

Glycemic Excursions in Diabetic Kidney Disease: Comparison of Three Therapeutic Arms

Abstract

Objectives/Aim of study: To assess the magnitude of glycemic variability (based on blood glucose levels) over 72 hours in patients with underlying diabetic kidney disease and HbA1c <8%, and to compare the effects of glimepiride, vildagliptin and insulin on glycemic variability.

Materials and Methods: Thirty patients of T2 DM and diabetic kidney disease were chosen whose HbA1C was less than 8%, fasting plasma glucose less than 150 mg/dL, two hour post prandial plasma glucose less than 200 mg/dl, eGFR- between 15 to 59 ml/min/1.73m². Exclusion criteria were pregnancy, pre-existing non diabetic kidney disease, decompensated heart failure, liver failure and systemic infections. Patients were categorized into three groups:- on glimepiride (n=10), on vildagliptin (n=10) and on basal bolus insulin (n=10). Medications were adjusted to patients' renal function. Patients were managed for their diabetes following the most recent ADA guidelines. Patients underwent CGM for 72 hours and the results were analyzed.

Results: Post dinner capillary blood glucose (CBG) was found to be significantly higher in the glimepiride (228 mg/dl \pm 37.66) cohort than vildagliptin (196 mg/dl \pm 40.43) cohort (p=0.043) and the predinner CBG was significantly higher in the insulin (130 mg/dl \pm 45.08) cohort than vildagliptin (92.89 mg/dl \pm 26.06) cohort (p=0.047). No significant difference in daytime as well as nocturnal hypoglycemia was noted among the three arms.

Conclusion: CGMS can reveal episodes of glycemic instability in a diabetic patient categorized as having stable glycemia by HbA1c, FPG and PPPG. Insulin, Glimepiride and Vildagliptin did not differ markedly in reducing glycemic variability in our study. Strict implementation of lifestyle modification and glycemic control can influence the extent of glycemic variability, which may have influenced the results. Small sample size was also a limiting factor in our study. However, rational and judicious use of antidiabetic medications may help in reducing glycemic variability and hypoglycemic episodes, even in diabetic kidney disease.

Keywords: Glycemic variability; Diabetic kidney disease

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Abbreviations: CBG: Capillary Blood Glucose; GV: Glycemic Variability; DKD: Diabetic Kidney Disease;

Introduction

The objective of optimal diabetes control is to maintain normal glycated hemoglobin (HbA1c) level in order to prevent diabetic complications. There is considerable evidence from landmark studies that HbA1c is linked to vascular complications of diabetes [1,2]. But HbA1c has its limitations too. Though being representative of an overall glycemic status, yet when incorporating all the components of glycemia, including fasting, preprandial and postprandial hyperglycemia, HbA1c level does not reflect their relative contribution towards glycemic control [3]. Moreover, HbA1c fails to capture glucose fluctuations and does not track glycemic excursions and 60% of these excursions are not revealed by SMBG alone.

Glycemic variability (GV) takes into account the glycemic excursions including episodes of hyper and hypoglycemia and is a risk factor for the development of diabetic complications independent from HbA1c. This parameter of glycemic control can be assessed using continuous glucose monitoring (CGM).

CGM identifies four times more glucose excursions than SMBG and is an upcoming area of research in the field of endocrinology. Lin et al showed annual FPG and HbA1c variability had a strong association with diabetic kidney disease in type 2 diabetes and impairment of renal function can affect the normal blood glucose metabolism⁴. So there is great clinical value of CGM in this population of patients. Moreover, patients with diabetic kidney disease (DKD) are more prone to hypoglycemic episodes which can be revealed by CGM.

There are conflicting reports regarding the effect of different antidiabetic agents on glycemic variability in Type 2 DM. Hypotheses have been made regarding the superiority of one agent over another on the basis of various studies, including some head to head comparisons [5-7]. Of particular interest in this respect have been the various insulin regimens and sulfonylureas. Also remarkable are the various DPP4 inhibitor agents, particularly in the context of the recent upsurge in their usage in clinical practice. A number of clinical trials have been done to prove the superiority of one agent over another as well as the superiority of DPP4 inhibitors over other antidiabetic agents [8]. Our study aims to evaluate the extent of glycemic

excursions in diabetic kidney disease in patients with HbA1c <8% and to make a comparative evaluation among the effects of glimepiride, vildagliptin and insulin on glycemic variability. Most of the studies done so far have been head to head comparison of two antidiabetic agents [9,10]. This study is unique in this aspect, evaluating and comparing the effects of three antidiabetic agents on glycemic variability in a relatively delicate group of patients with underlying diabetic kidney disease.

Materials and Methods

This was a cross sectional study of patients with T2DM complicated by diabetic kidney disease (DKD) treated at Department of Endocrinology, Nilratan Sircar Medical College, Kolkata. The study was approved by the Institutional Ethical Committee and informed consent was obtained from all the study subjects. All patients received an explanation of the procedure and possible disadvantages of participating in the study. Thirty patients with T2 DM and assumed to have diabetic kidney disease were chosen based on HbA1C < 8%, fasting plasma glucose less than 150 mg/dL, two hour post prandial plasma glucose less than 200 mg/dl, eGFR- between 15 to 59 ml/min/1.73m². Patients were categorized into three groups, on glimepiride (n=10), on vildagliptin (n=10) and on basal bolus insulin (n=10) as a unique antidiabetic medication regimen. Medications were adjusted based on renal function, and titrated for goal glucose levels as dictated by the 2016 ADA guidelines.

IPro2 CGM system (Medtronic) was used in this study. IPro2 digital recorder, MMT -7741 was used to collect and store data from a glucose sensor and was uploaded into CareLink iPro Therapy Management Software for Diabetes (CareLink iPro, MMT-7340) to generate reports. The IPro2 Docking station charges the iPro 2 and uploads data from iPro2 to CareLink iPro. The iPro2 digital recorder is intended to continuously record interstitial glucose levels in persons with diabetes mellitus and the information is intended to supplement the blood glucose information obtained using standard home glucose monitoring devices. The information collected by the IPro2 digital recorder was uploaded to a computer (with internet access) and reviewed [11-13].

The study was conducted inpatient. All the patients participating in this study were admitted to NRS Medical College, Kolkata beforehand to ensure proper compliance to medications and to BG monitoring. All the patients were through a patient instruction sheet to complete at least seven blood glucose readings per day in order to avoid data gap, including one blood glucose testing 1 hour after the iPro2 is connected to the sensor. The patients were told that blood glucose meter readings are required to calibrate the sensor data. The sensors were inserted in the abdomen after cleaning the insertion site with alcohol and allowed to air dry. Patients continued with their normal activities and a log sheet was maintained recording the meals, blood glucose, exercise and medications. The same glucose meter and same lots of strips were used for the entire study. Patients receiving insulin were asked to inject it at least 7.5 cm away from the sensor insertion site. The iPro2 were covered with Enlite sensor adhesive tab and it was ensured that the sensor fits firmly but comfortably to the insertion site. Patients underwent CGM for 72 hours and results were analyzed.

Statistical Method

Statistical tests used included the Kruskal-Wallis test with multiple comparison post-hoc bonferroni test, post-hoc multiple comparison Tukey's test, Ryan-Einot-Gabriel-Welsh multiple range test and Anova with post-hoc Bonferroni test.

Results

Patient Characteristics

The baseline characteristics of the patients in three groups are shown in Table 1. Other than age and lipid status, the baseline variables were equivalent in both groups.

CGM Values

Comparison among three therapeutic arms: The 24-hour glycemic results are shown in Table 2A & 2B. The mean blood glucose as well as the highest and lowest blood glucose levels within 2 hours before and after each major meal was noted to look into the preprandial and post prandial glycemic excursions. Then the preprandial and postprandial percentages of time the blood glucose levels were above 140 mg/dl and below 70 mg/dl, respectively were analyzed and compared. An important area in the interpretation of glycemic variability involves the nocturnal glycemic status, so several parameters were analyzed in the nocturnal period between 12 midnight and 6 am in the morning, including the mean blood glucose and percentages of time the blood glucose levels were above 140 mg/dl and below 70 mg/dl in the night. To get a more detailed description of the nocturnal glycemic profile, the nocturnal time span was divided into two halves-12 midnight to 3 am (early) and 3 am to 6 am (late) and the highest and lowest recorded blood glucose levels in these periods were analyzed and the data from the three arms were compared. In addition, the overall (over 72 hours) mean blood glucose levels and overall percentages of time the blood glucose levels were above 140 mg/dl and below 70 mg/dl were taken into account and the measures were statistically analysed.

One of the important areas where CGMS is undoubtedly unique is in providing a dependable picture of nocturnal glycemic status, particularly detecting previously unrecognized hypoglycemic events, both symptomatic as well as asymptomatic. Hypoglycemic troughs in the CGMS curve of each patient were identified and retrospectively labeled as symptomatic or asymptomatic based on a validated questionnaire on the symptoms of hypoglycemia and the number of events between the subjects receiving glimepiride, vildagliptin and basal-bolus insulin was compared. The percentages of time the blood glucose level was below 70 mg/dl between 12 midnight and 6 am as well as the early (12 midnight to 3 am) and late (3 am to 6 am) nocturnal lowest blood glucose values were also analyzed as they were representative of night time hypoglycemia.

Post dinner CBG was found to be significantly higher in the glimepiride (228±37.66) cohort than vildagliptin (196±40.43) cohort (p=0.043) and the predinner CBG was significantly higher in the insulin (130±45.08) cohort than vildagliptin (92.89±26.06) cohort (p=0.047). No significant difference in daytime as well as nocturnal hypoglycemia was noted among the three arms. Other parameters did not reach a statistical significance in this study, though a numerical difference in the study parameters was found between the three groups.

Table 1: Patient Characteristics.

	Glimepiride, N=10 Group 1			Insulin, N=10 Group 2			DPP4 Inhibitor, N=10 Group 3			P
	Median	Lower Quartile	Upper Quartile	Median	Lower Quartile	Upper Quartile	Median	Lower Quartile	Upper Quartile	
AGE	53.5	51	60	54	50	63	62.5	57	63	b,c
DM DURATION	20	19	22	18	17	21	19	16	23	ns
BMI	25.6	23.6	29.9	26.9	26.5	29	26.25	24.4	28.6	ns
A1C	6.8	6.6	7	7.6	7.3	7.9	7.35	6.5	7.8	ns
SBP	148	146	176	155	142	164	132	132	158	ns
DBP	80	68	88	86	80	88	75	70	86	ns
TG	165	146	218	183	134	186	142	122	190	ns
LDL-C	112	96	118	127	122	152	98	86	112	a, c
HDL-C	51	38	54	58.5	55	63	35	30	48	a, c
Creatinine	2.85	1.9	3.5	2.8	2.5	3.1	2.45	2	3.1	ns
Egfr	25.06	22.34	34.05	25.485	18.91	33.58	32.575	24.87	39.46	ns
Urine ACR	387	256	502	199	42	542	488	310	732	ns
BASELINE FPG	103	82	132	99	92	111	115.5	98	122	ns
BASELINE PPG	148	122	164	156.5	146	176	158	126	170	ns

a-significant difference between group 1&2, b-significant difference between group 1&3, c- significant difference between group 3&2, p<0.05 considered as statistically significant, p values computed by Kruskal-Wallis test with multiple comparison post-hoc bonferroni test and post-hoc multiple comparison Tukey's test and Ryan-Einot-Gabriel-Welsh multiple range test.

Table 2A: Comparison of glycemic parameters among three therapeutic arms.

Glycemic Parameters	Glimepiride, N=10			Insulin, N=10			Vildagliptin, N=10			P value
	Median	LQ	UQ	Median	LQ	UQ	Median	LQ	UQ	
MEAN GLUCOSE IN CGMS	114	99	126	122	99	145	120.5	110	156	NS
% OF TIME BG>140	13.5	7	18	15.5	12	21	14.5	9	22	NS
% OF TIME BG <70	2.5	0	4	2	2	4	2	0	5	NS
POST BF MEAN BG	119	113	143	131	117	140	121	118	132	NS
POST BF % OF TIME > 140	1	1	2	1	1	3	2	1	5	NS
POST BF % TIME<70	1	0	3	1	0	4	0	0	1	NS
POST LUNCH MEAN BG	143	121	160	131	117	145	132.5	120	142	NS
POST LUNCH % OF TIME > 140	2	1	3	1	0	3	2.5	1	4	NS
POST LUNCH % TIME<70	1	0	2	1	0	2	0	0	0	NS

POST DINNER MEAN BG	150	134	160	135	128	145	131	116	146	NS
POST DINNER % OF TIME > 140	1	0	2	0.5	0	2	1	1	3	NS
POST DINNER % TIME<70	1	0	2	1	1	2	0	0	1	NS
NOCTURNAL MEAN BG	121	116	127	124.5	118	134	121.5	110	132	NS
NOCTURNAL % OF TIME > 140	11.5	10	19	19.5	14	23	23	11	23	NS
NOCTURNAL % OF TIME <70	0	0	8	1	0	5	0	0	10	NS

a-significant difference between group 1&2, b-significant difference between group 1&3, c- significant difference between group 3&2, p<0.05 considered as statistically significant, a-significant difference between group 1&2, b-significant difference between group 1&3, c- significant difference between group 3&2, p<0.05 considered as statistically significant, p values computed by Kruskal-Wallis test with multiple comparison post-hoc bonferroni test and post-hoc multiple comparison Tukey's test and Ryan-Einot-Gabriel-Welsh multiple range test.

Table 2B: Comparison of glycemic parameters among three therapeutic arms.

Parameters	Insulin, N=10		Vildagliptin, N=10		Glimepiride, N=10		P
	Mean	SD	Mean	SD	Mean	SD	
Highest CBG Before BF	187.60	57.74	187.70	57.03	177.00	36.12	NS
Highest CBG After BF	228.10	47.93	232.20	53.79	230.10	48.59	NS
Lowest CBG Before BF	91.50	40.69	96.00	33.15	93.00	43.01	NS
Lowest CBG After BF	126.90	45.48	111.10	39.27	115.80	31.45	NS
Highest CBG Before Lunch	175.90	50.37	197.40	54.62	189.10	47.66	NS
Highest CBG After Lunch	209.60	34.35	222.60	44.73	232.60	38.80	NS
Lowest CBG Before Lunch	131.80	49.45	97.10	32.27	114.40	63.94	NS
Highest CBG Before Dinner	195.44	52.73	178.56	50.17	212.67	42.98	NS
Highest CBG After Dinner	209.44	40.78	196.00	40.43	228.56	37.66	c- 0.043
Lowest CBG Before Dinner	130.44	45.08	92.89	26.06	115.00	41.98	a-0.047
Lowest CBG After Dinner	132.70	29.82	118.33	24.14	127.89	33.26	NS
Early Nocturnal Highest CBG	189.22	24.23	168.22	30.24	187.22	36.70	NS
Early Nocturnal Lowest CBG	91.78	28.64	99.33	20.44	91.00	38.59	NS
Late Nocturnal Highest CBG	170.89	45.80	162.33	42.20	199.11	68.41	NS
Late Nocturnal Lowest CBG	73.11	20.59	82.67	23.00	100.00	45.44	NS
No Of Symptomatic Hypo	0.89	0.17	0.33	0.11	0.343	0.21	NS
No Of Asymptomatic Hypo	0.89	0.33	0.67	0.27	1.11	0.35	NS

p<0.05 considered as statistically significant as computed by ANOVA with post-hoc Bonferroni test, a-significant difference between insulin & vildagliptin, b-significant difference between insulin & glimepiride, c-significant difference between glimepiride & vildagliptin, NS - no significant difference between three groups.

Discussion

The management of type 2 diabetes has expanded in a large manner, initially centered around the holy trinity concept (fasting, postprandial blood glucose and HbA1c) and then including glycemic variability as a part of the glucose pentad [14]. HbA1c does not track glycemic excursions and 60% of these excursions are not revealed by SMBG alone, whereas continuous glucose monitors identifies four times more glucose excursions than SMBG alone. Glycemic variability is thus a HbA1c independent risk factor for the development of diabetic complications [15,16]. GV is another sign of dysglycaemia and according to the recent

clinical studies; GV is a significant predictor of mortality in T2DM [17,18]. The continuous interstitial glucose monitoring systems (CGMS) can detect unrecognized hypoglycemia [19] and other patterns that may require insulin dose adjustment, that is not detected with intermittent blood glucose monitoring [20,21]. Early uncontrolled studies [22,23] and cross-over trials [24] have shown benefit of using CGMS devices in stabilizing glycemic control. Randomized controlled trials done in diabetic populations, particularly in pregnant women with diabetes [25] and in uncontrolled type 1 diabetes [26] have recently thrown more light on this subject. The number of patients with diabetic kidney disease has gradually increased over the past decade and

type 2 diabetic patients with end-stage renal disease (ESRD) are an emerging threat to prevailing health care system [27,28]. Diabetic patients have a high mortality rate, mainly attributed to cardiovascular disease which is particularly marked in diabetic patients with renal impairment [29]. The physiology of insulin and glycemia differs markedly in diabetic patients with kidney disease from other diabetic subjects and that these patients are prone to hypoglycemia has been a matter of great clinical concern, particularly posing a problem for treating them with insulin and insulin secretagogues. There are conflicting reports of DPP4 inhibitors doing better than insulin and insulin secretagogues in terms of reducing glycemic excursions, with better long term prospects of reducing diabetic complications [30]. But very few studies are there involving subjects with diabetic kidney disease. The objective of the present study was to evaluate the clinical performance of a CGMS in type 2 diabetic patients with kidney disease and it is a pilot study comparing the effects of three antidiabetic agents simultaneously on glycemic excursions, all the agents being particularly relevant in the context of modern day diabetes management.

Although a high incidence of unrecognized hypoglycemia has been detected using the CGMS in patients with type 1 diabetes [31], extensive information about these events in type 2 diabetic subjects is not available. A recently published article on hypoglycemia and diabetes describes the presence of nondetected hypoglycemia in type 2 diabetic subjects, but only in those with a very long diabetes duration and final insulin deficiency [32]. In the present study group of type 2 diabetic subjects, the diabetes duration was not very long, and it did not demonstrate a high incidence of this event in type 2 diabetic patients.

Various antidiabetic agents have different effect on glycemic variability in patients with type 2 diabetes and most of the trials have compared between two agents. In this study the effect of vildagliptin, glimepiride and basal bolus insulin on glucose oscillations were compared, basal bolus insulin being closest to the physiological hormonal milieu and the other two agents having predominant post prandial activity. The glycemic parameters analyzed in this study did not show a statistically significant difference between the three agents, though a numerical difference was found. Logically glimepiride should cause less GV among sulfonylureas that is attributed to the extra pancreatic effect, rapid association and dissociation and effect on both phases of insulin secretion in patients with type 2 diabetes [33]. The insulin-releasing activity has been shown to be low with glimeperide, relative to other sulfonylureas in different studies [34]. Vildagliptin and other DPP-IV inhibitors increase endogenous GIP and GLP-1 by inhibiting their degradation. In the study by Yiwen Qiu et al. [35], they concluded that in T2DM patients with DKD, blood glucose fluctuation is an important factor affecting their survival rate and vildagliptin can reduce blood glucose fluctuation in this subset of patients. In another study looking into the efficacy of vildagliptin on glucose fluctuation in Japanese patients, it was concluded that vildagliptin when added to ongoing SU based OHA therapy for 12 weeks significantly improved glycemic fluctuation as well as glycemic control in Japanese patients with T2DM [36]. In another head to head comparative study between vildagliptin and glimepiride, it was revealed that Vildagliptin treatment was associated with

less fluctuation of glucose levels than glimepiride treatment as assessed by 24-h CGM device, suggesting vildagliptin may have the potential to offer long-term beneficial effects for patients with T2DM in preventing the development of complications of diabetes [37]. Several reports show DPP-4 inhibitors are non-inferior to insulin secretagogues in terms of reducing glycemic variability [38,39]. It is also reported that DPP-4 inhibitors are more efficacious in the Asians [40]. But the superiority of vildagliptin and basal bolus insulin over sulfonylureas as claimed in the literature was not supported in the present study.

The small number of patients was a limiting factor in this study. Another factor is the cost of CGMS and this is one of the reasons preventing diabetologists for using it liberally. In the present study, the patients attending this tertiary care hospital mostly belonged to lower socioeconomic status and CGMS could be done only in selected cases. Another limiting factor in this study was that the patients were being closely supervised and kept under strict glycemic control. Although hospital admission is not a prerequisite for performing CGMS, in this study all the patients were admitted prior to CGMS for proper calibration with self monitored blood glucose values and optimum procedural factors during 72 hours of CGMS, most patients being illiterate and lack enough of motivation. The data being collected inpatient may have been a source of bias in this study. Future studies done with a higher number of ambulatory patients may throw more light on this upcoming area of medical research.

Conclusion

Insulin, Glimepiride and Vildagliptin did not differ markedly in their impact on glycemic variability in DKD subjects in the inpatient setting under carbohydrate restricted diet. Hypoglycemic events (symptomatic as well as asymptomatic) also did not differ significantly in these three arms. Strict implementation of lifestyle modification and optimum glycemic control may have influenced the study results, small sample size being another limiting factor.

Acknowledgment

None.

Conflict of Interest

None.

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