Full Length Research Paper

Registry on Monitoring the Effectiveness and Tolerability of Basal (Plus/Bolus) Regimen with Insulin Glargine and Insulin Glulisine in T2 Diabetes Mellitus Patients in Everyday Practice in Saudi

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Type 2 Diabetes Mellitus (T2DM) has emerged as a major global health problem and is one of the most common chronic diseases worldwide. The prevalence of T2DM in Kingdom of Saudi Arabia (KSA) population is high (23%) and has increased by 10% in just one decade. Usually addition of basal insulin is considered as the simplest way to start insulin therapy in patients uncontrolled on oral antidiabetic agents (OADs). In KSA, the majority of patients(60%) recommended to use insulin are treated with premixed insulin.Currently there is limited availability of local (KSA) data documenting the switch from premixed insulin to a basal insulin (Plus/Bolus) regimen. To monitor the effectiveness and tolerability of basal (Plus/Bolus) using Insulin glargine and Insuline glulisine in T2DM patients switched from premixed insulin for achieving the glycemic goal (Glycatedhaemoglobin - HbA1c) as targeted by the treating physician. Multicenter, non-interventional prospective product registry was conducted nationwide across KSA. Males and females aged ≥ 21 years, with type 2 diabetes mellitus, uncontrolled on premixed insulin with HbA1C>7 % and Fasting Blood Sugar >120 mg/dL were selected for this study. Changes in HbA1C from baseline to the end of 6 months and the mean number of hypoglycemic episodes experienced by each patient were measured. Out of 619 enrolled patients, 543 patients completed all study visits. There was statistically significant mean change in HbA1c (2.02%) at visit 3 as compared to baseline. Forty-three percent reduction in hypoglycemia incidence (number of patients experiencing at least one hypoglycemic event) and a 30% reduction in event rate from base line till end of 6 months was also seen in this study. In everyday clinical practice, patients with type 2 diabetes inadequately controlled on premixed insulins experienced significant improvements in glycemic control over 24 weeks after switching to a glargine-based insulin regimen. There was also a significantly lower risk of hypoglycemia and a favorable tolerability profile with this regimen. These findings support the use of a basal-bolus glarginebased regimen in T2DM patients poorly controlled on premixed insulins in KSA.

Keywords: T2DM, Insulin Glargine, Insulin Glulisine, KSA, registry.

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INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is mainly caused by reduced response of the body's cells to insulin or by an impairment of beta cell function. Both of these factors alone would still not cause diabetes, but in combination may lead to a disturbance of glucose homeostasis (Cerf et al., 2013). T2DM develops mainly after an age of 40 years and therefore was formerly known as adult-onset diabetes (ADA, 2009).

In addition to genetic predisposition other triggering factors could be diet rich in fats, obesity and lack of exercise (Stumvoll et al., 2005). In recent years, the age of the first occurrence of T2DM has increasingly shifted downwards in certain populations. T2DM has emerged to a major global health problem and is one of the most common chronic diseases worldwide. The prevalence of T2DM in KSA population has been confirmed as high (23%) and has increased by 10% in just one decade. Based on these epidemiological findings, the implementation of diabetes management strategies might be one option to efficiently restrain the disease (Al-Daghri et al., 2011). Type 2 diabetes is characterized by insulin resistance and progressive β-cell deterioration (Bagust et al, 2003). With declining β-cell function, most T2DM patients treated with oral agents, in monotherapy or combination, will require insulin therapy. Usually addition of basal insulin is considered as the simplest way to start insulin therapy in patients uncontrolled on OADs. Even patients, who are adequately introduced to insulin, might need prandial insulin to achieve or maintain individual glycemic targets over time. The therapy with premixed insulin is an effective option. However, it is frequently associated with increased hypoglycemic risk, fixed meal schedules, and weight gain. Therefore a novel approach known as "basal plus strategy" has been developed as an alternative. This therapeutic approach is based on the fact that a meal has the major impact on postprandial glucose values, and therefore increasing injections of prandial insulin are administered in addition at the beginning of the meal. In cases where this option does not provide enough control, an even more intensive basal-bolus therapy is necessary (Ampudia-Blasco et al., 2011).

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus for the management of diabetes is a call to action as it recommends changing antidiabetic treatment-regimen from one single therapy to combination treatment-regimen including Insulins when glycemic target HBA1c is 7% [the value above which there is an exponential increase risk of cardiovascular diabetes-related complications] is not reached (Nathan et al., 2009). The United Kingdom Prospective Diabetes Study (UKPDS) study showed that each 1% reduction in HbA1c is associated with a risk reduction of complications that is clinically and statistically significant (deaths from diabetes -21%, Myocardial Infarction -14%, microvascular complications -37% and peripheral vascular disorders -43%). In KSA, the majority ofpatients treated with insulin are on premixed insulin (almost 60%) (Stratton et al, 2000).Currently, availability of local data is limited which documents the switch from premixed insulin to a basal insulin (Plus/Bolus) regimen (KSU data, year?). So, the aim of the present study was to monitor the effectiveness and tolerability of basal (Plus/Bolus) using Insuline glargine and Insulin glulisine in T2DM patients switched from premixed insulin for achieving the glycemic goal (HbA1c) as targeted by the treating physician.

SUBJECTS AND METHODS

This multicenter, non-interventional prospective product registry was conducted nationwide across KSA. Both public and private hospital based physicians were selected to get the data across the kingdom and to reflect the real hospital based practice independently from the hospital type to identify the number of patients who consented to their participation or declined to participate. Males and females aged ≥ 21 years, with type 2 diabetes mellitus, uncontrolled on premixed insulin and having HbA1C>7 % and Fasting Blood Sugar >120 mg/dL were selected for the study. Patients recruited were those in whom the physician had decided to change premixed insulin regimen to basal (Plus/Bolus) regimen and kept metformin after switching from premixes to Insulin Glargine + Insulin Glulisine. Patients who were undergoing current temporary insulin treatment for gestational diabetes, pancreatic cancer, surgery etc. and those who had contra-indications to Insulin Glargine and/or Insulin Glulisineas given in the prescribing information/summary of product characteristics (SPC) were excluded from the study. Pregnant and lactating women were not included in the study. Patients who were participating in other studies were also excluded. Written informed consent form was obtained from each patient prior to participation in the study. Local ethics committee approvals were taken for each hospital before the start of the study. This registry was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments.

The registry was a non-interventional investigation and consequently the medical assessment and the treatment follow the routine of the treating physician. Data were

Table 1. Patient disposition and eligible population

Patient Disposition	N(%)
Total number of enrolled patients	619(100)
Total number of patients who completed Visit 2	560(90.5)
Total number of patients who completed Visit 3	543(87.7)
Total number of patients who did not complete the study	76(12.3)

Table 2. Patient Demographics

Demographics	mean ± SD
Age (years)	51.8 ± 10.6
Gender	
Male	65.4%
Female	34.6%
Weight (kg)	90.8 ± 22.0
Mean Duration of Diabetes since diagnosis (years)	11.1± 6.5
Previous treatment: Premixed Insulin (%)	100
Duration of Premixed Insulin Treatment (months)	38.3 + 35.4
METFORMIN (mg)	1581 ± 754
HbA1c at baseline (%)	10.0 ± 1.6
FBG at baseline (mg/dl)	229.7 ± 73.7
Hypoglycemia episodes in last 3 month prior to baseline visit:	
Number of patients with hypoglycemic episodes (%)	98 (15.8%)
Mean number of episodes per patient	2.5
Severe hypoglycemia episodes (n)	64

collected at baseline (visit 1, V1), at 3 months (V2), and at 6 months (V3). Glycated haemoglobin test (HbA1C), Fasting Blood Glucose (FBG) in mg/dL and Post Prandial Blood Glucose (PPBG) were tested at every visit.

Statistical analysis was performed using SAS version 9.2. Sample size was calculated with reference to two studies that tested the efficacy and safety of basal (Plus/Bolus) regimen with Insulin Glargine and Insulin Glulisine in T2DM patients in real-world practice (6,7), where a mean reduction of 0.37% in pre-meal and post-meal HbA1c was observed. A sample size of 755 T2DM patients was calculated to allow estimating a mean change from baseline in HbA1c of 0.51% at 6 months using a two-sided 95% confidence interval with a precision of 2.5%. The study recruited 619 patients from 34 centers in KSA. Primary outcome measures were HbA1c at baseline and at six months were assessed using paired T-test. A *P* value <0.05 was considered statistically significant.Change in FBG and PPBG were also assessed using paired T-test. Mean number of hypoglycemic episodes experienced by each patient and adverse drug reactions (ADR) were also collected to assess the safety of the products studied.

RESULTS

A total of 619 patients were enrolled in the study from 34 centers and were included in the final analysis of baseline variables (eligible population). Fifty-nine patients were excluded from efficacy analysis because of non-availability of HbA1c within specific duration; hence 560 patients were included for the analysis of primary and secondary endpoints of the study.543 patients completedall study visits. (Table 1). Mean age of the study participants was found to be 51.79 years. The majority of participants were males (65 %) as shown in Table 2.

Mean Weight of the study participants was 90.8 Kg. Mean duration of diabetes was found to be 11.1 years from first diagnosis with a maximum duration of diabetes up to 51 years and minimum duration of 2 years. (Table 2)

Mean Duration of Premixed Insulin treatment in months prior to baseline was 38.3 months with a maximum of 276 months and a minimum of 1 month. Mean dose of Metformin at baseline was 1581 mg.

Table 3. Diabetes complication and comorbidities

Diabetic Comorbidities	N(%)
Hypertension	357 (57.7%)
Dyslipidemia	391 (63.2%)
Diabetic Complications	**N (%)**
Diabetic Foot Ulcer	2(0.3%)
Diabetic Nephropathy	7(1.1%)
Diabetic Neuropathy	42(6.8%)
Diabetic Retinopathy	2(0.3%)
Ischemic heart disease(IHD)	47(7.6%)
Coronary artery bypass grafting (CABG)	3(0.5%)
Coronary Artery Disease(CAD)	1(0.2%)
Chronic Heart Disease(CHD)	3(0.5%)
Peripheral artery disease (PAD)	2(0.3%)
Peripheral vascular disease (PVD)	1(0.2%)
Chronic Renal failure or Chronic Kidney Disease or renal insufficiency	14(2.3%)
Fatty Liver	2(0.3%)
Microalbuminuria	4(0.6%)

Table 4. HbA1c, FBG and PPBG levels at baseline and subsequent visits

HbA1c (%)	Baseline visit	V2 visit	V3 visit
Mean (SD)	10.00±1.62	8.70±1.45*	7.98±1.52*
FBG (mg/dL)			
Mean (SD)	229.7±73.7	164.8±62.9*	141.5±55.9 *
PPBG (mg/dL)			
Mean (SD)	315.5±86.3	221.6±53.9*	188.4±50.4*

*p<0.05 using paired T-test

A total of 98 patients (15.8% of all participants) reported 251 episodes of symptomatic hypoglycemia within the last 3 months prior to baseline visit and the mean number of hypoglycemic episodes experienced per patient was 2.5 episodes. Out of the 251 symptomatic hypoglycemia reported, 64 episodes were severe of which 3 episodes (1.2%) were associated with coma/loss of consciousness, 2 episodes (0.8%) were associated with seizures, 24 episodes (9.5%) required hospital visit and 35 episodes (13.9%) were leading to absence of work as seen in Table 2.

Dyslipidemia was found more frequently (63.2%) than hypertension (57.7%) as the co-morbid conditions with diabetes. Among other associated illnesses diabetic complications were separately assessed. Diabetic neuropathy (6.8%) and ischemic heart disease (7.6%) were found to be the most common late complication of diabetes, followed by chronic renal failure (2.3%) and diabetic nephropathy (1.1%). Other late complications included chronic heart disease, peripheral vascular diseases, diabetic foot ulcer, diabetic retinopathy, fatty liver and microalbuminuria (Table 3).

Mean change in HbA1c at V3 compared to baseline was 2.02%, which was found to be statistically significant when paired T-test was used to compare the mean values of HbA1c at these visits. Mean change in HbA1c at V2 compared to baseline visit was noticed as 1.3%, which was also found to be statistically significant (p=0.001) using paired T-test. Mean change in HbA1c between visit 2 and visit 3 (0.72%) was also found to be as statistically significant (p= 0.001) as seen in tTable 4 and f Figure 1.

Mean change in FBG at V3 compared to baseline was 88.2 mg/dL, which was found to be statistically significant when paired T-test was used to compare the mean values of FBG at these visits (p=0.001). Mean change in FBG at V2 compared to baseline visit was noticed as 64.9 mg/dL, which was also found to be statistically significant (p=0.001). Mean change in FBG between visit 2 and visit 3 (23.3 mg/dL) was also found to be statistically significant (p=0.001).Mean change in PPBG at V3 compared to baseline was 127.15 mg/dL, which was found to be statistically significant (p=0.001). Mean change in PPBG at V2 compared to baseline visit was
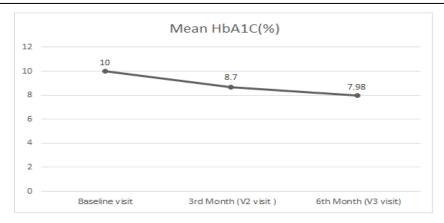
Mean HbA1C(%)

Figure 1

Mean Blood Glucose Levels

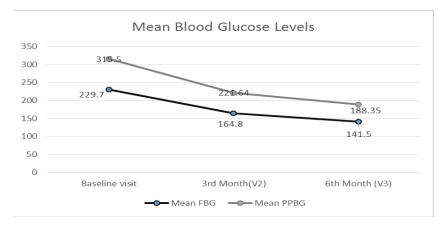Figure 2

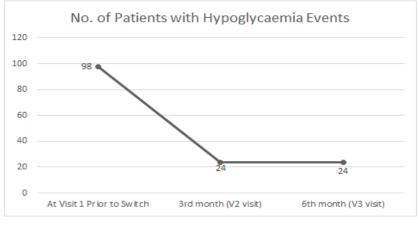**No. of Patients with Hypoglycaemia Events**

Figure 3

noticed as 93.9 mg/dL, which was also found to be statistically significant (p-value 0.001). Mean change in PPBG between visit 2 and visit 3 (33.25 mg/dL) was also found to be statistically significant (p=0.001) (Figure 2).

One of the secondary objectives of the study was to assess the safety of the glargine based regimens including the hypoglycemia and adverse events reported during the observational period. Symptomatic

Table 5. Hypoglycemic episodes prior and during the study

Variables	At Visit 1 Prior to Switch N (%)	V2 visit N (%)	V3 visit N (%)
No. of Patients with Hypoglycaemia Events	98(15.8)	24(3.9)	24(3.9)
No. Of Hypoglycaemia Events	251	38	37
Severity			
Mild	187*	36	30
Moderate	-	1	7
Severe	64	1	0

*Severity of mild/moderate episodes cannot be assessed from baseline data (reflecting 3 months before the study)

Table 6. Change in dosage levels of Insulin and Metformin from Baseline to End of Study

Variables	Baseline visit (starting dose)	V2 visit	V3 visit
Mean InsulinGlargine dose (U/day)	33.63±14.55	37.83±15.35	40.08±18.47
Mean insulin Glulisine dose (U/day)	37.46 ± 19.11	44.74 ± 22.89	47.00 ± 25.72
Mean Metformin Dose	1668.89 ± 722.42	1710.11 ± 771.5	1726.05 ± 754.77

hypoglycemia was defined on the basis of severity as mild; BG<70 mg/dl along with autonomic symptoms (tremors, palpitations, sweating, and excessive hunger), moderate; defined as BG between 70 mg/dl and 36 mg/dl along with autonomic and later signs of hypoglycemia which are neuroglycopenic symptoms (headache, mood changes, irritability, parasthesia, visual disturbances, confusion, difficulty speaking). Severe episodes were defined as an event with symptoms of hypoglycemia for which the patient required the assistance of another person and was associated with either a blood glucose (BG) level <35 mg/dL or a prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

As per the collected data in the current study, 98 patients (15.8%) reported prior history of symptomatic hypoglycemia with a total of 251 hypoglycemia episodes (3 months prior baseline). Sixty-four of these episodes were classified as severe hypoglycemic episodes with BG <36 mg/dL requiring hospitalization and loss of work day. There were a total of 75 hypoglycemic episodes recorded in 48 participants (7.8%) after switching to basal insulin glargine based treatment from baseline (V1) until end of observational period at month 6 (V3). For 42 patients (6.7%) recurrent hypoglycemia was reported at both 3 and 6 months (visit 2 and visit 3). Thirty-eight hypoglycemic episodes were reported at month 3 (Visit 2) in 24 patients and 37 hypoglycemic episodes were reported at month 6 in 24 patients. The majority of episodes were mild (66), 8 were moderate and only 1 (0.2%) was severe. Twenty-two episodes of hypoglycemia were related to Insulin Glargine and 52 episodes were related to Insulin Glulisine. One hypoglycemic episode was not related to either of the insulins (Table 5).

A non-statistically significant mean body weight change of 0.51 kg from baseline to 6 months was observed.

Regarding the diabetes treatment regimen, Insulin Glargine was initiated at at a mean daily dose of 33.63 U at baseline and the dose was increased to a mean daily dose of 37.83 U at 3 months and to 40.08 U at 6 months. Insulin Glulisine was commenced at a mean daily dose of 37.46 U at baseline and increased to a mean daily dose of 44.74 U at 3 months with a slightly further increase to 47.00 U per day at 6 months. Concomitant metformin medication was maintained stable during the study with a mean daily dose of 1668 mg at baseline and 1710 mg and 1726 mg at 3 and 6 months, respectively. (Table 6)

Thirty-two adverse events (5.2%) were reported during baseline to Visit 3. Thirteen(2.1%) were related to study products and 19 were unrelated to study Products. Among the 13 adverse events (AE) due to study products 4(0.6%) were possibly related to Insulin Glargine and 9(1.5%) were possibly related to Insulin Glulisine. Twelve of the 13 AEs were hypoglycemia episodes and one was a case of itching possibly related to Insulin Glulisine. One patient was withdrawn from the study due to intracranial hemorrhage post-surgery, which was not related to study products.

DISCUSSION

The progressive nature of T2DM requires insulin therapy to achieve and maintain good metabolic control. However, there are barriers for initiating insulin (including fear of hypoglycemia, fear of multiple injections, and weight gain). The new generation of insulin analogs enables many of these barriers to be overcome but the best method of initiating insulin remains a subject of

debate. Premixed insulins combine long- and short-acting insulins in a single preparation injected once or twice daily. They do not mimic physiological insulin profiles and are relatively inflexible; although newer analog mixtures may offer a closer equivalent (optimizing fasting blood glucose levels with premix, even the newer analog mixtures, may result in an increased risk of hypoglycemia and may not provide enough flexibility for patients to achieve optimal glycemic control). Furthermore, there is little information available regarding next-step therapeutic strategies for patients with inadequate glycemic control with premix.Insulin glargine was the first long-acting basal insulin analog for once-daily administration (Rosenstock et al., 2005). In patients with T2DM, glargine is associated with a lower risk of hypoglycemic events versus NPH insulin with at least equivalent glycemic control (Levin et al., 2011). The relentless, progressive nature of Type 2 diabetes results in an almost inevitable need for insulin supplementation and its intensification in an attempt to combat a worsening glycemic profile (Stolar et al, 2010; Stratton et al, 2000)including glycemic variability (Turnbull et al., 2009) and the associated increased risk of vascular complications (Stolar et al., 2010; Stratton et al., 2000; Turnbull et al., 2009; Huxley et al., 2006). Deteriorating glycemic control with disease progression is now understood to follow a sequence from an initial inadequacy in prandial glycemic control through to the addition of fasting hyperglycemia. This process usually begins with excess postprandial hyperglycemia during daytime, followed by fasting hyperglycemia because of increasing hepatic glucose production overnight, culminating in sustained hyperglycemia (Monnier et al., 2007). In T2DM patients, with time, oral anti-diabetic agents usually lose their effectiveness and patients need to seek exogenous insulin therapy. Generally, implementation of a successful insulin therapy requires three stages of treatment, which are insulin initiation, optimization and intensification (MEMS, 2011). For insulin intensification, when glycaemia is not achieved after the initiation and optimization of insulin, numerous recommendations exist in various guidelines for the selection of a second-line insulin regimen. Insulin therapy initiation with basal insulin or a premixed insulin regimen, has been recommended in several local and international practice guidelines as well as publications (Home et al., 2008; Kanatsuka et al., 2012; Lasserson et al., 2009; Mastura et al., 2011). However, for insulin intensification, when normo-glycaemia is not achieved after insulin initiation, various intensification recommendations exist, although there is no clear strategy for the selection of the second-line insulin regimen (Riddle et al., 2005). Among the recommendations for insulin intensification, switching to an intensified premixed insulin regimen (Gumprecht et al., 2009; Jang et al., 2008; Rosenstock et al., 2008). Basal-plus insulin regimen (Lankisch et al., 2008; Monnier et al., 2006; Raccah et al., 2007) or Basalbolus

insulin regimen (Herman et al., 2005) may be included.This study demonstrated the efficacy and safety of insulin glargine initiation and maintenance in T2DM patients poorly controlled on premixed insulins.

The study investigated glycemic control and safety in 619 patients switching from premixed insulin (premix) with or without (OADs) to once daily Glargine (OADs/prandial insulin). A 24-week, national, multicenter (34 centers), study, HbA1c levels significantly improved in the overall group (10.00 to 7.98; p < 0.001); fasting blood glucose levels also improved (229.7 to 141.5 mg/dL; p < 0.001). There was only singel incidence of severe hypoglycemia. The addition of prandial (OD, BD or >BD) insulin was associated with further improvements in glycemic control.

Hypoglycemic episodes were reduced around 49% from baseline till 3 months (78 episodes at baseline and 38 episodes after 3 months). The results from this analysis showed that in everyday clinical practice, switching to a basal-bolus glargine-based insulin regimen improves glycemic control in patients with type 2 diabetes inadequately controlled on a premix-based insulin regimen with less risk of hypoglycemia. The overall mean decrease in HbA1c was 1.99% observed 24 weeks after switching to a glargine-based regimen.

These findings are supported by data from other observational studies in patients with type 2 diabetes switching from premix to glargine-based regimen (Hammer et al., 2007; Schiel et al., 2007; Davis et al., 2008) and by a randomized comparison of a premix-based regimen versus a glargine-based regimen in patients with diabetes type 2 previously treated with a glargine-based regimen plus OADs (Stratton et al., 2000).

The UKPDS showed that a 1% reduction in HbA1C was associated with a 14% reduction in myocardial infarction, a 14% reduction in all-cause mortality and a 37% reduction in microvascular complications (Rosenstock et al., 2008). Therefore, the reduction in HbA1C of 2.00 % observed in the overall population, achieved by switching to an insulin glargine-based regimen can be considered clinically meaningful as these results may translate to long term clinical outcomes benefits.

Current evidence demonstrates that the basal-plus strategy provides a graduated advancement of insulin therapy based on individual requirements. This approach has been shown to be effective and accompanied by low rates of hypoglycemia and minimal weight gain. The basal-plus approach to insulin intensification in persons with Type 2 diabetes seems to be a promising alternative to the current options of either twice-daily premixed insulin or a full basal–bolus strategy, thereby providing a viable intermediate step between basal only and basal–bolus strategies, as recommended in the latest version of the ADA/EASD consensus guidelines. The basal-plus strategy is potentially suitable for a large number of individuals with Type 2 diabetes, and may delay their

progression to a full insulin replacement regimen, especially when the initiation of insulin therapy is not delayed. The results presented here demonstrate that patients with T2DM poorly controlled on premix can safely achieve improved glycemic control by transferring to a Glargine-based regimen (OADs). Optimization of FBG levels makes an important contribution to overall glycemic control, particularly if the HbA1c is greater than 8.4% (Benson et al., 2000).

The limitations of the study include its non interventional observational nature and lack of a control group, and the relatively short duration of follow-up, which might limit the generalizability of our results. A broader population and longer period of observation might have further supported our results. However, randomized controlled trials (RCTs)are also limited due to their strict inclusion/exclusion criteria. Thus, there is a need for registry studies designed to simulate real-life non-research settings.

In conclusion, In everyday clinical practice, patients with type 2 diabetes inadequately controlled on premixed insulins experienced significant improvements in glycemic control over 24 weeks after switching to a glargine-based insulin regimen with a significantly lower risk of hypoglycemia and a favorable tolerability profile. These findings support the use of a basal-bolus glargine based regimen in T2DM patients poorly controlled on premixed insulins in Saudi Arabia.

ACKNOLEDGEMENTS

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