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Remogliflozin: Add-on Therapy in Indian Uncontrolled Type 2 Diabetes Mellitus (T2DM) Patients

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Abstract
Background: T2DM is associated with abnormal high-regulation of sodium-glucose cotransporter-2 (SGLT2) protein leading to hyperglycemia. Remogliflozin etabonate has been demonstrated to be not only efficacious and safe but equivalent to currently available SGLT2 inhibitors. **Material and Methods:** This prospective and interventional study was carried out on eighty-one T2DM patients in Teerthanker Mahaveer Medical College & Research Center, Moradabad over a period of 18 months. **Results:** Out of 81 study subjects, 61.7% were male while 38.3% subjects were female. Majority of study subjects (46.9%) were in the age group 51-60 years. There was a decrease in the mean diastolic blood pressure (82.91 vs 80.86), weight (68.57kg vs 67.92kg), fasting blood sugar (177.68 mg/dl vs 162.83mg/dl) and 2 hour post prandial sugar (252.64 mg/dl vs 229.81mg/dl) from the baseline values. This difference was statistically significant with p-value <0.05. **Conclusion:** Add-on therapy with RE in T2DM patients on oral hypoglycemics demonstrates significant reduction in diastolic BP, body weight, FBS & PPBS within one month of therapy without significant change in systolic BP. This drug is not only well tolerated by T2DM patients but also has a very low risk of serious adverse events rarely requiring dose modification in T2DM patients with high-risk cardiovascular disease or renal impairment.
Keywords: Type-2 Diabetes Mellitus, Urinary Glucose Excretion, American Diabetes Association.

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Introduction

Diabetes mellitus (DM) encompasses group of metabolic disorders with common manifestation as hyperglycemia.[1] Complex interaction of genetic with environmental factors has led to the development of several distinct types of DM.[1] Alterations in metabolic regulation in DM secondarily affects and produces alterations in multiple organ systems leading to significant personal burden as well as the health care system.[1] T2DM is associated with abnormal high-regulation of sodium-glucose cotransporter-2 (SGLT2) protein leading to hyperglycemia.[2] Inhibition of these proteins leads to higher urinary glucose excretion (UGE) with subsequent fall in plasma glucose concentrations causing all glycemic parameters to improve significantly. It has been demonstrated in medical literature that SGLT2 inhibitors when used in T2DM patients produce sustained decrease in glycosylated hemoglobin (HbA1c), weight of body, blood pressure and uric acid levels in serum but also has beneficial effects on cardiovascular and renal functions.[2] Thus, commercial availability of economical SGLT2 Inhibitors in India such as Remogliflozin can be described as a positive step in reducing the financial burden.[3,4]

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend SGLT2 inhibitors in DM patients with cardiovascular (including cardiac failure) and, chronic renal disease.[5-7] Remogliflozin etabonate has been demonstrated to be not only efficacious and safe but equivalent to currently available SGLT2 inhibitors.[3,4] It is rapidly and almost completely absorbed within 10 minutes and has no correlation with food intake.[3,4] It reduces HbA1c levels by 0.5-1.0% on an average post-12week therapy in drug-naive patients with T2DM.[5] RE induces modest weight loss of ~2kg with low-risk of hypoglycemia and decrease in blood pressure.[5]

AIM

- To study the effectiveness of REMOGLIFLOZIN as an add-on therapy in type 2 diabetes mellitus (T2DM) patients inadequately controlled with a stable dose of Metformin and Glimepiride.

OBJECTIVES

To assess the effect of Remogliflozin on:

- Glycemic Parameters
- Lipid Profile
- BMI
- Blood Pressure
- To study the efficacy of Remogliflozin

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Methodology

This prospective and interventional study was carried out on eighty-one T2DM patients in Teerthanker Mahaveer Medical College & Research Center, Moradabad over a period of 18 months.

Inclusion Criteria

1. T2DM patients 30-70years of age with HbA1c 7-9% showing: -

- Inadequate control with Metformin 1-2gm per day & Glimepiride 1-4mg per day.
- Intolerance to further increase in dose of Metformin & Glimepiride.

Inadequate Glycemic Control,[6] is defined as:

Preprandial capillary plasma glucose	>130mg/dl
Peak postprandial capillary plasma glucose	>180mg/dl
HbA1c	7.0%-9.0%

Exclusion Criteria

- Patients on Insulin therapy.
- Patient needing any other antidiabetic medication after adding Remogliflozin to Metformin and Glimepiride.
- Patients needing alterations in Metformin or Glimepiride dosage.
- Patients with compromised renal function (GFR <30 mL/min/1.73m2).
- Patients with urinary tract infection and structural abnormalities of urinary tract.
- Patients with acute complications of DM.
- Patients with hypersensitivity to the drug.

RESULTS

Table 1: Distribution of cases according to Gender

Gender	Frequency (n=81)	Percentage (%)
Female	50	61.7
Male	31	38.3

Out of 81 study subjects, 61.7% were male while 38.3% subjects were female.

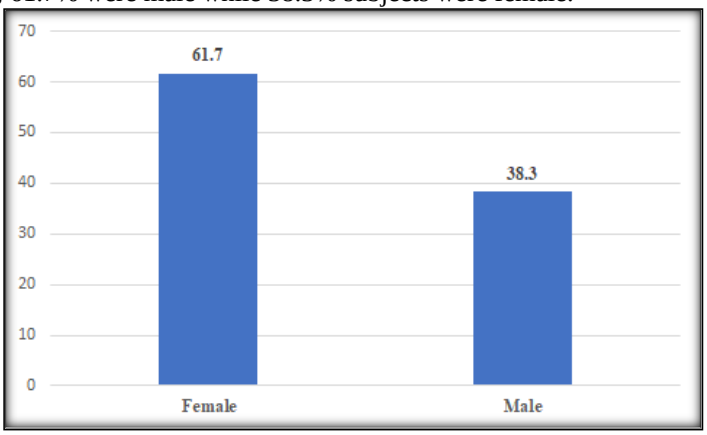

Figure 1: Distribution of cases according to Gender

Table 2: Distribution of cases according to Age

Age (years)	Frequency (n=81)	Percentage (%)
< 41	5	6.2
41 - 50	19	23.5
51 - 60	38	46.9
> 60	19	23.5

Majority of study subjects (46.9%) were in the age group 51-60 years followed by 23.5% in the age group 41-50 years and 23.5% were above 60 years while only 6.2% of subjects were below 40 years of age.

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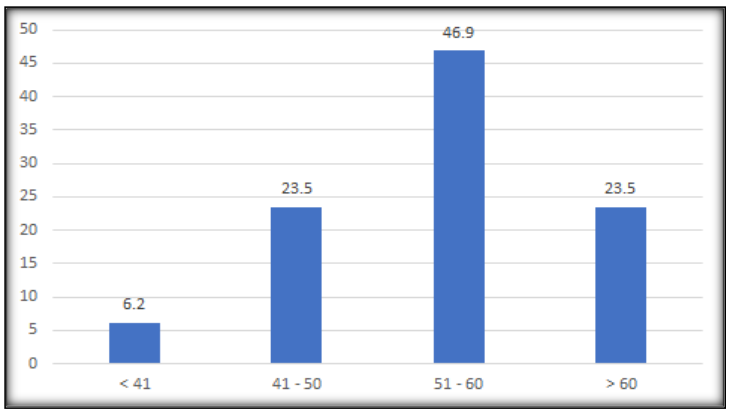

Figure 2: Distribution of cases according to Age

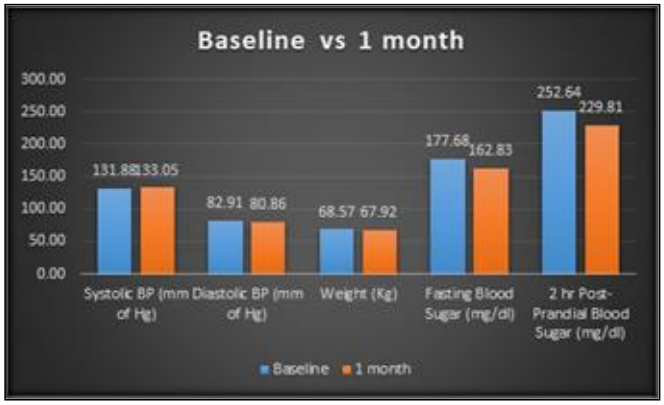

Figure 3: Comparison of characteristics at Baseline with 1 month follow up among the study groups

Figure 4: Comparison of characteristics at Baseline with 2 month follow up among the study groups

Figure 5: Comparison of characteristics at 2 month with 3 month follow up among the study groups

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Figure 6: Comparison of characteristics at 1 month with 3 month follow up among the study groups.

Table 3: Comparison of characteristics at Baseline with 1 month follow up among the study groups

Parameters	Baseline		1 month		Paired Differences		p-value
	Mean	SD	Mean	SD	Mean Difference	SD	
Systolic BP (mm of Hg)	131.88	15.90	133.05	12.89	-1.17	6.17	0.091
Diastolic BP (mm of Hg)	82.91	11.35	80.86	10.08	2.05	3.29	<0.001
Weight (Kg)	68.57	9.30	67.92	9.11	0.65	0.57	<0.001
Fasting Blood Sugar (mg/dl)	177.68	29.80	162.83	24.77	14.85	10.98	<0.001
2 hr Post-Prandial Blood Sugar (mg/dl)	252.64	61.96	229.81	55.94	22.83	19.58	<0.001

[Table 3 & Figure 3] shows comparison of clinical and biochemical characteristics at baseline with 1 month follow up among the study groups. There was a decrease in the mean diastolic blood pressure, weight, fasting blood sugar and 2 hour post prandial sugar from the baseline values. This difference was statistically significant with p-value <0.05.

Table 4: Comparison of characteristics at Baseline with 2 month follow up among the study groups

Parameters	Baseline		2 month		Paired Differences		p-value
	Mean	SD	Mean	SD	Mean Difference	SD	
Systolic BP (mm of Hg)	131.88	15.90	128.86	12.25	3.01	5.79	<0.001
Diastolic BP (mm of Hg)	82.91	11.35	77.83	8.60	5.09	5.64	<0.001
Weight (Kg)	68.57	9.30	67.32	9.15	1.25	0.69	<0.001
Fasting Blood Sugar (mg/dl)	177.68	29.80	149.12	19.64	28.56	15.81	<0.001
2 hr Post-Prandial Blood Sugar (mg/dl)	252.64	61.96	207.89	43.10	44.75	27.68	<0.001

[Table 4 & Figure 4] shows comparison of clinical and biochemical characteristics at baseline with 2 month follow up among the study groups. There was a decrease in the mean systolic & diastolic blood pressure, weight, fasting blood sugar and 2 hour post prandial sugar from the baseline values. This difference was statistically significant with p-value <0.05.

Table 5: Comparison of characteristics at 2 month with 3 month follow up among the study groups

Parameters	2 month		3 month		Paired Differences		p-value
	Mean	SD	Mean	SD	Mean Difference	SD	
Systolic BP (mm of Hg)	128.86	12.25	126.86	13.57	2.00	4.25	<0.001
Diastolic BP (mm of Hg)	77.83	8.60	78.74	9.07	-0.91	5.17	0.116
Weight (Kg)	67.32	9.15	66.93	9.15	0.39	0.61	<0.001
Fasting Blood Sugar (mg/dl)	149.12	19.64	138.57	17.81	10.56	7.77	<0.001
2 hr Post-Prandial Blood Sugar (mg/dl)	207.89	43.10	192.59	32.69	15.30	17.44	<0.001

[Table 5 & Figure 5] shows comparison of clinical and biochemical characteristics at 2 months with 3 month follow up among the study groups. There was a decrease in the mean systolic blood pressure, weight, fasting blood sugar and 2 hour post prandial sugar from the baseline values. This difference was statistically significant with p-value <0.05.

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Table 6: Comparison of characteristics at 1 month with 3 month follow up among the study groups.

Parameters	1 month		3 month		Paired Differences		p-value
	Mean	SD	Mean	SD	Mean Difference	SD	
Systolic BP (mm of Hg)	131.88	15.90	126.86	13.57	6.19	6.16	<0.001
Diastolic BP (mm of Hg)	82.91	11.35	78.74	9.07	2.12	4.90	<0.001
Weight (Kg)	68.57	9.30	66.93	9.15	0.99	0.68	<0.001
Fasting Blood Sugar (mg/dl)	177.68	29.80	138.57	17.81	24.26	13.78	<0.001
2 hr Post-Prandial Blood Sugar (mg/dl)	252.64	61.96	192.59	32.69	37.22	31.87	<0.001

[Table 6 & Figure 6] shows comparison of clinical and biochemical characteristics at 1 month with 3 month follow up among the study groups. There was a decrease in the mean systolic & diastolic blood pressure, weight, fasting blood sugar and 2 hour post prandial sugar from the baseline values. This difference was statistically significant with p-value <0.05.

Table 7: Comparison of characteristics at Baseline with 3 month follow up among the study groups

Parameters	Baseline		3 month		Paired Differences		p-value
	Mean	SD	Mean	SD	Mean Difference	SD	
Systolic BP (mm of Hg)	131.88	15.90	126.86	13.57	5.01	5.14	<0.001
Diastolic BP (mm of Hg)	82.91	11.35	78.74	9.07	4.17	5.09	<0.001
Weight (Kg)	68.57	9.30	66.93	9.15	1.64	0.91	<0.001
S. Creatinine	1.28	0.59	0.99	0.41	0.29	0.27	<0.001
Total Cholesterol	207.52	38.65	185.54	26.34	21.98	17.66	<0.001
Triglyceride	161.98	35.64	147.41	22.54	14.57	19.94	<0.001
HDL	41.24	9.59	44.25	8.04	-3.01	3.18	<0.001
Fasting Blood Sugar (mg/dl)	177.68	29.80	138.57	17.81	39.11	18.80	<0.001
2 hr Post-Prandial Blood Sugar (mg/dl)	252.64	61.96	192.59	32.69	60.05	36.54	<0.001
HbA1c	8.29	0.67	7.34	0.62	0.95	0.45	<0.001
Spot UACR (mg/g)	571.38	1455.76	291.10	958.30	280.27	570.03	<0.001

[Table 7 & Figure 7] shows comparison of clinical and biochemical characteristics at baseline with 3 month follow up among the study groups. There was a decrease in the mean systolic & diastolic blood pressure, weight, serum creatinine, total cholesterol, triglyceride, HDL, fasting blood sugar, 2 hour post prandial sugar, HbA1C and UACR from the baseline values. This difference was statistically significant with p-value <0.05.

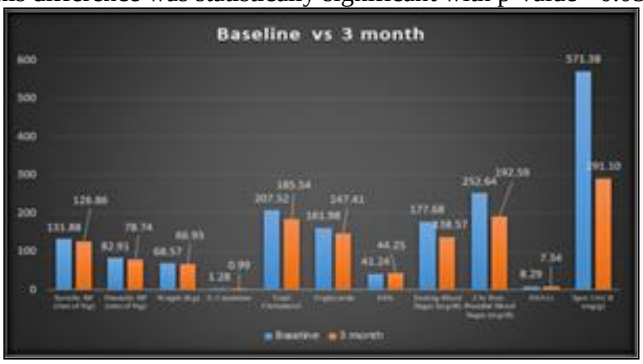

Table 7: Comparison of characteristics at Baseline with 3 month follow up among the study groups

DISCUSSION

Out of 81 study subjects, 61.7% were male while 38.3% subjects were female. Majority of study subjects (46.9%) were in the age group 51-60 years followed by 23.5% in the age group 41-50 years and 23.5% were above 60 years while only 6.2% of subjects were below 40 years of age. Over a period of One Month, there was a decrease in the

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mean diastolic blood pressure (82.91 vs 80.86), weight (68.57kg vs 67.92kg), fasting blood sugar (177.68 mg/dl vs 162.83mg/dl) and 2 hour post prandial sugar (252.64 mg/dl vs 229.81mg/dl) from the baseline values. This difference was statistically significant with p-value <0.05. Kuchay et al (2021) in their article described the benefit of SGLT2 inhibitors in reducing the Grade of fatty liver in NAFLD, improved cardiovascular & renal functions in addition to high glycemic control in T2DM patients receiving RE therapy.[2]

On comparison of clinical and biochemical characteristics at baseline with 2 month follow up among the study groups, there was a decrease in the mean systolic & diastolic blood pressure (82.91 vs78.74), weight (68.57kg vs 66.93kg), fasting blood sugar (177.68 mg/dl vs 138.57mg/dl) and 2 hour post prandial sugar (252.64 mg/dl vs 192.59mg/dl) from the baseline values. This difference was statistically significant with p-value <0.05. Atal et al (2020) described the advantages of weight and blood pressure reduction caused by SGLT-2 inhibitors during treatment of T2DM patients with known cardiac or kidney impairment. Our study also revealed a significantly reduced body weight, reduction in both systolic & diastolic BP, reduced serum creatinine & spot UACR, and reduced total cholesterol & triglyceride levels in addition to significant reduction in blood glucose levels (both FBS & PP) & HbA1c on addition of RE in T2DM patients.[7] S.R. Pattanaik (2020) in their study on 50 inadequately controlled T2DM patients observed significant reduction in weight in 24/50 patients, reduction in systolic BP in 40/50 patients and reduction in diastolic BP in 46/50 patients following RE administration.[8] Neal et al (2017) in their study on canagliflozin, SGLT2 inhibitor in 10,142 T2DM patients with increased cardiovascular risk reported lower rates of cardiovascular events compared to placebo in addition to the benefit in progression of albuminuria.[9] These conclusions are similar to the results of our study on 81 T2DM patients with 3-months RE coadministration with other oral hypoglycemic. Sykes et al (2015) in their 12-week, double-blinded, randomized control study on 336 treatment-naive T2DM subjects with HbA1c of 7.0-9.5% found significant reductions in HbA1c level versus placebo with significant reduction in weight.[10]

CONCLUSION

Based on the observations of our study, T2DM is common after 40years of age with 5th to 6th decade being the commonest decade of affection. Add-on therapy with RE in T2DM patients on oral hypoglycemics demonstrates significant reduction in diastolic BP, body weight, FBS & PPBS within one month of therapy without significant change in systolic BP. Significant reduction in both systolic & diastolic BP; body weight; FBS & PPBS levels; HbA1c level; total cholesterol & triglyceride level; serum creatinine & spot UACR value from baseline can be observed following 3-month add-on therapy with RE in T2DM patients on oral hypoglycemics with poor glycemic control associated with significant increase in HDL levels. SGLT2 inhibitors like Remogliflozin was very useful adjuncts to other oral hypoglycemics in type-2 diabetes mellitus patients with poor glycemic control. Increased urinary glucose excretion resulting in reduced fasting & 2-hour post-prandial blood sugar is the basic mechanism of action. This drug is not only well tolerated by T2DM patients but also has a very low risk of serious adverse events rarely requiring dose modification in T2DM patients with high-risk cardiovascular disease or renal impairment.

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