Effects of Voglibose on Glycemic Excursions, Insulin Secretion, and Insulin Sensitivity in Non-Insulin-Treated NIDDM Patients

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OBJECTIVE — To investigate the effects of voglibose, an α-glucosidase inhibitor, on daily glycemic excursions, insulin secretion, and insulin sensitivity in non–insulin-treated NIDDM patients.

RESEARCH DESIGN AND METHODS — An open prospective study was conducted in 27 NIDDM patients receiving diet therapy alone or treatment with a sulfonylurea drug. Of the study subjects, 14 patients were treated with voglibose; the remaining 13 patients served as the control group. The metabolic parameters were evaluated before treatment and at week 4 of treatment as follows: glycemic excursions by M-value and 1,5-anhydro-D-glucitol (1,5-AG), insulin secretion by area under the curve of daily serum insulin ($AUC_{insulin}$), and insulin sensitivity by the *K* index of the insulin tolerance test (K_{ITT}).

RESULTS — After the study treatment, HbA_{1c} and plasma glucose in the patients who had received voglibose were comparable to those of patients in the control group. M-value was lower in the patients treated with voglibose than in the control subjects (5.7 ± 0.9 vs. 9.8 ± 1.2, $P < 0.05$). 1,5-AG was higher in the patients treated with voglibose than in the control subjects (12.2 ± 1.0 vs. 8.2 ± 0.7 μg/ml, $P < 0.01$). A statistically significant decrease in $AUC_{insulin}$ occurred after treatment with voglibose (2,223.5 ± 390.6 to 1,546.7 ± 303.4 pmol · l^{-1} · h, $P < 0.05$), but no change occurred in the control group (2,364.5 ± 315.4 to 2,464.2 ± 269.3 pmol · l^{-1} · h, $P = 0.60$). Insulin sensitivity (K_{ITT}) was improved to a statistically significant level in both the patients treated with voglibose and the patients in the control group. K_{ITT} in the patients after voglibose treatment was comparable to that of the control group (3.18 ± 0.30 vs. 3.21 ± 0.23%/min, $P = 0.94$).

CONCLUSIONS — The results suggest that voglibose lowers the daily glycemic excursions and inhibits overwork of the pancreatic β-cells but has little effect on insulin sensitivity in NIDDM patients.

Voglibose (Takeda, Osaka, Japan) is a new α-glucosidase inhibitor. It delays the absorption of carbohydrates from the small intestine (1). Voglibose is reported to be ~20 to 30 times more potent than acarbose in inhibiting semipurified porcine small intestine disaccharidases (2). The delay in absorption of carbohydrates results in a reduction of postprandial glucose (3,4). It has therefore been suggested that this α-glucosidase inhibitor may suppress the daily glycemic excursions in NIDDM. Another reported advantage of α-glucosidase inhibitors is that they decrease postprandial glucose without inducing hypersecretion of insulin (3,4). This effect is desirable in treatment of NIDDM patients for at least two reasons: *1*) hyperinsulinemia may be related to the development of coronary artery disease (5–7), and 2) hypersecretion of insulin may result in exhaustion of the pancreatic β-cells (8,9). The effects of α-glucosidase inhibitor on the diurnal variations of insulin secretion, however, are not yet well established. The efficacy of α-glucosidase inhibitor on insulin sensitivity remains controversial (10–14).

This study was designed to evaluate in non–insulin-treated NIDDM patients the effects of voglibose treatment for 4 weeks on daily glycemic excursions, intrinsic insulin secretion, and insulin sensitivity.

RESEARCH DESIGN AND METHODS

— Twenty-seven NIDDM patients gave informed consent to participate in the study. The study protocol was approved by the institutional review board of the Sasebo Chuou Hospital. Patients were admitted to Sasebo Chuou Hospital because of poor control of diabetes. They had no disease of the heart, liver, or endocrine system nor any severe diabetic complications. They were receiving either diet therapy alone or treatment with a sulfonylurea (SU) drug. Of the 27 patients, 14 patients were treated with voglibose at a dosage of 0.2 mg three times daily before meals. The other 13 patients received diet therapy alone or treatment with an SU drug and served as control subjects. The demographic characteristics of the patients are shown in Table 1. The age, BMI, therapy for diabetes, and duration of the illness of the patients who received voglibose were comparable to those of the control patients. Diet therapy consisted of 25–30 kcal/kg of ideal body weight. Glibenclamide (1.25–5.0 mg/day) or gliclazide (20–80 mg/day) was in use as the SU drug. The dosage of voglibose and the diet therapy were not changed during the course of the study treatment. The dosage of the SU drug

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Abbreviations: 1,5-AG, 1,5-anhydro-D-glucitol; $AUC_{glucose}$, area under the curve of glucose; $AUC_{insulin}$, area under the curve of daily serum insulin; CV, coefficient of variation; FFA, free fatty acid; IGT, impaired glucose tolerance; K_{ITT}, *K* index of the insulin tolerance test; SU, sulfonylurea; TC, total cholesterol; TG, triglyceride.

Table 1—*Clinical characteristics of NIDDM patients*

	Voglibose-treated patients	Control patients
n (M/F)	14 (11/3)	13 (11/2)
Age (years)	62.0 ± 1.7	58.8 ± 1.8
BMI (kg/m²)	24.8 ± 0.8	23.9 ± 0.8
Treatment (diet/SU drug)	4/10	4/9
Duration of illness	5.6 ± 1.2	3.8 ± 0.6

Data are means ± SE.

in use was modified to achieve good glycemic control (fasting glucose <7.8 mmol/l and postprandial [2-h] glucose <11.1 mmol/l). Daily glycemic excursions, insulin secretion, and insulin sensitivity were measured before patients entered the study and 4 weeks after they started the study treatment. Blood samples were taken at 0700, 1000, 1130, 1400, 1730, 2000, and 2200 for determination of plasma glucose and serum insulin. HbA_{1c} and 1,5-anhydro-D-glucitol (1,5-AG) were measured in blood samples obtained at 0700. Glycemic excursion was assessed by M-value according to the method of Schlichtkrull et al. (15). Glycemic control was assessed by area under the curve of glucose ($AUC_{glucose}$), and insulin secretion was assessed by area under the curve of insulin ($AUC_{insulin}$). $AUC_{glucose}$ and $AUC_{insulin}$ were calculated by the trapezoidal method (16). Insulin sensitivity was assessed by the *K* index of the short insulin tolerance test (K_{ITT}) according to the method of Borona et al. (17). Briefly, the insulin tolerance test was performed after an overnight fast of 12–14 h. A butterfly needle was inserted into the antecubital vein with patency maintained by a slow drip of saline. The baseline blood samples were obtained 3 min before insulin infusion. A bolus of regular insulin (0.1 U/kg) (Humalin R [Shionogi, Osaka, Japan]) was infused, and blood samples were then obtained 3, 6, 9, 12, and 15 min after insulin infusion. K_{ITT}, an index of insulin sensitivity, was calculated from the formula $K_{ITT} = 0.693/t_{1/2}$ (17). Plasma glucose $t_{1/2}$ was calculated from the slope of least-squares analysis of plasma glucose concentration from 3 to 15 min after bolus injection of insulin. The mean K_{ITT} value (±SE) for 10 normal subjects who had normal oral glucose tolerance was 5.44 ± 0.29%/min. Total cholesterol (TC), HDL cholesterol, triglyceride (TG), and free fatty acid (FFA) were measured in the baseline blood samples.

Plasma glucose was measured with an automatic analyzer by the glucose oxidase method (Kyoto-Daiichi Kagaku, Kyoto, Japan). Intra- and interassay coefficients of variation (CVs) were <1.5%. Immunoreactive insulin was measured by a commercial radioimmunoassay kit (Shionogi). The intra-and interassay CVs were <7%. HbA_{1c} was measured by the high-performance liquid chromatography method (Kyoto-Daiichi Kagaku). Serum 1,5-AG was measured by the enzymatic method (Nippon Kayaku, Tokyo, Japan). TC, TG, and FFA were measured by the enzymatic methods (Kokusai Shiyaku, Kobe, Japan). HDL cholesterol was determined after isolation by the precipitation method (Kyowa, Tokyo, Japan). CVs for intra- and interassay in 1,5-AG, TC, TG, HDL cholesterol, and FFA were <3%.

Statistical analysis

Statistical analysis was conducted with the two-tailed Student's *t* test for paired and unpaired data. Data were presented as means ± SE. Differences were considered statistically significant at $P < 0.05$.

RESULTS — The baseline values of HbA_{1c} and $AUC_{glucose}$ of the patients on voglibose treatment were comparable to those of the control patients (Table 2). As shown in Fig. 1, the daily profiles of plasma glucose of the two groups of the patients before the study treatment were also comparable. After the study treatment, all study patients achieved a fasting glucose level of <7.8 mmol/l. However, two patients on voglibose treatment and six control patients could not reduce their postprandial glucose level to <11.1 mmol/l. Statistically significant decreases in HbA_{1c} and $AUC_{glucose}$ were observed in both groups, and the levels were comparable between the two groups (Table 2). Therefore, both groups of patients reached similar levels of glycemic control after the study treatment. There was a difference, however, in the graphed daily profiles of plasma glucose after the study treatment between the patients who had received voglibose and the control patients (Fig. 1*A* and *B*). Fluctuations in plasma glucose were larger in the control patients than in the patients on the voglibose treatment, especially after meals. Indeed, after the study treatment, the M-value, a marker of daily glycemic excursions, was lower in the patients treated with voglibose than in the control patients (5.7 ± 0.9 vs. 9.8 ± 1.2, $P < 0.05$). The 1,5-AG level was higher in the patients treated with voglibose than in the control patients (12.2 ± 1.0 vs. 8.2 ± 0.7 μg/ml, $P < 0.01$). These results indicate that lower daily glycemic excursions may be achieved by the use of voglibose.

Insulin secretion before the study treatment in the patients receiving voglibose was comparable to that of the control patients, as assessed by $AUC_{insulin}$ or the graphed daily profiles of serum insulin (Table 2, Fig. 1*C* and *D*). A statistically significant decrease in $AUC_{insulin}$ was

Table 2—*Glycemic control, glycemic excursions, insulin secretion, and insulin sensitivity in NIDDM patients before and after the study treatment*

	Voglibose-treated patients		Control patients	
	Before	After	Before	After
HbA_{1c}	9.7 ± 0.5	7.9 ± 0.2*	9.8 ± 0.7	8.0 ± 0.4*
1,5-AG (μg/ml)	3.8 ± 0.9	12.2 ± 1.0*†	4.0 ± 1.0	8.2 ± 0.7*
M-value	25.4 ± 2.9	5.7 ± 0.9*‡	30.0 ±4.4	9.8 ± 1.2*
$AUC_{glucose}$ (mmol · l⁻¹ · h)	168.9 ± 6.7	105.5 ± 3.6*	173.7 ± 10.7	106.3 ± 5.3*
$AUC_{insulin}$ (pmol · l⁻¹ · h)	2,223.5 ± 390.6	1,546.7 ± 303.4‡§	2,364.5 ± 315.4	2,464.2 ± 269.3
K_{ITT} (%/min)	2.47 ± 0.28	3.18 ± 0.30*	2.75 ± 0.23	3.21 ± 0.23§
Body weight (kg)	64.9 ± 3.1	63.0 ± 2.8§	65.5 ± 1.2	63.6 ± 1.0*

Data are means ± SE. *$P < 0.01$ vs. before treatment; †$P < 0.01$ vs. without voglibose; ‡$P < 0.05$ vs. without voglibose; §$P < 0.05$ vs. before treatment.

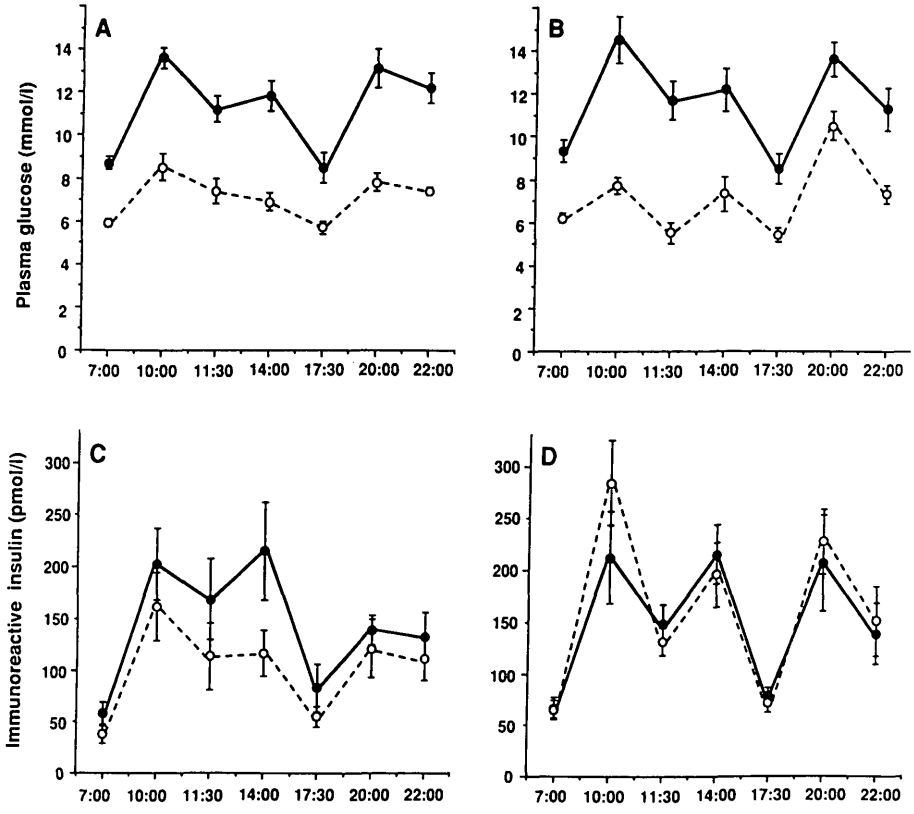

Figure 1—*Changes in daily plasma glucose and serum insulin levels before (—●—) and after (- - -○- - -) treatment. Data are presented as means ± SE. A: Plasma glucose levels in patients treated with voglibose. B: Plasma glucose levels in control patients receiving diet therapy alone or treatment with an SU drug. C: Serum insulin levels in patients treated with voglibose. D: Serum insulin levels in control patients receiving diet therapy alone or treatment with an SU drug.*

observed in the patients on voglibose after treatment (2,223.5 ± 390.6 to 1,546.7 ± 303.4 pmol · l^{-1} · h, $P < 0.05$). In contrast, $AUC_{insulin}$ did not change in the control patients after treatment (2,364.5 ± 315.4 to 2,464.2 ± 269.3 pmol · l^{-1} · h, $P = 0.60$). After patients were treated with voglibose, the decrease in the graphed serum insulin was observed for the whole day (Fig. 1*C*). In contrast, the graphed serum insulin level after breakfast tended to increase after treatment but, in general, did not change in the control patients during the day (Fig. 1*D*).

K_{ITT}, the index of insulin sensitivity used in the study, increased significantly after the study treatment in both the patients receiving voglibose (2.47 ± 0.28 to 3.18 ± 0.30%/min, $P < 0.01$) and the control patients (2.75 ± 0.23 to 3.21 ± 0.23%/min, $P < 0.05$) (Table 2). After the study treatment, there was no difference in K_{ITT} between both groups of patients. Therefore, insulin sensitivity was similarly improved after the treatment in both groups without any relation to the use of voglibose. A slight but statistically significant decrease in body weight (2.9%) was observed in both groups after the study treatment (Table 2).

TC, HDL cholesterol, and FFA levels did not change after treatment in both patient groups (Table 3). TG, however, decreased with statistical significance in both the patients on voglibose (1.27 ± 0.13 to 0.97 ± 0.07 mmol/l, $P < 0.01$) and the control patients (1.37 ± 0.14 to 1.09 ± 0.09 mmol/l, $P < 0.05$).

CONCLUSIONS — In the present study, M-value was lower in the patients treated with voglibose than in the control patients, and this difference was statistically significant. Furthermore, the patients treated with voglibose showed a statistically significant increase in 1,5-AG concentration compared with the control patients. Kishimoto et al. reported that 1,5-AG was useful in the evaluation of the daily glycemic excursions in the NIDDM patients, because M-value was found to correlate significantly with 1,5-AG concentrations (18). These results indicate that the voglibose treatment lowered the daily glycemic excursions more than the diet therapy alone or the treatment with an SU drug. The lower daily glycemic excursions may be considered attributable to the delay in the intestinal absorption of carbohydrates.

The insulin secretion ($AUC_{insulin}$) in the patients receiving diet therapy alone or treatment with an SU drug tended to increase, especially after breakfast (Fig. 1*D*). It is well known that long-standing hyperglycemia impairs insulin secretion in NIDDM patients. Such an effect of hyperglycemia has been referred to as glucose toxicity (19). It is therefore reported that an improvement in glycemic control is associated with an improvement in insulin secretion (20). In contrast, the patients treated with voglibose showed a statistically significant decrease in insulin secretion. These results agreed with reports of previous studies involving other α-glucosidase inhibitors (3,4,13,14), indicating that α-glucosidase inhibitors may reduce insulin secretion in NIDDM patients.

One possible explanation of the mechanism of decrease in insulin secretion in the patients treated with voglibose may be that the improvement in insulin sensitivity contributes to the decrease in insulin secretion. Kahn et al. reported that both insulin secretion and insulin sensitivity were important factors in determining glucose tolerance and that their relationship was hyperbolic (21). In our study, insulin sensitivity (K_{ITT}) increased with statistical significance both in the patients treated with voglibose and in the control patients. Furthermore, after the study treatment, K_{ITT} in the patients who had received voglibose was comparable to that in the control patients. These results suggested that the improvement in insulin sensitivity was probably attributable to the improvement in glycemic control (19) and not due to the direct effect of the voglibose treatment. As mentioned above, the mechanism of the decrease in insulin secretion that occurred after voglibose treatment could not be explained by the improvement in insulin sensitivity. A decrease in postprandial plasma glucose was recognized in the patients treated with voglibose and was probably due to the delay in absorption of the dietary carbohydrates. This decrease in postprandial plasma glucose may result in a decrease in the intrinsic insulin secretion and may inhibit the overwork of the pancreatic β-cells. Our study indicates that carbohydrate absorption as well as insulin secretion and insulin

Table 3—*Lipid data in NIDDM patients before and after the study treatment*

	Voglibose-treated patients		Control patients	
	Before	After	Before	After
TC (mmol/l)	4.76 ± 0.20	4.60 ± 0.21	5.06 ± 0.25	4.69 ± 0.22
TG (mmol/l)	1.27 ± 0.13	0.97 ± 0.07*	1.37 ± 0.14	1.09 ± 0.09†
HDL cholesterol (mmol/l)	1.13 ± 0.10	1.12 ± 0.07	1.18 ± 0.11	1.14 ± 0.09
FFA (g/l)	0.72 ± 0.06	0.59 ± 0.06	0.66 ± 0.05	0.54 ± 0.04

Data are means ± SE. *$P < 0.01$ vs. before treatment; †$P < 0.05$ vs. before treatment.

sensitivity is an important determinant of glycemic control in NIDDM patients.

Diet therapy and administration of an SU drug are the most common methods of treating NIDDM patients. It is well known, however, that treatment failure secondary to administration of the SU drug often occurs (22). The mechanism of this secondary failure is not yet well established, but some studies suggest the importance of the exhaustion of the pancreatic β-cells (8,9,23,24). It is therefore assumed that concomitant treatment with an SU drug and an α-glucosidase inhibitor may avoid this secondary failure. Further longitudinal study is necessary to elucidate this point.

In our report and in previous reports, the α-glucosidase inhibitor did not improve insulin sensitivity in NIDDM patients (10–12), whereas the drug has been shown to improve insulin sensitivity in patients with impaired glucose tolerance (IGT) and in nondiabetic hyperinsulinemic subjects (13,14). The major difference between the studies of NIDDM patients and nondiabetic subjects (including patients with IGT) is the difference in level of glycemic control in study subjects compared with that in the control subjects. In the studies of NIDDM patients, glycemic control level (such as HbA_{1c} or plasma glucose level) of the study patients was comparable to that of the control patients (10–12). In contrast, a significant decrease in $AUC_{glucose}$ in study subjects was observed, compared with $AUC_{glucose}$ in control subjects with IGT or nondiabetic subjects (13,14). Thus, plasma glucose level after treatment may, in part, affect insulin sensitivity.

A statistically significant decrease in TG level and no change in TC level were observed after the study treatment both in the patients treated with voglibose and in the control patients. Bruce et al. reported that insulin sensitivity was an important and independent determinant of the TG and FFA concentrations (25). Although a decline in FFA concentration after treatment was not statistically significant, FFA concentration tended to decrease both in the patients treated with voglibose and in the control patients. On the basis of these results, the authors suggested that the decline in TG levels after treatment may be associated with improvements in insulin sensitivity in both groups of patients.

In conclusion, we have demonstrated that voglibose is more effective in lowering the daily glycemic excursions in NIDDM patients than is either diet therapy alone or treatment with an SU drug. Furthermore, it has been demonstrated that voglibose treatment decreases intrinsic insulin secretion, probably via the delay in intestinal absorption of carbohydrates. Hence, voglibose is considered to be a drug beneficial in the treatment of NIDDM patients.

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