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PAKISTAN INSULIN STUDY (PINS) GLYCEMIC VARIABILITY AND EFFICACY OF NEW INSULINS IN TYPE 2 DIABETES

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ABSTRACT

Introduction: Type 2 diabetes is alarmingly increasing all over the globe. The oral anti diabetics and old insulins are frequently used by patients and doctors but exhibited high glycemic variability and more side effects profile. The newer insulins are better in term of reducing future complications.
Objective: To evaluate and assess the glycemic variability of new insulins in type 2 diabetes mellitus attended OPD of Liaquat University Hospital Hyderabad / Jamshoro Sindh, Pakistan
Study Design& duration: Randomized control trial.
Study Setting: OPDs of Liaquat University Hospital Hyderabad / Jamshoro Pakistan
Duration of Study: September 20 2023to January 2024
Methodology: All patients with type 2 DM for at least 4 years duration, already taking mixed insulin with or without Oral antidiabetic with age limit from 30-59 years of either gender were randomized by open clinical random software. Three insulin, Glargine 100, Glargine 300 and degludec have been studied. The glycemic variability of <50mg /dl and reduction in HbA1c of at least ≥0.5% from the baseline, at 3 months was considered as less glycemic variability and efficacious.
Results: Of 76 patients, the mean age was 41.24 ±4.89 years. There were 40 (66.7%) females and 36 (33.3%) males. The mean BMI was26±1,4kg/m^2 respectively. The mean pre and post HbA1c level were 7.78 ±1.43 and 6.73 ±1.39 respectively. Nine patients (12%) have shown reduction of HbA1c from 0.5 to 1% in 3 months, p value was 0.005 . Weight reduction was not significant in three groups. The less glycemic variability is shown in Glargine 300 p value 0.003 and degludec group 0.07
Conclusion: There was less glycemic variability and reduction of HbA1c was found Glargine 300 and Degludec using patients. All three insulins had better profile than pre mixed insulins.

Keywords: Efficacy, Glargine, Degludec, Hyderabad, Diabetes

Introduction

The increasing number of people with type 2 diabetes is alarming in most countries, two-thirds of adults with diabetes were living in low- and middle-income countries. The majority of patients of type 2 diabetes are between 40 and 59 years of age.

International Diabetes Federation published a report in 2022, 26.7% of adults in Pakistan were diabetics, making the total number of cases approximately 33,000,000. [1]

Insulin therapy is essential for many patients during the course of type 2 diabetes mellitus [2] and insulin is potent than any oral antidiabetic to lower Glycated hemoglobin.[3]

In type 1 diabetes, life is maintained with use of insulin and requires lifelong insulin therapy. While 20–30% of patients with type 2 eventually require insulin as a result of progressive pancreatic β-cell dysfunction. [4]

The earliest method for classifying therapeutic insulins was based on duration of action. More recently, therapeutic insulin, particularly those providing basal coverage have been classified by generation in order to less glycemic variability and less side effctd.[5]

First-generation analogue insulins (Glargine) are prepared to the standardized concentration of 100 units/mL (U-100). Second-generation insulins, in contrast, are prepared to a concentration of 200 units/mL (U-200), 300 units/mL (U-300), or 500 units/mL (U-500) [6].Second generation insulins are hepatic friendly and biosimilar to natural insulin.

Finally, third-generation insulins comprise inhaled insulin preparations, oral insulin preparations, ultra-rapid-acting insulin preparations [7], ultra-long-acting insulin preparations, fixed-ratio co-formulations of basal and prandial insulin , and fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) .[8]

Glargine U100 and Glargine U300 have different pharmacology profiles. The mean duration of action of U100 is 25.5 h. The single dose is calculated 0.3 U/kg.

Glargine U300 also has a flatter and more extended time-action profile than Glargine. U100 , and this may result in more stable and sustained glycemic control over the 24-h inter-dosing interval.

Patients with diabetes who do not achieve glycemic targets with once-daily or twice-daily dosing of a first-generation basal insulin may benefit from once-daily dosing of a second-generation basal insulin.[9]

The most recently Insulin degludec is a novel long-acting basal insulin analog with a half-life of 25 hours and a duration of action > 40 hours with no peaks.[10]

Insulin degludec, in most clinical trials, has been associated with significant lower rates of overall symptomatic and nocturnal hypoglycemic events.[11]. The prolonged duration of action and the uniform concentration throughout day , made this insulin as first choice .[12]

Insulin Degludec is formulated as a 100 unit/ml preparation and has demonstrated consistent efficacy and safety in numerous randomized controlled trials and real-world evidence studies [13] and represents the ‘gold standard’ against which new basal insulin analogues are assessed.

The main difference between Glargine 100 and glargine 300 is the same number of units of insulin, the volume of U300 is approximately one-third that of U100 .[14]

The older insulin like premixed regular and intermediate NPH shown fluctuations in blood sugar just before and after doses and made doctor and patient puzzled. This is known as glycemic variability(GV).

The new formula devised by David M Nathan, takes into consideration of multiple self-monitored blood glucose values and is depicted as ‘A1c Derived Average Glucose’ (ADAG): eAG (mg/dl) = 28.7 × A1C-46.[15]

The target Glycemic variability has been a topic of debate, it was proposed by Monnier *et al*. [16] that 40 mg/dl as the target level of glucose variability.Although HbA1c was traditionally considered as the gold standard for assessing glycemic control.[17]

There are predominantly two types of GV according to the length of time-interval: long-term GV, based on serial determinations over a longer period of time, involving HbA1c, serial fasting plasma glucose (FPG) and postprandial glucose (PPG) measurements, and short-term GV, represented by both within-day and between-day GV. Long-term GV, usually based on visit-to-visit measurements of HbA1c, FPG or PPG. [18]

Furthermore, short-term GV is calculated from self-monitoring of blood glucose (SMBG) measurements for a long time.

Moreover, a novel approach to measurement of with-day GV was presented by the continuous overlapping net glycemic action (CONGA) metric that calculates the SD of difference between a current blood glucose reading and a reading taken hours earlier.[19]

Accumulating evidence has suggested that GV, representing either short-term (with-day and between-day variability) or long-term GV, was associated with an increased risk of diabetic macro vascular and microvascular complications, hypoglycemia, mortality rates and other adverse clinical outcomes

Methods

Seventy six out patients type 2 diabetics attending diabetic /medical OPDs of Liaquat university hospital Hyderabad / Jamshoro were fulfilling the inclusion criteria registered in the study by using 30% prevalence of type 2 diabetics are on insulin from 20 September 2023 to January 2024 [20]. The purpose, procedure, risks and benefits were explained, and written consent was obtained from patients on Proforma written in Urdu and Sindhi.

This study was started after approval from Research ethical committee of LUMHS letter no LUMHS/REC/327.

The data was collected on pre-designed proforma including age, gender, BMI and duration of Diabetes. Baseline HBA1c level were noted .The BMI calculated by dividing the weight in kg with height in m^2. Patients were randomized on basis of Open Clinical Randomize software by cluster randomization.

Three group were randomized, matched almost for age, sex and demographic characteristics. Each group had insulin dose as per diet, HbA1c and BMI.

Group 1 kept on Glargine 100, group 2 was on Glargine U300 and group 3 was on Degludec admixed with Lispro.

All three group were kept on insulin as per initial HbA1c and 0.2-0.5 units/ Kg dose was started. There was clear instructions to patients for checking blood sugar random and fasting and record these reading on a chart provided by the author. The glycemic variability was considered by using A1c Derived Average Glucose' (ADAG): eAG (mg/dl) = 28.7 × A1C-46.

The reduction in HbA1c of at least ≥0.5% from the baseline, glycemic variability of < 50 mg at 6th week and 3 months was considered as good efficacy and low glycemic variability.

Inclusion criteria

All patients with type 2 DM for at least 2 years duration, already taking premix regular and NPH insulin or/ and NPH with oral anti diabetics of any group.

- HbA1c > 7.5%
- Age limit from 35-55 years of either gender.

Exclusion criteria

- Type 1 Diabetes mellitus
- Patients with end stage renal disease on dialysis
- Patients with inflammatory conditions; i.e. with raised CRP levels
- Patients with frequent urinary tract infections
- Patients with other endocrinopathies like thyroid, Addison's disease
- patients with pregnancy

Data analysis procedure

The data was analyzed by using SPSS version 22. The categorical variables such as gender, marital status, hypertension and efficacy were computed as numbers and percentages.

Normality of data was assessed by using Shapiro wilk test and the numerical data such as age, height, weight, BMI, baseline HbA1C and duration of diabetes were computed as mean and standard deviation or median (IQR) on the basis of normality.

The Pearson correlation was used for HbA1c and glycemic variability and duration of diabetes and hypertension.

The stratification was done for HbA1c, glycemic variability and duration of diabetes. The post stratification Chi-square test was applied on categorical variables at 95% confidence interval and the P-value ≤ 0.05 considered as statistically significant.

Results

76 patients were selected from OPDs of Liaquat university hospital. The female were more than males. (Chart 1). The major group of patients was insulin glargine 100. The glycemic variability was shown in able 2. The maximum reduction of HbA1c was associated to degludec .The demographic characteristics shown in table 1.

Baseline characteristics were similar between the three treatment-sequence arms (Table 1). The mean (SD) age was similar between treatment sequences for degludec/glargine U100/glargine 300.

The mean duration of diabetes was 4.1 years, HbA1c 7.9 %, and baseline mean blood glucose levels 137mg/dl Table 1.

The male; female ratio was 0.9 and BMI was same in all three groups and p value was 0.02 (chart1)

Chart 2

Type of insulin was used U100 because of easy availability and cost (49 patients, 65) and it is highlighted here

U100 Insulin

- This is the most commonly used type of insulin, indicating that the majority of patients prefer or require U100.

U300 Insulin:

- This type has a significant usage, but it is less common than U100.

DEG Insulin

- DEG insulin is the least used among the three types represented

- The blue line represents HbA1c levels, which appear to fluctuate between 7 and 9.5. This suggests some variability in the patients' long-term glucose control.
- The dotted blue line represents the linear trend of the HbA1c levels, which indicates a relatively stable average HbA1c level, slightly above 8.
- The flat red line indicates that no glycemic excursions above 40 mg/dl were detected (**Pearson's correlation 1**)

- The orange line represents HbA1c levels, which fluctuate between approximately 7 and 9.5 across the dataset.
- The variability in HbA1c levels suggests fluctuations in long-term blood glucose control among the patients
- The x-axis labels indicate the presence (Yes) or absence (No) of hypertension for each corresponding HbA1c measurement.
- Both patients with and without hypertension exhibit a range of HbA1c levels,

- Hypertension status alone may not be a significant determinant of HbA1c levels in this dataset.((**Pearson's correlation2**)
- Degludec demonstrated a significantly greater overall time in the tight glycemic range compared to glargine U100.
- Estimated Treatment Difference (ETD): 1.52% (95% CI: 0.15, 2.89), which corresponds to an additional 21.9 minutes per day spent in this range for patients using degludec.
- Both degludec and glargine U100 reported a mean of 136mg/dl..
- The treatment difference in glycaemic variability reached statistical significance.
- ETD: -0.06% (95% CI: -0.11, -0.01), indicating a slight but significant improvement with degludec.(**Table 2**)
- The HbA1c was reduced significantly with degludec group p value 0.005(table3)

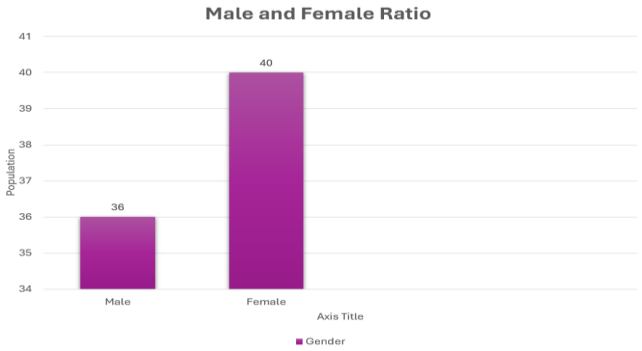
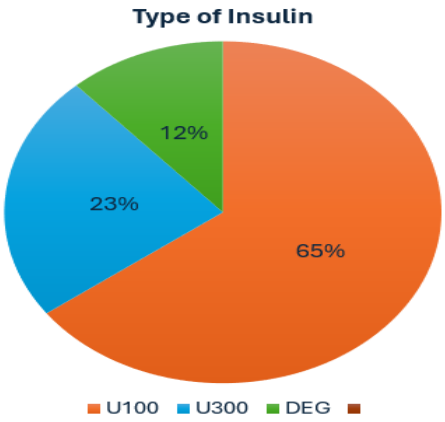


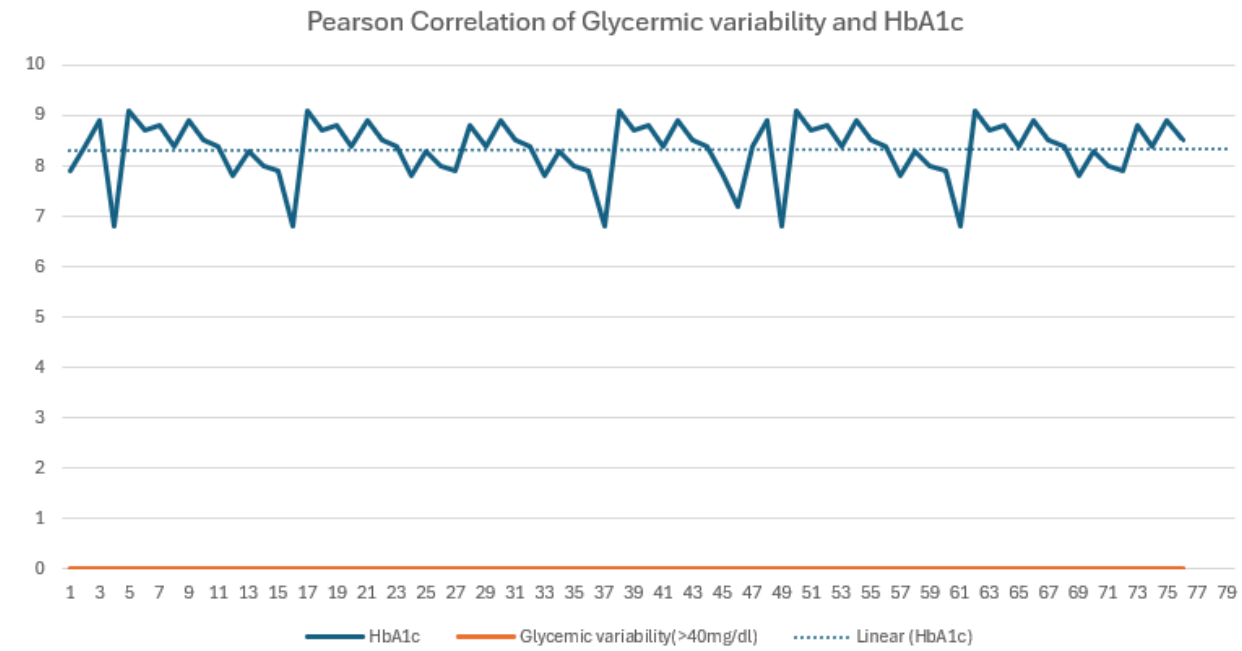
Table 1 Demographic characteristics of 76 patients

Variable	Group 1 (U100)	Group 2 (U300)	Group 3 (Deg)	P value
Sex (M /F)	49(65%)	18(23%)	9(12%)	0.034
Age years (mean)	45±2.3	46±1.9	44±1.7	0.077
Sugar(mean) Fasting	130±25	137±16	129±17	0.02
Duration of diabetes years(mean)	4 ±1.2	4±1.7	5±1.1	0.05
BMI(mean)	25±1.2	26±1,4	24±1.5	0.02
BP(mean) systolic	135±6.6	140±5.5	143±6.7	0.07
HbA1c	7.5±1.7	8±1.5	8.3±1.6	0.00

Chart 2



(Pearson's correlation1)



(Pearson's correlation2)

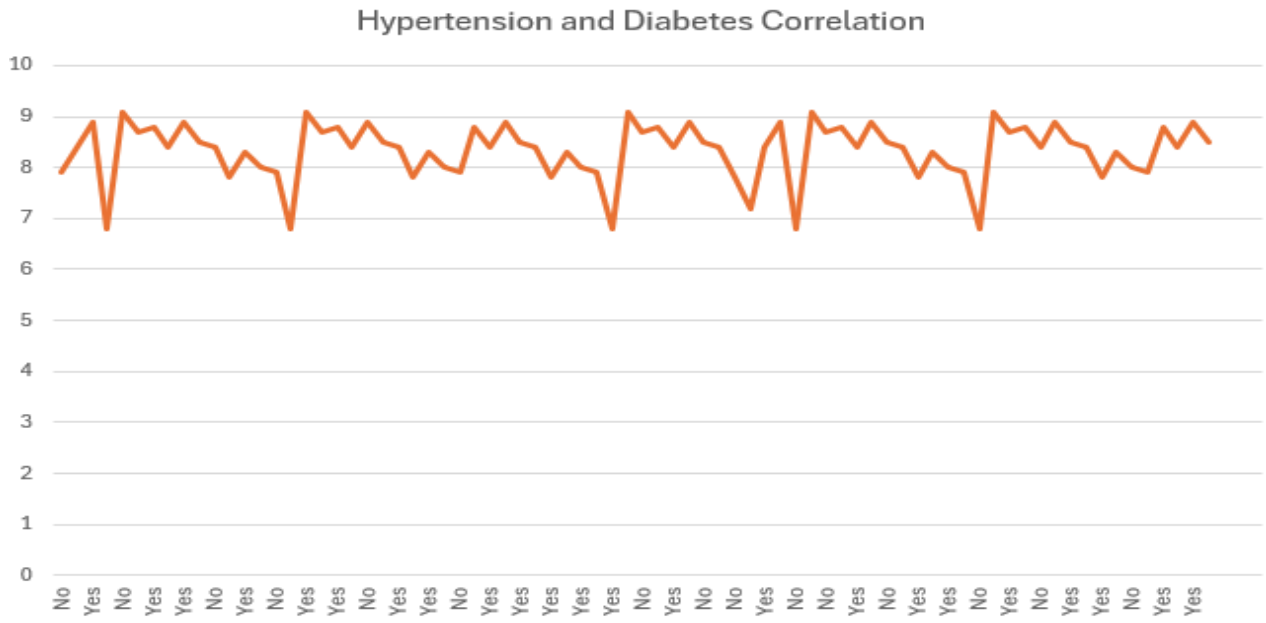


Table 2. Glycemic variability of three groups on different insulins

C	Group 1 (U100)	Group 2 (U300)	Group 3 (DEG)
76	49(65%)	18(23%)	9(12%)
Average Glucose' (ADAG):(mg/dl) = 28.7 × A1C-46	100	70	50
P value	0.001	0.003	0.07

Table 3 Mean reduction of HbA1c in three groups

HbA1c	Group 1	Group 2	Group 3
	0,4	0.8	0.9
P value	0.09	0.07	0..05

DISCUSSION

This is an exceptional RCT in Pakistan which has been compared various new insulin. At present majority of consultants are using mixed insulin which failed to control blood sugar after few years. As Mixed insulin is most instances shows very high glycemic variability which enhances chances of micro and macro vascular complications of diabetes.

The unique features of this study were female; male ratio, matched groups of patients and non-dropped out of patients.

Longer disease duration may be associated with a higher number and more serious diabetes-related complications and with longer insulin use. Multiple complications are important determinants of impaired health status, which underpins the importance of taking them into account.[21]

In our study Degludec demonstrated a significantly greater overall time in the tight glycemic range compared to glargine U100.Estimated Treatment Difference (ETD): 1.52% (95% CI: 0.15, 2.89), which corresponds to an additional 21.9 minutes per day spent in this range for patients using degludec and it is comparable to study done but Becker et al showed the ETD in HbA1c was −0.06% in favor of degludec.[22]

Our study was continued for 3 months and it represented that short term glycemic variability is reflection of long term glycemic control which was also shown by lachin et all that short-term GV is calculated from self-monitoring of blood glucose (SMBG) measurements for a long time.[23]

In our study, hypertension was correlated patients with and without hypertension exhibit a range of HbA1c levels, suggesting that hypertension status alone may not be a significant determinant of HbA1c levels in this dataset. This is not similar to one study which shows correlation of high HbA1c to left ventricular dysfunction.[24]

Various insulin have different profile but degludec is better than U 100 and U 300 in compliance and glycemic variability which has shown to one study and our study also shown this fact. [25]

Glargine 100 is good in controlling blood sugar after injection for few hours but Glargine U300 is better for long term control . Our study showed U300 exhibited less glycemic variability and better control with reduction of HbA1c over 3 months (table 3).[26]

CONCLUSION

Insulin use is mandatory step in type 2 diabetes treatment. The newer concepts focus the prevention of future complications than only control of blood sugar.

The newer insulins area safer, acceptable and provide less glycemic variability.

Over and above standard glycemic parameters like blood glucose and HbA1c, Glycemic variability can be a future target parameter for optimum glycemic control.

In spite of various formulas offered, simple and standard clinical tool to define Glycemic variability is yet to evolve.

Current database of diabetes focuses on Continuous glucose monitoring by various methods and this will lead to improve quality of life of diabetic patients.

This study highlighted new concepts and more prospective cohort would need for assessment of new insulin profile.

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