Original Article

Real-world Clinical Effectiveness on Glycaemic Parameters, Safety and Additional Benefits of Glargine U300 (Toujeo®) Initiation after Oral Antidiabetic Drug Failure in Insulin-naïve Patients with type 2 Diabetes Mellitus

Sanjay K. Shah, Mridul Bera[1], Guru Prasad Bhattacharya[2], Shambo Samrat Samajdar[3], Shatavisa Mukherjee[3]

Departments of Endocrinology, [1]Internal Medicine, [2]Consultant Physician, Narayana Super Specialty Hospital, Howrah, West Bengal, [3]Department of Clinical Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India

Abstract

Background: Several studies have proved the advantages of second-generation insulin analogs in lowering intra-individual variability in plasma insulin levels, flexibility in dosing, a sustained glucose-lowering effect, and decreasing the risk of hypoglycemia. Glargine 300 is one of the newer second-generation basal insulin analogs to have been approved for both type 1 and 2 diabetes. The present study aims to assess the real-world clinical effectiveness and safety of Glargine U300 (Toujeo®) initiation after oral antidiabetic drug failure in insulin-naïve patients with T2DM. **Methods:** A prospective, observational study was conducted where participants were interviewed regarding their basic demographics, body weight, and treatment details. Glycemic parameters (HbA1C%, Fasting Plasma Glucose, and Post Prandial Blood Glucose) were observed in the initial 6 months, and changes were noted and compared. Any hypoglycemic events or other complications were also noted. Data collected were statistically analyzed. **Results:** The study included a total of 188 patients. Treatment with glargine 300 significantly reduced the mean HbA1C level from 9.78% at baseline to 7.90% at the end of 6 months of treatment ($p < 0.001$). 10.60% of patients achieved the glycemic target of ≤7.0% by the end of 6 months, while only 6.90% were within the target range at baseline. Similarly, significant reduction in FPG was observed at the end of 6 months treatment period with Glargine U300. A significant increase in dose requirement was observed throughout the study phase ($p < 0.001$). Incidence of hypoglycemia was noted in 2.12% of subjects. **Conclusion:** The lower incidence statistics of hypoglycemia coupled with sustained positive glycemic effects, stands out to be a prominent advantage of Glargine U300 over its other congeners.

Keywords: Effectiveness, Glargine U300, safety, type 2 diabetes mellitus

Introduction

With the skyrocketing prevalence of diabetes worldwide, diabetes is now a major public health concern, which is posing a significant burden on healthcare resources. According to data from 2019, around 463 million people are suffering from diabetes worldwide, with the figure expected to reach up to 700 million by 2045.[1] At such a juncture, optimal glycemic control is extremely important to achieve death reduction owing to macro and microvascular complications. Insulin has been the mainstay treatment which has been considered the most effective diabetes treatment weapon. While type 1 diabetes mellitus (T1DM) patients require multiple daily injections of prandial bolus insulin and basal insulin or continuous subcutaneous insulin infusion via the pump, in type 2 diabetes mellitus (T2DM) patients, basal insulin is considered as second-line therapy for patients uncontrolled with oral antidiabetic drugs (OADs) or as first-line combination therapy in patients with very poor glycemic control.[2]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_57_23

Address for correspondence: Ms. Shatavisa Mukherjee, Department of Clinical Pharmacology, School of Tropical Medicine, Kolkata – 700 073, West Bengal, India.
E-mail: shatavisa100@gmail.com

Submitted: 10-Feb-2023 **Revised:** 25-Mar-2023
Accepted: 22-Apr-2023 **Published:** 30-Oct-2023

How to cite this article: Shah SK, Bera M, Bhattacharya GP, Samajdar SS, Mukherjee S. Real-world clinical effectiveness on glycaemic parameters, safety and additional benefits of Glargine U300 (Toujeo®) initiation after oral antidiabetic drug failure in insulin-naïve patients with type 2 diabetes mellitus. Indian J Endocr Metab 2023;27:426-30.

Some significant barriers to insulin usage are concerns regarding hypoglycemia, frequency of injection, and weight gain. Patients' fear of hypoglycemia is one of the most important concerns in insulin therapy, which could be responsible for the lack of adherence and the development of clinical inertia. This is responsible for developing a loss of glycemic control.[3,4] A majority of healthcare providers have indicated that they would manage diabetes more aggressively if there was no fear of hypoglycemia.[5] Due to suboptimal up-titration of the insulin dose following insulin initiation majority of them fail to achieve glycemic control. Fear of hypoglycemia or weight gain is mainly responsible for this. How to make insulin therapy safer and more effective for diabetics is the key research question in the field of insulin research and development. Lower intraindividual variability, flexibility in dosing, and sustained glycemic control without an increased risk of hypoglycemia are important advantages offered by newer basal insulin formulations.[6,7]

Recently introduced second-generation basal insulin analogs [for e.g., insulin glargine 300 U/mL (Gla-300) and insulin degludec] claim to have improved pharmacokinetic profiles with an intention to deliver steady insulin levels over a much longer period. Several randomized controlled and real-world studies have proven the resultant advantages of second-generation insulin analogs in lowering intra-individual variability in plasma insulin levels, flexibility in dosing, a sustained glucose-lowering effect, and decreasing the risk of hypoglycemia. Gla-300 is one of the newer second-generation basal insulin analogs to have been approved for both type 1 and 2 diabetes.[8,9] The present study thus aims to assess the real-world clinical effectiveness and safety of Glargine U300 (Toujeo®) initiation after oral antidiabetic drug failure in insulin-naïve patients with T2DM.

Methods

A prospective, observational study was conducted on insulin-naïve adults with type 2 diabetes who have been prescribed basal insulin treatment with Glargine U300 in Out Patient Department basis in a real-world setting. Permission for the conduct of the study was obtained from the institutional ethics committee (HREC-AARC/20). Written informed consent was obtained from the eligible participants, prior to inclusion into the study. The total study duration was 9 months, with 3 months of recruitment phase and a follow-up period of further 6 months respectively. Adult T2DM patients of either sex, uncontrolled on OADs or GLP-1 receptor agonists were included in the study. Those with HbA1C <7.5% or >11% at screening, or T2DM patients who have received any form of insulin in the last 1 year, or pregnant or lactating mothers, or having the end-stage renal disease (defined as estimated GFR <15 mL/min/1.73 m^2) or being on hemodialysis, or any contraindication to use of Gla-300 according to the National Product labeling; history of hypersensitivity to the active substance or to any of the excipients of Glargine U300, respectively were excluded.

Eligible patients were included for participation only if they consented to be a part of the study and provide written informed consent. Included participants were interviewed regarding their basic demographics. Body weight and treatment details were noted and observed for any changes in at Month 1, 2, 3, 4, 5, and 6 respectively. Glycemic parameters (HbA1C%, Fasting Plasma Glucose, and Post Prandial Blood Glucose) were noted for all time points. Any hypoglycemic events or other complications were noted.

The data collected was checked for completeness and analyzed using standard statistical software. Descriptive data were represented as mean or percentages. Different levels were expressed at a 95% Confidence Interval. A *P* value of less than 0.05 was considered statistically significant. Mean or median values were compared with hypothesis testing and correlation Analysis was attempted for various grades and scores obtained through prior analysis of data wherever applicable. All statistical analysis for various measures was performed using various statistical software packages like Statistical Package for the Social Sciences (Windows version 21.0; SPSS Inc, Chicago [IL], USA) and Microsoft Excel.

Ethical Clearance Statement

The study was approved by the Human Research Ethics Committee – AARC, Kolkata vide HREC-AARC/20 on 14.07.2022. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follow the guidelines laid down in the Declaration of Helsinki (1964).

Results

The study included a total of 188 patients, with a sex ratio of 1:1.05 (M:F). The mean age of the study population was 56.13 ± 14.45 years. 54.25% of study subjects were without any comorbid conditions. Comorbidities noted were mainly hypertension, chronic kidney disease, and hyperlipidemia observed in 38.29% (n = 72), 32.97 (n = 62), and 26.59% (n = 50) respectively.

Effectiveness analyses included changes in HbA1c, FPG, PPBG, and daily basal insulin dose from baseline to the end of 6 months' treatment. Treatment with glargine 300 significantly reduced the mean HbA1C level from 9.78% at baseline to 7.90% at the end of 6 months of treatment ($p < 0.001$). 10.60% of patients (n = 20) achieved the glycemic target of HbA1C ≤7.0% by the end of the treatment period, while only 6.90% (n = 13) patients were within the target HbA1C range at baseline. Similarly, significant reduction in FPG was observed at the end of 6 months treatment period with Glargine U 300. The mean FPG level reduced from 238.53 mg/dl at baseline to 113.19 mg/dl by the end of 6 months of treatment ($p < 0.001$). 84.6% of patients (n = 159) achieved the glycemic target of FPG ≤130 mg/dL by the end of the treatment period, while only 11.20% (n = 21) patients were within the target FPG range at baseline. [Table 1 and Figure 1].

Table 1: Effectiveness of Glargine U300 on Glycaemic Parameters

	Mean±SD (95% CI)	Mean Change from Baseline	*P*
Glycosylated Hemoglobin (in %)			
Baseline	9.78±1.35 (9.59–9.97)		
3rd Month	8.69±1.03 (8.54–8.84)	1.09±0.71	<0.001
6th Month	7.90±0.75 (7.79–8.00)	1.88±0.98	<0.001
Fasting Plasma Glucose (in mg/dl)			
Baseline	238.53±89.65 (225.71–251.34)		
2nd Month	178.91±59.03 (170.47–187.35)	59.62±66.65	<0.001
3rd Month	144.16±32.09 (139.57–148.75)	94.37±76.63	<0.001
4th Month	129.68±24.40 (126.19–133.17)	108.85±80.33	<0.001
5th Month	120.77±22.70 (117.52–124.01)	117.76±85.69	<0.001
6th Month	113.19±19.76 (110.36–116.01)	125.34±87.18	<0.001
Post Prandial Plasma Glucose (in mg/dl)			
Baseline	339.13±129.55 (320.61–357.65)		
2nd Month	280.03±97.35 (266.11–293.95)	59.10±65.06	<0.001
3rd Month	221.71±55.30 (213.80–229.61)	117.41±91.82	<0.001
4th Month	187.37±32.73 (182.69–192.05)	151.76±107.34	<0.001
5th Month	168.94±23.09 (165.64–172.24)	170.19±120.48	<0.001
6th Month	156.23±19.68 (153.42–159.04)	182.90±128.06	<0.001
Insulin Dose (in Units)			
Baseline	16.82±5.70 (16.00–17.63)		
2nd Month	17.71±5.86 (16.87–18.55)	0.89±1.93	0.1363
3rd Month	18.26±6.10 (17.39–19.13)	1.44±2.97	0.0185
4th Month	18.70±6.48 (17.77–19.63)	1.88±4.12	0.003
5th Month	19.16±7.15 (18.14–20.18)	2.35±4.83	<0.001
6th Month	19.49±7.26 (18.45–20.53)	2.67±5.41	<0.001
Weight (in kg)			
Baseline	64.39±12.60 (62.59–66.19)		
2nd Month	64.37±12.55 (62.58–66.16)	0.02±0.22	0.9877
3rd Month	64.29±12.46 (62.58–66.16)	0.10±0.45	0.9384
4th Month	64.15±12.40 (62.38–65.92)	0.25±0.76	0.8524
5th Month	64.08±12.34 (62.32–65.84)	0.31±0.96	0.8097
6th Month	63.69±12.09 (61.96–65.42)	1.38±7.07	0.5829

In assessing the contribution of Glargine U300 in reducing 2 hours postprandial blood glucose (PPBG), the mean levels reduced from 339.13 mg/dl at baseline to 156.23 mg/dl at the end of 6 months ($p < 0.001$). The daily basal insulin dose gradually increased from baseline to the endpoint (6th month). The mean daily basal insulin requirement stepped from 16.82 units at baseline to 19.49 units at the 6th month. A significant increase in dose requirement was observed throughout the study phase ($p < 0.001$) [Table 1].

No significant change in body weight was noted throughout the various time points in the study or by the end of the study period. The mean body weight of the population was recorded as 64.39 kgs at baseline, which maintained the level to 63.39 kgs after 6 months of treatment. ($p = 0.5829$) [Table 1]. The mean drop in glycemic indices was represented graphically in Figure 2.

Of the total study population, biguanides were used by 89.89% (n = 169) study population, followed by Sulfonylureas by 85.64% (n = 161), thiazolidinediones by 20.74% (n = 39) and alpha-glucosidase inhibitors by 3.19% (n = 6) study population.

Incidence of hypoglycemia was noted in 4 cases, accounting for 2.12% of the study population [Figure 3]. Severe hypoglycaemia was not noted in any cases, all cases of hypoglycemia were self-managed, and did not necessitate hospitalization. No incidence of nocturnal hypoglycemia was however noted. No other safety concerns were noted during the study.

Discussion

Due to the progressive loss of β-cell function, insulin initiation is extremely crucial for many patients with T2DM. Insulin, either alone or in combination with other OADs in unstable T2DM or acutely decompensated patients; is recommended. Early initiation and short-term use of insulin could be associated with long-term benefits and optimum glycemic control in the early part of diabetes. It would produce legacy effects and good metabolic memory.[10] For the maintenance of blood glucose at a consistent level during fasting periods, basal insulin is required. Sustaining physiologic insulin levels between meals and mitigating the risk of hypoglycemia, particularly at night

are two primary goals of basal insulin therapy. Commencement of insulin therapy is required when a combination of ≥3 OAD fails to reach optimal glycemic control. A combination of basal insulin and OADs could be utilized as an effective regimen in first-line insulinization.[11] They exhibit longer duration, flatter action profiles, lower risk of severe and nocturnal hypoglycemia, and less glycemic variability, compared to older basal insulins. Chronic sustained hyperglycemia and glycemic variability both contribute to diabetic cardiovascular complications causing excessive protein glycation and oxidative stress.[12] Insulin glargine is an acidic solution that forms microprecipitates following its subcutaneous administration from which dissolution slowly occurs. Insulin glargine concentration was thought to be inversely related to this redissolution rate, and with this viewpoint, insulin glargine 300 units/mL was developed to provide more consistent insulin absorption and a longer duration of action than its predecessor, glargine 100 units/mL.[13]

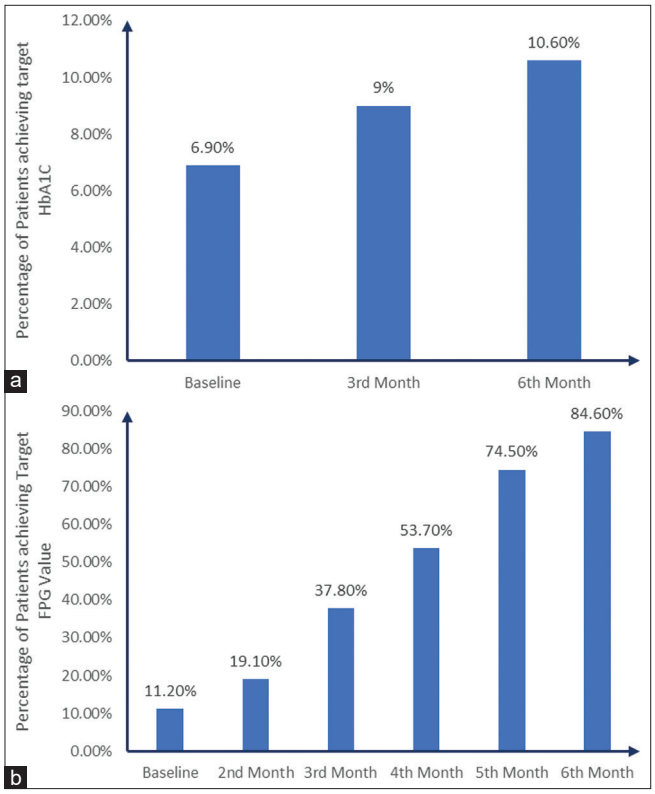

Figure 1: Proportion of Patients achieving the target glycaemic control in terms of (a) HbA1C (b) FPG

The present study focused on the effectiveness and safety of Glargine U 300 (Toujeo®) initiation after oral antidiabetic drug failure in insulin-naïve patients with T2DM. The study assessed the effects of Glargine U300 in a cohort of 188 patients, where a significant decrease in glycemic indices like HbA1C, fasting, and post-prandial glucose was noted throughout the study timeframe. Significant dose intensification by the end of the study period was observed. 10.60% and 84.6% of patients achieved glycemic targets of HbA1C and fasting glucose respectively. Incidence of hypoglycemia was noted in only 2.12% of the study population, with no incidence of nocturnal hypoglycemia.

In the DELIVER-2[14] and DELIVER-3[15] studies, Gla-300 showed greater improvements in glycemic control and

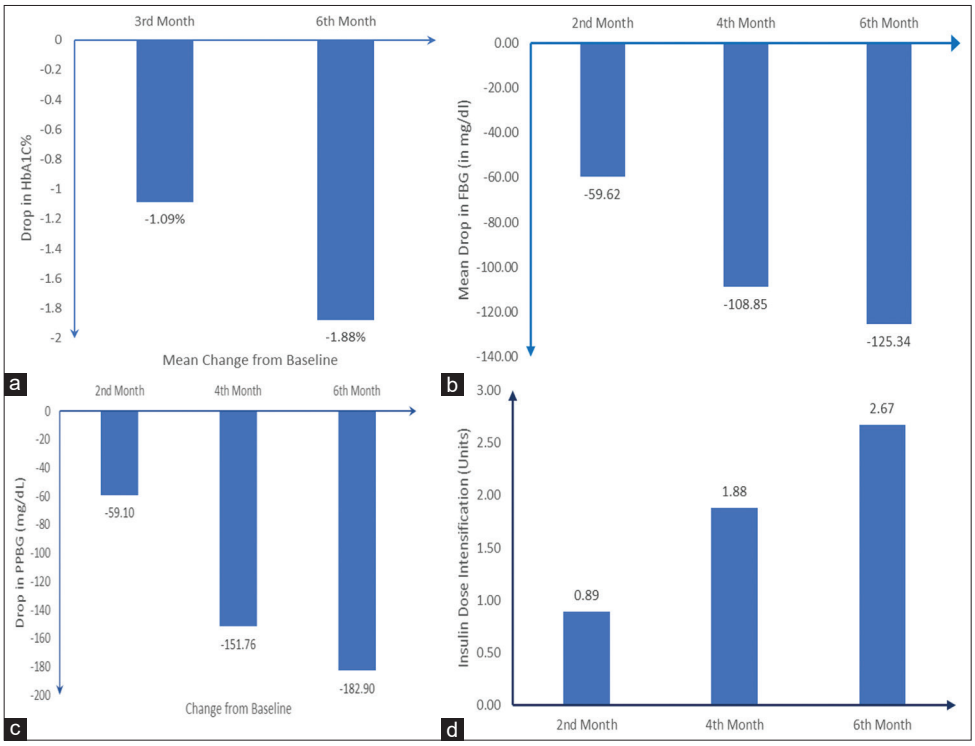

Figure 2: Mean change from baseline for (a) HbA1C (b) FPG (c) PPPG (d) Insulin Dose

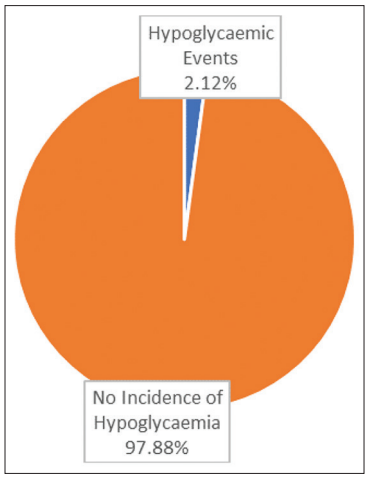

Figure 3: Incidence of Hypoglycaemia

reduced the risk of hypoglycemia in T2D on switching from Gla-100. Similar effects were found with the insulin degludec switching as observed in the prospective real-world study conducted by Fadini *et al*., in which the switch to degludec from another basal insulin was significantly associated with lower rates of hypoglycemia and improved glycemic control.[16] The effectiveness of Gla-300 in real-world settings is thus of paramount importance. The present study depicted acceptable effectiveness and safety profile with Gla-300.

However, there exist a few limitations of this study. The absence of a comparator group in the study challenges the generalizability of the results. Matched population cohort design can also help to get a better glimpse of the real-world effectiveness of the Gla-300 in subgroup populations. Continuous glucose monitoring data would have helped to understand the variability in-depth. Future research should try to overcome these limitations.

Conclusion

As a second-generation basal insulin analog, insulin glargine 300 U/mL (Gla-300) proves to be both an effective and safe option in the treatment of T2DM patients after oral antidiabetic drug failure in insulin-naïve patients. The lower incidence statistics of hypoglycemia coupled with sustained positive glycemic effects stands out to be a prominent advantage of Glargine U300 over its other congeners.

Financial support and sponsorship

The study received a financial grant from the Howrah Diabetes Society for its due conduct.

Conflicts of interest

There are no conflicts of interest.

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, *et al*. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843. doi: 10.1016/j.diabres. 2019.107843.
2. Silver B, Ramaiya K, Andrew SB, Fredrick O, Bajaj S, Kalra S, *et al*. EADSG guidelines: Insulin therapy in diabetes. Diabetes Ther 20189:449-92.
3. Weinger K, Beverly EA. Barriers to achieving glycemic targets: Who omits insulin and why? Diabetes Care 2010;33:450-2.
4. Ahrén B. Avoiding hypoglycemia: A key to success for glucose-lowering therapy in type 2 diabetes. Vasc Health Risk Manag 2013;9:155-63.
5. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational global attitudes of patients and physicians in insulin therapy study. Diabet Med 2012;29:682-9.
6. Ovalle F, Segal AR, Anderson JE, Cohen MR, Morwick TM, Jackson JA. Understanding concentrated insulins: A systematic review of randomized controlled trials. Curr Med Res Opin 2018;34:1029-43.
7. Chun J, Strong J, Urquhart S. Insulin initiation and titration in patients with type 2 diabetes. Diabetes Spectr 2019;32:104-11.
8. Cheng A, Bailey TS, Mauricio D, Roussel R. Insulin glargine 300 U/mL and insulin degludec: A review of the current evidence comparing these two second-generation basal insulin analogues. Diabetes Metab Res Rev 2020:e3329. doi: 10.1002/dmrr. 3329.
9. Ghosh S, Ghosh R. Glargine-300: An updated literature review on randomized controlled trials and real-world studies. World J Diabetes 2020;11:100-14.
10. Samajdar SS, Mukherjee S, Tripathi SK, Joshi SR, Pal J, Joshi SR. Early initiation of insulin therapy in newly diagnosed patients with type 2 diabetes and exploring the legacy effect—A single-arm prospective observational study. Bengal Physician J 2020;7:52–4.
11. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): An open randomised controlled trial. Lancet 2008;371:1073-84.
12. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res 2010;107:1058-70.
13. Dunn CJ, Plosker GL, Keating GM, McKeage K, Scott LJ. Insulin glargine: An updated review of its use in the management of diabetes mellitus. Drugs 2003;63:1743-78.
14. Zhou FL, Ye F, Berhanu P, Gupta VE, Gupta RA, Sung J, *et al*. Real-world evidence concerning clinical and economic outcomes of switching to insulin glargine 300 units/ml vs other basal insulins in patients with type 2 diabetes using basal insulin. Diabetes Obes Metab 2018;20:1293–7.
15. Bailey TS, Wu J, Zhou FL, Gupta RA, Menon AA, Berhanu P, *et al*. Switching to insulin glargine 300 units/mL in real-world older patients with type 2 diabetes (DELIVER 3). Diabetes Obes Metab 2019;21:2384–93.
16. Fadini GP, Feher M, Hansen TK, de Valk HW, Koefoed MM, Wolden M, *et al*. Switching to degludec from other basal insulins is associated with reduced hypoglycemia rates: A prospective study. J Clin Endocrinol Metab 2019;104:5977–90.