Effectiveness and safety of insulin glargine plus glimepiride after 6 months of treatment among patients with type 2 diabetes mellitus who failed premixed insulin: An observational study conducted in Egypt

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Objective
This study aimed to evaluate the effectiveness and safety of insulin glargine in combination with glimepiride treatment in daily practice in patients who failed premixed insulin with or without oral antidiabetic (OAD) regimen.
Patients and methods
This 6-month, prospective, multicenter, observational study conducted in Egypt included adult patients with type 2 diabetes mellitus on premix with or without OAD (glimepiride plus metformin), with glycated hemoglobin (HbA1c) greater than 8.5% and for whom the investigator decided to switch to insulin glargine in addition to glimepiride. Overall, three mandatory visits (baseline, 3 months, and 6 months) and seven phone calls were performed by the investigator for each eligible patient. Patients were assessed according to the value of HbA1c and fasting blood glucose (FBG).
Results
At the end of this study, the results showed effectiveness of combining insulin glargine plus glimepiride in reducing the mean baseline level of HbA1c% by 1.79 and 2.5% at visit 2 (week 12) and visit 3 (week 24), respectively ($P<0.001$). The percentage of patients reaching target HbA1c less than 7% in visit 2 (week 12) and visit 3 (week 24) was 5 and 24.3%, respectively. They also showed a significant reduction ($P<0.001$) in the mean FBG at visit 2 (week 12) and visit 3 (week 24) of 97.44 and 104.4 mg/dl, respectively, whereas the mean percent reductions were 44.37 and 47.54%, respectively. The percentage of patients who reaching FBG less than or equal to 100 mg/dl was 26.7 and 32.2%, in visit 2 (week 12) and visit 3 (week 24), respectively. There was no significant change in mean body weight between baseline and visit 3 ($P>0.05$). The mean 2-h postprandial blood glucose level was decreased significantly ($P<0.001$) at visit 2 to 171.93±68.2 mg/dl and at visit 3 to 155.88±56.61 mg/dl. The mean reductions of 2-h postprandial blood glucose at weeks 12 and 24 were 140.8 and 156.8 mg/dl, respectively, and the mean percentage reductions were 45 and 50.1%, respectively.
A total of 50 adverse events were reported by 41 patients during the study. The most frequently reported adverse event was hypoglycemia, which included 37 episodes reported by 31 patients, where nocturnal hypoglycemia was represented in 12 episodes, with percentage of 32.4%.
Conclusion
The results showed that a combination therapy of insulin glargine and glimepiride improved glycemic control in patients with type 2 diabetes mellitus, who failed premixed with or without OAD (glimepiride plus metformin). In addition, safety analysis showed high patient tolerability to glargine and glimepiride regimen.

Keywords:
glimepiride, HbA1c, insulin glargine, oral anti-diabetics (OAD), premixed insulin, type 2 diabetes (T2DM)

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Introduction

Diabetes mellitus is a common disease affecting ~8.3% of the population [1]. Type 2 diabetes (noninsulin-dependent diabetes mellitus) accounts for 90% of patients with diabetes mellitus [2]. Patients with diabetes have an approximately two-fold to three-fold risk for all cardiovascular diseases [3,4], and their relative risk of death from all causes is increased by 75% [5,6]. As of yet, there is no conclusive evidence that improved glucose control with oral agents' leads to a decrease in the complications of type 2 diabetes.

There is some evidence that improved glucose control delays the onset of complications in type 2 diabetes. In a cohort study of 114 patients followed for 5 years, the incidence of progression of retinopathy increased linearly as a function of the glycated hemoglobin (HbA1c) level, 2% in those with HbA1c less than 0.070 and 62% in those with HbA1c greater than 0.090 [7]. In a randomized secondary prevention intervention trial of diabetic patients (majority type 2 diabetes) who had experienced Myocardial Infarction (MI), those patients had intensive insulin treatment and thus resulted in an absolute reduction of mortality by 11% (44 vs. 33%) compared with the regular therapy group after 3.4 years of follow-up [8]. In a randomized trial of 110 patients with type 2 diabetes, patients who received multiple insulin injections had an absolute reduction in the progression of retinopathy by 24%, and of nephropathy by 20% after 6 years of follow-up, when compared with a conventional therapy group [9].

Basal supported oral therapy [insulin glargine plus oral antidiabetic (OAD) treatment] makes antidiabetic treatment easier for physicians and patients with advanced type 2 diabetes mellitus (T2DM), that is, more flexibility in meal frequency, less variability of insulin dosage caused by insufficient mixing of premixed insulin as well as a lower risk for hypoglycemia. The aforementioned reasons makes basal supported oral therapy much more comfortable compared with insulin therapy with premixed insulin. Physicians may decide to change premixed insulin therapy to basal supported oral therapy to overcome hypoglycemic events.

The efficacy and safety of patients treated with basal insulin and OAD therapy after pretreatment with premixed insulin therapy in daily practice were investigated in this observational study.

Patients and methods

Study design

This was a national, multicenter, prospective, observational study. The study was conducted in 26 sites all over Egypt to study the effectiveness and safety of insulin glargine plus glimepiride after 6 months of treatment among patients with T2DM who failed premixed insulin. It was planned to enroll 321 patients, but only 280 satisfied the eligibility criteria and were enrolled in the study. The estimated enrollment duration was 1 year. Overall, three mandatory visits (baseline, 3 months, and 6 months) and seven phone calls were performed by the investigator for each eligible patient. Data were collected at each visit/phone call. Sample size determination was based upon a reference study that assured a sample size of 288 patients would guarantee a study power of 96% and a confidence level of 95%. Considering a dropout rate of 15%, another 43 patients were to be enrolled, so the total number of patients was planned to be 321.

Ethical statement

This study was conducted in accordance with the principles established by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by it, as well as the ICH guidelines for good clinical practice. This study was conducted in compliance with all national and international laws and regulations. Written informed consent was obtained from all participants in this study. The study protocol was approved by the ethics committee of Faculty of Medicine, Alexandria University, Faculty of Medicine, Minia University, and Faculty of Medicine, Zagazig University prior to patient enrollment.

Observation

At the start, all eligible patients were treated with insulin glargine: subcutaneous injection and glimepiride, in the form of oral tablet. Criteria for selecting the dose were based on prior clinical experience. Prescription and titration was left to physician discretion; the physician was guided by the seven-point profile and the summary of product characteristics. All enrolled patients were assessed at baseline visit, visit 2, and visit 3 for HbA1c%, fasting blood glucose (FBG) levels, and hematological and biochemical analyses. In addition, patients were assessed for occurrence of adverse events (AEs) including hypoglycemic episodes and for other criteria outlined in the study activities.

Patients

Only patients with T2DM, aged more than 18 years who failed premix with or without OAD (glimepiride plus metformin), with HbA1c greater than 8.5%, and for whom the investigator has decided to switch to insulin glargine in addition to glimepiride were eligible to participate in this study. Patients considered ineligible for participation included those having diabetic nephropathy with impaired renal function, severe impaired hepatic functions (alanine aminotransferase/aspartate aminotransferase >3× upper normal level), active proliferate diabetic retinopathy, pregnancy, and breast-feeding women.

Outcomes

In this study, primary efficacy outcome was to evaluate the change of HbA1c% from the start to end of study (after 6 month of treatment) and to evaluate the percentage of patients achieving glycemic control (HbA1c<7% and FBG≤100 mg/dl). The secondary efficacy outcomes were to evaluate number and percentage of patients reaching target HbA1c (reduction by 1% compared with baseline); compare FBG values at baseline visit, visit 2, and visit 3; and measure the change in patients' weight during the study. The primary safety outcome was to assess all AEs that occurred during the 6-month study duration (both patient-reported and investigator-reported events), and the incidence of hypoglycemic events.

Statistical analysis

All study patients were described by demographic variables, background variables, and other variables with appropriate statistics: frequency tables (count and percent) for categorical variables and/or descriptive statistics (mean, SD, minimum, median, mode, and maximum) for continuous variables. Repeated measure analysis of variance was used to test the change significance of HbA1c and FBG between study visits. Change in patients' body weight was tested using paired dependent Student's *t*-test between baseline and 24-week visits. Safety analyses were performed on all patients enrolled in the study who attended the relevant study visits. Safety analyses were performed on all AEs that were recorded during the 6-month study duration, both those observed by the investigator or reported by the patient. Incidences of hypoglycemic events were recorded. Statistical analysis of hypoglycemic episodes (including grade, type, symptoms, and countermeasures) and that of AEs were performed using frequency and percentages.

Results

Recruitments

A total of 280 patients were enrolled and eligible for the study. One patient was lost to follow-up after visit 2 and was excluded from efficacy analysis at visit 3, and a total of 279 patients completed the study.

Study dates

Date first patient enrolled: 5 November 2008.

Date last patient completed: 6 December 2010.

Patient baseline characteristics and demographics

The study population consisted of 54.3% males and 45.7% females, with a mean age 51.2±9.6 years. The mean height was 169.92±7.77 cm, the mean weight was 89.6±13.45 kg, and the mean BMI was 31.03±4.5 kg/m^2. The mean baseline heart rate was 80±6.88 beat/min. The mean baseline systolic and diastolic blood pressures were 134.04±14.20 and 83.46±8.03 mmHg, respectively. Regarding diabetes mellitus characteristics at baseline, the mean HbA1c% was 10.35±1.60%, the mean FBG level was 234.53±70.55 mg/dl, and the mean 2-h postprandial blood glucose was 312.7±95 mg/dl. The mean duration of diabetes mellitus was 8.12±5.06 years. Overall, 85.4% of the patients had family history of the disease. The mean daily doses of insulin glargine and glimepiride were 20.69±9.19 IU and 3.62±1.39 mg, respectively, at baseline. All the enrolled 280 (100%) patients were on insulin premix with a mean dose of 41.55±17.57 IU. In contrast, only 56 patients were on OAD metformin with a mean dose of 1575.89±420.82 mg.

Outcomes

Efficacy outcome

Glycemic control was improved in all patients with significant improvements observed for HbA1c% and FBG levels. At the start of the study, the mean HbA1c % was 10.35±1.6%, which then decreased significantly at visit 2 to reach 8.55±1.28% and finally reached to 7.85±1.29% at the end of the study ($P<0.001$).

There was a significant reduction in HbA1c level, as the mean reductions of HbA1c at visits 2 and visit 3 were 1.7 and 2.5%, respectively, whereas the mean percent reductions were 17.3 and 24.1%, respectively ($P<0.001$). At visit 2, 187 (66.7%) patients experienced HbA1c reduction of 1% compared with baseline values and 14 (5%) patients reached the target levels for HbA1c less than 7%, whereas at visit 3, 233 (83.5%) patients experienced HbA1c reduction by 1% compared with baseline values and 68 (24.3%) patients reached the target levels for HbA1c less than 7%.

Regarding the mean FBG level, it was 219.6±73.6 mg/dl at baseline, which then decreased significantly at visit 2 to reach 122.16±41.9 mg/dl and to finally reach 115.2±62.4 mg/dl at visit 3 ($P<0.001$). The mean reductions of FBG at visits 2 and visit 3 were 97.44 and 104.4 mg/dl, respectively, whereas the mean percent reductions were 44.3 and 47.5%, respectively. Regarding target FBG (≤100 mg/dl), 75 (26.7%) patients reached the target at visit 2, and this number was increased at visit 3 to reach 90 (32.2%) patients. The number of patients who experienced reduction of FBG by 1% compared with baseline values and reached target levels for FBG less than or equal to 100 mg/dl was 54 (19.2%) and 76 (27.1%) at visit 2 and visit 3, respectively (Table 1).

At baseline, the mean 2-h postprandial blood glucose level was 312.71±95.04 mg/dl, which decreased significantly ($P<0.001$) at visit 2 to 171.93±68.2 mg/dl and at visit 3 to 155.88±56.61 mg/dl. The absolute mean reductions of 2-h postprandial blood glucose level at weeks 12 and 24 were 140.8 and 156.8 mg/dl, respectively and the mean percent reductions were 45 and 50.1%, respectively.

Regarding vital signs at baseline, the mean baseline systolic and diastolic blood pressures were 134.04±14.20 and 83.46±8.03 mmHg, respectively. These values were significantly reduced ($P<0.001$) at visit 3 to reach 128.25±10 and 79.74±5.17 mmHg, respectively. Moreover, a significant decrease ($P<0.001$) of the heart rate was observed in visit 3; the mean heart rate at baseline was 80±6.88 beat/min, which then decreased to reach 77.55±6.73 beat/min at end of study visit.

The effect on mean values of the seven-point blood glucose profile

The mean baseline blood glucose values at all seven points were significantly decreased ($P<0.001$) at weeks 12 and 24 (Table 2).

There was no significant difference in patients' weight between baseline visit and visit 3 ($P>0.05$). The mean weight at baseline was 89.6±13.45 kg whereas at visit 3, it was 90.03±13.43 kg. This indicated that the use of basal-bolus with glimepiride did not lead to weight gain.

Regarding hematologic tests, hemoglobin concentration, red blood cell count, white blood cell count, and platelets count were measured for each patient at the three consequent study visits whenever applicable, whereas for biochemistry tests, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum creatinine, triglycerides, cholesterol, high-density lipoprotein and low-density lipoprotein concentrations were measured for each patient at the three consequent study visits whenever applicable (Table 3).

Safety outcome

A total of 50 AEs were reported by 41 (14.64%) patients. No serious AE was experienced during this study by any patients. AEs included 37 (6.61%) episodes of hypoglycemia reported by 31 (11.07%) patients, and 13 (2.32%) episodes of reactions at the injection site of insulin reported by 10 (3.57%) patients. Percentages are calculated based on total number of follow-up visits done for all patients (N=560).

Hypoglycemia is a condition characterized by abnormally low blood glucose (blood sugar) levels, usually less than 70 mg/dl. Hypoglycemia is categorized as follows:

Table 1 Number and percentage of patients reaching target glycated hemoglobin less than 7% and target fasting blood glucose less than or equal to 100 mg/dl and those who experienced glycated hemoglobin reduction by 1% and fasting blood glucose reduction by 1%

Achieved the target	Patients reaching target HbA1c<7% [*n* (%)]		Patients reaching target FBG ≤100 mg/dl [*n* (%)[a]]	
	Visit 2	Visit 3	Visit 2	Visit 3
Yes	14 (5)	68 (24.37)	75 (26.79)	90 (32.26)
No	266 (95)	211 (75.63)	205 (73.21)	189 (67.74)
	Patients who experienced HbA1c reduction by 1% from baseline levels [*n* (%)]		Patients who experienced FBG reduction by 1% and reached target levels for FBG£100 mg/dl from baseline levels [*n* (%)]	
	Visit 2	Visit 3	Visit 2	Visit 3
Yes	233 (85.51)	68 (24.37)	54 (19.29)	76 (27.14)

FBG, fasting blood glucose; HbA1c, glycated hemoglobin. [a]Percentages are calculated out of 279, as one patient was lost to follow-up after visit 2.

Table 2 Comparison between mean values of the seven-point blood glucose profile at baseline, visit 2, and visit 3

Blood glucose values (mg/dl)	Baseline	Visit 2	Visit 3	Repeated measure ANOVA (*P* value)
Fasting before breakfast	210.45±61.47	120.48±31.57	113.97±30.40	<0.001
Two hours after breakfast	289.55±82.25	163.71±45.75	155.79±50.16	<0.001
Before lunch	207.81±76.31	126.38±35.04	121.85±34.28	<0.001
Two hours after lunch	286.74±82.23	175.03±48.95	165.49±49.96	<0.001
Before dinner	212.2±63.28	131.66±34.80	123.58±32.13	<0.001
Two hours after dinner	264.53±74.62	166.9±42.43	157.84±45.41	<0.001
Bed time	233.24±69.80	149.47±36.44	140.66±37.41	<0.001

ANOVA, analysis of variance.

Table 3 Summary of laboratory changes at visit 3 from baseline visit

	Baseline visit (week 0)	Visit 3(week 24)	Paired sample *t*-test (*P* value)
Hematology			
Hemoglobin (g/dl)	13.1±1.8	13.4±1.5	<0.001
RBC ($\times 10^6$/ml)	4.8±0.7	4.8±0.5	<0.001
WBC ($\times 10^3$/ml)	6.5±1.8	13.6±20.7	0.581
Platelet count ($\times 10^3$/ml)	248.1±65.8	244.3±62.6	<0.001
Blood chemistry			
SGOT (IU/l)	24.2±11.7	24.4±10.2	<0.001
SGPT (IU/l)	29.1±17.0	28.1±14.2	<0.001
Serum creatinine (mg/dl)	1.187±1.87	1.057±0.31	0.774
Triglycerides (mg/dl)	181.55±95.38	147±49.03	<0.001
Cholesterol (mg/dl)	230.93±153.42	182.8±32.6	0.051
HDL (mg/dl)	50.09±36.64	50.5±40.59	0.106
LDL (mg/dl)	140.48±41.68	119.36±32.7	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein; RBC, red blood cell; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

(a) asymptomatic hypoglycemia is defined as a measured blood glucose level less than 70 mg/dl not associated with clinical symptoms; (b) symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to result from hypoglycemia (confirmed or not by a blood glucose measurement <70 mg/dl); (c) nocturnal hypoglycemia, which occurs while the patient is asleep, after bedtime and before getting up in the morning; and (4) severe symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to result from hypoglycemia in which the patient requires the assistance of another person because the patient cannot treat her/himself owing to acute neurological impairment directly resulting from the hypoglycemia (assistance by another person when the patient could have treated her/himself is not considered as requiring assistance).

A total of 25 (67.6%) episodes of the experienced hypoglycemic episodes were non-nocturnal. Overall, 30 (81.1%) were symptomatic, 12 (32.4%) were nocturnal, and seven (18.9%) were asymptomatic. In the 37 episodes of hypoglycemia, the most prevalent symptoms were sweating in 30 (81.1%) patients, hunger in 24 (64.96%) patients, tremors in 21 (56.8%) patients, dizziness and headache in 14 (37.8%) patients, and nervousness in nine (24.3%) patients. In total, 34 (91.89%) patients recovered from their hypoglycemic events with administration of carbohydrates, two (5.41%) patients without any countermeasures, and one (2.7%) patient with the use of glucagon.

Discussion

T2DM is a progressive disease characterized by co-existing insulin deficiency (relative) and insulin insensitivity. Both FBG and postprandial blood glucose levels are elevated, exposing the patient to acute and chronic complications owing to microvascular and macrovascular angiopathy. Improving glycemic control has been demonstrated to lower the risk of these complications. It is necessary to maintain glycemic control. Insulin therapy is required when dietary and lifestyle modifications combined with oral hypoglycemic agents fail to provide adequate glycemic control. Adding an optimized dose of basal insulin to the existing oral therapy is a simple and widely used method for initiating insulin therapy [10]. However, despite an effective control of fasting hyperglycemia, further intervention to control postprandial hyperglycemia may become necessary to achieve HbA1c targets. Strategies for the addition of prandial insulin include administering short-acting (or rapid-acting) insulin analogues before each meal or twice-daily administration of premixed insulin. As a single large meal often contributes to the greatest part of daytime hyperglycemia, an alternative strategy is emerging with the addition of a single injection of prandial insulin before the meal that induces the largest postprandial blood glucose excursion measured 2 h after the start of the meal. Over time, additional prandial boluses of insulin may be required to sustain daytime glycemic control. This strategy offers a simple, stepwise approach to progress from basal insulin to a basal-bolus regimen. Studies are needed to validate this method and better define specific titration tactics [10].

In a recent observational study of 12 216 patients with T2DM poorly controlled with OADs alone (HbA1c: 8.7±1.4%; FBG: 202±56 mg/dl), addition of once-daily insulin glargine was associated with improvements in FBG (133±33 mg/dl) and HbA1c (7.2±0.9%) at 3 months, which were maintained at 9 months [11].

In this study, the mean HbA1c% reached 7.85±1.29% and FBG levels reached 115.2±62.4 mg/dl at the end of the study. Moreover, 68 (24.37%) patient reached the target level of HbA1c% less than 7, and 233 (83.51%) patient showed reduction by 1% from baseline levels; 90 (32.26%) patient reached target level of FBG less than or equal to 100 mg/dl, and 76 (27.14%) patient showed reduction by 1% from baseline levels. Another study compared the use of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Results showed a decrease in mean HbA1c from baseline, which was significantly more pronounced (−1.64 vs. −1.31%, P=0.0003), and more patients reached HbA1c less than or equal to 7.0% without confirmed nocturnal hypoglycemia. FBG decrease was greater with glargine plus OAD, and more patients reached target FBG less than or equal to 100 mg/dl with glargine plus OAD. Patients on glargine plus OAD had fewer confirmed hypoglycemic episodes [12].

Preliminary results of a large prospective randomized trial, that examined the relationship of glucose control to complications of diabetes in type 2 diabetics, showed an improvement in HbA1c levels in patients who received treatment, whether with sulfonylurea, metformin, or insulin [13]. In contrast, there is strong evidence that near-normalization of blood glucose levels with insulin can delay the development and progression of retinopathy, nephropathy, and neuropathy of patients with type 1 diabetes mellitus (insulin-dependent diabetes mellitus) [14]. However, weight gain is a seemingly unavoidable occurrence with initiation of insulin therapy in T2DM [15]. In a 28-week study comparing initiation of insulin therapy with either biphasic insulin aspart (70/30) or insulin glargine, once-daily insulin glargine was associated with significantly less weight gain compared with twice-daily biphasic insulin aspart (+3.5 vs. +5.4 kg, P<0.01) [16]. However, in this study there was no significant effect on reducing weight gain. Furthermore, educational programs, if combined with insulin glargine therapy, may help prevent the weight gain otherwise associated with insulin therapy [17].

Nowadays, regimens using combination therapy of insulin glargine and OADs have become widely used worldwide as an initiation of insulin therapy which has a positive effect on glycemic control [10,13]. An increased necessity for combined therapies was clearly acknowledged by the physicians in the UK Prospective Diabetes Study. Assessment of the results of 9 years of monotherapy with several agents showed that fasting plasma glucose was maintained below 140 mg/dl in only 18% of participants using metformin, 24% using a sulfonylurea, and 42% using insulin [18]. Parallel values for maintaining A1c below 7% were 13% with metformin, 24% with a sulfonylurea, and 28% with insulin. Regardless of which agent was used as initial therapy, a progressive worsening of glycemic control arose, and this is because of continuing decrease of endogenous insulin production. A substudy embedded in the UK Prospective Diabetes Study compared early addition of basal insulin to a sulfonylurea with insulin alone and showed that after 6 years of treatment the combined regimen resulted in lower median A1c (6.6 vs. 7.1%) and also less major hypoglycemic events (1.6 vs. 3.2% annually) [19]. The UK Study investigators concluded that "the majority of patients need multiple therapies to attain these glycemic targets in the longer term" [18]. Moreover, combined therapy (insulin plus oral agents) is widely used and has been proved to be effective in successful glycemic control in many studies. The reason for using combined therapies is to minimize the dose of antihyperglycemic agents and thus their unfavorable adverse effects. The combined therapies enhance either the availability or effectiveness of endogenous insulin and glycemic stability with less hypoglycemia [19].

Furthermore, endogenous insulin secretion is more physiological than subcutaneous insulin injection; therefore, continuing glimepiride may remain valuable, partly through enhancing insulin secretion, in individuals with a long duration of diabetes and basal–prandial insulin therapy [20].

Another study carried by Standl *et al.* [21] suggested that flexible dosing with simple glimepiride/glargine regimens achieved significant and practically meaningful improvements in glycemic control, regardless of administration time and without differences in hypoglycemia. This flexibility should facilitate initiation of and adherence to insulin therapy and thus lead to improvements in glycemic control [21].

In our study, patients who failed to reach glycemic control with premixed insulin were evaluated after treatment with insulin glargine plus glimepiride for 6 months for its effectiveness and safety. At baseline, HbA1c levels in 80% of patients who failed premixed insulin had HbA1c levels more than 8.5%. Moreover, they experienced high rates of hypoglycemia in 7.14% of patients, and blood glucose fluctuation in 12.86% of patients.

There was a significant reduction in HbA1c levels, as mean percent reductions were 17.34 and 24.17% after 3 and 6 months of treatment, respectively ($P<0.001$). At visit 2, 187 (66.79%) patients experienced HbA1c reduction of 1% compared with baseline values, and 14 (5%) patients reached the target levels for HbA1c less than 7%, whereas at visit 3, 233 (83.51%) patients experienced HbA1c reduction by 1% compared with baseline values, and 68 (24.37%) patients reached the target levels for HbA1c less than 7%.

Regarding the mean FBG level, it decreased significantly after 3 months of treatment to reach 122.16±41.9 mg/dl and to finally reach 115.2 ±62.4 mg/dl after 6 month of treatment ($P<0.001$). The mean percent reductions at visit 2 and visit 3 were 44.37 and 47.54%, respectively. Regarding achieving target FBG (≤100 mg/dl), 75 (26.79%) patients achieved the target at visit 2, and this number increased at visit 3 to reach 90 (32.26%) patients. Regarding the patients weight, there were no significant differences between baseline and end of treatment which indicate that combined therapy did not result in long-term weight gain.

At the end of this study, the effects of therapy and glycemic control on the hematological indices were a significant increase in the mean hemoglobin level and red blood cells count with significant decrease in the mean platelet count ($P<0.001$) and no effect on the mean TLC. In addition, the mean concentration of serum glutamic oxaloacetic transaminase was significantly ($P<0.001$) increased, whereas the mean concentration of serum glutamic pyruvic transaminase was significantly ($P<0.001$) decreased. No significant change was observed in the mean concentration of serum creatinine level; the effect of therapy on cholesterol level and high-density lipoprotein was insignificant statistically, but was of clinical significance. Significant decrease was noticed in serum low-density lipoprotein from 140.48 ±41.684 ng/dl to 119.36±32.703 mg/dl at the end of the study ($P<0.001$).

Vital signs (systolic and diastolic blood pressure) and heart rate were significantly decreased ($P<0.001$) which is an indicator of lower risk of cardiovascular, hepatic, and renal complications of diabetes mellitus, which is consistent with previous studies [12].

As for observations, insulin glargine plus glimepiride was tolerated by patients. A total of 50 AEs were reported by 41 patients. Hypoglycemia was the most frequent reported AE. Moreover, 37 episodes of hypoglycemia were reported by 31 patients, of which nocturnal hypoglycemia represented 12 episodes. No SAEs were reported during this study.

Doses of glimepiride were significantly increased from mean dose of 3.62±1.39 mg at baseline to 5.09 ±1.88 mg at the end of the study ($P<0.001$). Moreover, doses of basal insulin were significantly increased from mean dose of 20.69±9.19 IU at baseline to 29.86±11.86 IU at the end of the study ($P<0.001$). Moreover, at the end of the study, number of patients who were on OAD (metformin) decreased from 56 patients to 15 patients. Dose of metformin was significantly increased from 1575.89±420.82 to 1880±508.78 mg ($P<0.001$).

Statistical results of this study showed an increase in the response to treatment from baseline to the end of the study and an increase in number of patients reaching the target of study at the end point; moreover, maintaining and increasing the doses of therapy will lead to a better response, as the dose of both insulin glargine and insulin glimepiride was increased at the end of the study significantly ($P<0.001$), which is consistent with other studies [12–14].

This study demonstrates that initiation of combination therapy of insulin glargine plus glimepiride improves glycemic control in patients with T2DM who were poorly controlled with premixed insulin before the observation period. Significant improvements ($P<0.001$) in both HbA1c and FBG were observed from the start to the end point of the study.

Conclusion

The study treatments showed that patients who failed premix with or without OAD (glimepiride plus metformin) and switched to insulin glargine in addition to glimepiride resulted in statistically significant ($P<0.001$) reduction in both HbA1c% and FBG values at 3 and 6 months of treatment. Regarding mean HbA1c%, reductions of −1.79 and −2.5% from baseline value were observed at visit 2 and visit 3, respectively. Moreover, mean FBG level at baseline demonstrated significant reductions ($P<0.001$) of −97.44 and −104.4 mg/dl at visit 2 and visit 3, respectively. There was no significant change in mean body weight between baseline visit and visit 3 ($P>0.05$). AEs were reported in 41 patients. Overall, 37 episode of hypoglycemia were reported by 31 patients during the study period, where nocturnal

hypoglycemia represented 12 episodes. No SAEs were reported during this study.

In conclusion, the results showed that a combination therapy of insulin glargine plus glimepiride markedly improved glycemic control in patients with T2DM, who failed premix with or without OAD. In addition, it was well tolerated with low rates of hypoglycemic events reported.

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Conflicts of interest
There are no conflicts of interest.

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