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A comparison study on efficacy, insulin sensitivity and safety of Glimepiride/Metformin fixed dose combination versus glimepiride single therapy on type 2 diabetes mellitus patients with basal insulin therapy

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ABSTRACT

Aim: The aim of this study was to analyze the efficacy, insulin sensitivity and safety in the event of administering sulfonylurea-based drugs and metformin in combination with basal insulin.

Methods: A randomized, open-label, parallel, 16-week trial was conducted across four study centers. The 97 type 2 diabetic patients were selected and randomized into two groups, the insulin glargine plus fixed-dose combination glimepiride 1 mg and metformin 500 mg twice daily group (the G/M group) and the insulin glargine plus glimepiride 4 mg once daily group (the G group). The primary endpoint evaluated was change in HbA1c. The secondary endpoints evaluated were changes in fasting blood glucose (FPG), 2-h post prandial glucose (PPG 2 h), insulin, and C-peptide levels.

Results: The G/M group was found to have experienced a significantly greater decrease in HbA1c, as well as PPG 2 h compared to the G group. While no significant intergroup difference was found regarding FPG in the ITT, the G/M group in the PP set experienced a significantly greater decrease in FPG.

Conclusion: Comparison of combined therapy consisting of either the G/M group or the G group indicated that both forms of therapy are relatively safe but that the former more effectively decreases blood glucose levels.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic diseases and glycemic control usually begins with administration of an oral hypoglycemic agent. According to the UKPDS analysis results, however, glycemic control using an oral hypoglycemic agent alone is likely to be ineffective and become increasingly ineffective over time, thus unavoidably requiring the addition of other agents for adequate blood glucose control [1]. Therefore, many patients will require combination therapy to achieve their target glucose level.

Many clinical trials have reported the superiority of combination therapy consisting of sulfonylurea-based drugs and metformin, either in combined use [2,3] or as a pre-dosed composite [5], compared to all possible combinations of agents in maintaining glycemic control. The combined use of sulfonylurea-based drugs and metformin may be an ideal combination therapy, as it appears simultaneously capable of counteracting "insulin secretion disorder" and "insulin resistance," the two pathophysiologic mechanisms underlying T2DM [2,3].

On the other hand, insulin monotherapy or combination therapy with an oral hypoglycemic agent may be considered for patients for whom use of an oral hypoglycemic agent alone does not provide adequate glycemic control, as manifested by a decrease in β-cell function in tandem with the duration of the disease [4]. However, combination therapy with several drugs may reduce compliance and cause failure of blood glucose control.

In accordance, this clinical trial aimed to assess and compare the efficacy and safety of fixed-dose combinations (FDC) of glimepiride/metformin and single high-dose glimepiride formulations with basal insulin for type 2 diabetic patients.

2. Materials and methods

2.1. Patients

2.1.1. Inclusion criteria

All enrolled patients met all the following criteria at screening: (1) previous diagnosis of T2DM; (2) age 20 or older; (3) inadequate glycemic control despite continuous administration of glimepiride, metformin, or both agents over three months at the maximum safe or the maximum tolerable dose; (4) glycated Hemoglobin A1c (HbA1c) level between 7% and 11%; (5) body mass index (BMI) between 21 kg/m^2 and 30 kg/m^2; (6) need for an additional insulin therapy, as judged by the researcher, for adequate glycemic control; (7) ability to provide informed consent before trial initiation; and (8) ability and willingness to conduct self-monitoring of blood glucose and record the values in a trial diary.

2.1.2. Exclusion criteria

Any potential patients characterized by one or more of the following conditions were precluded from further consideration: (1) had undergone a medication regimen consisting of single-agent therapy with glimepiride or metformin in addition to other oral hypoglycemic agents within three months of screening; (2) had experienced acute metabolic complications within three months of screening; (3) was pregnant or lactating; (4) had a history of drug or alcohol abuse; (5) had a known hypersensitivity to glimepiride, metformin, or insulin; (6) was experiencing inconsistent sleep patterns, such as those that result from performing night-shift work; (7) was undergoing insulin therapy at the time of screening or had undergone insulin therapy continuously or non-continuously over seven days within three months of screening; (8) had been treated with clinical trial drugs within three months of screening; (9) was in a medical state, as judged by the researcher, that could have significantly affected clinical and/or laboratory values, resulting in abnormal test values or the completion or results of the study; (10) had serum creatinine values exceeding 1.5 mg/dL (men) or 1.4 mg/dL (women); and (11) had an alanine transaminase (ALT) level and/or an aspartate aminotransferase (AST) level >3 × upper normal limit (UNL) at the time of screening.

2.2. Study design and protocol

2.2.1. Study design

This study was a multi-center, randomized, parallel-group, open-label clinical trial conducted in four institutions in South Korea. Over the 16 weeks that the trial was conducted, screening was performed from weeks 1 to 4 (Supplementary Fig. 1). All patients found eligible then underwent screening for one to four weeks before being randomly assigned to one of two treatment groups: the insulin glargine plus a fixed-dose glimepiride/metformin composite (Amaryl M®, Handok) 1/500 mg twice-a-day (BID) group (hereinafter referred to as the G/M group) or the insulin glargine plus glimepiride (Amaryl®, Handok) 4 mg once-a-day (QD) group (hereinafter referred to as the G group). Both groups were instructed to follow uniform dietary and exercise plans throughout the duration of the trial. After administration of the initial dose of insulin glargine (Lantus Inj Solostar®, Sanofi-aventis) at baseline (0.2 IU/kg × body weight), dose control monitoring was conducted for three consecutive days by measuring morning fasting blood glucose (FBG) level (Table 1).

2.2.2. Randomized medication trial

To ensure performance of a scientific and objective clinical trial procedure, the sponsor conducted assignment of the medication groups to each of the four study centers by block randomization via preparation of pre-assigned random tables that were supplied to the study centers prior to trial initiation. After screening all potential patients to determine whether they met all the inclusion criteria and none of the exclusion criteria, a random number was assigned to each patient found eligible according to order of enrollment. The pre-assigned random table was then scratched to reveal either of the medication groups, followed by corresponding medication. The randomly-assigned G/M-to-G ratio was set at 1:1.

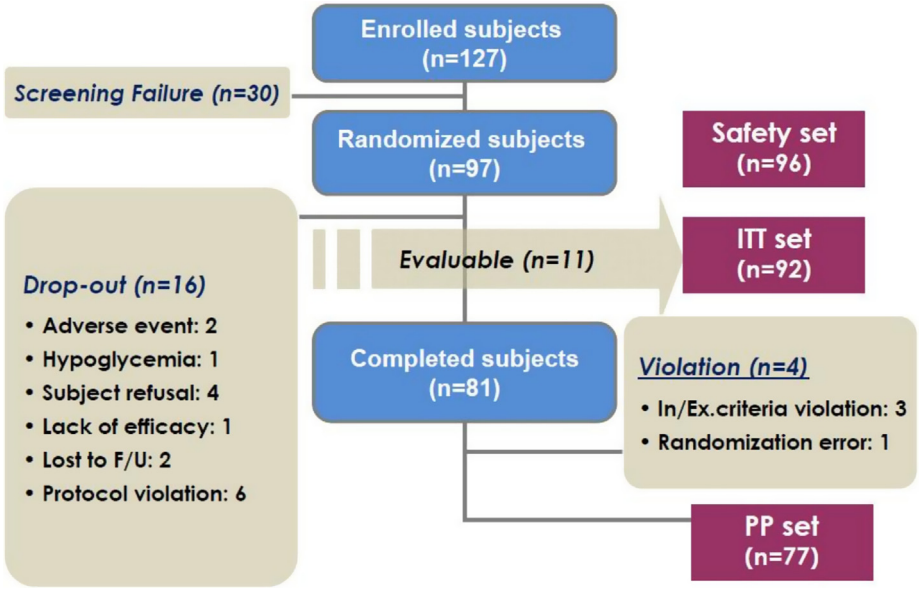

Fig. 1 – Patient disposition (ITT & PP). A total of 127 patients were enrolled in this clinical trial, of whom 30 (23.6%) were excluded due to screening failure. The remaining 97 patients were randomly assigned to the G/M group (*n* = 49), of whom 10 dropped out during the trial and 39 completed the trial, and to the G group (*n* = 48), of whom 6 dropped and 42 completed the trial. Of the 97 randomized patients, 96 patients of safety set (G/M group 48, G group 48), 92 patients of intent to treat (ITT) set (G/M group 46, G group 46) and 77 patients of per protocol (PP) set (G/M group 36, G group 41) were selected.

2.3. *Endpoints of the clinical trial*

2.3.1. *Primary endpoint*

The primary endpoint of this clinical trial was to evaluate and compare the extent of HbA1c decrease in the G/M and G groups.

2.3.2. *Secondary endpoint*

The secondary endpoint of this clinical trial was to evaluate and compare the changes in FPG, 2-h post prandial glucose (PPG2h), insulin, C-peptide levels, insulin sensitivity and the incidence of hypoglycemia and other adverse events in the G/M and G groups.

Table 1 – Insulin glargine dose control algorithm.

Average fasting SMBG (mg/dl) for 3 consecutive days	G/M group	G group
Initial dose	0.2 IU/kg × Body weight	
≤100, or Hypoglycemia**	0, −2	
100< and <120	+2	
120≤ and <140	+4	
***140≤ and <180	+6	
≥180	+8	

SMBG = self-monitoring blood glucose.
** More than 2 events of FPG less than 80 mg/dl with/without hypoglycemic symptoms.
*** For average SMBG ≥ 140 mg/dl, insulin dose change was confirmed with physician.

2.4. *Efficacy, insulin sensitivity and safety analysis*

2.4.1. *Efficacy*

The primary efficacy parameter examined was change in HbA1c level from baseline to final visit. The secondary efficacy parameters examined were changes in FPG, PPG2h, insulin, and C-peptide levels; response rates to HbA1c and FPG at the final visit; and insulin glargine dose and medication compliance at baseline (initiation visit), during the trial (week 8 interim monitoring visit), and at the end of the trial (week 16 final visit).

2.4.2. *Insulin sensitivity*

Homeostatic model assessment (HOMA) was used for the evaluation of change in insulin resistance (IR) and pancreatic β-cell function (HOMA-β) between at the baseline (initiation visit) and the end of the trial (week 16 final visit). We used updated HOMA model (i.e., HOTMA2, the computer model) for calculation with C-peptide and FPG.

2.4.3. *Safety*

The safety assessments were evaluated on incidence of hypoglycemia and other adverse events during the treatment.

2.5. *Medication compliance*

A medication compliance rate <80% or ≥120% was considered an indication of noncompliance. To ensure precise measurement of medication compliance, the patients were instructed to return any remaining study drugs and empty packages and containers during each visit and all remaining study drugs at the end of the trial. Medication

compliance was evaluated by comparing actual medication administration according to the prescribed use and dose to the number of remaining tablets. The investigators encouraged the patients to maintain at least 80% compliance.

2.6. Statistical analysis

Continuous efficacy data, clinical lab test values, and vital signs were presented as descriptive statistics in terms of changes exhibited during the trial. Efficacy was evaluated by dividing the patients into two analysis sets—the intent to treat (ITT) set (i.e., the randomly assigned group) and the per protocol (PP) set (i.e., the compliance group)—and targeting the PP set for equivalence testing of the primary efficacy parameter. To examine the equivalence of the extent of HbA1c change, which was the primary efficacy parameter, the two-sided 95% confidence interval (CI) was calculated for the difference in HbA1c change between the two treatment groups; if the value fell within the pre-determined equivalence range of −0.4% to +0.4%, it was considered equivalent. The statistical analysis was performed by using the analysis of covariance (ANCOVA) model. The ITT set was targeted for analysis of secondary efficacy parameters as superiority test. ANCOVA and the *t*-test were performed to examine differences in FPG and PPG2h changes and medication compliance.

All enrolled patients who took at least one dose of a study drug underwent safety assessment. Changes in incidence of hypoglycemia and adverse events were analyzed using the Fisher's exact test.

3. Results

3.1. Patient

3.1.1. Patients and clinical trial procedure

A total of 127 patients participated in this clinical trial, of whom 30 (23.6%) were excluded during screening. Among the remaining 97 patients, 49 were randomly assigned to the G/M group, 39 completed the trial, and 48 to the G group, 42 completed the trial (Fig. 1). The 16 of the 97 patients who withdrew from the clinical trial did so for the following reasons: protocol violations ($n = 6$; 2 from the G/M and 4 from the G group), patient request ($n = 4$; 3 from the G/M group and 1 from the G group), adverse events including hypoglycemia (3 from the G/M group), insufficient efficacy (1 from the G/M group), and inability/unwillingness to engage in follow-up ($n = 2$; 1 each from the G/M and G groups).

3.1.2. Protocol violation

Of the 97 patients randomly assigned to treatment groups, 81 completed the trial before the statistical analysis began. Of these pre-analysis patients, 8 were excluded from the PP set, of whom 4 (3 from the G/M and 1 from the G group) were excluded for major protocol violations, 3 (2 from the G/M and 1 from the G group) for violation of inclusion criteria, and 1 for assignment error.

3.1.3. Analysis groups

Of the 97 patients randomly assigned to either treatment group, 96 were included in the safety assessment group (48 each from the GM and G groups). The ITT set ($n = 92$) consisted of 46 patients each from the G/M and G groups and the PP set ($n = 77$) of 36 patients from the G/M group and 41 patients from the G group (Fig. 1). Of the randomly assigned patients, 5 were excluded from the ITT set (3 from the G/M and 2 from the G group) because they delivered no efficacy analysis data after assignment. Of the 77 patients initially included in the PP set, 36 of the 49 patients in the G/M group remained after the exclusion of 10 patients who had withdrawn and 3 who had engaged in major protocol violations, while 41 of the 48 patients in the G group remained after the exclusion of 6 patients who had withdrawn and 1 who had engaged in major protocol violations.

3.1.4. Patient demographic characteristics and basic data

No significant intergroup differences were found regarding any of the demographic characteristics of the patients randomly assigned to the clinical trial groups (Table 2).

3.2. Medical history

3.2.1. Diabetes-related medical history

Diabetes-related concomitant diseases were identified in 41 (44.6%) of the 92 patients in ITT group, of whom 21 (45.7%) were among the 46 in the G/M group and 20 (43.5%) of the 46 in the G group. The major diabetes-related concomitant diseases observed were DM neuropathy ($n = 25$) and DM retinopathy ($n = 17$) (Supplementary Table 1).

3.2.2. Concomitant diseases

In the ITT set, 78 (84.8%) of the 92 patients were found to have concomitant diseases, of whom 38 (82.6%) were among the 46 G/M patients and 40 (87.0%) among the 46 G patients. The major concomitant diseases identified were cardiovascular disorders (57.6%), which affected 54.3% of the G/M group and 60.9% the G group, and metabolic and nutritional disorders (51.1%), which affected 43.5% of the G/M group and 58.7% of the G group. Other concomitant diseases identified were gastrointestinal disorders, liver and biliary disorders, coronary artery diseases, visual disturbances, and musculoskeletal diseases (Supplementary Table 1).

3.3. Efficacy

3.3.1. Primary efficacy parameter

The primary efficacy parameter was the change in HbA1c level between baseline and the final visit. No significant difference ($p = 0.7671$) was found in HbA1c level between the G/M and G groups at baseline (8.62% and 8.56%, respectively). During the study period, the mean decrease in HbA1c was 0.99% (adjusted mean: 0.97%) in the G/M group, from 8.62% to 7.62%, and 0.20% (adjusted mean: 0.22%) in the G group, from 8.56% to 8.36%, yielding an adjusted mean difference of −0.76% between the two treatment groups (Table 3). As the 95% two-sided CI for the difference in the change in HbA1c between the two groups (−1.10% to −0.42%) did not

Table 2 – Patients' demographic and baseline data.

Variables	G/M group N = 46	G group N = 46	Total N = 92	p-value (t-test)
Age (years)	54.0 ± 9.6	55.3 ± 11.6	54.7 ± 10.6	0.5709
Sex (male/female)	45.7/54.3	45.7/54.3	45.7/54.3	1.0000*
Weight (kg)	64.5 ± 11.4	63.8 ± 9.0	64.1 ± 10.2	0.7236
Height (cm)	161.1 ± 9.4	161.3 ± 8.3	161.2 ± 8.8	0.9031
BMI (kg/m^2)	24.7 ± 2.8	24.5 ± 2.4	24.6 ± 2.6	0.6111
Duration of diabetes (yrs)	10.6 ± 7.1	10.5 ± 5.8	10.6 ± 6.4	0.9616
Age at onset of diabetes (yrs)	43.7 ± 8.6	45.1 ± 10.5	44.4 ± 9.5	0.4806

M = male, F = female, BMI = body mass index.
* (Chi-square test).

lie within the equivalence interval (−0.4% and +0.4%), the value failed to satisfy the criterion for equivalence. Therefore, an additional significance test was performed, which resulted in detection that the G/M group had experienced a significantly greater decrease in HbA1c compared to the G group ($p < 0.0001$). As in the ITT set, the difference in the change in HbA1c in the PP set (adjusted mean change: −0.79%; two-sided 95% CI: −1.18% to −0.41%) did not satisfy the criterion for equivalence. As in the ITT set, the G/M group was found to have experienced a significantly greater decrease in HbA1c compared to the G group ($p < 0.0001$, Table 3).

3.4. *Secondary efficacy parameters*

3.4.1. *Change in FPG and PPG2h levels from baseline to study end or withdrawal*

In the ITT set, the mean decrease in FPG level was 53.3 mg/dL (adjusted mean: 51.2 mg/dL) in the G/M group and 37.6 mg/dL (adjusted mean: 39.8 mg/dL) in the G group (Table 3). No statistically significant difference was found between the G/M and G groups regarding change in FPG level ($p = 0.1807$; adjusted mean intergroup difference: −11.3 mg/dL; two-sided 95% CI: −28.0 mg/dL to 5.4 mg/dL). In contrast, a significant difference was found between the groups in the PP set ($p = 0.0439$) regarding decrease in FPG level (adjusted mean: −18.1), which was found to be 64.2 mg/dL (adjusted mean: 59.8 mg/dL) and 37.9 mg/dL (adjusted mean: 41.8 mg/dL) for the G/M and G groups, respectively (Table 3). As with the mean decrease in FPG level, the mean decrease in PPG2h level in the ITT set was greater in the G/M group (adjusted mean: −69.7 mg/dL) than the G group (adjusted mean: −37.8 mg/dL; $p = 0.0349$, Table 2). Compared to the ITT set, the decrease in PPG2h level was slightly greater in the PP set and compared to the change until the endpoint, being found to be −77.9 mg/dL for the G/M group and −40.8 mg/dL for the G group. As had that of the ITT set, analysis of the intergroup difference in the adjusted mean change (-37.0 mg/dL) revealed the existence of a significant intergroup difference ($p = 0.0172$; Table 3).

3.4.2. *Insulin and C-peptide changes from baseline to study end or withdrawal*

In the ITT set, the mean increase in insulin level was 0.62 μU/mL (adjusted mean: 0.49 μU/mL, range: 6.49 to 7.11 μU/mL) in the G/M group and 1.27 μU/mL (adjusted mean intergroup difference: 1.40 μU/mL, range: 7.14 to 8.40 μU/mL) in the G group (Table 3). No statistically significant difference was found between the adjusted mean change in insulin in the groups (adjusted mean intergroup difference: −0.91 μU/mL; $p = 0.4564$). In the PP set, the mean increase in insulin level was 0.60 μU/mL (adjusted mean: 0.43 μU/mL, range: 6.16 to 6.76 μU/mL) in the G/M group and 1.42 μU/mL (adjusted mean: 1.57 μU/mL, range: 6.98 to 8.41 μU/mL) in the G group. No statistically significant difference was found between the groups regarding adjusted mean change in insulin level (adjusted mean intergroup difference: −1.14 μU/mL; $p = 0.3822$). In the ITT set, the mean decrease in C-peptide level was −0.58 ng/mL (adjusted mean: −0.61 ng/mL) in the G/M group and −0.65 ng/mL (adjusted mean: −0.62 ng/mL) in the G group. No statistically significant difference was found between the groups regarding adjusted mean change in C-peptide level (adjusted mean intergroup difference: 0.004 ng/mL; $p = 0.9702$, Table 3). In the PP set, the mean decrease in C-peptide level was −0.58 ng/mL (adjusted mean: −0.61 ng/mL) in the G/M group and −0.66 ng/mL (adjusted mean: −0.63 ng/mL) in the G group. No statistically significant difference was found between the groups regarding adjusted mean change in C-peptide level (adjusted mean intergroup difference: 0.016 ng/mL; $p = 0.8949$; Table 3).

3.4.3. *Rates of achievement of therapeutic goals*

The therapeutic goal of a decrease in HbA1c of less than 7.0% was achieved by 28.3% of the G/M group and 2.2% of the G group, yielding a relatively large difference (26.1%) that was found to be statistically significant ($p = 0.0005$). The therapeutic goal of achievement of an FPG level of 140 mg/dL was achieved by 72.7% of the G/M group and 65.1% of the G group, yielding a smaller intergroup difference (7.6%) that was not found to be statistically significant ($p = 0.4430$). Although no significant intergroup difference was found regarding the combined response rate of satisfying at least one of these two indicators, the G/M group was found to have a significantly higher combined response rate of satisfying both indicators (Table 4).

3.4.4. *Rate of medication compliance and change in insulin dose*

Review of the data regarding actual drug administration revealed that the mean medication compliance rate was 93.6% for the G/M group and 97.0% for the G group, a relatively small difference (3.4%) that was not found to be statistically

Table 3 – Equivalence and efficacy analysis on parameters change at the endpoint.

ITT	A1c		FPG		PPG2h		insulin		C-peptide	
	G/M group $n = 46$	G group $n = 46$	G/M group $n = 44$	G group $n = 43$	G/M group $n = 42$	G group $n = 43$	G/M group $n = 43$	G group $n = 43$	G/M group $n = 44$	G group $n = 43$
Baseline (mean)	8.62	8.56	175.0	168.3	315.4	312.8	6.49	7.14	1.95	2.15
End of study (mean)	7.62	8.36	121.7	130.7	244.7	275.9	7.11	8.40	1.37	1.49
Change (mean)	−0.99	−0.20	−53.3	−37.6	−70.6	−36.9	0.62	1.27	−0.58	−0.65
Change (adjusted mean)	−0.97	−0.22	−51.2	−39.8	−69.7	−37.8	0.49	1.40	−0.61	−0.62
Difference between adjusted means	−0.76		−11.3		−31.9		−0.91		0.004	
95% CI for the difference	(−1.10, −0.42)		(−28.0, 5.4)		(−61.6, −2.3)		(−3.33, 1.51)		(−0.23, 0.23)	
p-value (ANCOVA)	$P < 0.0001$		0.1807		0.0349		0.4564		0.9702	
PP	A1c		FPG		PPG2h		insulin		C-peptide	
	G/M group $n = 46$	G group $n = 46$	G/M group $n = 36$	G group $n = 41$	G/M group $n = 36$	G group $n = 41$	G/M group $n = 35$	G group $n = 41$	G/M group $n = 36$	G group $n = 41$
Baseline (mean)	8.67	8.60	181.3	167.0	322.4	311.0	6.16	6.98	1.93	2.14
End of study (mean)	7.59	8.37	117.1	129.1	240.5	273.8	6.76	8.41	1.35	1.48
Change (mean)	−1.07	−0.24	−64.2	−37.9	−81.9	−37.3	0.60	1.42	−0.58	−0.66
Change (adjusted mean)	−1.05	−0.26	−59.8	−41.8	−77.9	−40.8	0.43	1.57	−0.61	−0.63
Difference between adjusted means	−0.79		−18.1		−37.0		−1.14		0.016	
95% CI for the difference	(−1.18, −0.41)		(−35.6, −0.5)		(−67.3, −6.8)		(−3.72, 1.44)		(−0.22, 0.25)	
p-value (ANCOVA)	$P < 0.0001$		0.0439		0.0172		0.3822		0.8949	

ITT = intention to treat, PP = per protocol.

Table 4 – Response rate at the endpoint (ITT).

		G/M group	G group	p-value*
HbA1c response	*n*	46	46	0.0005
(HbA1c < 7%)	*n* (%)	13 (28.3%)	1 (2.2%)	
FPG response	*n*	44	43	0.4430
(FPG < 140 mg/dl)	*n* (%)	32 (72.7%)	28 (65.1%)	
Combined response I	*n*	44	43	0.4430
(HbA1c < 7% or FPG < 140 mg/dl)	*n* (%)	32 (72.7%)	28 (65.1%)	
Combined response II	*n*	46	46	0.0005
(HbA1c < 7% and FPG < 140 mg/dl)	*n* (%)	13 (28.3%)	1 (2.2%)	

Hemoglobin A1c = HbA1c, FPG = fasting blood glucose.
* Chi-square test.

significant ($P = 0.142$). The mean increase in insulin glargine dose between baseline and final visit was 6.6 IU, from 12.8 to 19.4 IU, in the G/M group and 12.5 IU, from 12.5 to 25.0 IU, in the G group. Analysis of these changes revealed that the mean rate of increase in insulin glargine in the G/M group was significantly lower compared to that of the G group ($P = 0.0204$).

3.5. *Insulin sensitivity*

3.5.1. *HOMA-Ir*

Analysis of homeostasis model assessment of insulin resistance (HOMA-IR) values revealed a mean HOMA-IR value decrease of 0.55, from 2.85 to 2.30, in the G/M group ($n = 41$) and 0.05, from 3.02 to 2.96, in the G group ($n = 43$). Although the rate of decrease was higher for the G/M group, the difference between the group rates did not reach a level of statistical significance (Supplementary Table 2).

3.5.2. *Homa-β*

Assessment of pancreatic β-cell function (HOMA-β) values revealed a mean HOMA-β value increase of 26.5, from 36.2 to 62.7, in the G/M group ($n = 41$) and 39.3, from 29.9 to 69.2, in the G group ($n = 44$). Although the rate of increase was higher for the G group and the G/M group had a higher median value (9.2 vs. 3.6), the differences between the group rates and values did not reach a level of statistical significance ($P > 0.05$, Wilcoxon's rank sum test; Supplementary Table 3).

3.6. *Safety*

3.6.1. *Incidence of hypoglycemia*

In the G/M group, 79 hypoglycemic events were experienced by 19 (39.6%) of the 48 patients, while 50 events were experienced by 20 (41.7%) of the 48 patients in the G group. Among these events, 63 events experienced by 18 patients (37.5%) in the G/M group and 44 experienced by 17 (35.4%) in the G group were symptomatic, and 14 events experienced by 9 patients (18.8%) in the G/M group and 18 experienced by 9 (18.8%) in the G group were cases of nocturnal hypoglycemia. Although the rate of hypoglycemia was slightly higher in the G/M group, the intergroup difference did not reach a level of statistical significance ($P = 1.000$). Both groups experienced symptoms such as sweating, tremor, hunger, weakness/fatigue, and dizziness during these hypoglycemic events at similarly high rates (Supplementary Table 4).

3.6.2. *Adverse events*

Prior to the administration of study drugs, six patients (3.7%) reported experiencing more than eight adverse events, one of whom reported three (blood sugar problems, insomnia, and chest tightness). During the study, 19 adverse events were reported by 12 of the 48 patients (25.0%) in the G/M group and 15 by 10 of the 48 (20.8%) in the G group, yielding an intergroup difference that did not reach a level of statistical significance (p = 0.8086). Adverse events that were attributed to the study drugs were one case of nausea and one case of itching at the injection site, both of which were reported by G patients. Four cases of serious adverse events were experienced by four patients (8.3%) in the G/M group and two cases by one patient (2.1%) in the G group. The most frequently reported adverse events were gastrointestinal tract problems (6.3% of all patients), followed by central and peripheral nervous system and musculoskeletal system problems (4.2%) and problems with other body organs. One gastrointestinal adverse event was reported by one G/M patient (2.1%) and six events were reported by five G patients (10.4%). Although the rate of the G group was higher, the intergroup difference did not reach a level of statistical significance (p = 0.2038, Fisher's exact test; Supplementary Table 4).

4. Discussion

The primary therapy objective in treating T2DM patients is preventing or delaying the onset and progression of these chronic diseases through maintaining strict glycemic control [1,6].

According to the guidelines for the treatment of T2DM, the therapeutic target should be an HbA1c level of <7.0% [7]. Although most diabetic patients follow special regimens to improve their dietary habits and lifestyle for the maintenance of the recommended blood sugar level, the majority ultimately must also begin a medication regimen to ensure adequate glycemic control. Metformin has been used for over 40 years as an oral hypoglycemic agent that suppresses hepatic glucose production, restores insulin secretion, and improves insulin sensitivity [8,9]. It is generally chosen as the first T2DM drug because of its proven efficacy in lowering blood glucose and sustaining weight loss, low risk of hypo-

glycemia, and cost effectiveness [10]. If metformin monotherapy fails to ensure adequate glycemic control, combination therapy consisting of metformin and another hypoglycemic agent that acts according to a mutually complementary mechanism is recommended.

Many studies have demonstrated the therapeutic efficacy of combination therapy consisting of metformin and sulfonylurea-based glibenclamide, glipizide, or glimepiride for treatment of T2DM [11–15]. Among these, glimepiride is a sulfonylurea-based third-generation drug associated with a lower risk of hypoglycemia than other sulfonylurea-based hypoglycemic agents due its regulation of insulin secretion through physiological stimulation of β-cell secretion [16,17] and ability to increase the insulin-sensitizing activity of peripheral tissues through a variety of mechanisms [3,18].

The pathophysiology of T2DM is characterized by insulin secretion disorder and insulin resistance. Thus, the combined use of sulfonylurea-based drugs and metformin may theoretically be considered an ideal combination therapy capable of simultaneously counteracting insulin secretion disorder and insulin resistance [3,14].

However, the rate of compliance in the combined use of two or more oral hypoglycemic agents by T2DM patients for an unspecified duration, one of the most common causes of poor glycemic control by T2DM patients who need combination therapy, has been found to be relatively low. Therefore, administration of a composite drug of two oral hypoglycemic agents as a more convenient form of medication can be an effective alternative method for improving patient compliance and thus ensuring long-term glycemic control [5,19,20].

Developing a therapy that combines administration of oral hypoglycemic agents and insulin therapy was proposed as a means of eliciting the synergistic effect of each agent's complementary mechanisms. In support of this proposal, various reports have demonstrated the superior efficacy of early administration of combined intensive oral hypoglycemic agent and insulin therapy in recovering and maintaining β-cell function and sustaining adequate glycemic control compared to oral hypoglycemic agent monotherapy [21].

This study was designed to investigate the efficacy and safety of the combination therapy of conventional oral hypoglycemic agents and insulin injection based on the results of previous studies. To this end, the efficacy and safety data including the HbA1c changes were compared between the fixed-dose glimepiride/metformin composite 1/500 mg BID group (G/M group) and glimepiride 4 mg QD group (G group) as administered in addition to the insulin glargine QD. A total of 127 patients were enrolled in four study centers, of whom 97 were randomly assigned to either group and 81 successfully completed the clinical trial, with 16 withdrawals. Of the 97 patients randomly assigned, 92 were targeted for the ITT analysis, thus satisfying the target trial sample size of 44 per group. As for the patients' basic data, there were no statistically significant intergroup differences in demographic characteristics. The primary efficacy endpoint was the HbA1c change; its intergroup difference was −0.76% (two-sided 95% confidence interval: −1.10%, −0.42%), which did not lie within the equivalence range. Therefore, additional significance tests were performed to obtain more accurate results. The intergroup significance test revealed that the decrease in HbA1c was significantly greater in the G/M group than the G group (ITT/PP analysis sets, $p < 0.0001$). The result reveals that the G/M group had a greater effect in lowering HbA1c compared to the G group, as expected.

In our study result, the decrease in HbA1c within the G group was relatively low when compared to other studies using glimepiride [15,16]. Glimepiride can improve blood sugar control; however, it may lose its effectiveness over time. Patients in our study group have had diabetes for over 10 years, and several patients had already taken glimepiride. Therefore, the G group of single glimepiride might be relatively less effective.

Of the secondary endpoints, the G/M group showed a significantly greater decrease in the PPG2h than the G group (ITT set: $p = 0.0349$; PP set $p = 0.0172$) which reveals that the G/M group had better effect in lowering PPG2h compared to the G group. FPG of both groups did not show significant differences in the ITT set ($p = 0.1807$), whereas the G/M group showed a significantly greater decrease rate than the G group in the PP set ($p = 0.0439$). In other secondary efficacy parameters, i.e. insulin, C-peptide, and medication compliance, no significant intergroup differences could be confirmed. On the other hand, the insulin glargine dose increased to a lesser extent in the G/M group (ITT set: $p = 0.0204$; PP set: $p = 0.0154$). The result of serum insulin and C-peptide could be biased as the dosage of glimepiride were different between two groups and the G group had more increased insulin glargine dose. And for compliance rate, the G group had higher mean compliance rate of 97.0% compared to the G/M group 93.6%, but there was no statistical significance and median value was 99.1% for the G group and 98.7% for the G/M group which both group had similar values. The result could be revealed that the G/M group has good compliance as well as the G group.

HOMA is a quantifying mathematical method for assessing insulin resistance and β-cell function from basal glucose and insulin or C-peptide concentrations [22,23]. HOMA-IR and HOMA-β are based on the assumption that under normal conditions a certain serum insulin concentration is required to achieve normoglycemia in the fasting normal state. Any requirement of more insulin to maintain normoglycemia or any hyperglycemia occurring at similar insulin levels is an indicator of deteriorated homeostasis due to insulin resistance and/or β-cell dysfunction [22,24]. Given that the G/M composite can counteract insulin resistance and insulin secretion disorder by improving the insulin sensitivity and pancreatic β-cell function, it was expected in this study that the G/M group would yield greater decrease in HOMA-IR and greater increase in HOMA-β. And also, there was one study supporting our study, which had shown that metformin plus low-dose glimepiride significantly improves HOMA-IR and HOMA-β [25].

In our study result, the mean HOMA-IR value had decreased both on the G/M (2.85 to 2.30) and the G group (3.02 to 2.96). G/M group had more decrease (−0.55 vs −0.05) which seemed obvious as insulin sensitizer was added, however, there was no statistical significance. The mean HOMA-β value had increased both on the G/M (36.2 to 62.7) and G group (29.9 to 69.2) with the G group showing a larger increase rate contrary to the prediction. In terms of mean mean ± SD, however, the G/M group showed a greater median value (9.2 vs.

3.6) with 8.0 ± 116.3 vs. 27.5 ± 140.7, wherein the G group showed a larger standard deviation.

There could be several reasons for unexpected HOMA data in our study. First, as the G/M and G group had different dosage of glimepiride, the data could be biased. Second, as sulfonylurea has effect of driving β-cell secretion, it would not be appropriate for using HOMA-β during treatment with glimepiride. There was a study that had shown that false positive result of HOMA-β could come out, especially for patients treated with drugs driving β-cell secretion, such as sulfonylureas or glinides [26]. So, HOMA itself cannot be an independent factor for analyzing the whole concept of insulin resistance and β-cell function, but rather, it could be used as a quantifying parameter. As a result, the G/M and G group both had improved HOMA and we cannot definitely conclude that the G/M group was superior to the G group on HOMA, however there was tendency toward improved HOMA-IR.

Safety was assessed on the basis of hypoglycemia, adverse events, clinical test values, vital signs, physical examination. While the overall incidence rate of hypoglycemia did not vary between the two treatments groups, its frequency was relatively high in the G/M group. It was expected that the G group would have had greater hypoglycemic events since the dosage of glimepiride was higher (4 mg vs 2 mg) and higher dose of insulin glargine was injected, but contrary result had come out. This could paradoxically have thought that even with low dose of glimepiride (2 mg), adding metformin can have better hypoglycemic effect compared to high dose glimepiride alone. Nor was there any significant intergroup difference in the incidence rate of adverse events.

Limitations of this study were the short follow-up period and small sample size. Therefore, long-term studies in large populations are required to prove the efficacy and safety of the GM group relative to the G group. Further, we carefully interviewed each patient; however, some patients may have been afraid of insulin uptitration and experiencing hypoglycemia unawareness. However, this study demonstrates a combination of more appropriate oral medications for uncontrolled type 2 diabetic patients who require insulin initiation.

5. Conclusion

Comparison of the efficacy and safety of combined therapy consisting of either insulin glargine plus glimepiride/metformin 1/500 mg BID or insulin glargine plus glimepiride 4 mg QD indicated that both forms of therapy are relatively safe but that the former more effectively decreases HbA1c and blood glucose levels. Thus, use of glimepiride/metformin 1/500 mg BID as the oral hypoglycemic agent in combination therapy with insulin glargine will likely yield better outcomes than use of glimepiride QD in the treatment of T2DM patients with inadequate glycemic control.

Ethical approval and consent to participate

Clinical Trials.gov Identifier: NCT 00913367.

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Declaration of Competing Interest

None.

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