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Research Article

A Prospective Multicenter Open-label Study to Assess Effect of Remogliflozin on Glycemic Variability Compared to Dapagliflozin Using Continuous Glucose Monitoring (REMIT - GV study)

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Abstract

Background: Remogliflozin has shown similar glycemic control to dapagliflozin in phase III study; however, its impact on glycemic variability (GV) was unknown. The objective was to evaluate the effect of remogliflozin on GV and compare with dapagliflozin, using continuous glucose monitoring (CGM) in T2DM patients with inadequate glycemic control.

Methods: A 6-weeks randomized, open-label, active-controlled, parallel-group multicenter study was conducted in four centers across India. Eligible T2DM patients were randomized to either remogliflozin 100 mg twice daily or dapagliflozin 10 mg once daily, in addition to standard of care. CGM device was implanted twice to collect baseline and post-treatment data. The efficacy endpoints included mean change in CGM derived GV parameters and HbA1c, while safety assessment was done through adverse events reporting.

Results: The final analysis set of 65 patients included 33 patients in remogliflozin and 32 in dapagliflozin group. There was a significant improvement in GV parameters and HbA1c in both remogliflozin and dapagliflozin group from baseline to end of study; however, no significant difference was seen between the two groups. Significant reduction in the mean post-prandial glucose excursion (MPPGE), PP 1-hour and PP 2-hour was seen in remogliflozin group, but not in dapagliflozin group. The 24-hour mean of mean change in glucose profile showed overall better glycemic control in remogliflozin group, as compared to dapagliflozin group.

Conclusion: Remogliflozin showed significant improvement in PP variability parameters, which was not observed with dapagliflozin; hence, remogliflozin might be a better option to control post-prandial GV in Indian T2DM patients.

Keywords: Remogliflozin; Dapagliflozin; Glycemic variability; Continuous glucose monitoring; Post-prandial

Abbreviations: GV: Glycemic Variability; CGM: Continuous Glucose Monitoring; PP: Post-Prandial; MPPGE: Mean Post-Prandial Glycemic Excursion; CV: Coefficient of Variation; TIR: Time in Range; MAGE: Mean Amplitude Glycemic Excursion; LAGE: Largest Amplitude Glycemic Excursion

Introduction

Diabetes Mellitus is a growing concern in India with an estimate of 74.2 million diabetes and 9.6% diabetic population in the age range of 20-79 years in 2021, and by 2030, nearly 93 million people are expected to get affected by the disease [1]. Management of diabetes include modification in the food and lifestyle habits combined with oral or injectable anti-diabetic medications that either increase insulin secretion (sulphonlyureas [SUs], Dipeptidyl peptidase 4 [DPP4] inhibitor, sodium glucose co-transporter 2 [SGLT2] inhibitor) or improve insulin sensitivity and increase glucose utilization (biguanides, thiazolinediones) [2]. Modulation of renal glucose handling is a promising approach for improving hyperglycemia in type 2 diabetes mellitus (T2DM) patients. SGLT2, primarily expressed on the luminal side of the renal proximal tubule, is considered as a major pathway for renal glucose re-absorption. Inhibiting this pathway has been shown to inhibit re-absorption of glucose and enhance urinary glucose excretion, and thus reduce the blood glucose levels [3]. SGLT2 inhibitors such as canagliflozin, dapagliflozin and empagliflozin have shown to be effective in the management of T2DM and are approved as monotherapy as well as in combination with other anti-diabetic agents [4-7]. Remogliflozin etabonate is orally bioavailable prodrug of remogliflozin, which is a potent and selective inhibitor of SGLT2 [8], and has been approved for the treatment of T2DM in India.

Although HbA1c, FPG and PPG levels are useful for monitoring patient's response to treatment, they do not capture variability in plasma glucose levels i.e. glycemic variability (GV) across 24 hours. The use of continuous glucose monitoring (CGM) for measuring GV has been shown to reduce time spent outside of glucose targets, and more accurately identify hypoglycemic episodes, thereby helping to characterize hypoglycemia risk. Additionally, CGM provide short time and intermediate-time glycemic markers that supplements HbA1c to predict long-term outcomes related to morbidity and mortality in people with type 2 diabetes [9].

The twice-daily regimen of remogliflozin has been shown to provide equivalent glycemic control to once-daily dapagliflozin in Phase III study [10]; however, the impact of remogliflozin twice-daily regimen on glycemic variability is unknown. Also, this twice-daily regimen of remogliflozin may potentially offer a better post-prandial control compared to once-daily regimen of other SGLT2 inhibitors in Indian patients, as our dietary pattern usually consist of carbohydrate rich meals. In STARCH study conducted in five regions of India revealed that carbohydrates constitute 64.1% of total energy from diet in T2DM patients, which is above the recommended guidelines [11]. Therefore, this study was conducted to evaluate the effect of remogliflozin on 24-hour glucose profile assessed through CGM and compare with dapagliflozin in Indian T2DM patients.

Materials and Methods

Study design

This prospective multicenter randomized open label, active controlled comparative study of 6 weeks' duration was conducted at four institutions/hospital across India from 22 March 2021 to 06 December 2021. Ethics committee approval to conduct this study was taken from all the four hospitals by respective study investigators. Study was conducted as accordance with Declaration of Helsinki, ICH GCP, ICMR guidelines and applicable regulatory guidelines.

Study endpoints

The primary endpoint was to evaluate the mean change in glycemic variability parameters (Glycated haemoglobin [HbA1c], fasting blood glucose [FPG], time in range [TIR], maximum amplitude glycemic excursion [MAGE], coefficient of variation [CV], largest amplitude glucose excursion [LAGE], mean post-prandial glucose excursion [MPPGE], post prandial 1 hour [PP 1hr] and post prandial 2 hour [PP 2 hr]) from baseline with remogliflozin and compare with mean change in these parameter with dapagliflozin. The CGM based glycemic parameters included TIR (70-180mg/dl), MAGE, CV, LAGE and post prandial glycemic parameters i.e. MPPGE, PP 1 hr and PP 2 hr. The secondary endpoints were to compare safety and tolerability of remogliflozin with dapagliflozin.

Sample size

Based on the study by Vianna AGD, et al. the authors reported a mean TIR % change of 24.9 (18.6-31.2) in dapagliflozin group and 17.4 (11.6 - 23.3) in gliclazide group from their respective baselines [12]. Assuming that in the proposed study, the mean percent change in TIR after administering remogliflozin could be 20% with a standard deviation of 5.25%, and considering 1% tolerable margin, resulted into a sample of 30 patients per group. The sample is expected to provide the assumed mean within the error range, with 95% confidence and 80% power. Considering 20% loss to follow up, the number of patients needed comes out to be 75.

Methodology

T2 DM patients with age > 18 years of either gender,

with HbA1c between 7-9%, on stable (>6 weeks) metformin or metformin plus DPP4 inhibitor therapy, with random glucose level < 300 mg/dl and willing to comply with study requirements were included in the study. The exclusion criteria were: hypersensitivity to study medications, evidence of diabetic ketosis or non-ketotic hyperosmolar coma, presence of cardiac arrhythmias, acute coronary syndrome, elevated liver enzymes, eGFR < 60 ml/min/1.73m^2, evidence of acute infection, anemia and pregnant or lactating women. Informed consent was obtained from all study participants prior to the screening and enrolment procedures.

All the eligible patients were randomized in ratio of 1:1 using computer generated randomization list to receive one of the two treatments i.e. remogliflozin 100 mg twice daily orally or dapagliflozin 10 mg once daily orally for a period of 42 days. A CGM device was implanted on visit 1 at least 3 days before randomization, with proper care and glycemic data was recorded, referred as baseline data. On visit 2 i.e. day 0, patients were randomized to receive either of the two treatments for next 42 days. On visit 3 i.e. day 7/8 from randomization, which was 14 days from the day of implantation of CGM device, the device was removed. The period from day of randomization to removal of CGM device constitute phase I of the study. On visit 4 i.e. 28 ± 1 day after randomization, CGM device was again implanted and data was recorded till day 42. This 14 days' duration of CGM device constitute phase II of the study. At final visit or visit 5, i.e. 42 days after randomization, CGM device was removed. The patients were provided with uniform meal plan to be followed during the study period. The meal diary was assessed for any deviations in the meal plan during follow up visits. The first patient was enrolled on 22 March 2021 and the last patient completed last visit on 06 December 2021. The ongoing anti-diabetic medication that patients received at baseline was not altered during study duration. Patients visited the site at pre-determined intervals for assessment (Figure 1).

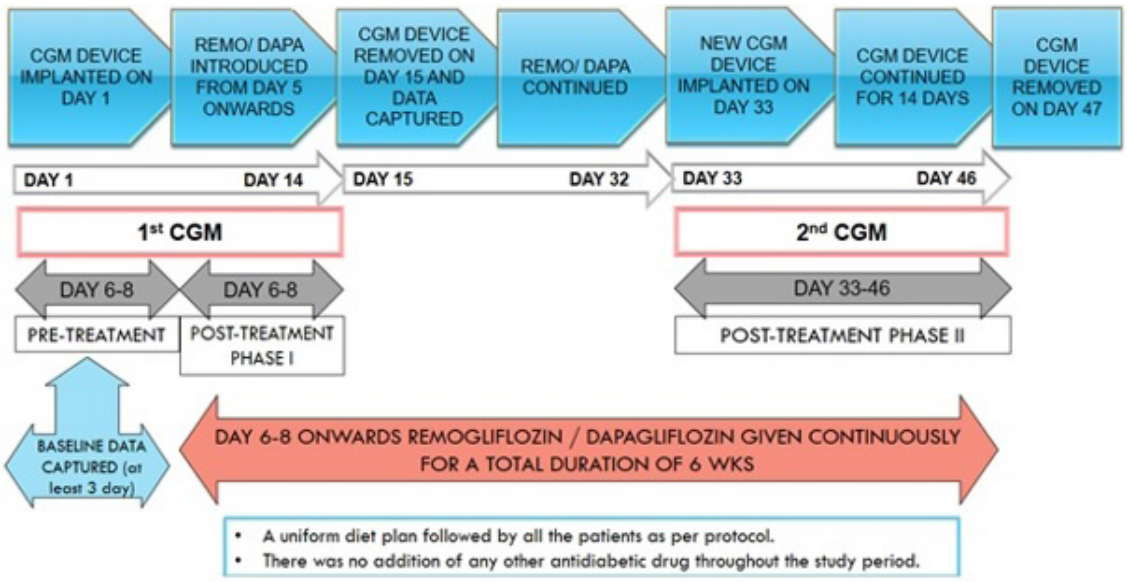

Figure 1: Study flow diagram.

REMO – Remogliflozin, DAPA – Dapagliflozin, CGM – Continuous glucose monitoring

Statistical analysis

Continuous data was summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max). The categorical variables were summarized using the frequency count (n) and percentage for each possible value. The comparison of mean change in glycemic parameters within the group was done using paired t-test from baseline to phase I and phase II, whereas comparison between the groups using unpaired t-test. The change in the mean glucose level between baseline and phase II, across 24-hrs time scale, was obtained for each patient and mean of this mean change in glucose level across patients in each treatment groups was analyzed and compared between two treatment groups. The CGM parameters were obtained using *iglu* library from R – 3.4.3 and were compared statistically using SPSS version 26.0 (IBM Corp. ARMONK USA). The statistical significance was considered if p value is <0.05 (5% level).

Results

Of the 75 patients enrolled, 38 patients were in remogliflozin group and 37 patients in dapagliflozin group. Out of 38 patients in remogliflozin group, CGM data was available on 33 patients, while in dapagliflozin arm, out of 37 patients, CGM data was available on 34 patients. In dapagliflozin group, two patients showed extreme mean values and were ignored as statistical outliers. Thus, the final analysis set consisted of 33 patients in remogliflozin and 32 patients in dapagliflozin group (Figure 2).

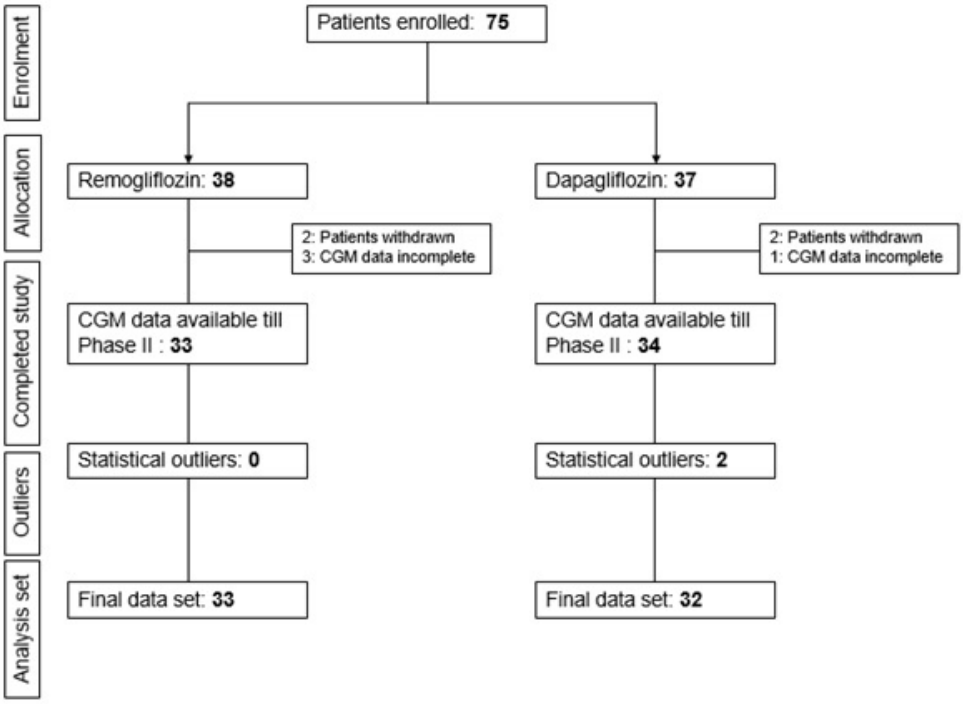

Figure 2: Flow diagram of patient enrolment.

The descriptive statistics for various characteristics for per protocol population at baseline are given in Table 1. The mean age of patients in remogliflozin group was 51.73 ± 10.09 years, while that of dapagliflozin group was 50.37 ± 9.62 years. There was no statistical difference between the two groups in various characteristic except in mean duration of diabetes in two groups differed significantly (p = 0.047), with remogliflozin group having higher duration of diabetes than dapagliflozin at baseline (Table 1).

Parameter		Group		P-value
		Remogliflozin (N=33)	Dapagliflozin (N=32)	
Age in years [Mean ± SD; Min, Max]		51.73 ± 10.09; 20, 74	50.37 ± 9.62; 34, 71	0.583*
Gender [n (%)]	Male	24 (72.7)	19 (59.4)	0.255‡
	Female	9 (27.3)	13 (40.6)	
Duration of DM (months) [Mean ± SD; Min, Max]		61.76 ± 51.84; 4, 240	39.59 ±34.29; 4, 120	0.047*
BMI (kg/m^2) [Mean ± SD; Min, Max]		27.82 ± 6.37; 19.11, 52.16	27.44 ±5.04; 16.02, 43.94	0.794*
Concomitant medication [Median; Min, Max]		1; 1,3	1; 1, 3	0.461†
*Using t-test for independent samples; ‡Using Chi-square test; †Using Mann-Whitney U test SD – Standard deviation, DM – Diabetes mellitus, BMI – Body mass index				

Table 1: Descriptive statistics for various characteristics of patients at baseline in two treatment arms

The comparison of mean baseline glycemic parameters between the two groups was shown in Table 2. All the parameters were found to be similar (p>0.05) between two groups. The comparison of mean change in glycemic parameters from baseline to phase I and phase II within each treatment group is shown in Table 3. In remogliflozin group, significant reduction is seen in all the glycemic parameters i.e. HbA1c, FPG, TIR, MAGE, LAGE, MPPGE, PP 1hr and PP 2hr except coefficient of variance (CV) at both phase I and phase II compared to baseline. Whereas, in dapagliflozin group, significant reduction is seen in FPG, TIR, MAGE, LAGE, and PP 2hr at phase I compared to baseline and in HbA1c, TIR, MAGE and LAGE at phase II compared to baseline (Table 3). The comparison of mean change in glycemic parameters from baseline to phase II between two groups was shown in Table 4. There was no statistically significant difference found between the two groups.

Parameter	Remogliflozin (N=33)	Dapagliflozin (N=32)	P-value*
	Mean ± SD	Mean ± SD	
HbA1c (%)	8.24 ±1.30	8.42 ±1.55	0.597
Mean glucose (mg/dl)	153.57 ± 57.69	152.05 ± 39.77	0.902
TIR70-180	66.65 ± 27.43	69.56 ± 22.60	0.643
MAGE (mg/dl)	114.87 ± 40.42	110.22 ± 28.69	0.596
CV	28.05 ± 5.94	27.77 ± 6.07	0.85
LAGE (mg/dl)	150.02 ± 54.45	146.67 ± 34.83	0.769
MPPGE (mg/dl)	74.89 ± 29.8	62.62 ± 20.55	0.058
Post-prandial – 1hr (mg/dl)	170.22 ± 62.31	164.25 ± 37.02	0.642
Post-prandial – 2 hr (mg/dl)	179.03 ± 68.76	173.07 ± 40.95	0.674

*Using t-test for independent samples; HbA1c – Glycated haemoglobin, TIR – Time in range (70-180 mg/dl), MAGE - Mean amplitude of glycemic excursions, CV - Coefficient of variation, LAGE – Largest amplitude of glycaemic excursion, MPPGE: Mean post prandial glycaemic excursion

Table 2: Comparison of CGM parameters at baseline between two treatment arms.

Parameter	Remogliflozin (N=33)					Dapagliflozin (N=32)				
	Mean ± SD					Mean ± SD				
	Baseline (a)	Post-treatment		P-value*	P-value*	Baseline (a)	Post-treatment		P-value*	P-value*
		Phase I (b)	Phase II (c)	a vs. b	a vs. c		Phase I (b)	Phase II (c)	a vs. b	a vs. c
HbA1c (%)	8.24 ± 1.30	-	7.64 ± 1.04	-	**0.015**	8.42 ± 1.55	-	7.83 ± 1.10	-	**0.002**
Mean glucose (mg/dl)	153.57 ± 57.69	132.45 ± 37.60	131.74 ± 48.11	**0.001**	**0.014**	152.05 ± 39.77	139.52 ± 31.31	138.86 ± 41.09	**0.019**	0.139
TIR70-180 (%)	66.65 ± 27.43	75.55 ± 20.05	76.77 ± 23.48	**0.001**	**0.014**	69.56 ± 22.6	78.42 ± 19.12	78.56 ± 21.68	**0.009**	**0.044**
MAGE (mg/dl)	114.87 ± 40.42	102.69 ± 38.79	98.49 ± 39.31	**0.009**	**0.002**	110.22 ± 28.69	99.80 ± 32.12	96.07 ± 29.62	**0.002**	**0.004**
CV	28.05 ± 5.94	28.56 ± 7.59	28.13 ± 6.65	0.629	0.935	27.77 ± 6.07	26.33 ± 6.46	26.74 ± 4.59	0.167	0.351
LAGE (mg/dl)	150.02 ± 54.45	137.54 ± 48.21	134.58 ± 52.22	**0.018**	**0.011**	146.67 ± 34.83	133.57 ± 41.92	129.05 ± 39	**0.003**	**0.005**
MPPGE (mg/dl)	74.89 ± 29.8	63.75 ± 27.86	61.39 ± 27.39	**0.001**	**< 0.0001**	62.62 ± 20.55	58.23 ± 21.77	54.54 ± 19.71	0.093	0.053
Post-prandial – 1hr (mg/dl)	170.22 ± 62.31	145.94 ± 36.45	142.51 ± 48.19	**0.005**	**0.01**	164.25 ± 37.02	153.03 ± 35.98	149.49 ± 48.31	0.063	0.141
Post-prandial – 2 hr (mg/dl)	179.03 ± 68.76	152.50 ± 43.17	149.41 ± 54.27	**0.003**	**0.005**	173.07 ± 40.95	157.89 ± 35.99	153.99 ± 49.05	**0.018**	0.072

*Using paired t-test; Bold p-value indicate statistical significance
HbA1c – Glycated haemoglobin, TIR – Time in range (70-180 mg/dl), MAGE - Mean amplitude of glycemic excursions, CV - Coefficient of variation, LAGE – Largest amplitude of glycaemic excursion, MPPGE: Mean post prandial glycaemic excursion

Table 3: Comparison of glycemic parameters between baseline and phase I as well as phase II in each treatment arm.

Parameter	Remogliflozin (N=33)	Dapagliflozin (N=32)	P-value*
	Mean ± SD	Mean ± SD	
HbA1c (%)	0.50 ± 1.09	0.62 ± 1.03	0.889
Mean Glucose (mg/dl)	21.84 ± 48.37	13.20 ± 49.16	0.478
TIR70-180 (%)	10.12 ± 22.33	9.00 ± 24.31	0.848
MAGE (mg/dl)	16.38 ± 27.44	14.15 ± 25.94	0.737
CV	-0.08 ± 5.77	1.03 ± 6.16	0.455
LAGE (mg/dl)	15.44 ± 32.80	17.62 ± 33.27	0.791
MPPGE (mg/dl)	13.51 ± 19.00	8.08 ± 22.73	0.299
Post-prandial – 1hr (mg/dl)	27.70 ± 58.43	14.76 ± 55.21	0.362
Post-prandial – 2 hr (mg/dl)	29.62 ± 55.73	19.08 ± 57.87	0.457

*Using t-test for independent samples; HbA1c – Glycated haemoglobin, TIR – Time in range (70-180 mg/dl), MAGE - Mean amplitude of glycemic excursions, CV - Coefficient of variation, LAGE – Largest amplitude of glycaemic excursion, MPPGE: Mean post prandial glycaemic excursion

Table 4: Comparison of change in glycemic parameters from baseline to phase II between two treatment arms.

From baseline to phase II, mean reduction in PP glycemic parameters i.e. MPPGE, PP 1 hr and PP 2 hr was found to be numerically higher and statistically significant in remogliflozin group compared to dapagliflozin group in which these reductions were found to be statistically non-significant (Table 3). Mean changes in PP glycemic parameters were also analyzed according to meal times i.e. breakfast, lunch and dinner from baseline to phase II. Mean reduction in MPPGE was found significant post breakfast and dinner in remogliflozin group, whereas only post dinner in dapagliflozin group. Mean reduction in PP 1hr was found significant post all meals in remogliflozin group but not in dapagliflozin group after any meal. Again mean reduction in PP 2hr was found significant post all meals in remogliflozin group, whereas post breakfast and dinner in dapagliflozin group (Table 5, Figure 3). The mean of mean change in glucose profile across 24 hour of the two treatment groups from baseline to phase II is shown in Figure 4. It shows that change in remogliflozin group is more than that of dapagliflozin group at all the time points including nighttime, although these differences were not statistically significant.

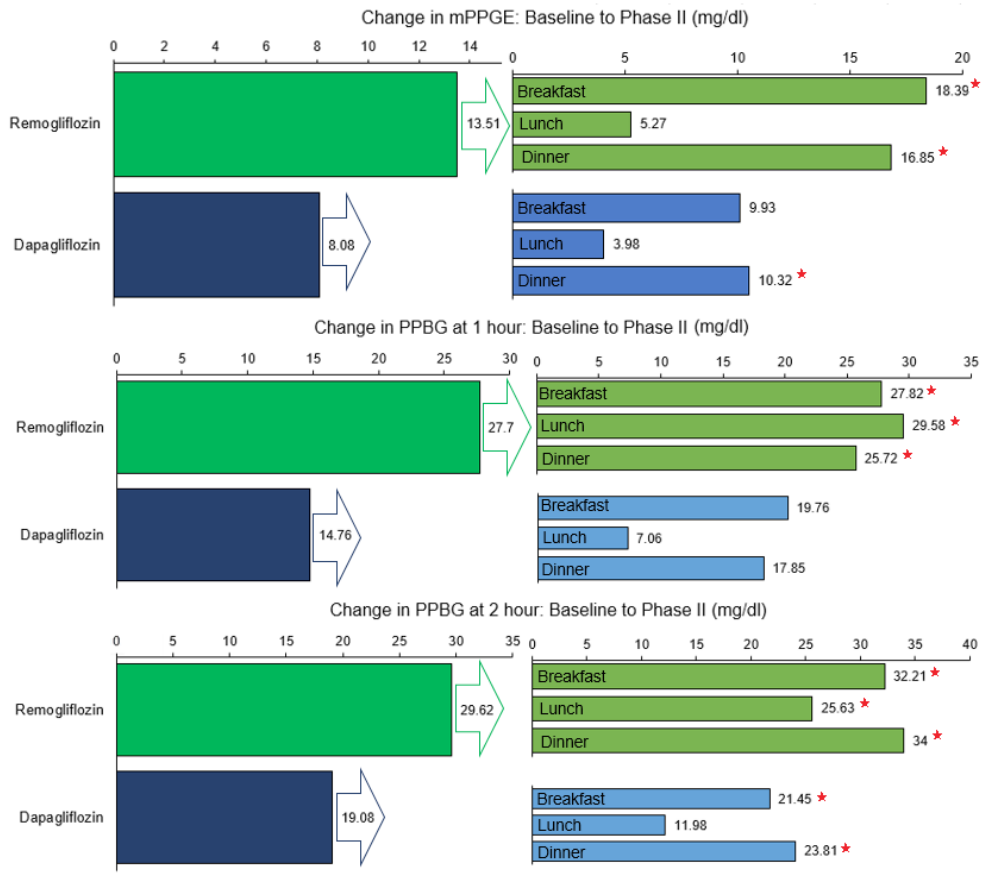

Figure 3: Comparison of mean change in post-prandial glycemic parameters from baseline to phase II in two treatment groups according to meal times (*P-value < 0.05).

Parameter	Meal	Stage	Remogliflozin (N=33)		Dapagliflozin (N=32)	
			Mean ± SD	P-value*	Mean ± SD	P-value*
MPPGE	Breakfast	Baseline	81.81 ± 35.7	**0.001 (S)**	70.44 ± 26.4	0.087 (NS)
		Phase II	63.42 ± 27.42		60.51 ± 25.91	
	Lunch	Baseline	67.75 ± 35.53	0.270 (NS)	63.15 ± 32.2	0.565 (NS)
		Phase II	62.47 ± 25.32		59.17 ± 24.92	
	Dinner	Baseline	75.14 ± 41.28	**0.001 (S)**	54.26 ± 28.25	**0.049 (S)**
		Phase II	58.28 ± 43.97		43.94 ± 29.4	
PP - 1hr	Breakfast	Baseline	171.26 ± 63.64	**0.028 (S)**	168.79 ± 47.21	0.067 (NS)
		Phase II	143.44 ± 52.06		149.43 ± 55.77	
	Lunch	Baseline	168.53 ± 68.77	**0.016 (S)**	154.79 ± 39.31	0.480 (NS)
		Phase II	138.95 ± 49.04		147.73 ± 44.36	
	Dinner	Baseline	170.86 ± 65.16	**0.015 (S)**	169.16 ± 43.71	0.138 (NS)
		Phase II	145.14 ± 52.84		151.31 ± 51.35	

PP - 2hr	Breakfast	Baseline	176.88 ± 68.19	**0.012 (S)**	172.19 ± 42.94	**0.040 (S)**
		Phase II	144.67 ± 56.61		150.74 ± 55.89	
	Lunch	Baseline	173.68 ± 70.13	**0.017 (S)**	166.89 ± 47.31	0.281 (NS)
		Phase II	148.05 ± 49.93		154.91 ± 45.11	
	Dinner	Baseline	186.54 ± 75.42	**0.001 (S)**	180.14 ± 44.64	**0.048 (S)**
		Phase II	155.51 ± 64.64		156.33 ± 52.47	

*Using paired t-test; CGM: Continuous glucose monitoring, MPPGE: Mean post-prandial glycaemic excursion; PP: Post-prandial

Table 5: Comparison of post prandial glycaemic parameters between baseline and phase II at each mealtime within group.

There was no serious adverse events (SAEs) were reported during the study duration in either groups. There were total 15 adverse events (AEs) reported in the study, 10 of them were from remogliflozin group and 5 from dapagliflozin group. All the AEs were mild in intensity, and resolved eventually without any intervention. Most of these AEs were declared as not related or associated with the study drugs (Table 6).

S. No.	Adverse event	Remogliflozin (N= 37)	Dapagliflozin (N= 38)
1	Hypoglycemia	1(2.7%)	0
2	Weakness	3(8.1%)	0
3	Headache	1(2.7%)	0
4	Bronchospasm	0	1(2.6%)
5	Neuropathic pain	0	1(2.6%)
6	Giddiness	1(2.7%)	0
7	Heel pain	2(5.4 %)	0
8	Insomnia	1(2.7%)	0
9	Microalbuminuria	1(2.7%)	1(2.6%)
10	Burning feet	0	1(2.6%)
11	Fever	0	1(2.6%)

Table 6: List of adverse events between the two treatment groups.

Discussion

Management of diabetes has evolved from assessment of long term GV parameters (HbA1c or FPG) for glycemic control to short term (day to day or within day variation) GV parameters like TIR, MAGE, CV, LAGE, MPPGE etc. Also GV is not expressed by HbA1c properly, particularly in patients having good metabolic control. Thus, relying on HbA1c alone may end up with false negative or positive interpretations. Significant GV can worsen onset and progression of various complications associated with diabetes especially with hypoglycemia [13]. Among various glycemic variability parameters, TIR is most accepted among health care professionals for monitoring glycemic control and now included in recent American diabetes association guidelines [14]. CGMs utilize a monitoring system that detects the blood glucose levels at regular intervals of time, and enables the researchers and physicians to have a more precise picture of the glycemic variability.

In the current study, we aimed to evaluate short-term glycemic variability using CGM in addition to HbA1c & FPG of remogliflozin. We hypothesized that twice daily dosing of remogliflozin might provide a better PP control compared to other once-daily approved SGLT2 inhibitors like dapagliflozin. Both the treatment groups were balanced in terms to baseline characteristics and glycemic variability parameters (Table 1, 2). Duration of diabetes was found significantly more in remogliflozin group at baseline, which was an incidental finding. The meal pattern was standardized before start of study treatment and assessment throughout the study duration using patient meal diary to detect any major deviation, which was not observed.

We found significant improvement in glycemic parameters (HbA1c, TIR, MAGE and LAGE) in both the treatment groups from baseline to phase I and phase II. However, change in CV was not seen in both the groups after 6 weeks of therapy (Table 3). In one of the phase III study, remogliflozin showed similar reduction in glycemic efficacy parameters i.e. HbA1c, PPG and FPG in comparison to dapagliflozin [10]. Also, similar glycemic control was observed with other molecules in the SGLT2 class, i.e., empagliflozin, dapagliflozin, and canagliflozin [17-19]. This adds to the evidence of similar glycemic efficacy among SGLT2 inhibitors.

In our study, significant improvement in PP glycemic parameters (MPPGE, PP 1hr, PP 2hr) from baseline to phase II was observed only in remogliflozin group, but not in dapagliflozin group. However, between the treatment groups improvement in PP glycemic parameters was not found statistically significant. (Table 3) This could be due to short duration of study i.e. 6 weeks.

Moreover, analysis of these PP glycemic parameters according to meal time, shows that significant improvement was seen in most of meal times (8 out of 9) with remogliflozin compared to dapagliflozin (3 out of 9) from baseline to phase II. This difference was seen at all mealtime in PP 1hr values. (Table 5) The PP hyperglycemia is an independent risk factor for CVD and further increases the risk of CV events in diabetic patients [15]. This is a major concern in Indian diabetic patients who consume high carbohydrate rich meals that contributes to increased PP hyperglycemia [11]. Also a sudden increase in blood glucose level has been shown not only detrimental effect on blood vessels leading to macrovascular and microvascular complications but also causes significant impairment of beta cell function [16]. Thus, PP hyperglycemia control can not only reduce the risk of CV events associated with diabetes, but also slow progression of diabetes.

The mean of mean change in glucose level across 24 hr from baseline to phase II found more reduction in remogliflozin group as compared to dapagliflozin group. Especially more reduction in remogliflozin group was seen post each mealtime especially after lunch and dinner. Moreover, more reduction was seen across whole night in remogliflozin group compared to dapagliflozin. (Figure 4) We hypothesize that this could be due to two blood peak of remogliflozin as according to its twice daily dosing which leads to better reduction compared to dapagliflozin especially post dinner.

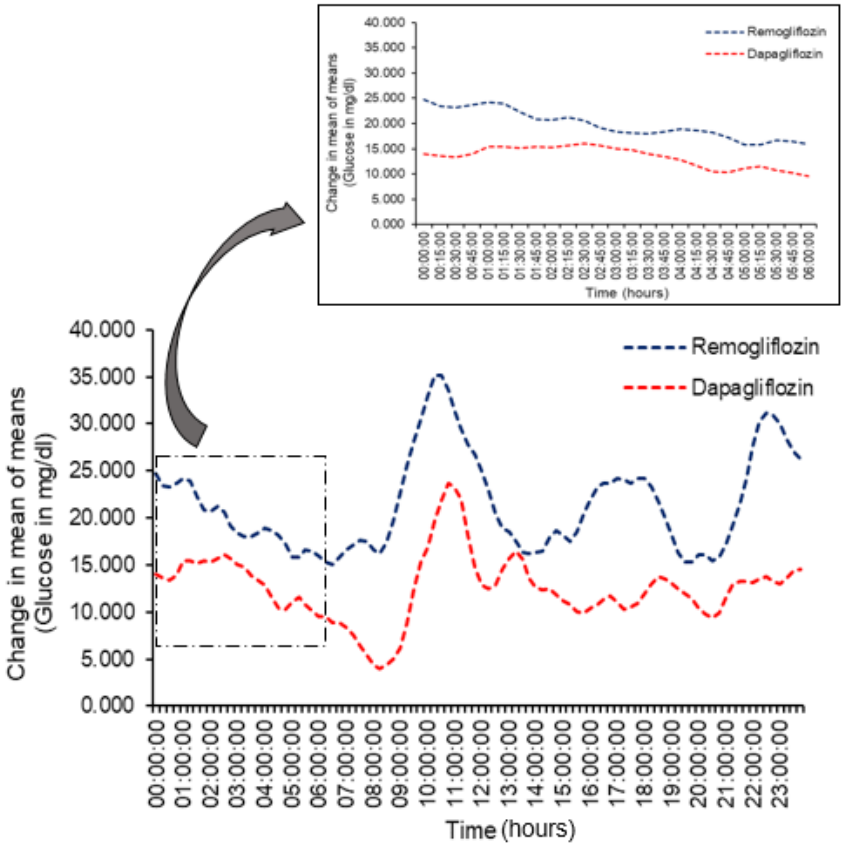

Figure 4: Change in mean of mean glucose level from baseline to phase II according to time in two treatment groups.

The adverse events were found similar between the two groups and found to be mild in intensity and does not lead to any discontinuation of therapy. This reinforce the safety and tolerability of SGLT2 inhibitors including remogliflozin seen in various randomized studies and real world evidence [4-6,12,17-19].

Our study has few limitations like a smaller sample size and short treatment duration. However, this study is proof of concept study justifying smaller sample size. Moreover, studies involving CGM usually have small sample size and short treatment duration. Still, this study provides important insights of the effect of twice-daily dosing regimen remogliflozin in managing the glycemic variability. Long-term study with larger sample size is required to confirm these findings.

Conclusion

In summary, patients with T2D require strict control of GV especially post-prandial hyperglycemia, which directly correlate with CV morbidity and mortality associated with diabetes and its progression. Remogliflozin treatment (100 mg twice daily) was able to improve GV parameters similar to dapagliflozin 10 mg once daily after 6 weeks of therapy. However, post-prandial parameters were significantly improved with remogliflozin treatment but not with dapagliflozin. This suggests that remogliflozin twice-daily regimen might be a better option to control post-prandial hyperglycemia compared to once-daily regimen of other SGLT2 inhibitors in Indian T2DM patients having high carbohydrate rich meal.

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