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# Efficacy and Safety of Miglitol- or Repaglinide-Based Combination Therapy with Alogliptin for Drug-Naïve Patients with Type 2 Diabetes: An Open-Label, Single-Center, Parallel, Randomized Controlled Pilot Study

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**Background:** Combination therapy with an alpha-glucosidase inhibitor or glinide plus a dipeptidyl peptidase-4 inhibitor is thought to be effective for glycemic control because of its effects on postprandial hyperglycemia. However, no studies have directly compared these two combination therapies in relation to efficacy and safety.

**Methods:** Eighteen patients with type 2 diabetes were studied. All had diabetes not adequately controlled with diet and exercise therapy, an HbA1c level of ≥7.5%, and were not receiving any medication for diabetes. The patients were randomized to either miglitol- or repaglinide-based combination therapy with alogliptin. Patients received miglitol or repaglinide monotherapy for 3 months (the miglitol and repaglinide groups, respectively), after which alogliptin was added to each group as combination therapy for 3 months. A meal tolerance test (MTT) was performed before the start of treatment and at the end of monotherapy and combination therapy.

**Results:** During the study period, decreases in HbA1c and glycated albumin were significantly greater in the repaglinide group than in the miglitol group; however, there was no significant difference between treatment groups at the end of the study. At the end of monotherapy, insulin secretion relative to glucose elevation ($ISG_{0\text{-}30}$: area under the curve of insulin from 0 to 30 min during MTT [$AUC_{0\text{-}30}$ of IRI]/$AUC_{0\text{-}30}$ of plasma glucose) was significantly higher only in the repaglinide group; $ISG_{0\text{-}30}$ did not significantly increase in either group after the addition of alogliptin.

**Conclusions:** The addition of alogliptin to repaglinide monotherapy did not cause glucose-independent inappropriate insulin secretion and did not appear to increase the incidence of hypoglycemia.

(J Nippon Med Sch 2021; 88: 71–79)

**Key words:** miglitol, repaglinide, alogliptin, postprandial hyperglycemia

## Introduction

The primary aim of diabetes treatment is prevention of diabetic complications, including microvascular and macrovascular complications. Clinical trials showed that hyperglycemia was an independent risk factor for diabetic complications[1–4]. In addition, reduction of HbA1c level, a marker of mean plasma glucose level, prevented incidence and progression of microvascular complications[1,2]; however, previous studies reported difficulties in preventing macrovascular complications by reducing HbA1c with sulfonylureas, biguanides, and/or insulin[5–7]. Moreover, some clinical trials showed that hypoglycemia increased the risk of macrovascular complications, especially cardiovascular death[8,9]. Therefore, hypoglycemia must be avoided during medical treatment for diabetes.

Postprandial hyperglycemia has a greater effect than fasting hyperglycemia on the incidence of coronary artery disease (CAD)[10,11]. Acarbose, an alpha-glucosidase inhibitor (αGI), improved postprandial hyperglycemia and reduced CAD incidence in patients with impaired glu-

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https://doi.org/10.1272/jnms.JNMS.2021_88-205
Journal Website (https://www.nms.ac.jp/sh/jnms/)

cose tolerance[12] and type 2 diabetes[13]. Among oral antidiabetics, αGIs and glinides directly suppress postprandial plasma glucose (PG) levels by delaying intestinal absorption of glucose[14] and producing immediate insulin secretion[15], respectively. We and other researchers reported that incretin-related drugs such as glucagon-like peptide-1 (GLP-1) receptor agonists[16] and dipeptidyl peptidase-4 (DPP-4) inhibitors[17,18] also improve postprandial hyperglycemia. A previous report showed that combination therapy with an αGI and DPP-4 inhibitor was effective for glycemic control because of the synergistic effect on postprandial elevation of plasma GLP-1 levels[19]. To our knowledge, only one study compared the effect of glinide monotherapy and combination therapy with DPP-4 inhibitors and glinides on PG and serum insulin levels after a meal load in humans[20]. In that report, combination therapy with nateglinide and vildagliptin resulted in lower postprandial PG levels and higher postprandial serum insulin levels, as compared with nateglinide monotherapy, within 30 min after a meal load in patients with type 2 diabetes. However, no previous study directly compared the efficacy and safety of αGI- or glinide-based combination therapy with a DPP-4 inhibitor. We hypothesized that glinide-based combination therapy with a DPP-4 inhibitor would result in better glycemic control but would be more likely than αGI-based combination therapy to cause hypoglycemia.

In the present study, we compared the efficacy and safety of adding alogliptin to miglitol and repaglinide monotherapy for drug-naïve patients with type 2 diabetes inadequately controlled with diet alone.

## Materials and Methods

### Participants

The patients were aged 20-75 years and initially consulted the outpatient clinic of Nippon Medical School Chiba Hokusoh Hospital for diabetes treatment during the period from March 2012 through January 2014. All consecutive patients who did not need hospitalization attended a lecture on diabetes and diet therapy, and those with an $HbA_{1c}$ level of ≥7.5% after diet therapy but no use of antidiabetic medication for >3 months were enrolled. A total of 22 patients were assessed for eligibility, and four were excluded because consent was not obtained. Ultimately, 18 patients with type 2 diabetes were selected and enrolled in an unblinded randomized study. Total daily caloric intake (kcal/d) was calculated as 27.5 (kcal) × ideal body weight (IBW). IBW (kg) was calculated as 22 × [height (m)]$^2$, in accordance with the Japan Diabetes Society evidence-based practice guideline for diabetes treatment in Japan. The daily diet consisted of 55% carbohydrate, 25% fat, and 20% protein. Participants were excluded if they were treated with antidiabetic medication (including insulin), had a positive result for antiglutamic acid decarboxylase antibody, or had a history or evidence of recent myocardial infarction, heart failure, cerebral vascular disease, endocrine disease, or any carcinoma.

### Study Protocol and Treatment

The study protocol was approved by the ethics committee of Nippon Medical School Chiba Hokusoh Hospital (No. 523018) and conforms to the provisions of the Declaration of Helsinki. The protocol was registered at UMIN Clinical Trials Registry (UMIN000016011). Written informed consent was obtained from all participants. A table of random sampling numbers (block size, 4) was used to randomly assign all patients to receive either miglitol and alogliptin (miglitol group, n = 9) or repaglinide and alogliptin (repaglinide group, n = 9). One author (F.O.) generated the random allocation sequence and enrolled and assigned all participants.

Before starting medication, a meal tolerance test (MTT) was performed, after an overnight 12-hour fast, by giving test meal A—a standard test meal authorized by the Japan Diabetes Association[21]—and 35 g of oral fat tolerance test cream (Jomo Shokuhin, Takasaki, Japan) to each patient. Blood samples were drawn before and at 30, 60, 90, 120, 180, and 240 min after meal ingestion, and PG, serum immune-reactive insulin (IRI), glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) levels were measured. In accordance with their assigned group, all participants started miglitol (50 mg) or repaglinide (0.25 mg) t.i.d. just before the meal after the first MTT. The MTT was performed again at 3 months after starting medical treatment. After the second MTT, alogliptin 25 mg q.d. after breakfast was added. The third MTT was performed at 3 months after the addition of alogliptin. Insulin secretion relative to glucose elevation (ISG) was calculated by using the following equations:

$ISG_{0\text{-}30}$ = [area under the curve (AUC) of IRI from 0 to 30 min / AUC of PG from 0 to 30 min] × 100

$ISG_{0\text{-}240}$ = (AUC of IRI from 0 to 240 min) / AUC of PG from 0 to 240 min) × 100

### Biochemical Measurement

PG was measured by using the glucose oxidase method, HbA1c was measured with high-performance liquid chromatography, glycated albumin (GA: Lucica

Table 1 Baseline demographics and patient characteristics

| Parameter | Miglitol group | Repaglinide group |
|---|---|---|
| Number of patients (male) | 9 (6) | 9 (6) |
| Age (years) | 58 ± 5 | 62 ± 5 |
| Duration of diabetes (years) | 5 ± 3 | 3 ± 2 |
| BMI (kg/m$^2$) | 24.3 ± 1 | 24.7 ± 0.9 |
| FPG (mg/dL) | 161 ± 28 | 153 ± 24 |
| HbA1c (%) | 8.3 ± 0.9 | 8.1 ± 0.9 |
| GA (%) | 22.1 ± 2.4 | 20.4 ± 5.7 |
| 1,5AG (μg/mL) | 6.4 ± 5.1 | 7.6 ± 6.6 |
| IRI (μU/mL) | 8.1 ± 4.2 | 8.6 ± 7.9 |
| ALT (U/L) | 28 ± 15 | 27 ± 19 |
| AST (U/L) | 30 ± 19 | 35 ± 43 |
| GGT (U/L) | 45 ± 35 | 34 ± 21 |
| Cre (mg/dL) | 0.64 ± 0.06 | 0.62 ± 0.06 |
| Complication | | |
| Absent Achilles tendon reflex (n) | 2 | 2 |
| U-Alb (mg/d) | 30.2 ± 12.8 | 22 ± 17.7 |
| Diabetic retinopathy (DR) | | |
| none (n) | 6 | 6 |
| simple DR (n) | 2 | 3 |
| preproliferative DR (n) | 1 | 0 |
| proliferative DR (n) | 0 | 0 |

BMI, body mass index; FPG, fasting plasma glucose; $HbA_{1c}$, glycated hemoglobin; GA, glycated albumin; 1,5AG, 1,5-anhydroglucitol,1,4-anhydro(-D)-glucitol; IRI, immunoreactive insulin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gammaglutamyl transpeptidase; Cre, creatinine; U-Alb, urinary albumin.
Data are expressed as mean ± standard deviation.

GA-L, Asahi Kasei Pharma) was measured by enzymatic methods, 1,5 anhydroglucitol,1,4-anhydro(-D)-glucitol (1,5 AG) was measured with an enzymatic colorimetric assay (Lana 1,5AG auto liquid; Nippon Kayaku, Tokyo, Japan), and IRI level was measured with a chemiluminescent immunoassay (Siemens Healthcare Diagnostics). As described previously[22], hormones were measured with a human total GLP-1 (ver. 2) assay kit (K150JVC-2; Mesoscale Discovery, Gaithersburg, MD, USA) for total GLP-1 and a human GIP (total) ELISA kit (EZHGIP-54K; Merck Millipore, Darmstadt, Germany) for total GIP. Blood samples for measurement of total GLP-1 and total GIP were collected directly into BD P800 Blood Collection Tubes (BD, Franklin Lakes, NJ, USA) containing a DPP-4 inhibitor and the other peptidase inhibitors. The samples were immediately centrifuged to prevent degradation of intact GLP-1 and GIP by DPP-4.

**Statistical Analysis**

We performed all analyses with the JMP 12.2 software package (SAS Institute, Cary, NC) at Nippon Medical School Chiba Hokusoh Hospital. Values are presented as mean ± SD. The $\chi^2$ test was used for statistical analysis of sex differences and diabetes complications at baseline. Differences in baseline characteristics between the two treatment groups were analyzed with the Student t-test. Changes in HbA1c and GA after the start of treatment and MTT variables were analyzed with repeated-measures multivariate analysis of variance (MANOVA) and analysis of variance (ANOVA). The Tukey-Kramer test was used for post-hoc analysis. A P value of $<0.05$ was considered to indicate statistical significance.

## Results

We enrolled 18 patients with type 2 diabetes (men, 67%; mean age, 58 ± 13 years; body mass index, 24.5 ± 2.6 kg/m$^2$; diabetes duration, 5 ± 7 years; HbA1c, 8.2% ± 0.9%; and GA, 21.2% ± 4.4%). All participants were assigned to a group and received treatment for the study duration. There were no significant differences in baseline characteristics between the two groups (**Table 1**).

Repeated-measures MANOVA showed that decreases in HbA1c and GA levels during the study period were significant (P = 0.011 for HbA1c; P = 0.001 for GA) and that HbA1c values and GA levels were significantly

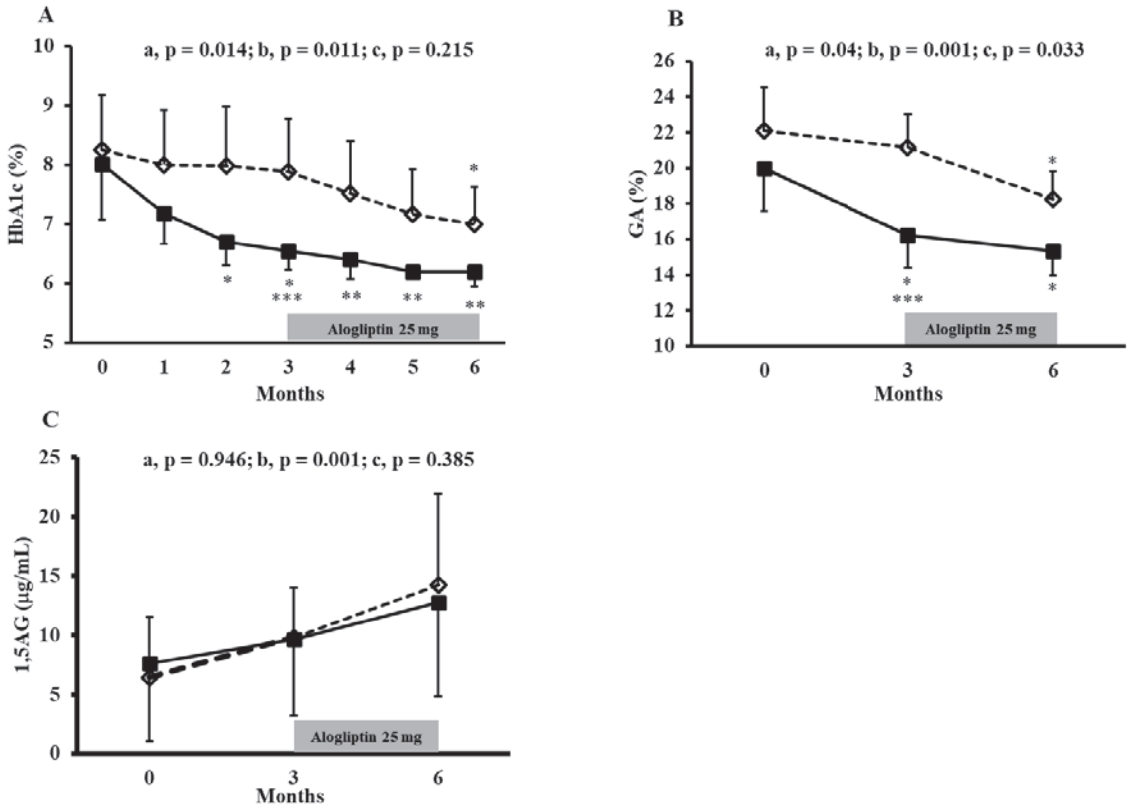


Fig. 1 Changes in HbA1c (A), GA (B), and 1,5AG (C) levels in the miglitol and repaglinide groups
Data are expressed as mean ± SD in the miglitol group (open diamonds and dotted lines; n = 9) and repaglinide group (filled squares and solid lines; n = 9). P values reflect differences in relation to treatment (a), time course (b), and interaction of treatment and time course (c), as calculated by repeated multivariate analyses of variance. The Tukey–Kramer method was used for post-hoc analysis
*P < 0.05 vs. 0 months in the same treatment group;
**P < 0.01 vs. 0 months in the same treatment group;
***P < 0.05 vs. another treatment group in the same month.
HbA1c, glycated hemoglobin; GA, glycated albumin; 1,5 AG, 1,5-anhydroglucitol,1,4-anhydro(-D)-glucitol

lower in the repaglinide group than in the miglitol group (P = 0.014 for HbA1c; P = 0.044 for GA). The interaction of treatment and time course was statistically significant for GA but not for HbA1c. During the first 3 months of monotherapy, HbA1c values decreased from 8.3% ± 0.9% to 7.9% ± 0.9% in the miglitol group and from 8.0% ± 0.9% to 6.5% ± 0.3% in the repaglinide group (mean ± SD). GA values decreased from 22.1% ± 2.4% to 21.2% ± 1.8% in the miglitol group and from 20% ± 2.4% to 16.2% ± 1.8% in the repaglinide group. Because the interaction of treatment and time course was statistically significant for GA, post-hoc analysis was performed with the Tukey-Kramer test. The decreases in HbA1c and GA levels in the first 3 months were significant only in the repaglinide group (P = 0.011 for HbA1c; P = 0.041 for GA), and HbA1c and GA levels were significantly lower in the repaglinide group than in the miglitol group at 3 months, ie, the end of monotherapy (P = 0.033 for HbA1c; P = 0.021 for GA; **Fig. 1**). At 6 months (the end of combination therapy), HbA1c and GA levels were 7.5% ± 0.6% and 18.2% ± 1.6%, respectively, in the miglitol group and 6.2% ± 0.3% and 15.3% ± 1.4% in the repaglinide group. As compared with levels at 0 months (before treatment), HbA1c and GA levels at 6 months were significantly lower in both treatment groups (miglitol: P = 0.045, P = 0.049, respectively; repaglinide: P = <0.001, P = 0.011, respectively). There was no significant difference between treatment groups at the end of combination therapy. The values for %change in HbA1c and GA levels from 0 months were −4.5% ± 4.1% and −3.9% ± 6.5%, respectively, in the miglitol group and −16.2% ± 8.8% and −16 ± 11.3% in the repaglinide group at 3 months, and −14.8% ± 6.5% and −17.1% ± 6.7% in the miglitol group and −20.5% ± 9% and −20.9% ± 14.7% in the repaglinide group at 6 months (**Fig. 2**).

The %reduction in HbA1c and GA levels was signifi-

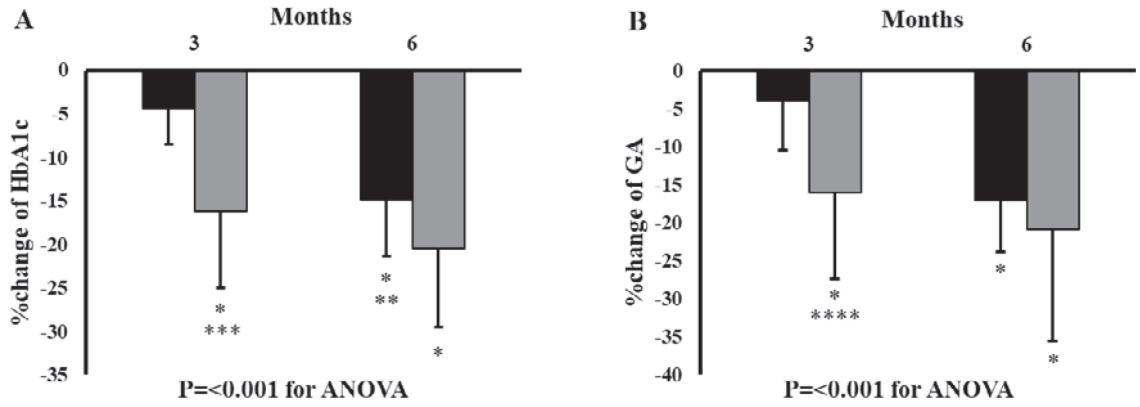


Fig. 2 Percentage change from baseline in HbA1c and GA levels

Percentage change in HbA1c (A) and GA (B) levels in the miglitol (black bars; n = 9) and repaglinide (gray bars; n = 9) groups.

Data are expressed as mean ± SD.

The variables were analyzed with ANOVA.

The Tukey–Kramer method was used for post-hoc analysis.

*P < 0.01 vs. 0 months in the same treatment group;

**P < 0.05 vs. 3 months in the same treatment group;

***P < 0.01 vs. another treatment group in the same month;

****P < 0.05 vs. another treatment group in the same month.

HbA1c, glycated hemoglobin; GA, glycated albumin; ANOVA, analysis of variance

cant in the repaglinide group at 3 months (P < 0.001 for both) and in both treatment groups at 6 months (P < 0.001 for all comparisons). The %reductions in HbA1c and GA levels were significantly larger in the repaglinide group than in the miglitol group at 3 months (P = 0.008, P = 0.023). In addition, the %reduction in HbA1c level in the miglitol group was significantly larger at 6 months than at 3 months (P = 0.033).

Increments in 1,5AG levels during the study period were significant (P = 0.001), and 1,5AG levels did not differ between the treatment groups (P = 0.946). The interaction of treatment and time course was statistically significant for 1.5AG (P = 0.385). In post-hoc analysis, 1,5AG level did not significantly differ between treatment groups at any time point and did not significantly increase after treatment in either treatment group.

The AUC of PG during the MTT performed at 3 months was lower than at 0 months only in the repaglinide group and was lower in the repaglinide group than in the miglitol group (**Fig. 3**, **Table 2**). The AUC of PG was lower at 6 months than at 0 months in both treatment groups but did not differ between treatment groups at 0 or 6 months. The AUC values of IRI at 0, 3, and 6 months did not significantly differ in either treatment group or between treatment groups at any time point. The AUC values of GLP-1 and GIP did not significantly different at 3 months from the respective values at 0 months and did not differ from each other in any treatment group. The AUC value of GLP-1 was significantly higher at 6 months than at 0 and 3 months in both treatment groups. The AUC value of GLP-1 at 6 months was significantly higher in the miglitol group than in the repaglinide group. The AUC value of GIP at 3 months did not significantly differ from that at 0 months in either treatment group. The AUC value of GIP was higher at 6 months than at 3 months only in the repaglinide group and was higher in the repaglinide group than in the miglitol group at 6 months. As compared with ISG ($ISG_{0\text{-}30}$, $ISG_{0\text{-}240}$) values at 0 months, values at 3 months were higher only in the repaglinide group and differed from those in the miglitol group at 3 months.

In the repaglinide group, one patient developed symptomatic hypoglycemia at 2 months after the addition of alogliptin but quickly recovered after oral glucose intake. No musculoskeletal complaints or new abnormalities in blood test results were observed.

## Discussion

This study compared the efficacy and safety of combination therapy with miglitol or repaglinide plus alogliptin in drug-naïve patients with type 2 diabetes. Control of blood glucose was significantly better for repaglinide monotherapy than for miglitol monotherapy. The addi-

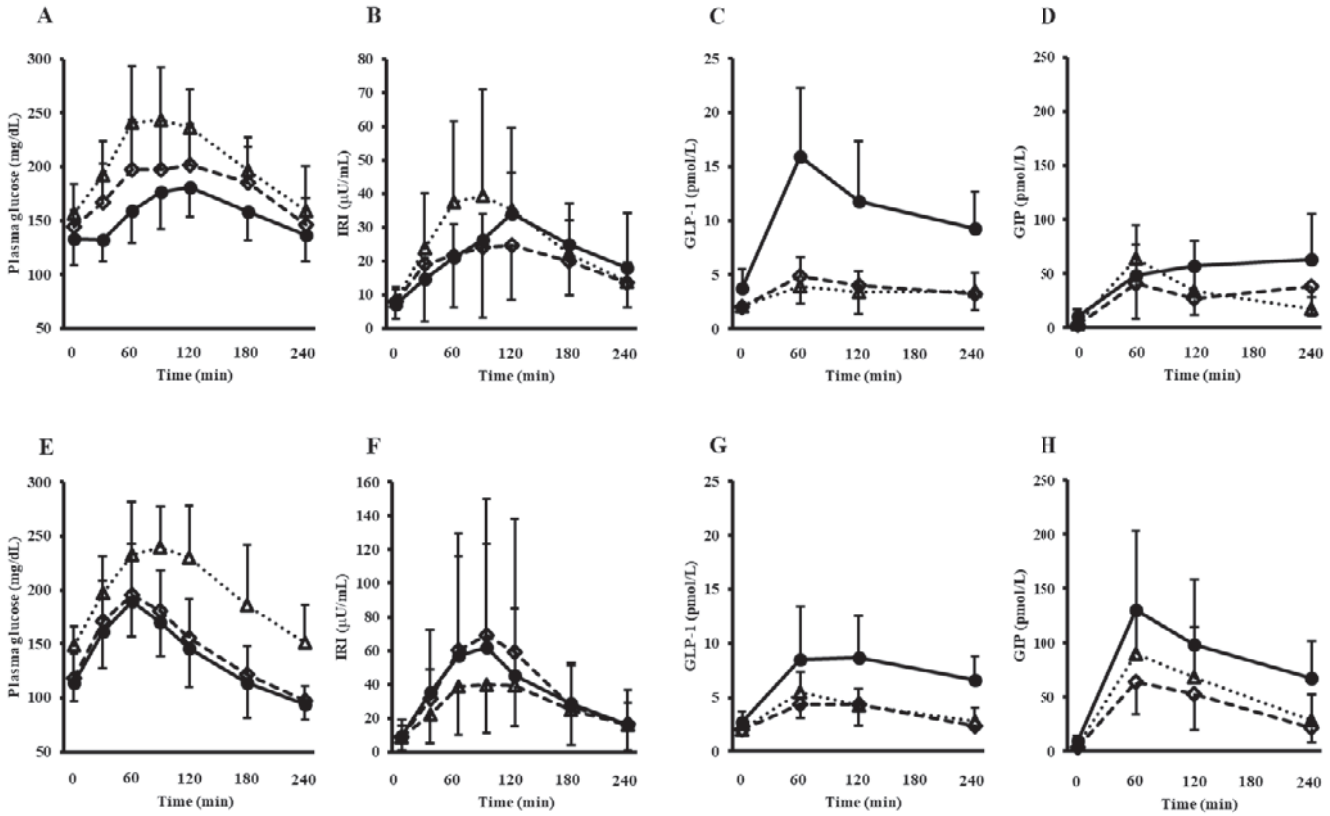


Fig. 3 Results of meal tolerance testing

Mean plasma glucose (A, E), serum insulin (B, F), plasma glucagon-like peptide-1 (C, G), and mean plasma glucose-dependent insulinotropic polypeptide (D, H) levels during meal tolerance testing in the miglitol (A–D) and repaglinide (E–H) groups at baseline (open triangles and dotted lines; n = 9), 3 months (open squares and dotted lines; n = 9), and 6 months (filled circles and solid lines; n = 9).

Data are expressed as mean ± SD

tion of alogliptin did not cause inappropriate secretion of insulin resulting in hypoglycemia at 30 or 240 min after a meal. To our knowledge, this is the first study to directly compare αGI- and glinide-based combination therapy with a DPP-4 inhibitor in drug-naïve patients with type 2 diabetes.

In the present study, we chose miglitol, repaglinide, and alogliptin as the respective αGI, glinide, and DPP-4 inhibitor because miglitol is believed to have the strongest effect on glycemic control among αGIs[23] and because repaglinide and alogliptin were reported to have beneficial effects on carotid atherosclerosis[24,25]. HbA1c and GA levels during the present study were significantly lower in the repaglinide group than in the miglitol group. Although post-hoc analysis showed that reductions in HbA1c and GA levels were significantly greater for repaglinide monotherapy than for miglitol monotherapy, the difference in blood glucose control between the repaglinide-alogliptin and miglitol-alogliptin combination therapies was not significant, perhaps because of the small sample size or because the addition of alogliptin could not significantly reduce the HbA1c and GA levels (6.5% and 16.2%, respectively) that had already been achieved at the end of repaglinide monotherapy. If repaglinide monotherapy could not improve glycemic control in the present study, the addition of alogliptin to repaglinide monotherapy might be able to reduce levels of HbA1c and GA significantly, and HbA1c and GA levels might be significantly lower for repaglinide-alogliptin combination therapy than for miglitol-alogliptin combination therapy at the end of combination therapy. The 1,5 AG concentration reflects the level of postprandial hyperglycemia because hyperglycemia inhibits renal reabsorption of 1,5AG[26]. Peak postprandial PG during the MTT was nearly identical between the treatment groups at 3 months and 6 months, although the AUC values of PG were significantly lower in the repaglinide group at 3 months. Therefore, 1,5AG levels did not differ between treatment groups at 3 or 6 months.

DPP-4 inhibition increases GIP and GLP-1 levels, which are secreted by K and L cells, respectively. These cells are present in the upper and lower intestine, respec-

Table 2 Changes in meal tolerance test variables

| | | 0M | 3M | 6M | p value for ANOVA | p value for 0M vs 3M | p value for 0M vs 6M | p value for 3M vs 6M |
|---|---|---|---|---|---|---|---|---|
| AUC of PG (mg/dL*h) | miglitol | 951 ± 151 | 827 ± 135 | 720 ± 106 | <0.001 | NS | 0.02 | NS |
| | repaglinide | 895 ± 181 | 636 ± 77 | 625 ± 96 | | 0.02 | 0.005 | NS |
| | p value between treatment groups | NS | 0.04 | NS | | | | |
| AUC of IRI (μU/mL*h) | miglitol | 126.5 ± 78.6 | 91.8 ± 58.9 | 107.8 ± 40 | NS | NS | NS | NS |
| | repaglinide | 124.6 ± 91.3 | 177.5 ± 217.1 | 154.1 ± 159.4 | | NS | NS | NS |
| | p value between treatment groups | NS | NS | NS | | | | |
| AUC of GLP-1 (pmol/L*h) | miglitol | 13.6 ± 4.7 | 15 ± 3.2 | 44.7 ± 10.7 | <0.001 | NS | <0.001 | <0.001 |
| | repaglinide | 17.6 ± 5.3 | 14.9 ± 3.5 | 32 ± 6.6 | | NS | 0.018 | 0.008 |
| | p value between treatment groups | NS | NS | 0.008 | | | | |
| AUC of GIP (pmol/L*h) | miglitol | 133.2 ± 57.7 | 120.8 ± 60.6 | 202.5 ± 81 | 0.003 | NS | NS | NS |
| | repaglinide | 232.8 ± 116.2 | 171.1 ± 85.2 | 364.2 ± 175.5 | | NS | NS | 0.025 |
| | p value between treatment groups | NS | NS | 0.048 | | | | |
| $ISG_{0\text{-}30}$ (μU/mg) | miglitol | 9.08 ± 5.72 | 8.54 ± 4.93 | 8.23 ± 3.28 | NS | NS | NS | NS |
| | repaglinide | 8.59 ± 5.83 | 15.78 ± 7.37 | 15.3 ± 11.55 | NS | 0.028 | NS | NS |
| | p value between treatment groups | NS | 0.03 | NS | | | | |
| $ISG_{0\text{-}240}$ (μU/mg) | miglitol | 13.2 ± 8.07 | 10.9 ± 5.98 | 15.01 ± 5.4 | NS | NS | NS | NS |
| | repaglinide | 14.4 ± 8.27 | 27.98 ± 10.32 | 26.68 ± 22.74 | NS | 0.035 | NS | NS |
| | p value between treatment groups | NS | 0.012 | NS | | | | |
| AUC insulin/glucose | miglitol | 0.13 ± 0.08 | 0.11 ± 0.06 | 0.15 ± 0.05 | NS | NS | NS | NS |
| | repaglinide | 0.14 ± 0.09 | 0.27 ± 0.31 | 0.24 ± 0.23 | NS | NS | NS | NS |
| | p value between treatment groups | NS | NS | NS | | | | |

Continuous glucose monitoring values before discharge are presented as mean ± SD.

$ISG_{0\text{-}30}$ = (AUC of IRI from 0 to 30 min)/(AUC of PG from 0 to 30 min);

$ISG_{0\text{-}240}$ = (AUC of IRI from 0 to 240 min)/(AUC of PG from 0 to 240 min).

Variables were analyzed with ANOVA and the Tukey–Kramer method for post-hoc analysis.

AUC, area under the curve; PG, plasma glucose; IRI, immunoreactive insulin; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; ANOVA, analysis of variance

tively. αGI inhibits digestion and delays absorption of dietary carbohydrates, which allows these molecules to reach the lower intestine. Therefore, as was noted in a previous report[19], we found that GLP-1 levels were significantly higher, and GIP levels were lower, after miglitol-alogliptin combination therapy than after repaglinide-alogliptin combination therapy.

Repaglinide stimulates immediate and short-term insulin secretion from pancreatic beta cells after oral intake. Glinide closes the K-ATP channel at the pancreatic beta cell membrane and inhibits $K^+$ efflux[15]. Closure of the K-ATP channel promotes a rise in intracellular $Ca^{2+}$ by increasing $Ca^{2+}$ influx through voltage-dependent $Ca^{2+}$ channels. This elevation in intracellular $Ca^{2+}$ leads to insulin secretion. GLP-1 binds the GLP-1 receptor expressed on the surface of pancreatic beta cells and increases cyclic AMP (cAMP) by activating adenyl cyclase[27]. Elevated cAMP augments insulin secretion initiated by elevation of intracellular $Ca^{2+}$. Therefore, DPP-4 inhibitors might increase insulin secretion initiated by repaglinide, thus causing hypoglycemia. In the present study, addition of alogliptin to repaglinide did not increase ISG, which suggests that alogliptin does not augment insulin secretion stimulated by repaglinide. The drug information leaflet from Sumitomo Dainippon Pharma Co., Ltd. reports that, after multiple repaglinide administrations

for 5 days, serum repaglinide exhibited a Tmax of 31.7 ± 4.1 min and a T1/2 of 88.6 ± 11.0 min in Japanese with type 2 diabetes. Therefore, in the present study, the effect of repaglinide might have already peaked when serum GLP-1 increased after meal ingestion; thus, alogliptin did not synergistically stimulate insulin secretion in patients treated with repaglinide. Although a previous report showed that $ISG_{0\text{-}30}$ increased during combination treatment with nateglinide and vildagliptin[20], it did not increase in the current study, perhaps because we did not measure serum IRI at 15 minutes after meal ingestion, ie, when it was elevated in the previous study. This increase in IRI at 15 min after meal ingestion could be important in hypoglycemia development.

These data suggest that to improve glycemic control—especially in the postprandial state—with miglitol, repaglinide, and/or alogliptin, drug-naïve type 2 diabetic patients undergoing diet therapy with HbA1c levels around 8% should initially receive miglitol monotherapy. Many previous studies showed that miglitol improved postprandial hyperglycemia and had the lowest risk of hypoglycemia among the three drugs used in the current study, even though miglitol monotherapy did not reduce HbA1c or GA levels in the present study. If miglitol monotherapy does not adequately control HbA1c, the addition of alogliptin should be considered as the next step, because of the lower risk of hypoglycemia. If glycemic control is not optimal with miglitol-alogliptin combination therapy, repaglinide should added as the last step. Hypoglycemia risk is greater for repaglinide monotherapy than for miglitol or alogliptin monotherapy. However, addition of repaglinide to alogliptin does not increase hypoglycemia risk, because it does not induce inappropriate insulin secretion.

This study had some limitations. We were unable to identify any previous studies comparing αGI- and glinide-based combination therapy with a DPP-4 inhibitor and thus could not perform a power analysis to determine sample size. Because few patients with diabetes are both drug-naïve and have an HbA1c of ≥7.5%, the sample size was small. In addition, the unblinded trial design and small sample size might have affected the results.

In conclusion, the glucose lowering effect of repaglinide monotherapy was significantly stronger than that of miglitol monotherapy. Repaglinide-alogliptin combination therapy controlled blood glucose, but the difference with miglitol-alogliptin combination therapy was not significant. Addition of alogliptin to repaglinide monotherapy did not lead to inappropriate insulin secretion, independent of glucose level, and therefore is unlikely to increase the risk of hypoglycemia. Future studies should investigate the efficacy and safety of DPP-4 inhibitor combination therapy with glinide and αGI (eg, by assessing glycemic viability with continuous glucose monitoring during daily life in a larger sample).

**Acknowledgements:** This study was supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (#23653070). The authors are grateful to the study participants and clinical staff in the outpatient clinic of Nippon Medical School Chiba Hokusoh Hospital.

**Conflict of Interest:** H.S. received research funds from Ono Pharmaceutical Co. The funder had no role in the research design, results, or manuscript preparation.

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(Received, September 12, 2019)
(Accepted, April 20, 2020)
(J-STAGE Advance Publication, May 30, 2020)