An Importance of Carbohydrate Ingestion for the Expression of the Effect of α-Glucosidase Inhibitor in NIDDM

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OBJECTIVE — To examine the usefulness of α-glucosidase inhibitors in glycemic control of patients with NIDDM. The involvement of carbohydrate ingestion in manifestation of the effects of α-glucosidase inhibitors was also investigated.

RESEARCH DESIGN AND METHODS — A total of 41 patients hospitalized with NIDDM (22 patients receiving sulfonylurea and 19 receiving insulin therapy) were given α-glucosidase inhibitors during the period when their blood glucose levels were well controlled. They were followed for 3 weeks as inpatients and for an additional 6 months as outpatients. They were retrospectively divided into two groups according to the percentage of carbohydrates in all sources of calories during outpatient management: the <50% group and the >50% group. Between these two groups, we compared circadian variation in blood glucose levels, HbA_{1c}, and urine C-peptide.

RESULTS — Treatment with α-glucosidase inhibitors during the hospital stay markedly improved circadian variation in blood glucose levels and HbA_{1c} and decreased urine C-peptide in both groups. While HbA_{1c} returned to its pretreatment level at 6 months after the treatment in the <50% group, HbA_{1c} had further improved in the >50% group at 6 months.

CONCLUSIONS — α-glucosidase inhibitors are useful for glycemic control in patients with NIDDM and the percentage of carbohydrate in all calorie sources is an important factor for the expression of their effects.

The Diabetes Control and Complications Trial demonstrated that long-term strict control of blood glucose levels is indispensable for preventing the development of diabetic complications (1). Although oral hypoglycemic agent therapy and insulin therapy (frequent injections of insulin or continuous subcutaneous insulin infusion) are often used to achieve better blood glucose control (2,3), it is very difficult to achieve an ideal circadian variation in blood glucose levels. α-glucosidase inhibitors are known to inhibit salivary and pancreatic α-amylase as well as glucoamylase, sucrase, and maltase in a reversible antagonistic manner (4,5). Animal studies have revealed that oral ingestion of α-glucosidase inhibitors with food suppresses the hydrolysis of glucose in the intestinal lumen and delays the uptake of glucose or fructose into systemic circulation, resulting in correction of the postprandial hyperglycemia (4–6). In addition, many investigators suggested the clinical usefulness of α-glucosidase inhibitors for controlling the blood glucose levels of diabetic patients (7–15). However, the relationship between diet and the effect of α-glucosidase inhibitors has been analyzed only by Toeller (16,17) from the viewpoint that α-glucosidase inhibitors selectively delay the absorption of carbohydrates. The present study was undertaken to examine the usefulness of α-glucosidase inhibitors in patients with NIDDM who were receiving sulfonylurea or insulin therapy. We also investigated the relationship between the effects of α-glucosidase inhibitors and the amount of carbohydrates ingested.

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H-CHO, high carbohydrate; L-CHO, low carbohydrate.

RESEARCH DESIGN AND METHODS

Patients

Patients with NIDDM, who had been receiving sulfonylurea therapy or insulin therapy (secondary failure to sulfonylurea therapy), were admitted to our hospital. Of these patients, the 41 patients whose sulfonylurea or insulin dosage had become constant and whose blood glucose levels had become stable during the first 3 weeks of their hospital stay were selected for this study (Table 1). Of these subjects, 22 were on sulfonylurea therapy and 19 were on insulin therapy. The sulfonylurea used was tolbutamide in 9 patients and glibenclamide in 13. Of the 19 patients on insulin therapy, 5 received one injection (in the morning) every day, and 14 received two injections (one in the morning and one at night) every day. During their hospital stay, all patients (and the wives of married male patients) learned how to plan therapeutic diet meals, while taking into account the patient's previous diet style. After discharge, each subject reported their meals for at least seven days of the month. This report was made monthly for 6 months. On the basis of these reports, we calculated daily calorie ingestion and the percentage of carbohydrates in total calorie sources during the outpatient management period after discharge. Depending on the average amount of carbohydrates ingested during the 6-month period after discharge, the subjects were retrospectively divided into two groups: the low carbohydrate (L-CHO) group (patients in whom the percentage of carbohydrates in total calorie sources was <50%) and the high carbohydrate (H-CHO) group (patients in whom the percentage of carbohydrates in total calorie sources was >50%). There

Table 1—*Clinical profiles of patients*

	Total	L-CHO	H-CHO
n	41 (23/18)	19 (12/7)	22 (11/11)
α-glucosidase inhibitor			
Acarbose	21 (12/9)	10 (6/4)	11 (6/5)
Voglibose	20 (11/9)	9 (6/3)	11 (5/6)
Treatment			
Sulfonylurea group	22 (15/7)	9 (7/2)	13 (8/5)
Insulin group	19 (8/11)	10 (5/5)	9 (3/6)
Age (years)	56.9 ± 10.8	54.1 ± 12.9	59.2 ± 8.3
BMI (kg/m^2)	22.2 ± 2.9	21.8 ± 3.1	22.6 ± 2.8
Duration of diabetes (years)	13.7 ± 7.5	14.9 ± 8.5	12.5 ± 6.5

Data are *n* (number of men/number of women) or means ± SD. Low carbohydrate (L-CHO) group: the percentage of carbohydrate in total calorie sources was <50%; high carbohydrate (H-CHO) group: the percentage of carbohydrate in total calorie sources was >50%.

was no significant difference between these two groups in terms of background variables such as therapeutic method, age, BMI, duration of diabetes, and 24-h urine C-peptide elimination.

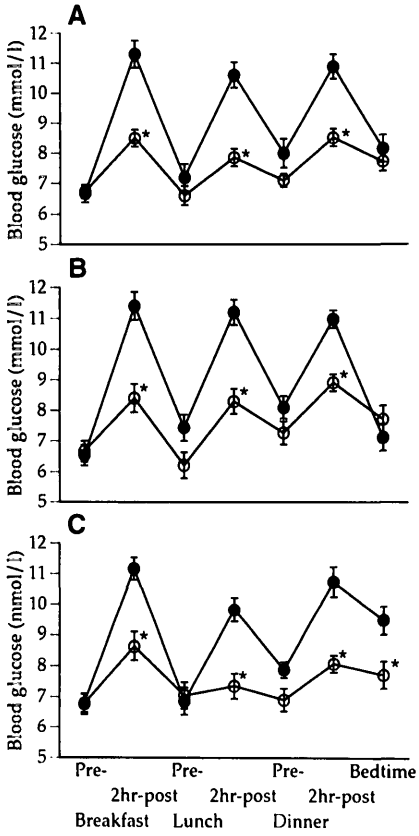

Figure 1—*Changes in circadian variations in blood glucose levels before (●——●) and after (○——○) treatment with α-glucosidase inhibitor for 3 weeks. Total cases (A), low carbohydrate (L-CHO) group (B), and high carbohydrate (H-CHO) group (C). For the L-CHO group, the percentage of carbohydrate in total calorie sources was <50%. For the H-CHO group, the percentage of carbohydrate in total calorie sources was >50%. Results are means ± SE. *P < 0.05 vs. before treatment.*

Protocols

The subjects were followed throughout their 6-week hospital stay period and for 6 months after discharge (the outpatient follow-up period). Immediately after admission, each patient received strict diet therapy, and the sulfonylurea or insulin dosage was adjusted. After the first 3 weeks, when blood glucose was well controlled, treatment with α-glucosidase inhibitor was started. The sulfonylurea or insulin dosage was adjusted again 3 weeks after the start of α-glucosidase inhibitor treatment. Patients were discharged when control of their blood glucose levels became stable. After discharge, the patients were seen at our outpatient clinic. An α-glucosidase inhibitor, voglibose (0.3 mg tablets) or acarbose (100 mg tablets), was used. Each patient ate three meals and took one tablet of voglibose or acarbose three times a day (immediately before breakfast, lunch, and dinner). During the outpatient period, the dosage of sulfonylurea or insulin was not changed, and the use of any drug that might potentiate or weaken the effects of sulfonylurea or insulin was avoided.

Immediately before and 3 weeks after the start of α-glucosidase inhibitor treatment, circadian variations in blood glucose levels were determined, accompanied by evaluation of the dosage of sulfonylurea and insulin, the frequency of insulin injections, and the frequency of extra meals. To determine circadian variations in blood glucose levels, blood glucose levels were measured seven times per day, i.e., immediately before and 2 h after each meal and at bedtime. The *M* value, which is an indicator of variation in blood glucose levels, was calculated using the method of Schlichtkrull (18). Body weight, HbA_{1c}, triglyceride, total cholesterol, and HDL cholesterol were measured at the beginning of the α-glucosidase inhibitor treatment and at 1 month and 6 months after the start of outpatient management.

During the observation period, each patient was instructed to ingest 30 kcal/kg ideal body weight every day, to distribute the prescribed total calories equally to three meals, and to take a snack only when they had hypoglycemia. During their hospital stay period, the percentages of each nutrient in the total calorie sources were set at 57–61% (carbohydrates), 23–26% (fat), and 16–18% (protein). The main carbohydrates were starch, sucrose, and fructose, and the relative proportion of these three carbohydrates were 90–95, 2–4, and 2–4%, respectively. At the beginning of α-glucosidase inhibitor therapy, many patients complained of flatulence or bloating. However, these symptoms were not severe and endurable. There were no significant differences in the incidence of these side effects between the two groups. During the outpatient period, the same percentages were 32–62% (carbohydrates), 22–40% (fat), and 16–28% (protein). During the observation period, discontinuation of α-glucosidase inhibitors was not necessitated by adverse reactions by any patient. In all 41 patients, the drugs were used as instructed throughout the observation period.

Table 2—*Changes in M value, 24-h urine C-peptide response, the regimens of sulfonylurea/insulin therapy, and frequency of extra meals before and after treatment with α-glucosidase inhibitor for 3 weeks*

	Total		L-CHO		H-CHO	
	Before	After	Before	After	Before	After
M value	13.3 ± 0.9	4.5 ± 0.5*	13.1 ± 1.1	4.7 ± 0.4*	13.4 ± 1.6	4.3 ± 0.6*
24-h urine C-peptide (μg/day)	36.9 ± 5.4	23.3 ± 4.2*	38.2 ± 7.3	23.4 ± 6.3*	35.5 ± 8.3	23.1 ± 5.7*
Dosage of sulfonylurea						
Tolbutamide (mg/day)	583 ± 83 (250~1000)	389 ± 44* (250~500)	625 ± 125 (500~1000)	438 ± 63 (250~500)	550 ± 122 (500~1000)	350 ± 61 (250~500)
Glibenclamide (mg/day)	3.0 ± 0.3 (1.25~5.00)	2.0 ± 0.3* (1.25~5.00)	3.0 ± 0.5 (2.50~5.00)	2.0 ± 0.3 (1.25~2.50)	3.0 ± 0.5 (1.25~5.00)	2.0 ± 0.5 (1.25~5.00)
Dosage of insulin (units/day)	24.6 ± 1.7	18.5 ± 1.9*	24.2 ± 2.4	17.2 ± 3.0*	25.1 ± 2.6	20.0 ± 2.3*
Frequency of insulin injections (times/day)	1.7 ± 0.1	1.2 ± 0.1*	1.8 ± 0.1	1.1 ± 0.1*	1.7 ± 0.2	1.2 ± 0.1*
Frequency of extra meals (cases)	5	1	3	1	2	0

Data are means ± SE. Low carbohydrate (L-CHO) group (n = 19): the percentage of carbohydrate in total calorie sources was <50%; high carbohydrate (H-CHO) group (n = 22): the percentage of carbohydrate in total calorie sources was >50%. *P < 0.05 vs. before treatment.

Statistical analysis

The data were expressed as means ± SD or SE. Statistical difference was assessed in a nonparametric manner. Wilcoxon's test was used for paired comparison, and the Mann-Whitney *U* test was used for unpaired comparison.

RESULTS

Circadian variation in blood glucose levels, *M* value, and urine C-peptide during the hospital day

Analysis of the data for the entire group revealed no significant change in blood glucose levels before any meal or at bedtime after the start of α-glucosidase inhibitor treatment. However, the blood glucose level at 2 h after each meal decreased significantly after the start of treatment (breakfast: 11.3 ± 0.5 vs. 8.5 ± 0.3 mmol/l; lunch: 10.6 ± 0.4 vs. 7.9 ± 0.3 mmol/l; dinner: 10.9 ± 0.4 vs. 8.5 ± 0.3 mmol/l; $P < 0.05$)(Fig. 1*A*). The *M* value and urine C-peptide elimination decreased significantly after treatment (Table 2). These effects of α-glucosidase inhibitor treatment were of a similar degree in both the L-CHO and H-CHO group (Fig. 1*B*,*C* and Table 2). No significant differences between the effect of acarbose and that of voglibose were observed. The mean blood glucose levels at 2 h after breakfast in the acarbose and voglibose therapy groups were 8.7 ± 0.5 and 8.1 ± 0.6 mmol/l, respectively, in the L-CHO group and 8.2 ± 0.6 and 9.2 ± 0.7 mmol/l in the H-CHO group. Similar results were obtained at 2 h after lunch and dinner.

Dosage of sulfonylurea and insulin and frequencies of insulin injections and extra meals (Table 2)

In each group, severe hypoglycemia often resulted if the dosage of sulfonylurea or insulin was unchanged after the start of α-glucosidase inhibitor treatment from the dosage used before the start of this treatment. For this reason, the dosage of sulfonylurea was reduced for 4 of 9 patients in the L-CHO group and for 6 of 13 patients in the H-CHO group; the dosage of insulin was reduced for 7 of 10 patients in the L-CHO group and for 8 of 9 patients in the H-CHO group; and the frequency of insulin was reduced for 5 of 10 patients in the L-CHO group and for 5 of 9 patients in the H-CHO group. After the dosage of sulfonylurea or insulin was reduced, blood glucose levels became highly stable in all but two patients who showed mild hypoglycemia. As a result, the frequency of extra meals was also reduced significantly after the start of α-glucosidase inhibitor treatment. The changes in the regimens of sulfonylurea/insulin therapy and the frequency of extra meals after the start of α-glucosidase inhibitor treatment did not differ significantly between the two groups.

Changes in HbA_{1c}

When the changes in HbA_{1c} in relation to the percentage of carbohydrates in all calorie sources (L-CHO and H-CHO) were analyzed separately in the sulfonylurea therapy group and the insulin therapy

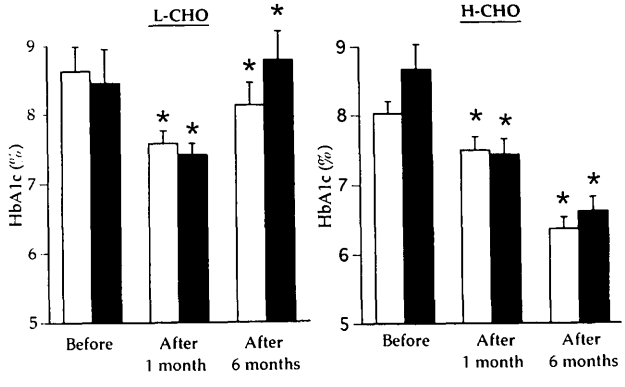

Figure 2—*Changes in HbA_{1c} before as well as after the treatment with α-glucosidase inhibitor. Low carbohydrate (L-CHO) group: the percentage of carbohydrate in total calorie sources was <50%; high carbohydrate (H-CHO) group: the percentage of carbohydrate in total calorie sources was >50%.* □: *sulfonylurea therapy group,* ■: *insulin therapy group. Results are means ± SE.* *P < *0.05 vs. before treatment,* **P < *0.05 vs. after 1-month treatment.*

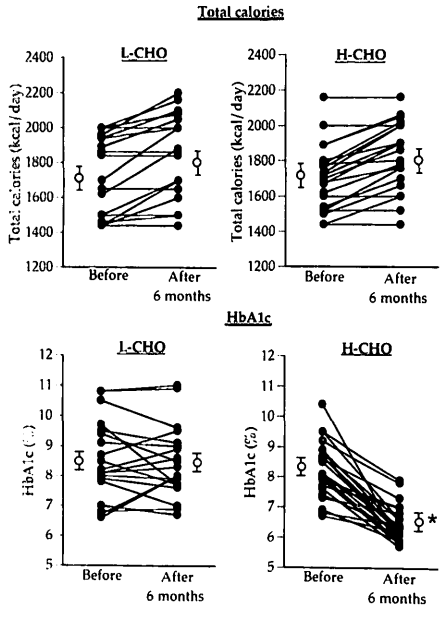

Figure 3—*Changes in the total calorie sources and HbA_{1c} before and after 6-months treatment with α-glucosidase inhibitor. Results are means ± SE. *P < 0.05 vs. before treatment. Low carbohydrate (L-CHO) group: the percentage of carbohydrate in total calorie sources was <50%; high carbohydrate (H-CHO) group: the percentage of carbohydrate in total calorie sources was >50%.*

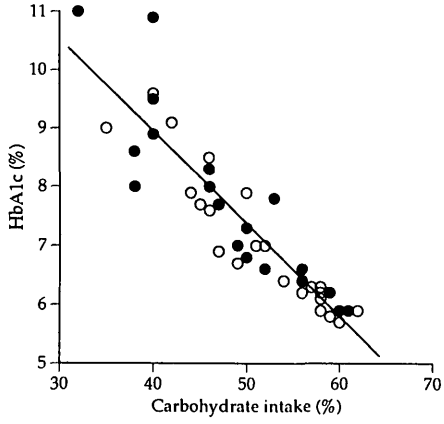

Figure 4—*Correlation between carbohydrate intake (percentage of total calorie sources) and HbA_{1c}. ○: sulfonylurea therapy group; ●: insulin therapy group. n = 41; r = 0.909; P < 0.001.*

group (Fig. 2), similar changes were observed in both therapy groups. That is, 1 month after the start of treatment, this parameter was significantly lower than its pretreatment level in both the L-CHO and H-CHO groups. After 6 months of treatment, HbA_{1c} in the L-CHO group was significantly higher than its level at 1 month and was equal to its pretreatment level. In the H-CHO group, the HbA_{1c} after 6 months of treatment was significantly lower than its level at 1 month and was very close to the normal level. Twelve patients in the L-CHO group and 15 patients in the H-CHO group showed an increase in total calorie ingestion at 6 months after the start of treatment from that before the start of treatment. There was, however, no significant difference in this parameter between the two groups or between the two points of measurement in any group. HbA_{1c}, on the other hand, increased in eight patients and decreased in seven patients in the L-CHO group. The L-CHO group thus showed no significant change in HbA_{1c}. In the H-CHO group, all patients showed a decrease in HbA_{1c}. The H-CHO group thus showed a marked decrease in HbA_{1c} (Fig. 3). A significant negative correlation was noted between HbA_{1c} and the percentage of carbohydrates in total calorie sources, as measured after 6 months of treatment, irrespective of the therapy used (sulfonylurea or insulin therapy) (Fig. 4).

Body weight and serum lipids

No significant difference was seen between the L-CHO and H-CHO groups in terms of body weight or serum lipids. None of these parameters showed any significant change during the observation period.

CONCLUSIONS — Considering that diet therapy is the basis of treatment of diabetes and that α-glucosidase inhibitor exert its actions through delaying carbohydrate absorption by the intestine, there may be a close relationship between the expression of the effects of α-glucosidase inhibitors and diet. Before the present study, however, no study of this relationship had been reported.

Some investigators recommended the use of reinforced insulin therapies as a means of strict glycemic control (2,3). These therapies, however, cause great stress to patients and involve a high risk of inducing hypoglycemia. It is doubtful that blood glucose levels can be controlled satisfactorily by using these therapies. Although hyperglycemia, which occurs ~2 h after a meal, can be suppressed by short-acting insulin, additional food may be needed by the patient because of hypoglycemia, which develops 3–4 h after an injection of short-acting insulin. The necessity of extra meals often hampers the control of blood glucose. Circadian variations in blood glucose levels and the *M* value, calculated from circadian variations, serve as indicators of changes in blood glucose levels. Schlichtkrull found that blood glucose control is good when the *M* value is 18 or less, fair when it is between 19 and 31, and poor when it is 32 and over (18). In the present study, adjustment of the dosage of sulfonylurea or insulin for hospitalized patients under strict diet therapy allowed the blood glucose levels of these patients to be well controlled, and further improvement of postprandial hyperglycemia and *M* value was obtained by the addition of α-glucosidase inhibitor treatment. The reduction in urine C-peptide elimination with decreased dosage of sulfonylurea and insulin and better glycemic control suggests that insulin resistance in NIDDM patients was ameliorated by the treatment with α-glucosidase inhibitor. The decrease in the dosage of sulfonylurea and insulin is also favorable in avoiding hyperinsulinemia, which can precipitate arteriosclerosis (19). These results, which support the previously reported usefulness of α-glucosidase inhibitors, were, however, derived from hospitalized patients under strict diet therapy. It is difficult for outpatients to continue ideal diet therapy for long periods of time.

It is thought that excessive ingestion of carbohydrates can induce a sharp increase in postprandial blood glucose levels and excessive secretion of insulin, thus precipitating obesity or hyperlipidemia (20). For this reason, ingestion of carbohydrates by diabetic patients has been limited. However, excessive limitation of carbohydrate ingestion increases the use of fatty acids and amino acids as sources of energy, leading to a further decrease in glucose utilization and more severe disturbances of glucose metabolism (21). At present, therefore, the view that >50% of all calories should be ingested in the form of carbohydrates, proposed by the American Diabetes Association and the British Diabetes Association, has been accepted widely as a basic guideline (22,23). In patients in whom the percentage of carbohydrates among all calorie sources was low, blood glucose control became less satisfactory with time after discharge. In patients in whom this percentage was high, blood glucose control remained good after discharge, accompanied by a further decrease in HbA_{1c} in the

present study. Because each patient received guidance about meals during their hospital stay, the difference between the prescribed daily calorie ingestion and the actual daily calorie ingestion after discharge was less than ~5%, and the actual daily calorie ingestion did not differ significantly between the two groups. Therefore, the changes in the blood glucose control status after discharge cannot be attributable to an increase in daily calorie ingestion. Furthermore, since no significant differences were noted between these two groups in terms of any background variable, it is unlikely that the observed differences in blood glucose control reflect differences in the patients' ability to secrete insulin. In the L-CHO group, about half the patients showed an increase in HbA_{1c}, and in most of the other patients in this group, glycemic control after discharge was less satisfactory than that during the hospital stay period under α-glucosidase inhibitor treatment, although HbA_{1c} remained unchanged or improved after discharge, as compared with its level before treatment. The worsening of blood glucose control after discharge of these patients can be explained as follows. During the hospital stay period with strict diet therapy, blood glucose levels could be well controlled, thanks to the effects of α-glucosidase inhibitors, even after the dosage of sulfonylurea or insulin or the frequency of insulin injections was reduced. After discharge, however, the effects of α-glucosidase inhibitors were lost in these patients because their ingestion of carbohydrates decreased and their ingestion of fat and protein increased (data not shown).

It has been widely recognized by multicenter double-blind studies (13–15) that α-glucosidase inhibitors are useful in achieving good blood glucose control. To date, however, α-glucosidase inhibitors have been regarded as only an auxiliary therapy for conventional diet therapy or drug therapy. The present study, however, revealed that in diabetic patients whose blood glucose levels have been well controlled by drugs, blood glucose control can be further improved by α-glucosidase inhibitors. The study also revealed that the percentage of carbohydrates in all calorie sources is an important factor for the expression of the effects of α-glucosidase inhibitors. In cases where the percentage of carbohydrates is low even when the total calorie ingestion is kept at the prescribed level, blood glucose control is not improved by α-glucosidase inhibitors. α-glucosidase inhibitors improve blood glucose control only when the percentage of carbohydrates is high. We therefore conclude that when α-glucosidase inhibitors are used for glycemic control in NIDDM, it is essential to pay adequate attention not only to total calorie ingestion but also to the percentage of carbohydrates in total calorie sources so that optimum blood glucose control can be achieved.

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