Efficacy of α-glucosidase inhibitors combined with dipeptidyl-peptidase-4 inhibitor (alogliptin) for glucose fluctuation in patients with type 2 diabetes mellitus by continuous glucose monitoring

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ABSTRACT

Aims/Introduction: The combination therapy of dipeptidyl-peptidase (DPP)-4 inhibitor and α-glucosidase inhibitors (α-GIs) is highly effective in suppressing postprandial hyperglycemia. The aim of the present study was to compare the effects of voglibose and miglitol on glucose fluctuation, when used in combination with DPP-4 inhibitor by using continuous glucose monitoring (CGM).

Materials and Methods: In a randomized cross-over study, 16 patients with type 2 diabetes who presented with postprandial hyperglycemia despite alogliptin (25 mg) were treated with voglibose (0.9 mg) or miglitol (150 mg). We measured standard deviation (SD); mean amplitude of glycemic excursions (MAGE), and mean, minimum and maximum glucose measured by CGM during three phases (alogliptin monotherapy, dual therapy of alogliptin and voglibose, and dual therapy of alogliptin and miglitol). The primary outcome measure was SD between α-GIs.

Results: SD was significantly improved by the addition of either voglibose (18.9 ± 10.1) or miglitol (19.6 ± 8.2) to alogliptin monotherapy (36.2 ± 8.7). MAGE improved significantly with the addition of either voglibose (57.5 ± 26.1, $P < 0.01$) or miglitol (64.6 ± 26.2, $P < 0.01$) to alogliptin monotherapy (101.5 ± 21.5). There was no significant difference in glucose fluctuation between α-GIs. There were no differences between two groups in mean (132.6 ± 21.4 and 138.7 ± 25.4) and maximum (184.3 ± 48.7 and 191.9 ± 38.3). The minimum glucose under alogliptin plus voglibose (94.9 ± 20.2) was significantly lower than that under alogliptin and miglitol (105.3 ± 21.0).

Conclusions: Glucose fluctuation was improved by the addition of voglibose or miglitol to alogliptin. Glucose fluctuations and postprandial hyperglycemia were similar between α-GIs. This trial was registered with the University Hospital Medical Information Network (no. UMIN R000010028). (J Diabetes Invest, doi: 10.1111/jdi.12059, 2013)

KEY WORDS: Alpha-glucosidase inhibitor, Continuous glucose monitoring, Dipeptidyl-peptidase-4 inhibitor

INTRODUCTION

The aim of treatment of diabetes mellitus is to achieve quality of life (QOL) and a life expectancy similar to those of healthy subjects. Studies such as the Diabetes Epidemiology Collaborate Analysis of Diabetic Criteria in Europe (DECODE)[1] and Funagata study[2] showed that plasma glucose levels at 2 h in the 75-g oral glucose tolerance test correlated with macroangiopathy. The Diabetes Intervention Study (DIS)[3] identified that postprandial hyperglycemia is an independent risk factor for macroangiopathy, which could lead to cardiovascular disease and cerebral infarction. In contrast, many large-scale cohort studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[4] and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) studies[5], have shown that severe hypoglycemia is also a risk factor of cardiovascular disease and mortality.

Dipeptidyl-peptidase (DPP)-4 inhibitor stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner, and improves postprandial glucose levels without inducing hypoglycemia. Single administration of alogliptin, a DPP-4 inhibitor, has been shown to improve glycated hemoglobin (HbA_{1c}) by 0.56% (alogliptin 12.5 mg/day) and 0.59% (alogliptin 25 mg/day) after 26 weeks. However, we often experience patients treated with DPP-4 inhibitors only who present

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with insufficient postprandial glucose control, thereby requiring additional medications.

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial[6] has shown that α-glucosidase inhibitors (α-GIs) prevent cardiovascular events. α-GIs are also recommended in the International Diabetes Federation (IDF) guidelines for management of postprandial glucose, published in 2008[7,8], with the highest evidence level.

Furthermore, α-GIs have been reported to increase glucagon-like peptide-1 (GLP-1)[9,10], and are expected to have a synergistic effect in combination with DPP-4 inhibitors. Mori[11] reported a case of significant improvement in glucose fluctuations by adding miglitol to alogliptin. To prevent or suppress the progression of diabetic vasculopathies, it is important to minimize glucose fluctuations by lowering postprandial glucose levels and avoiding hypoglycemia, in addition to improvement of HbA_{1c} levels. However, there is no information on the comparative effects of different α-GIs used in combination with DPP-4 inhibitors. Based on the common knowledge that the standard deviation (SD) value of glucose measured through continuous glucose monitoring (CGM) reflects glucose fluctuation, we used the SD of glucose as the primary outcome measure in the present study. The present study was designed to assess and compare the effects of miglitol and voglibose on glucose fluctuation in combination with alogliptin with regard to their impact on postprandial hyperglycemia by CGM.

METHODS

Patients

The study participants were patients with type 2 diabetes mellitus, aged 20–79 years, who presented with postprandial hyperglycemia despite treatment with 25 mg/day alogliptin for more than 1 week, and were hospitalized at the University of Occupational and Environmental Health Japan, Department of Endocrinology, Metabolism and Diabetes in Kitakyushu, Japan, between October 2010 and December 2011. Patients using insulin therapy, those who were or might have been pregnant and those with severe liver dysfunction (level of transaminases three times the upper normal levels) were excluded. Each participant provided a signed informed consent to participate in the study. The study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan.

Study Protocol

The study was designed as a randomized cross-over study, and participants were allocated to either group A or B (Figure 1). Throughout the study period, patients of both groups were treated with alogliptin at 25 mg/day. In group A, participants were treated with 50 mg miglitol before each meal from day 6 of admission (150 mg/day), and 5 days later (from day 11 of admission), they were switched to 0.3 mg voglibose before each meal (0.9 mg/day). In group B, participants were treated with 0.3 mg voglibose before each meal from day 6 of admission (0.9 mg/day), and 5 days later (from day 11 of admission), they were switched to 50 mg miglitol before each meal (150 mg/day). All participants wore a continuous glucose monitoring system (CGMS® System Gold™; Medtronic Inc., Fridley, MN, USA) from the night of day 2 of admission for 3 days for continuous monitoring of glucose fluctuations while on alogliptin treatment alone. Similarly, the participants wore the CGM device from day 2 of each α-GI administration for 3 days. Thus, a 3-day CGM monitoring was carried out three times in each patient, followed by assessment of glucose levels. The data used for analysis were obtained on day 3 of CGM to ensure stability. No changes were made to diet or exercise therapy or drugs (except the α-GIs).

Measurements of Biochemical Variables

The CGM system used to monitor glucose fluctuations measures glucose levels every 5 min, 288 times per day. This device causes glucose oxidase to react with glucose concentration in the subdermal interstitial fluid, producing an electrical signal. Although the CGM measures interstitial glucose concentration, the measured values have been reported to

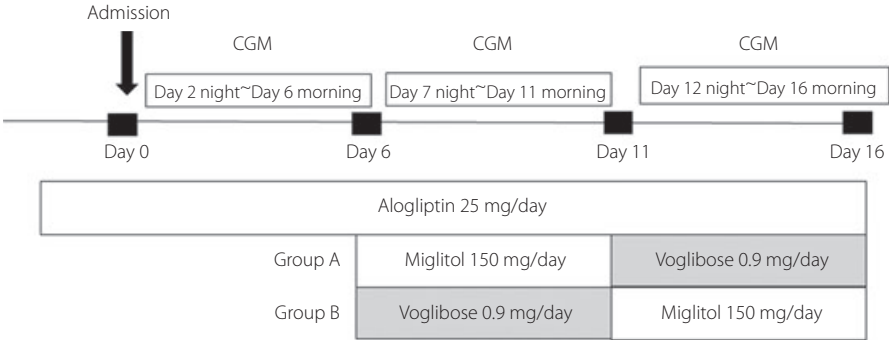

Figure 1 | Study design. The study design was a randomized cross-over study, and participants were allocated to either group A or B. Patients were treated with either voglibose (0.9 mg/day) or miglitol (150 mg/day) in combination with alogliptin (25 mg/day). Each participant wore a continuous glucose monitoring (CGM) device from the night of day 2 of admission for 3 days. Similarly, the participant wore a CGM device from day 2 of each α-GI administration for 3 days. Thus, each patient underwent 3-day CGM three times, followed by assessment of glucose level.

correlate well with venous blood glucose levels[12], and are adjusted for self-monitoring blood glucose (SMBG) values. For convenience, the glucose concentration values measured by the CGM device were therefore considered to represent blood glucose levels. The mean ± SD glucose level, minimum and maximum glucose levels, area under the curve for glucose above 180 mg/dL (AUC > 180), and area under the curve for glucose above 140 mg/dL (AUC > 140) were analyzed by CGM. The American Diabetes Association (ADA) recommends that peak postprandial glucose levels should not exceed 180 mg/dL at any time after a meal[13], whereas the glucose level at 2 h after a meal was recommended to be maintained at 140 mg/dL or less by the IDF 2007 guidelines[8], and at 160 mg/dL or less by the 2011 version of the same guidelines. For this reason, we used AUC > 180 and AUC > 140 as outcome measures.

HbA_{1c} (%) was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value, which was calculated as HbA_{1c} (NGSP) (%) = HbA_{1c} (Japan Diabetes Society [JDS]) (%) + 0.4%, considering the relationship of $HbA1_c$ (NGSP) values to HbA_{1c} (JDS) (%) values measured by the Japanese standard and measurement method[14]. Homeostasis model assessment for insulin resistance (HOMA-R), which represents insulin resistance, was calculated (formula: HOMA-R = fasting glucose level × fasting insulin level/405). Blood samples were collected during fasting, and urinary C-peptide reactivity (u-CPR) levels were measured in 24-h urine samples.

The primary outcome measure was SD of glucose, and this was compared between the two α-GIs (both being used in combination with alogliptin). The mean glucose level, MAGE of glucose, AUC > 180, AUC > 140, and maximum and minimum glucose levels were used as secondary outcome measures to determine the difference between the two α-GIs.

Statistical Analysis

Data were expressed as mean ± SD. The efficacies of voglibose and miglitol within each group were compared by using the Wilcoxon matched-pairs signed-rank test. The efficacies of alogliptin and combination therapy of alogliptin and voglivose or miglitol within each group were compared by using the Wilcoxon matched-pairs signed-rank test. In all analyses, $P < 0.05$ was considered statistically significant. Statistical analyses were carried out with PASW Statistics 18.0 software (formerly SPSS Statistics; SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Demographics

Table 1 shows the baseline characteristics of the patients. Consent was obtained from 16 patients (13 men and 3 women). The mean age, body mass index, HbA_{1c}, HOMA-R, and u-CPR were 53.3 ± 10.5 years, 25.2 ± 4.8 kg/m^2, 9.3 ± 1.3%, 2.5±1.9, and 112.3 ± 75.0 μg/day, respectively.

Table 1 | Patient profile on admission

Sex (male : female)	16 (13:3)
Age (years)	53.3 ± 10.5 (range 32–73)
Other drugs	Pioglitazone 4 patients (30 mg: 3 patients, 15 mg: 1 patient)
Bodyweight (kg)	69.5 ± 16.2 (range 52.2–114.1)
Body mass index (kg/m^2)	25.2 ± 4.8 (20.2–38.1)
Diabetic neuropathy (%)	56
Diabetic retionopathy (%)	25
Diabetic nephropathy (%)	19
HbA_{1c} (NGSP; %)	9.3 ± 1.3 (range 7.0–11.9)
Fasting plasma glucose (mg/dL)	147.2 ± 26.0 (range 111–195)
Insulin (μU/mL)	6.0 ± 3.7 (range 2.7–16.2)
HOMA-R	2.5 ± 1.9 (range 0.9–6.9)
u-C peptide (μg/day)	112.3 ± 75.0 (range 30.5–257.0)

Data are mean ± standard deviation or *n*. Glycated hemoglobin (HbA_{1c}) levels were converted to National Glycohemoglobin Standardization Program (NGSP) levels (formula: NGSP = Japan Diabetes Society + 0.4%). HOMA-R, homeostasis model assessment insulin resistance.

CGM Data

The glucose fluctuation, the SD of glucose levels detected by CGM, in diabetes patients treated with alogliptin alone (36.2 ± 8.7 mg/dl) was markedly and significantly improved by combination with either voglibose (18.9 ± 10.1 mg/dL, $P < 0.01$) or miglitol (19.6 ± 8.2 mg/dL, $P < 0.01$; Figure 2). Also, the MAGE of glucose levels detected by CGM improved significantly by the addition of either voglibose (57.5 ± 26.1 mg/dL, $P < 0.01$)

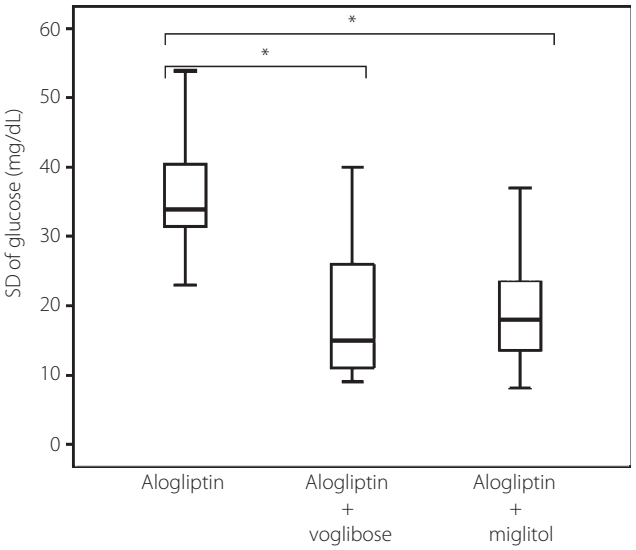

Figure 2 | The standard deviation (SD) of glucose levels in each therapy (95% confidence intervals). Data are shown as box and whisker plots showing medians, 25th and 75th quartiles, and complete data range. *$P < 0.01$ vs alogliptin (by Wilcoxon test).

or miglitol (64.6 ± 26.2 mg/dL, $P < 0.01$) to alogliptin monotherapy (101.5 ± 21.5 mg/dL). The combination treatment of alogliptin with either of the α-GIs also resulted in a significant improvement in outcome measures including AUC > 180, AUC > 140, the mean, and minimum and maximum glucose levels compared with alogliptin alone (Table 2). However, there was no statistically significant difference in the SD of glucose levels between α-GIs in combination with voglibose (18.9 ± 10.1 mg/dL) and with miglitol (19.6 ± 8.2 mg/dL; Figure 2 and Table 2).

Analysis of the secondary outcome measures showed no significant difference between voglibose and miglitol (in combination with alogliptin) in AUC > 180, AUC > 140 and in mean or maximum glucose levels. Also, there was no statistically significant difference in the MAGE of glucose levels between α-GIs in combination with voglibose (57.5 ± 26.1 mg/dL) and with miglitol (64.6 ± 26.1 mg/dL; Table 2). Interestingly, the minimum glucose level, however, was significantly lower in voglibose (94.9 ± 20.2 mg/dL) than in miglitol (105.3 ± 21.0 mg/dL). The combination treatment of alogliptin with either of the α-GIs resulted in a significant improvement in outcome measures in postmeal glucose after 1 h and 2 h, compared with alogliptin alone. However, there was no significant difference in the results between α-GIs (Table 2). The mean values of 3-days continuous glucose levels detected by CGM in all the participants who were treated with either miglitol or voglibose in combination with alogliptin are shown in Figure 3. Glucose fluctuation of voglibose in combination with alogliptin was 133 ± 19 mg/dL, and glucose fluctuation of miglitol in combination with alogliptin was 139 ± 20 mg/dL. Glucose fluctuations during treatment with voglibose and miglitol were comparable. Although there was no statistically significant difference, improvement in glucose level after lunch and dinner was slightly better for voglibose.

DISCUSSION

It is important to minimize glucose fluctuations by lowering postprandial glucose levels and avoiding hypoglycemia, in addition to improving HbA_{1c} levels to prevent the progression diabetic macro- and/or microvasculopathy. It is well known that the SD value of glucose measured through CGM reflects glucose fluctuation; we, therefore, compared the efficacy of α-GIs, miglitol (150 mg) and voglibose (0.9 mg) when used in combination with alogliptin (25 mg) by measuring glucose levels by CGM, and used the SD of glucose as the primary outcome measure in the present study. We found that the glucose fluctuation detected with the SD of glucose levels by CGM in patients treated with alogliptin combined with either of the α-GIs was significantly improved, compared to those with alogliptin alone. The combination treatment of alogliptin with α-GIs also had an advantage in the improvement of AUC > 180, AUC > 140, the mean, and minimum and maximum glucose levels, compared with alogliptin alone. The minimum glucose level with alogliptin plus voglibose (94.9 ± 20.2 mg/dL) was significantly lower than that with alogliptin and miglitol (105.3 ± 21.0 mg/dL). The difference in the CGM data shown in Figure 3 is probably a result of glucose suppression during the night-time. In this regard, Narita *et al.*[15] compared the GLP-1 concentration between voglibose monotherapy and miglitol monotherapy, and found no statistically significant difference between α-GIs. Although there are no reports that have compared different α-GIs under DPP-4 inhibitors, and because we did not measure serum GLP-1 and glucagon concentrations in the present study, we could not

Table 2 | Continuous glucose monitoring data according to the type of α-glucosidase inhibitor

	Voglibose plus alogliptin	Miglitol plus alogliptin	*P*-value	Alogliptin alone
SD of glucose (mg/dL)	18.9 ± 10.1**	19.6 ± 8.2**	0.679	36.2 ± 8.7
MAGE of glucose (mg/dL)	57.5 ± 26.1**	64.6 ± 26.2**	0.365	101.5 ± 21.5
Average plasma glucose (mg/dL)	132.6 ± 21.4**	138.7 ± 25.4**	0.187	164.1 ± 27.9
Area under the curve >180 (mg/dL per day)	1.9 ± 5.5**	2.9 ± 7.7**	0.139	12.4 ± 13.0
Area under the curve > 140 (mg/dL per day)	7.6 ± 13.7**	11.9 ± 17.9**	0.102	31.4 ± 21.2
Maximum plasma glucose (mg/dL)	184.3 ± 48.7**	191.9 ± 38.3**	0.535	266.3 ± 41.5
Minimum plasma glucose (mg/dL)	94.9 ± 20.2*	105.3 ± 21.0	0.029+	110.6 ± 21.5
Blood glucose level 1 h after breakfast (mg/dL)	141.9 ± 29.5**	150.3 ± 26.3**	0.173	216.8 ± 39.3
Blood glucose level 1 h after lunch (mg/dL)	139.5 ± 25.4**	135.4 ± 26.0**	0.518	209.4 ± 24.2
Blood glucose level 1 h after dinner (mg/dL)	153.7 ± 30.2**	137.3 ± 30.8**	0.132	206.9 ± 23.8
Blood glucose level 2 h after breakfast (mg/dL)	141.2 ± 31.3**	153.3 ± 27.2**	0.173	208.0 ± 51.2
Blood glucose level 2 h after lunch (mg/dL)	136.6 ± 19.1**	148.8 ± 22.5**	0.056	197.8 ± 56.6
Blood glucose level 2 h after dinner (mg/dL)	147.2 ± 30.3**	166.9 ± 40.5**	0.155	219.4 ± 32.2

Data are mean ± standard deviation (SD). $^{+}P < 0.05$, voglibose combined with alogliptin vs Miglitol combined with alogliptin; $*P < 0.05$, voglibose or miglitol vs alogliptin alone. $**P < 0.01$, voglibose or miglitol vs alogliptin alone. *P*-values indicate the difference between voglibose combined with alogliptin, and miglitol combined with alogliptin, by Wilcoxon test. The efficacies of alogliptin and combination therapy of alogliptin and voglivose or miglitol within each group were compared by using the Wilcoxon test. MAGE, mean amplitude of glycemic excursions.

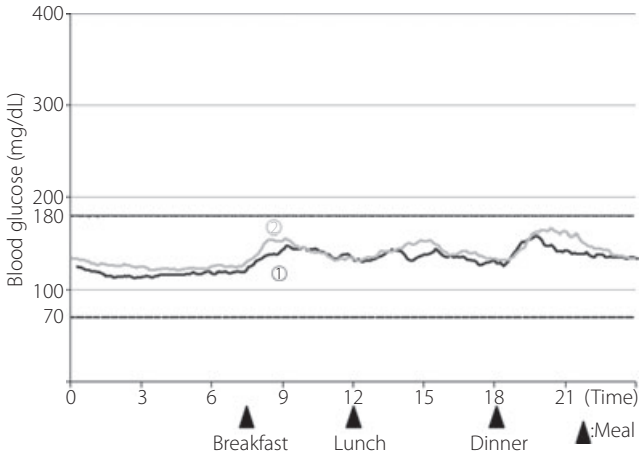

Figure 3 | The mean values of 3-days continuous plasma glucose levels detected by continuous glucose monitoring in all the participants who were treated with either miglitol or voglibose in combination with alogliptin. ①, Glucose fluctuation of voglibose in combination with alogliptin; ②, glucose fluctuation of miglitol in combination with alogliptin.

establish the exact mechanism of voglibose-induced suppression of minimum glucose level. However, it is likely that the combination treatment of alogliptin and voglibose improved glucose levels during the night-time by increasing GLP-1 concentration and reducing glucagon concentration.

We also compared the efficacy of voglibose and miglitol on glucose fluctuations when administered with alogliptin by using CGM. Except for the effect on minimum glucose, however, there were no significant differences in SD of glucose, MAGE of glucose, AUC > 180, AUC > 140, the mean and maximum glucose level during treatment by either of the two α-GIs. Glucose levels in the voglibose arm of the study were generally lower for all parameters compared with miglitol, and the minimum glucose level was significantly lower with voglibose. Meta-analysis of α-GI monotherapy showed a positive effect on HbA_{1c} levels of 0.47% with voglibose and 0.68% with miglitol. In addition, a study that compared glucose levels 1 h after meals showed regulation of 43.2 mg/dL with voglibose and of 48.6 mg/dL with miglitol; thus, miglitol monotherapy was considered to be slightly more effective[16].

The results of the present study contradicted these findings. We assume that the lack of significant differences between voglibose and miglitol is due to the study; the inclusion of patients who were already treated with alogliptin. α-GIs suppress postprandial hyperglycemia by blocking the absorption of glucose after meals, and are also reported to affect incretin. α-GIs suppress the secretion of gastric inhibitory peptide (GIP) from K cells in the upper small intestine, but enhance GLP-1 secretion from L cells in the lower small intestine[9,10]. With regard to the efficacy of α-GIs on incretin, one study of incretin secretory reaction compared a control group with a treatment group (healthy individuals administered voglibose first, followed by 75 g of sucrose). Voglibose suppressed sucrose-induced GIP secretion, but increased GLP-I reaction[17]. Analysis carried out after a meal challenge test also showed similar results[18]. A previous study that compared miglitol with placebo in obese female type 2 diabetics showed that miglitol significantly increased GLP-1 secretion after a meal challenge test[9]. In another study involving non-obese type 2 diabetic patients, miglitol suppressed GIP secretion and stimulated GLP-1 secretion after a meal challenge test[10]. The combination therapy of DPP-4 inhibitor plus α-GI could synergistically enhance GLP-1, leading to a different result compared with studies using a single α-GI.

In a cross-over study using CGM, Tsujino *et al.*[19] compared the short-term efficacy of α-GI monotherapy, miglitol (50 mg) and acarbose (100 mg) before each meal in 10 patients with type 2 diabetes. In that study, the range of increase in glucose levels at 30 and 60 min after lunch and 30, 60 and 90 min after dinner was significantly smaller in miglitol treatment compared with acarbose treatment. However, no significant differences were observed between the two agents with regard to the range of increase in glucose levels from baseline to peak, time to peak postprandial period and to 3 h after each meal. To our knowledge, similar comparative studies for miglitol and voglibose, or voglibose and acarbose are not available at present. Miglitol is absorbed in the small intestine, as observed during the manifestation of pharmaceutical efficacy, and provides early suppression of postprandial hyperglycemia. Although miglitol is partially absorbed in the small intestine and excreted from the kidney unchanged, voglibose is minimally absorbed from the intestine. Miglitol thus suppresses the glucose level for 1 h after meals, whereas acarbose and voglibose suppress glucose levels for 2 h after meals[20].

The combination therapy of DPP-4 inhibitor plus α-GI is potentially useful in clinical medicine, as it has been shown to improve progressive diabetes in murine experiments[21]. In an experiment that compared a monotherapy group (0.2 mg voglibose before each meal) with a dual therapy group (0.2 mg voglibose combined with 12.5 mg of alogliptin or 0.2 mg voglibose and 25 mg alogliptin), the changes in HbA_{1c} levels after 12 weeks were 0.06%, −0.96% and −0.91%, respectively, showing a difference of approximately 1% between voglibose monotherapy and the dual therapy[22]. These results suggest the high efficacy of the combination therapy of alogliptin and α-GI. Further long-term studies should be carried out to investigate the difference in efficacy between α-GIs when used alone or in combination with DPP-4 inhibitors.

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