic patients and normal subjects are also listed in Table 1. The acute insulin response to intravenous glucose ($AIR_{glucose}$) and SI were similar between the two groups. There was no significant difference in KG between the two groups. On the other hand, SG and GEZI were significantly diminished in bulimic patients compared with normal controls. No significant difference was observed for BIE between the two groups.

DISCUSSION

In the present study, we investigated glucose kinetics in bulimic patients using the minimal model method of Bergman.[12] This approach enables us to estimate insulin sensitivity, insulin secretion, and glucose effectiveness simultaneously. Our bulimic patients had normal insulin sensitivity and normal insulin secretion, indicating that the insulin-dependent glucose uptake in response to intravenous glucose is normal.[24] On the other hand, SG and GEZI were decreased, suggesting an impairment in insulin-independent glucose uptake in response to intravenous glucose.[24] Glucose effectiveness is reported to be low not only in non–insulin-dependent diabetes mellitus (NIDDM) patients but also in impaired glucose tolerance (IGT) subjects.[15,16,25] Evidence has been provided that the ability of hyperglycemia to promote its own glucose uptake is impaired in NIDDM patients.[26] Our bulimic patients had normal glucose tolerance and no family history of NIDDM. Thus, the reason that our bulimic patients had decreased glucose effectiveness ($0.011 \pm 0.002\ min^{-1}$) similar to that reported in NIDDM patients ($0.011 \pm 0.002\ min^{-1}$ [15] and $0.014 \pm 0.001\ min^{-1}$ [25]) or IGT subjects ($0.014 \pm 0.001\ min^{-1}$ [16]) is not known at present. Of particular interest is that glucose effectiveness was similarly decreased but a lower insulin sensitivity and higher $AIR_{glucose}$ were observed in bulimic patients in comparison to restrictive anorectic patients reported by our group.[10] Eating behavior differs between bulimic and anorectic patients. Thus, it can be speculated that factors other than eating behavior decrease glucose effectiveness in patients with bulimia nervosa.

Glucose effectiveness is defined as the ability of glucose to normalize its own concentration at basal insulin. Therefore, it may be considered that two organs contribute to glucose effectiveness: liver and muscle. There are three reports suggesting that the organ contributing to glucose effectiveness is muscle.[26-28] DeFronzo et al[26] reported that although the suppression of hepatic glucose production by hyperglycemia is normal, the ability of hyperglycemia per se to enhance glucose uptake is impaired in NIDDM. We previously showed that physically trained subjects had not only higher insulin sensitivity but also higher glucose effectiveness.[27] Marchesini et al[28] demonstrated that glucose effectiveness was significantly correlated with the ratio of urinary creatinine to height, which is an indirect

measure of muscle mass in cirrhotic patients. However, it remains to be clarified whether glucose-mediated glucose disposal is disturbed in muscle of bulimic patients.

In summary, our present study demonstrated that normal glucose-tolerant bulimic patients without a family history of NIDDM had decreased glucose effectiveness, normal insulin sensitivity, and normal $AIR_{glucose}$. Although the reason that bulimic patients had a decreased glucose effectiveness is not known at present, the abnormality in glucose effectiveness may reflect a disturbance similar to that found in NIDDM or IGT. This syndrome thus provides an excellent experimental model to study the progress of the metabolic abnormalities found in NIDDM.

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