Improvement of Insulin Sensitivity and Dyslipidemia With a New α-Glucosidase Inhibitor, Voglibose, in Nondiabetic Hyperinsulinemic Subjects

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This study was undertaken to investigate the effect of voglibose, a new α-glucosidase inhibitor, on glucose and lipid metabolism in nondiabetic hyperinsulinemic subjects. Sixteen nondiabetic subjects with hyperinsulinemia participated in the study. They were divided into two groups of eight subjects with normal (NGT) and impaired (IGT) glucose tolerance. A meal tolerance test and a 75-g oral glucose tolerance test (OGTT) were performed at the beginning (baseline phase) and end (treatment phase) of the 12-week treatment. Serum lipid levels were measured every 4 weeks throughout the treatment phase and follow-up phase (8 weeks). All patients received 1 0.2-mg tablet of voglibose before each test meal (3 tablets per day). We also measured insulin sensitivity using a steady-state plasma glucose (SSPG) method in eight normotensive hyperinsulinemic subjects and in eight age- and body mass index (BMI)-matched control subjects before and after the drug treatment. Voglibose significantly decreased the responses of plasma glucose and insulin on the meal tolerance test. The area under the curve for 2-hour insulin during the 75-g OGTT decreased after treatment, whereas that for 2-hour glucose did not change before and after treatment. SSPG was reduced after treatment, indicating improvement of insulin sensitivity. Moreover, treatment with voglibose resulted in a significant decline of triglyceride level and an elevation of high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I. These values returned to near-baseline levels after the drug was discontinued. Consequently, we conclude that this agent not only has a direct hypoglycemic effect through decreased absorption of carbohydrate, but also a hypoinsulinemic and hypolipidemic effect via improved insulin sensitivity.

IT IS NOW well established through clinical studies[1] and population studies[2-6] that there is an association between hyperinsulinemia and cardiovascular disease. Recently, it was suggested that a cluster of risk factors such as dyslipidemia, hypertension, glucose intolerance, hyperinsulinemia, and obesity are associated not only with obstructive coronary artery disease,[7,8] but also with vasospastic angina.[9] Therefore, it is probably necessary to correct hyperinsulinemia by improving insulin resistance and normalizing glucose tolerance in both diabetic subjects and nondiabetic subjects. It is well known that weight reduction and exercise therapy can improve peripheral insulin sensitivity and pancreatic β-cell function.[10] Certain polysaccharides, ie, those rich in fiber, such as pectins, have also been shown to improve insulin binding to its receptor in diabetic subjects.[11]

Voglibose (Takeda, Osaka, Japan), a newly identified disaccharidase inhibitor, is a potent competitive inhibitor of intestinal α-glucosidase that delays the digestion and absorption of maltose and sucrose.[12] In an animal experiment, voglibose showed approximately 20- to 30-fold more potent inhibition of semipurified porcine small intestine disaccharidases as compared with acarbose, a typical α-glucosidase inhibitor.[13] Previous studies have shown that α-glucosidase inhibitors (acarbose and miglitol) are effective in reducing postprandial glucose and insulin levels in groups of patients with non–insulin-dependent diabetes mellitus (NIDDM).[14,15] As yet, no clinical study demonstrating the efficacy of this compound in the improvement of insulin sensitivity has been reported. The purpose of this study was to investigate the effects of voglibose treatment on endogenous insulin secretion, plasma glucose level, lipid levels, and insulin action in nondiabetic subjects with hyperinsulinemia.

SUBJECTS AND METHODS

Subjects

Sixteen nondiabetic subjects with hyperinsulinemia (10 men and six women) were randomly selected from patients at the outpatient clinic of the National Cardiovascular Center (Suita, Osaka, Japan). The diagnosis of hyperinsulinemia was based on the following laboratory findings: area under the plasma insulin concentration-time curve after oral administration of 75 g glucose greater than 110 μU/mL · h (normal mean reference value [mean ± 2 SD], 62 ± 48 μU/mL · h). The participants were classified into the following two groups based on initial oral glucose tolerance test (OGTT) results according to World Health Organization criteria[16]: eight subjects with normal glucose tolerance (NGT group) and eight with impaired glucose tolerance (IGT group). The two groups were comparable with respect to age (mean ± SEM: 56.5 ± 3.8 and 56.8 ± 3.4 years for NGT and IGT, respectively) and body mass index ([BMI] 24.2 ± 0.7 and 24.1 ± 0.5 kg/m^2, respectively). Five subjects had hypertension, and another six were overweight ($24 \leq BMI < 26.4$). In Japan, overweight is defined as a mean BMI of 24.8 in men and 25.1 in women aged 50 to 60 years. All subjects had normal liver, kidney, and thyroid function, and no subject had a history of coronary artery disease or obesity ($BMI \geq 26.4$). Subjects who were taking any lipid-lowering drugs, β-adrenergic–blocking drugs, or diuretics that might have a confounding effect on carbohydrate or lipid metabolism were excluded from the study. Informed consent was provided by all patients, and the study protocol was approved by the Ethics Committee of the National Cardiovascular Center.

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Study Protocol

All patients received one 0.2-mg tablet of voglibose 5 to 15 minutes before breakfast, lunch, and dinner (daily dose, 0.6 mg). The patients were evaluated at 4-week intervals in the outpatient clinic, and were instructed to continue their regular diet and exercise routines throughout the study period. Before the start of treatment and at the beginning and end of each 4-week segment of the 12-week treatment period, body weight was recorded and blood was collected for measurement of hemoglobin A_{1c} (HbA_{1c}), total cholesterol, high-density lipoprotein (HDL) cholesterol, apolipoprotein A-I, and apolipoprotein B levels. At the beginning and end (week 12) of the treatment period, we performed a meal tolerance test and a 75-g OGTT in all patients. Five to 15 minutes before each meal test, the subjects received 0.2 mg voglibose orally; we performed this test to evaluate the acute and chronic effects of voglibose on blood glucose and insulin responses. To determine whether voglibose reversed insulin resistance and altered plasma insulin levels, we also measured insulin sensitivity using the steady-state plasma glucose (SSPG) method in eight (four each with NGT and IGT) normotensive hyperinsulinemic subjects (age, 54.3 ± 3.5 years; BMI, 22.9 ± 0.4 kg/m^2) before and after 12 weeks of treatment, and compared the results with those obtained in eight (four each with NGT and IGT) age- and BMI-matched healthy control subjects (age, 54.1 ± 3.4 years; BMI, 22.8 ± 0.4 kg/m^2).

The test meal contained 500 kcal total energy consisting of 60% carbohydrate (75 g), 20% fat (10 g), and 20% protein (25 g) and was eaten at 9 AM after an overnight fast. The test meal was ingested within 20 minutes, and blood samples for glucose and insulin assay were obtained under fasting conditions and 1 and 2 hours after ingestion of the test meal. A standard 75-g OGTT (Trelan G 75; Shimizu, Shizuoka, Japan) was performed after an overnight fast, and plasma glucose and insulin levels were measured under fasting conditions and 30, 60, and 120 minutes after a 75-g glucose load. As compared with the test meal, Trelan G (liquid glucose) has a relatively high glucose content (34% glucose, 36% maltose, 16.5% polysaccharide, and 13.5% oligosaccharide). Therefore, results of the 75-g OGTT may reflect a secondary effect of the α-glucosidase inhibitor on glucose utilization.

Plasma glucose was determined by the glucose oxidase method,[17] and plasma insulin by double-antibody radioimmunoassay.[18] HbA_{1c},[19] total cholesterol,[20] triglyceride,[21] HDL cholesterol,[22] and apolipoproteins A-I and B[23] were determined as previously described. BMI was calculated as weight in kilograms divided by height in meters squared.

Insulin Sensitivity Test

Insulin sensitivity tests were performed in eight patients with hyperinsulinemia (four each with NGT and IGT) and eight age- and BMI-adjusted control subjects (four each with NGT and IGT). Insulin sensitivity was estimated by the SSPG method using Sandostatin (Sandoz, Basel, Switzerland),[24] as originally described by Harano et al.[25] After an overnight fast, glucose (6 mg/kg/min), KCl (0.5 μEq/kg/min), Novolin R 40 insulin (7.5-mU/kg bolus followed by continuous 0.77-mU/kg/min infusion [Novo, Copenhagen, Denmark] using an insulin infusion pump SP-3HQ; [Nipro, Osaka, Japan]), and Sandostatin (1.25 μg/min) were simultaneously infused for 2 hours at the rate of 3 mL/kg/h via an antecubital vein using a constant-infusion pump (Nipro SP-10). Blood samples were obtained at 0, 30, and 120 minutes for determination of plasma glucose and insulin. Levels of both in samples obtained at 120 minutes were almost equal to the steady-state levels, as confirmed previously using glucose monitoring.[26] Under these steady-state conditions, plasma glucose is inversely correlated with insulin sensitivity: the higher the SSPG, the greater the insulin resistance.

Statistical Analyses

Results are presented as the mean ± SEM. Comparisons were made within each group to determine the effects of the drug on glucose and lipid metabolism. The areas under the concentration (C) curves for glucose (2-hour glucose area) and insulin (2-hour insulin area) were determined using the trapezoidal rule,[27] as follows: area under the curve = $[(C_0 + C_{30})/2 \times 0.5] + [(C_{30} + C_{60})/2 \times 0.5] + [(C_{60} + C_{120})/2]$. The significance of differences between control and hyperinsulinemic subjects was determined by ANOVA. Statistical analysis was performed using the paired Student's *t* test and paired Wilcoxon's signed rank test, respectively, for parametric data (BMI, total cholesterol, HDL cholesterol, apolipoprotein A-I, and apolipoprotein B) and nonparametric data (HbA_{1c}, immunoreactive insulin, steady-state plasma insulin [SSPI], SSPG, and triglyceride), with *P* less than .05 indicating significance.

RESULTS

Mean plasma glucose and insulin levels during the OGTT before and after voglibose treatment are shown in Figs 1 and 2. Although posttreatment plasma glucose values were lower than pretreatment values at each point of measurement throughout the 120-minute period and 2-hour glucose area, none of the differences reached statistical significance. Almost without exception, plasma insulin responses were lower posttreatment compared with pretreatment, especially at 60 to 120 minutes. After voglibose treatment, the 2-hour insulin area decreased from 151.5 ± 16.8 to 107.5 ± 14.9 μU/mL · h in the NGT group ($P < .01$) and from 161.6 ± 18.1 to 108.1 ± 17.1 mg/dL · h in the IGT group ($P < .01$). In contrast, the 2-hour glucose area did not differ in either the NGT or IGT group before (270.4 ± 13.7 and 365.7 ± 21.4 mg/dL · h, respectively) and after (273.2 ± 25.1 and 349.8 ± 16.7 mg/dL · h, respectively) voglibose treatment.

In subjects with NGT, voglibose treatment significantly reduced plasma glucose levels at 60 minutes and plasma insulin levels at 60 and 120 minutes with the meal tests, whereas fasting plasma insulin levels were not affected (Table 1). In subjects with IGT, voglibose treatment significantly reduced plasma glucose levels at 60 and 120 minutes and plasma insulin levels at 0 and 120 minutes with the meal tests.

Within each group studied, baseline lipid and lipoprotein assays showed low HDL cholesterol and high triglyceride levels (Table 2). BMI and systemic blood pressure remained constant throughout the 20 weeks of study. Although HbA_{1c} showed a slight reduction during the 12-week treatment period in both groups, none of the differences reached statistical significance. No significant differences (as compared with baseline levels) were found for fasting total cholesterol or apolipoprotein B during the 12-week period of treatment. Moreover, this agent did not affect low-density lipoprotein cholesterol levels (data not shown). Treatment with voglibose resulted in a significant decline in triglyceride levels after 4 weeks of treatment, followed by a return to near-baseline values after discontinuation of the

drug. The treatment was associated with a significant increase of HDL cholesterol and apolipoprotein A-I.

SSPG levels of the two age- and BMI-matched control (n = 8) and hyperinsulinemic (n = 8) groups are shown in Fig 3. The mean SSPG level (196.6 ± 15.5 mg/dL) before treatment in hyperinsulinemic subjects was significantly higher than in control subjects (controls, 97.1 ± 6.2 mg/dL; NGT, 86.4 ± 4.7; IGT, 104.3 ± 5.6). SSPG level significantly ($P < .05$) decreased to 157.1 ± 18.3 mg/dL after voglibose treatment. Of eight insulin-resistant subjects, seven exhibited a reduction of SSPG level, indicating improvement of insulin sensitivity for glucose utilization at the SSPI level. SSPI levels before and after voglibose treatment were 55.7 ± 3.5 and 54.4 ± 4.6 μU/mL · h, respectively, which were not significantly different.

Administration of voglibose was associated with softening of the stool in two patients (13%), flatulence in one patient (6%), and abdominal distension in two patients (13%). These side effects tended to diminish during the course of treatment. No patients developed severe side effects or failed to complete the study.

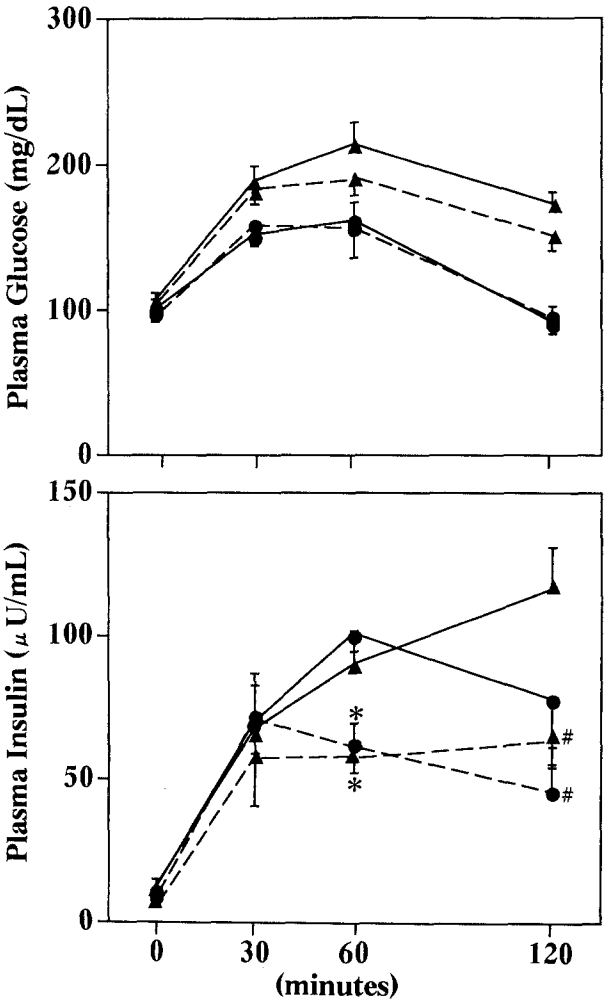

Fig 1. Plasma glucose and insulin responses to 75-g OGTT before and after treatment with voglibose in study subjects. NGT (●); IGT (▲); before treatment (——); after treatment (----). *$P < .05$, #$P < .01$: *v* before treatment.

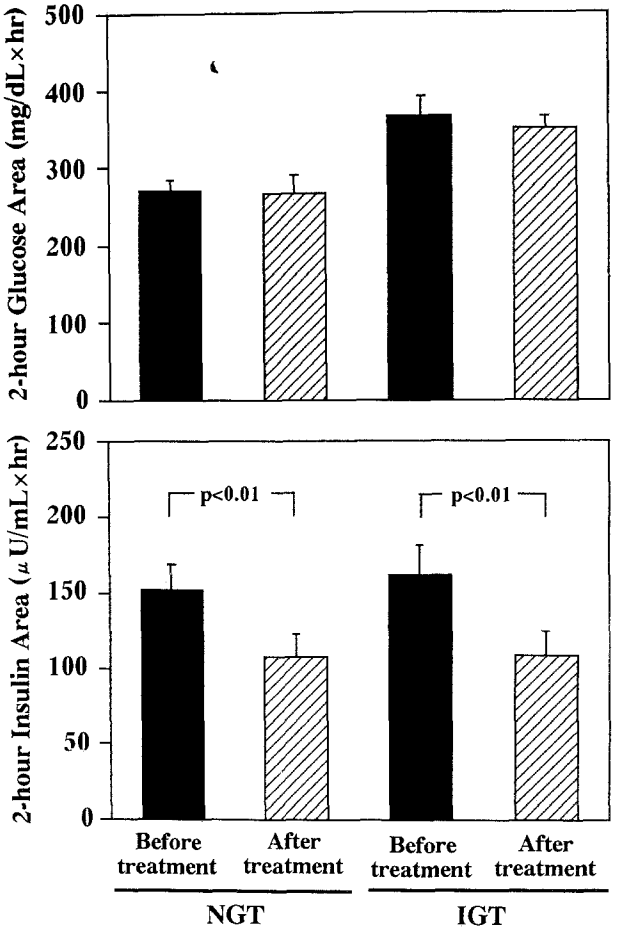

Fig 2. Plasma glucose and insulin areas during 75-g OGTT before and after treatment with voglibose in study subjects.

DISCUSSION

Twelve weeks of treatment with the α-glucosidase inhibitor, voglibose, not only produced an appreciable decrease in the postprandial plasma glucose level after a test meal, but also decreased the insulin level following meal ingestion. The observed effect of this agent on the meal tolerance test result may be indicative of a direct action of this drug in delaying or partly inhibiting starch and sucrose digestion, leading to a slower entrance of glucose into the circulation.[28] In addition, voglibose treatment significantly reduced the SSPG level (by 20%), indicating enhancement of insulin sensitivity for glucose utilization. During the OGTT, insulin responses were significantly reduced, with no change in glycemic excursions. Because this agent does not directly affect glucose absorption and because Trelan G has a relatively high glucose content (34%), the hypoinsulinemic effect of this agent in the case of Trelan G ingestion is thought to include a secondary effect resulting from improvement of peripheral insulin sensitivity. On the other hand, SSPI levels at 2 hours in this study (41.7 to 75.0 μU/mL) did not differ before and after treatment, and were comparable

Table 1. Effect of 12-Week Treatment With Voglibose on Glucose Metabolism During Meal Tolerance Test

Variable	NGT (n = 8)			IGT (n = 8)		
	Before Treatment	After Treatment	P	Before Treatment	After Treatment	P
PG (mg/dL)						
Fasting	102.8 ± 5.2	100.2 ± 5.4	NS	101.3 ± 3.5	93.8 ± 4.0	NS
1-hour	145.4 ± 12.8	123.7 ± 9.5	<.05	153.9 ± 15.8	128.6 ± 8.8	<.05
2-hour	122.9 ± 8.5	114.9 ± 6.9	NS	147.5 ± 12.5	113.5 ± 6.0	<.01
IRI (μU/mL)						
Fasting	9.4 ± 1.7	8.4 ± 1.2	NS	10.8 ± 3.4	6.4 ± 0.7	<.05
1-hour	53.4 ± 4.4	35.9 ± 5.9	<.05	59.2 ± 5.8	50.7 ± 7.5	NS
2-hour	53.8 ± 7.4	30.1 ± 3.1	<.01	58.3 ± 10.0	38.7 ± 5.6	<.05

NOTE. Values are the mean ± SEM.

Abbreviations: PG, plasma glucose; IRI, immunoreactive insulin.

to the physiological meal-stimulated level typically observed in hyperinsulinemic subjects in Japan.

α-Glucosidase inhibitors impair the conversion of disaccharides to monosaccharides in the small intestine, leading to a reduced increase in postprandial blood glucose.[29] Clinical investigation of acarbose[14] and the two other α-glucosidase inhibitors, miglitol and emiglitate, has shown that they improve glycemic control in both NIDDM and insulin-dependent diabetes mellitus (IDDM) patients.[30] Some studies have demonstrated a significant decrease in postprandial insulin levels, which may be particularly important in obese and NIDDM patients presenting with insulin resistance and hyperinsulinemia.[31,32] However, no previous reports have indicated an improvement of insulin sensitivity in these subjects. Baron et al[33] reported that short-term (2-week) acarbose treatment produced a small improvement in hepatic insulin sensitivity but had no effect on peripheral insulin sensitivity in NIDDM patients. Recently, Jenney et al[34] found that a lower dose of acarbose decreased postprandial glycemic excursion without changes in insulin sensitivity in NIDDM patients. In the present study of nondiabetic subjects, SSPG levels were significantly reduced after 12 weeks of voglibose treatment, indicating a long-term enhancing effect on insulin sensitivity.

Prolonged clinical administration of acarbose is known to induce intestinal adaptation, resulting in a reduction of the effect of the drug.[35] In an animal experiment, in contrast, this adaptation was not observed after treatment with voglibose 1 mg/kg for 4 weeks.[36] Since an inverse relationship was noted between plasma insulin level and number of

Table 2. Effect of 12-Week Treatment With Voglibose on Serum Lipid, Lipoprotein, Apolipoprotein, and Other Relevant Variables

Variable	Baseline Phase	Treatment Phase			Follow-up Phase	
		Week 4	Week 8	Week 12	Week 4	Week 8
BMI (kg/m²)						
NGT	24.2 ± 2.4	24.0 ± 2.5	24.0 ± 2.9	24.5 ± 3.0	24.2 ± 3.0	24.1 ± 2.9
IGT	24.4 ± 1.3	24.5 ± 1.1	24.3 ± 1.1	24.5 ± 1.2	24.4 ± 1.3	24.0 ± 1.0
HbA_{1c} (%)						
NGT	4.88 ± 0.16	4.58 ± 0.15	4.56 ± 0.14	4.62 ± 0.14	4.78 ± 0.12	4.76 ± 0.11
IGT	4.90 ± 0.19	4.91 ± 0.16	4.98 ± 0.15	4.83 ± 0.16	4.92 ± 0.22	4.87 ± 0.12
Total cholesterol (mg/dL)						
NGT	205.1 ± 11.5	202.1 ± 16.0	209.7 ± 18.1	211.5 ± 12.1	211.8 ± 19.8	207.6 ± 12.2
IGT	200.4 ± 14.5	202.8 ± 17.5	197.6 ± 15.8	202.9 ± 15.0	198.9 ± 19.7	196.4 ± 18.1
HDL cholesterol (mg/dL)						
NGT	42.8 ± 3.2	43.3 ± 4.6	43.6 ± 4.6	46.2 ± 4.7*	42.3 ± 3.4	42.1 ± 4.5
IGT	41.1 ± 4.2	45.5 ± 4.2	44.3 ± 3.6	46.8 ± 3.7*	44.6 ± 4.6	43.8 ± 4.9
Triglyceride (mg/dL)						
NGT	200.8 ± 26.1	158.1 ± 25.6*	157.4 ± 30.4*	146.4 ± 18.5*	174.8 ± 25.6	180.4 ± 25.1
IGT	194.2 ± 28.4	146.2 ± 20.5*	146.4 ± 18.9*	139.4 ± 22.7*	159.6 ± 20.3	178.9 ± 20.7
Apolipoprotein A-I (mg/dL)						
NGT	108.2 ± 5.3	121.8 ± 4.8	123.7 ± 7.0	129.4 ± 4.8†	118.0 ± 6.7	117.0 ± 7.9
IGT	111.3 ± 7.3	118.9 ± 5.1	122.8 ± 5.2*	126.4 ± 8.7*	122.0 ± 11.3	114.8 ± 8.0
Apolipoprotein B (mg/dL)						
NGT	106.7 ± 7.4	108.9 ± 7.2	109.0 ± 9.6	111.0 ± 7.1	111.6 ± 9.9	109.9 ± 7.2
IGT	113.8 ± 7.3	113.2 ± 8.1	106.7 ± 7.4	108.7 ± 6.5	111.0 ± 9.5	112.4 ± 10.4

NOTE. Values are the mean ± SEM; n = 8 for NGT and IGT. The means ± 2 SD at our laboratory are as follows: total cholesterol, 186.6 ± 54.2 mg/dL; HDL cholesterol, 49.2 ± 13.7 mg/dL; triglyceride, 117.9 ± 75.6 mg/dL; apolipoprotein A-I, 133.1 ± 36.3 mg/dL; and apolipoprotein B, 106.6 ± 33.7 mg/dL.

*$P <$.

†$P < .01$: *v* before treatment.

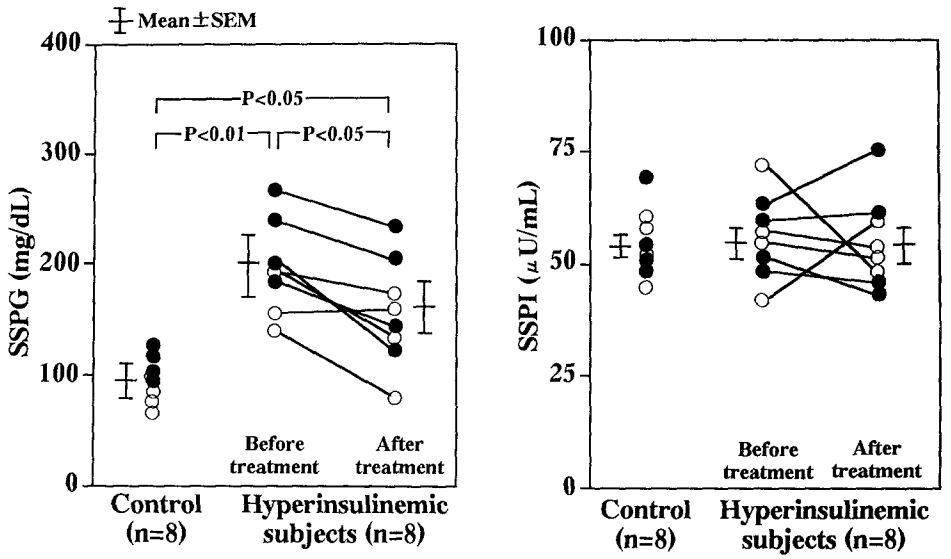

Fig 3. Effect of 12-week treatment with voglibose on insulin sensitivity determined by SSPG methods. NGT (○); IGT (●). Results expressed as the mean ± SEM.

insulin receptors in obese humans,[37] a decreased plasma insulin level may have resulted in an upregulation of insulin receptors and its transduction systems.

Voglibose showed a favorable effect on fasting serum lipid levels over the 12-week period of treatment, with a reversal of increased triglyceride and decreased HDL cholesterol levels, but these ultimately returned to baseline values after cessation of treatment. The reduction of fasting triglyceride level after the 4-week voglibose treatment is compatible with the long-term effect reported for acarbose.[31] On the other hand, Samad et al[15] reported that miglitol had no effect on serum lipid levels. Reaven et al[38] reported that plasma insulin level is directly associated with very-low-density lipoprotein production rate, and adipose tissue lipoprotein lipase (LPL) activity is also known to be regulated by insulin.[39] Therefore, a reduction of the insulin level and/or an improvement of insulin action may be associated with a decline in the rate of very-low-density lipoprotein production and an increase in LPL activity. The increase of HDL cholesterol may be due in part to the increased LPL activity, resulting in a concomitant increase of apolipoprotein A-I.

The subjects maintained almost constant BMI throughout the treatment period, but it appears unlikely that weight reduction would improve their insulin sensitivity. There is considerable evidence that an increase in triglyceride level and a decrease in HDL cholesterol level are the result of insulin resistance associated with hyperinsulinemia.[40] Recent studies have indicated that plasma insulin and HDL cholesterol levels are inversely related, and that as plasma insulin level increases, the fractional catabolic rate of HDL increases and HDL cholesterol level declines.[41] In this regard, it is conceivable that the favorable effects of voglibose on glucose and lipid metabolism may be attributable, at least in part, to the improvement of peripheral insulin sensitivity.

We did not measure glucose or insulin levels after cessation of drug treatment (follow-up phase), nor did we perform an objective evaluation of change in diet or physical activity. We cannot completely rule out the possibility that other factors may have influenced glucose and lipid metabolism during the observation period. However, treatment with voglibose resulted in a significant decline in triglycerides after 4 weeks of treatment, followed by a return to near-baseline values after discontinuation of the drug. Moreover, treatment with this agent resulted in a slight (but not significant) decline in HbA_{1c} as compared with baseline values, whereas no differences were found for BMI throughout the 20 weeks of study. Gastrointestinal side effects were mild enough to have no effect on the subjects' eating habits, and these side effects tended to decline during the course of treatment. Therefore, it is unlikely that the observed improvement of insulin sensitivity was due to any change of diet or exercise.

Since glucose intolerance is associated with insulin resistance and compensatory hyperinsulinemia in many patients, we believe the results obtained in the present study may have important clinical implications for the management of IGT or the initial stage of NIDDM. In fact, in our separate study, similar favorable results were observed in two NIDDM subjects with hyperinsulinemia. A review of data from clinical trials involving IDDM and NIDDM patients treated with acarbose showed that 58% of the subjects complained of gastrointestinal symptoms[42]; in this study, in contrast, adverse symptoms were infrequently observed in association with voglibose treatment, and there was a tendency for these side effects to decline over the course of voglibose treatment.

In conclusion, voglibose may be an effective treatment for correction of postprandial hyperglycemia, hyperinsulinemia, and dyslipidemia in nondiabetic subjects with hyperinsulinemia. In addition to a direct effect of inhibiting carbohydrate digestion, a long-term effect by which insulin sensitivity for glucose metabolism is enhanced was demonstrated.

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