Cross-Over Study Comparing Postprandial Glycemic Increase After Addition of a Fixed-Dose Mitiglinide/Voglibose Combination or a Dipeptidyl Peptidase-4 Inhibitor to Basal Insulin Therapy in Patients with Type 2 Diabetes Mellitus

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Although the efficacy of combination therapy consisting of basal insulin and oral hypoglycemic agents (OHAs) has been shown, which OHAs are the most efficient remains unclear.

Material/Methods: Five patients with type 2 diabetes were enrolled and treated with insulin degludec and metformin as a basal therapy. The patients were randomized in a cross-over fashion to receive a combination of mitiglinide (10 mg) and voglibose (0.2 mg) (M+V) 3 times daily or linagliptin (5 mg) (L) once daily for 8 weeks. After 8 weeks, 2 kinds of meal tolerance tests were performed as breakfast on 2 consecutive days. The first breakfast contained 460 kcal (carbohydrates, 49.1%; protein, 15.7%; fat, 35.2%), while the second contained 462 kcal (carbohydrates, 37.2%; protein, 19.6%; fat, 43.2%). Self-monitoring blood glucose levels were measured at 0, 30, 60, and 120 min after the meal tests, and the increase in the postprandial area under the curve $(AUC)_{0–120 min}$ was determined. The HbA1c, glycated albumin, and 1,5-anhydroglucitol (AG) levels were measured, and continuous glucose monitoring was performed.

Results: The increase in the postprandial $AUC_{0–120 min}$ was significantly smaller in the M+V group than in the L group after both meals. The 24-h average, 24-h standard deviations, 24-h AUC, and mean amplitude of glycemic excursion (MAGE) were similar for both groups and after both meals. The change in 1,5-AG was higher in the M+V group than in the L group.

Conclusions: The combination of M+V with basal therapy improved postprandial glucose excursion more effectively than L in T2DM patients.

MeSH Keywords: **Dipeptidyl Peptidase 4 • Hyperglycemia • Incretins**

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Background

The impairment of β cells in type 2 diabetes is a progressive process that occurs before diagnosis and throughout the disease course [1,2]. Therefore, many patients who are initially treated with oral hypoglycemic agents (OHAs) eventually require the addition of insulin therapy. One treatment strategy that includes insulin is a combination of basal insulin with OHAs. Using this regimen, the insulin dose can be easily titrated to minimize the number of hypoglycemic episodes and weight gain, compared with multiple insulin injections or mixed insulin therapy [3,4]. However, a drawback of this regimen is that it provides poor support against sustained postprandial hyperglycemia, resulting in glucose fluctuations that can increase the risks of both cardiovascular disease [5–8] and microvascular disease [9,10].

We previously reported that the 2-step addition of 2 postprandial hypoglycemic agents, an alpha-glucosidase inhibitor and a glinide, to basal insulin therapy was potentially effective and safe for decreasing both the fasting and postprandial glucose levels [11]. While these basal insulin therapies are commonly used for patients with insufficient glycemic control using only OHAs, which OHAs are the most efficient for use in combination with basal insulin therapy remains unclear. We next compared a fixed-dose mitiglinide/voglibose combination and a dipeptidyl peptidase-4 (DPP-4) inhibitor. Mitiglinide is categorized as a glinide and voglibose is categorized as an alpha-glucosidase inhibitor. In comparison, DPP-4 inhibitors have a different mechanism of action for reducing postprandial hyperglycemia. Although some studies [12–15] have shown these OHAs can reduce postprandial glucose levels, few studies have examined the combination of basal insulin therapy with these OHAs.

Accordingly, we proposed a regimen consisting of a fixed-dose mitiglinide/voglibose combination or a dipeptidyl peptidase-4 inhibitor to basal insulin therapy to target postprandial hyperglycemia. Here, we compare the effects of these regimens on the postprandial response after meals containing different amounts of carbohydrates and on the participants' daily lives.

Material and Methods

Patients

We enrolled patients with type 2 diabetes who were outpatients at the National Center for Global Health and Medicine (NCGM) Hospital between April 2014 and December 2014. Candidate subjects were ages 30–79 years, were being treated with insulin therapy, and had an HbA1c level below 8.5%. Patients with severe renal dysfunction (estimated glomerular
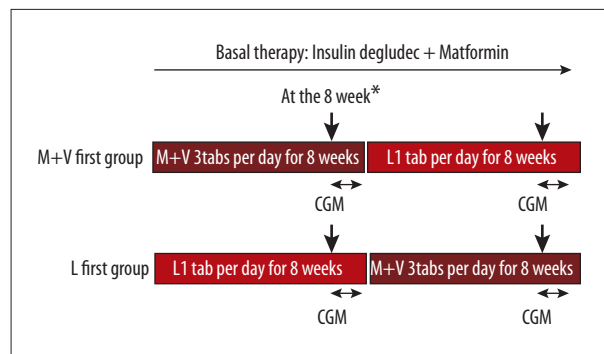
Figure 1. Cross-over study protocol. Basal therapy: the patients were treated once daily with an injection of insulin degludec and metformin as a basal therapy throughout the treatment course. The first M+V group additionally received M+V (mitiglinide10 mg and voglibose 0.2 mg) (3 tablets per day) for 8 weeks and were then switched to L (5 mg) (1 tablet per day) for 8 weeks. The first L group received L for 8 weeks and were then switched to M+V for 8 weeks. * HbA1c, GA, and 1,5-AG were measured and CGM was recorded for 1 week at the end of each 8-week treatment period.

filtration rate <30 mL/min/1.73 m^2 or continuous hemodialysis), severe liver dysfunction, type 1 diabetes, glutamic acid decarboxylase antibody positivity, malignancy, or other causes of hyperglycemia were excluded from this study.

All the patients provided written informed consent at an outpatient hospital prior to enrollment in the trial. The study protocol was approved by the Ethics Committee of NCGM (NCGM-G-001555-01) and was implemented in accordance with the provisions of the Declaration of Helsinki. This study was also registered at the UMIN Clinical Trial Registry as UMIN000013689.

Study design

After enrollment, the patients were treated with a once-daily injection of insulin degludec and metformin as a basal therapy. The metformin dosage was set as high as possible after considering the patient's age, renal function, and other adverse effects.

The subjects were randomized in an open-label, cross-over fashion to receive a combination of mitiglinide (10 mg) and voglibose (0.2 mg) (M+V) for 8 weeks 3 times daily immediately before each meal, or linagliptin (5 mg) (L) once daily for 8 weeks. The treatment groups were then switched (Figure 1).

The first M+V group took the M+V combination immediately before every meal (3 times daily) for 8 weeks. For the first 4 weeks, insulin degludec titration was performed once a week to achieve a target fasting glucose level of 70–130 mg/dL, based

on telephone contact. After 8 weeks, laboratory measurements were performed and 2 kinds of meal tolerance tests were administered. Then, this group of patients was switched to the L regimen, and insulin degludec titration was performed again for the first 4 weeks. After 8 weeks of the second regimen, the clinical measurements were performed a second time and the 2 meal tolerance tests were administered.

The first L group took L after breakfast for 8 weeks. Insulin degludec titration, laboratory measurements, and meal tolerance tests were performed in the same way as described above. Then, this group of patients was switched to the M+V regimen. The clinical measurements were then performed and the 2 meal tolerance tests were administered after 8 weeks, similar to the protocol described above.

Biochemical and clinical measurements

Before and 8 weeks after the start of M+V or L administration, the HbA1c, glycated albumin (GA), and 1, 5-anhydroglucitol (AG) levels were measured after an overnight fast.

Two kinds of morning meal tolerance tests were performed on 2 consecutive days after a 7-h overnight fast. The breakfast on the first day of testing contained 460 kcal (carbohydrates, 56.5 g [49.1%]; protein, 18.0 g [15.7%]; fat, 18.0 g [35.2%]; Test meal: JANEF E460F18, Q.P. Co., Tokyo, Japan), while that on the second day contained 462 kcal (carbohydrates, 43.0 g [37.2%]; protein, 22.6 g [19.6%]; fat, 22.2 g [43.2%]; low-carbohydrate meal [LC meal]: milk, corn flakes, cheese, and fish sausage). The self-monitoring blood glucose (SMBG: OneTouch® UltraVue™; Johnson & Johnson) level was measured at 0, 30, 60, and 120 min after meal intake. The increase in the postprandial area under the curve $(AUC)_{0-120\ min}$ based on the SMBG measurements was then determined.

The glucose levels were recorded over a period of 4 days using continuous glucose monitoring (CGM) (iPro™; Medtronic Inc.). The CGMS device was calibrated 4 times a day. We used 3 different measurement periods: 1) the day of the Test meal (first day), 2) the day of the LC meal (second day), and 3) 2 consecutive days of their daily lives (third and fourth days). As part of their daily lives' glucose profiles, we evaluated the average CGM data for the third and fourth days. The CGM results were then used to calculate the 24-h average, the standard deviation (SDs) of the 24-h values, the 24-h AUC, and the mean amplitude of glycemic excursion (MAGE [16]) using glucose values observed every 5 min.

Primary and secondary outcomes

The primary endpoint was the difference in the postprandial $AUC_{0-120\ min}$ increase after the Test meal between the M+V group and the L group. The difference in the postprandial $AUC_{0-120\ min}$ increase after the LC meal was also compared between the M+V group and the L group.

We calculated the 24-h average, the SDs of the 24-h values, the 24-h AUC, and the MAGE of the CGM data obtained on the days of the Test meal, the LC meal, and the average of 2 consecutive days of daily life. Then, we compared the difference in the postprandial $AUC_{0-120\ min}$ increase between the Test meal and the LC meal for both the M+V group and the L group.

The HbA1c, GA, and 1,5-AG levels were evaluated between the M+V group and the L group. For these 3 glycemic indexes, we calculated the changes between baseline and 8 weeks and between 8 and 16 weeks, which we then used to evaluate the effects of the corresponding administered drug(s), i.e., M+V or L.

Statistical analysis

Continuous variables were compared using the Wilcoxon rank sum test. A 2-sided *P* value <0.05 was regarded as significant. The results were described using the median and interquartile ranges. The statistical analysis was performed using Stata IC 11.

Results

We enrolled 6 patients (5 males and 1 female) with type 2 diabetes who were outpatients of our institution. The female patient was excluded because she developed hyperglycemia and began to require multiple insulin injections after her inclusion in the study. Therefore, all the enrollees were male patients. These 5 patients completed the study. The median age was 63 years, the duration of diabetes was 8 years, the BMI was 23.5 kg/m^2, and the HbA1c level was 7.1% (Table 1).

The blood glucose levels as determined using SMBG are shown in Figure 2. The postprandial $AUC_{0-120\ min}$ increase for the M+V group after the Test meal was significantly lower than that for the L group (*P*=0.04) (Figure 2A). The glucose levels at 60 min after the Test meal tended to be lower in the M+V group than in the L group, while the levels at 0, 30, and 120 min were similar for the 2 groups.
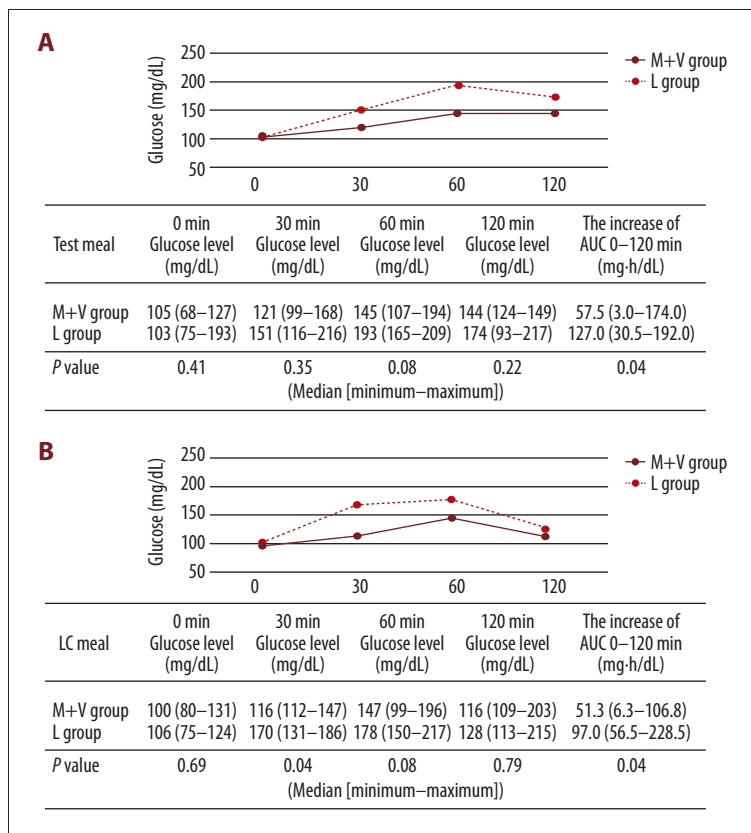
After the LC meal, the postprandial $AUC_{0-120\ min}$ increase for the M+V group was also lower than that for the L group (*P*=0.04) (Figure 2B).

In the M+V group, the glucose level at 30 min after the LC meal was significantly lower and the level at 60 min tended to be lower than in the L group. The glucose levels at 0 and 120 min were similar for the 2 groups.

Table 1. Patient characteristics at baseline.

	Age (year)	Duration of diabetes (year)	BMI (kg/m²)	Prescription of anti-diabetic agents		HbA1c (%)	GA (%)	1,5-AG (µmol/L)	1-mg glucagon stimulated test Serum C peptide (nmol/L)		eGFR (mL/min/ 1.73 m²)
				Ins-Deg (units)	Metformin (mg)				0 minutes	6 minutes	
Case 1	47	7	29.2	24	1000	8.3	18.1	17.7	0.57	0.97	94.9
Case 2	53	10	24.4	22	1500	6.8	17.1	54.8	0.53	0.87	64.2
Case 3	63	1	20.3	8	1000	6.7	19.6	152.9	0.63	1.76	87.3
Case 4	66	8	23.5	15	2250	7.6	16.2	22.5	0.67	1.43	74.7
Case 5	72	32	21.5	13	500	7.1	19.9	77.4	0.37	0.60	85.3
Median	63	8	23.5	15	1000	7.1	18.1	54.8	0.57	0.97	85.3

All the patients were male.

Test meal	0 min Glucose level (mg/dL)	30 min Glucose level (mg/dL)	60 min Glucose level (mg/dL)	120 min Glucose level (mg/dL)	The increase of AUC 0–120 min (mg·h/dL)
M+V group L group	105 (68–127) 103 (75–193)	121 (99–168) 151 (116–216)	145 (107–194) 193 (165–209)	144 (124–149) 174 (93–217)	57.5 (3.0–174.0) 127.0 (30.5–192.0)
P value	0.41	0.35	0.08	0.22	0.04
		(Median [minimum–maximum])			

| LC meal	0 min Glucose level (mg/dL)	30 min Glucose level (mg/dL)	60 min Glucose level (mg/dL)	120 min Glucose level (mg/dL)	The increase of AUC 0–120 min (mg·h/dL)
M+V group L group	100 (80–131) 106 (75–124)	116 (112–147) 170 (131–186)	147 (99–196) 178 (150–217)	116 (109–203) 128 (113–215)	51.3 (6.3–106.8) 97.0 (56.5–228.5)
P value	0.69	0.04	0.08	0.79	0.04
		(Median [minimum–maximum])			

Figure 2. Comparison of the SMBG profiles of the M+V and L groups after each kind of meal tolerance test. (**A**) The SMBG profiles of the M+V and L groups after the Test meal. The solid line represents the M+V group and the dot line represent the L group. (**B**) The SMBG profiles of the M+V and L groups after the LC meal. The solid line represents the M+V group and the dot line represents the L group.

No differences in the glucose levels after the Test meal and the LC meal were seen for either the M+V group or the L group (Figure 3A, 3B).

Regarding the CGM data, we found no significant differences between the M+V group and the L group in the 24-h average, the 24-h AUC, the SDs of the 24-h values, the proportion of time in hyper- and hypoglycemia, or the MAGE on the day of the Test meal and the day of the LC meal. These indexes were also similar in the average of 2 consecutive days of daily life between the 2 groups (Table 2).

When the results after the 2 test meals were compared, no significant differences in the 24-h average (P=0.69), the 24-h AUC (P=0.69), the SD of 24-h (P=0.35), or the MAGE (P=0.35) were observed between the Test meal data and the LC meal
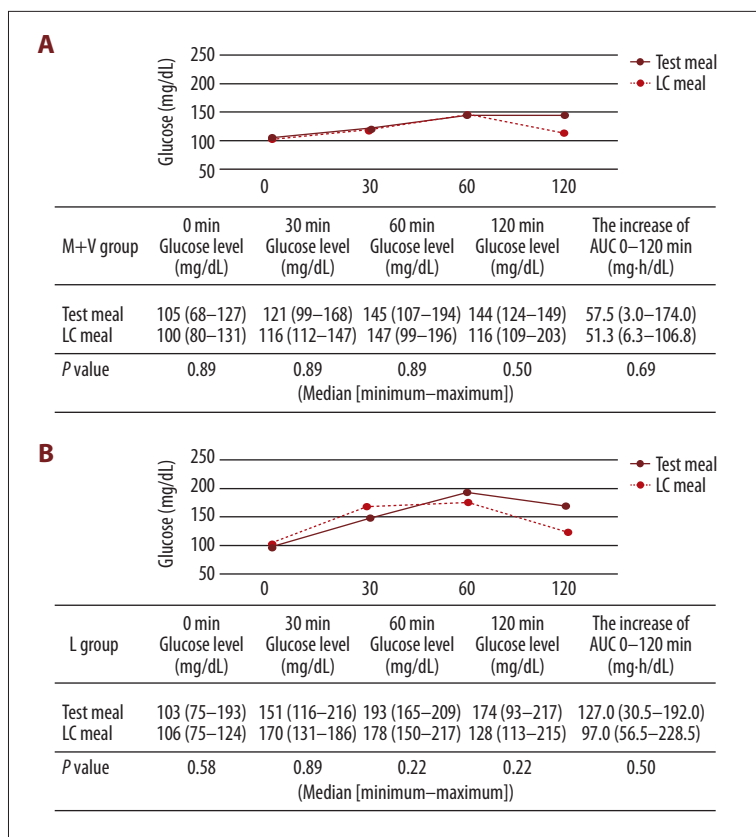
Figure 3. Comparison of the SMBG profiles after the Test meal and the LC meal between the M+V and L groups. The data shown in Figure 2 was re-plotted to evaluate the difference between the meal tolerance tests. (**A**) SMBG profiles after the Test and LC meals in the M+V group. (**B**) SMBG profiles after the Test and LC meals in the L group. The solid line represents Test meal and the dot line represents LC meal.

M+V group	0 min Glucose level (mg/dL)	30 min Glucose level (mg/dL)	60 min Glucose level (mg/dL)	120 min Glucose level (mg/dL)	The increase of AUC 0–120 min (mg·h/dL)
Test meal	105 (68–127)	121 (99–168)	145 (107–194)	144 (124–149)	57.5 (3.0–174.0)
LC meal	100 (80–131)	116 (112–147)	147 (99–196)	116 (109–203)	51.3 (6.3–106.8)
P value	0.89	0.89	0.89	0.50	0.69
		(Median [minimum–maximum])			

L group	0 min Glucose level (mg/dL)	30 min Glucose level (mg/dL)	60 min Glucose level (mg/dL)	120 min Glucose level (mg/dL)	The increase of AUC 0–120 min (mg·h/dL)
Test meal	103 (75–193)	151 (116–216)	193 (165–209)	174 (93–217)	127.0 (30.5–192.0)
LC meal	106 (75–124)	170 (131–186)	178 (150–217)	128 (113–215)	97.0 (56.5–228.5)
P value	0.58	0.89	0.22	0.22	0.50
		(Median [minimum–maximum])			

data among the subjects in the M+V group. In the L group, compared with 2 test meals, no significant differences in the 24-h average (*P*=0.69), the 24-h AUC (*P*=0.69), or the SD of 24-h (*P*=0.69) were observed between the Test meal data and the LC meal data, while the MAGE of the LC meal data was significantly higher than that of the Test meal data (*P*=0.04) (Supplementary Table 1).

The insulin degludec dose of each patient at CGM is shown in Table 3. The HbA1c and the GA levels were similar in the M+V group and the L group. The median HbA1c change was −0.3 (in the M+V group) *vs*. −0.2 (in the L group) (*P*=0.50), while the median GA change was −0.7 (in the M+V group) *vs*. −0.2 (in the L group) (*P*=0.14). The 1,5-AG level was higher in the M+V group than in the L group. The median 1,5-AG change was 15.2 (in the M+V group) *vs*. −9.7 (in the L group) (*P*=0.04) (Table 3).

Discussion

This study is the first to investigate the difference in effects of M+V versus L on postprandial hyperglycemia in patients receiving basal insulin therapy support. The M+V group exhibited a smaller postprandial AUC$_{0–120 \text{ min}}$ increase, compared with the L group, after both the Test meal and the LC meal. The 24-h average, the SDs of the 24-h values, the 24-h AUC, and the

MAGE of the CGM data were similar between the 2 groups for data obtained on the day of the Test meal, the day of the LC meal, and the average of 2 days in daily life. When the results after the meal tests were compared, in the L group the MAGE was significantly higher for the day of the LC meal, compared with the value for the day of the Test meal. Furthermore, the 1,5-AG value was higher in the M+V group than in the L group.

Some previous studies have assessed the effects of oral postprandial hypoglycemic agents used in combination with basal therapy. We previously reported that a 2-step regimen consisting of the addition of the postprandial hypoglycemic agents miglitol and mitiglinide to basal insulin therapy enabled more than 80% of the patients to achieve a good glucose profile [11]. CGM also showed the effectiveness of miglitol and mitiglinide in lowering the daytime blood glucose levels without inducing hypoglycemia. Linagliptin added to basal insulin therapy also reportedly improved glycemic control relative to a placebo without increasing hypoglycemia or body weight over a 52-week period [17]. Although some studies have indicated that a combination of basal insulin and OHAs can reduce postprandial hyperglycemia, a comparable investigation of the combination of mitiglinide/voglibose and DPP-4 inhibitors with basal insulin has not been previously performed.

Table 2. Continuous glucose monitoring profiles for the day of the Test meal, the day of the LC meal, and two consecutive days in the patients' daily life.

	24-h average glucose levels (mg/dL)	AUC for 24-h glycemic fluctuation (mg·h/dL)	the SDs of the 24-h values (mg/dL)	Proportion of time (%) in hypoglycemia (<70 mg/dL)	Proportion of time (%) in hyperglycemia (>140 mg/dL)	Proportion of time (%) in hyperglycemia (>180 mg/dL)	MAGE
Test meal							
M+V group	120.3 (109.1–125.4)	2887.8 (2616.9–3010.0)	24.1 (21.6–58.8)	2.1 (0.0–7.3)	22.9 (19.8–25.3)	0 (0.0–2.1)	58.3 (52.3–60.0)
L group	129.1 (117.1–135.7)	3101.0 (2805.1–3257.5)	32.6 (16.6–52.7)	0 (0.0–0.0)	34.4 (21.9–47.6)	17.0 (0–19.8)	65.8 (47.7–91.8)
P value	0.22	0.22	0.69	0.78	0.22	0.28	0.69
LC meal							
M+V group	120.2 (114.0–120.4)	2885.2 (27336.5–2890.0)	37.5 (22.1–41.8)	1.7 (0.0–17.0)	33.3 (19.8–35.1)	6.9 (6.6–8.3)	77.0 (73.3–86.3)
L group	124.0 (121.4–129.1)	2977.7 (2909.7–3094.9)	30.6 (14.4–66.2)	0 (0.0–2.1)	25.0 (21.5–43.1)	3.5 (0.0–21.9)	103.0 (55.0–105.5)
P value	0.14	0.14	0.89	0.78	0.69	0.89	0.69
Average of two consecutive day of daily life							
M+V group	125.6 (125.6–137.1)	3012.4 (3011.8–3290.9)	30.9 (21.7–41.8)	0.3 (0.0–6.9)	37.0 (29.5–43.1)	8.2 (5.2–18.8)	72.6 (64.2–85.5)
L group	136.0 (115.7–140.0)	3265.3 (2776.7–33361.1)	22.6 (17.6–39.6)	0 (0.0–0.0)	38.9 (13.4–40.5)	5.9 (4.5–22.7)	62.1 (60.13–73.2)
P value	0.69	0.50	0.22	0.09	0.50	0.50	0.69

(Median [minimum-maximum])

Table 3. HbA1c, GA, and 1,5-AG levels at baseline and at 8 and 16 weeks.

	Baseline				At 8 weeks				At 16 weeks			
	Ins-Deg (units)	HbA1c (%)	GA (%)	1,5-AG (μmol/L)	Ins-Deg (units)	HbA1c (%) (ΔHbA1c (%))	GA (%) (ΔGA(%))	1,5-AG (μmol/L) (Δ1,5-AG (μmol/L))	Ins-Deg (units)	HbA1c (%) (ΔHbA1c (%))	GA (%) (ΔGA (%))	1,5-AG (μmol/L) (Δ1,5-AG (μmol/L))
Case 1	24	8.3	18.1	17.7	32	8.0 (−0.3)	17.4 (−0.7)	30.5 (12.8)	34	8.0 (0.0)	20.9 (3.5)	9.7 (−20.8)
Case 2	22	6.8	17.1	54.8	22	6.6 (−0.2)	16.3 (−0.8)	48.1 (−6.7)	22	7.0 (0.4)	16.6 (0.3)	59.7 (11.6)
Case 3	8	6.7	19.6	152.9	8	6.2 (−0.5)	17.0 (−2.6)	207.1 (54.2)	8	5.9 (−0.3)	16.5 (−0.5)	213.8 (6.7)
Case 4	15	7.6	16.2	22.5	15	6.7 (−0.9)	13.5 (−2.7)	43.2 (20.7)	15	6.4 (−0.3)	13.3 (−0.2)	33.5 (−9.7)
Case 5	13	7.1	19.9	77.4	13	7.1 (0.0)	19.9 (0.0)	53.6 (−23.8)	13	6.9 (−0.2)	19.3 (−0.6)	68.8 (15.2)

The solid cells and the normal cells at 8 and 16 weeks indicate the data after a period of M+V and L, respectively. The data in the parentheses are differences from the previous time point for each parameter. Ins-Deg – insulin degludec dose at each time point.

In the present study, 5 patients were treated with as high a dose of metformin as they could tolerate; metformin is recommended as the drug of first choice in combination with insulin degludec [18]. We also used 2 kinds of postprandial hypoglycemic agents: M+V (a combination of voglibose/mitiglinide) and L (linagliptin).

Voglibose is an alpha-glucosidase inhibitor that delays the absorption of carbohydrates in food, reducing the postprandial glucose level without inducing the secretion of insulin [19]. As a result of this unique mechanism, alpha-glucosidase is effective for patients even if they have a relatively long duration of diabetes and a severe deterioration of insulin secretion.

Mitiglinide is a glinide that is a short-acting insulin secretagogue; it functions through the K_{ATP} channel inhibition of β cells [20].

Linagliptin is a selective inhibitor of DPP-4, which the enzyme responsible for cleavage of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Linagliptin increases the availability of active GLP-1 and GIP, which stimulate glucose-dependent insulin release from β-cells while reducing glucagon secretion from α-cells [15].

These drugs effectively decrease postprandial hyperglycemia while causing fewer episodes of hypoglycemia and are relatively safe for patients with renal dysfunction and for elderly patients. In addition, alpha-glucose inhibitors and glinides are particularly safe for long-term use.

The comparative effects of these agents on glucose reduction have been previously investigated. Ono et al. [13] reported that the combination of M+V increased early-phase insulin secretion at 30 min after the test meal, sustained GLP-1 production, and reduced postprandial glucose excursion, compared with the baseline period. Moreover, the combination of M+V reportedly reduced the postprandial glucose levels, compared with either mitiglinide or voglibose alone, particularly at 30–90 min [14]. The combination of M+V was also reported to enable better control of postprandial glucose excursion, compared with sitagliptin, in 20 drug-naïve patients with type 2 diabetes in a randomized cross-over trial [12].

In our study, the postprandial glucose excursion after the Test meal for breakfast was lower at 60 min in the M+V group than in the L group. The glucose level after the LC meal for breakfast was also lower at 30 min and 60 min in the M+V group compared with the L group. Although we did not measure the C peptide level, early-phase insulin secretion might also suppress the glycemic excursion.

Regarding long-term glycemic indexes, the 1,5-AG level was higher in the M+V group than in the L group. The 1,5-AG level reflects the 2-h postprandial glucose values for the 2 previous weeks [21]; therefore, M+V might be more effective at increasing the 1,5-AG level, compared with L, since M+V suppressed the postprandial $AUC_{0-120\ min}$ increase more effectively than L. The HbA1c and GA levels were similar in the M+V and L groups. Because HbA1c is a measure of glycemia over the prior 3 months [22], the preregistration HbA1c levels might have affected the present results.

We compared the postprandial glucose profiles after 2 kinds of meals. The Test meal consisted of a moderate-carbohydrate meal (carbohydrates: 56.5 g, 49.1%), while the LC meal consisted of a moderately low-carbohydrate meal (carbohydrates: 43.0 g, 37.2%) [23]. After the LC meal, the glucose level for the M+V group was significantly lower than that for the L group at 30 min; after the Test meal, the M+V group exhibited a reduced glucose excursion at 60 min. The LC meal contained cornflakes, which have a high glycemic load and likely contributed to the postprandial glycemic excursion; consequently, the early insulin secretion induced by M+V might have enabled a more effective reduction at 30 min after the LC meal.

CGM showed similar levels between the M+V group and the L group after both the Test meal and the LC meal. When the meal tolerance tests were compared, the MAGE on the day of the LC meal was significantly higher than that on the day of the Test meal in the L group. Although the reason for this result is unclear, a low-carbohydrate/high-fat diet is known to lead to an insufficient first-phase insulin release and an increase in the postprandial glucose level [24]. Thus, an insufficient amount of carbohydrate in the LC meal for breakfast might have led to glycemic excursion after lunch and dinner, and M+V might reduce postprandial hyperglycemia more effectively than L.

In the present study, severe hypoglycemia, gastrointestinal symptoms, and other adverse effects were not observed. In the CGM data, the frequency of a glucose level of less than 70 mg/dL was the same between the M+V group and the L group.

This study had several strengths. First, we utilized a cross-over design that enabled us to compare these treatments under similar conditions. Second, we were able to confirm the effects of these treatments using different types of test meals as well as the effects on the patients' daily lives. However, the study also has several limitations. First, the number of subjects was relatively small, partly because the Test meal was discontinued shortly after starting the study. Second, other metabolic indexes that affect the glycemic profile, such as the C peptide, GLP-1, GIP, and glucagon levels, were not measured. Future investigations involving a larger number of subjects and examining the effects of the combination of these OHAs with basal insulin more precisely are needed.

Conclusions

The combination of M+V (10 mg/0.2 mg immediately before each meal) with basal therapy improved postprandial glucose excursion more effectively than linagliptin in type 2 diabetic patients.

Supplementary Table

Supplementary Table 1. Continuous glucose monitoring profiles compared two test meals in the M+V group and the L group.

	24-h average glucose levels (mg/dL)	AUC for 24-h glycemic fluctuation (mg·h/dL)	The SDs of the 24-h values (mg/dL)	Proportion of time (%) in hypoglycemia (<70 mg/dL)	Proportion of time (%) in hyperglycemia (>140 mg/dL)	Proportion of time (%) in hyperglycemia (>180 mg/dL)	MAGE
M+V group							
Test meal	120.3 (109.1–125.4)	2887.8 (2616.9–3010.0)	24.1 (21.6–58.8)	2.1 (0.0–7.3)	22.9 (19.8–25.3)	0 (0.0–2.1)	58.3 (52.3–60.0)
LC meal	120.2 (114.0–120.4)	2885.2 (27336.5–2890.0)	37.5 (22.1–47.3)	1.7 (0.0–17.0)	33.3 (19.8–35.1)	6.9 (6.6–8.3)	77.0 (73.3–86.3)
P value	0.69	0.69	0.35	0.40	0.35	0.41	0.35
L group							
Test meal	129.1 (117.1–135.7)	3101.0 (2805.1–3257.5)	32.6 (16.6–52.7)	0 (0.0–0.0)	34.4 (21.9–47.6)	17.0 (0–19.8)	65.8 (47.7–91.8)
LC meal	124.0 (121.4–129.1)	2977.7 (2909.7–3094.9)	30.6 (14.4–66.2)	0 (0.0–2.1)	25.0 (21.5–43.1)	3.5 (0.0–21.9)	103.0 (55.0–105.5)
P value	0.69	0.69	0.69	0.16	0.10	0.85	0.04

(Median [minimum-maximum]). The CGM data of table 2 is reclassified by the M+V group and the L group to compare with two test meals.

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