Original Research Paper

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RETROSPECTIVE, OBSERVATIONAL STUDY TO EVALUATE EFFECT DAPAGLIFLOZIN ON BODY WEIGHT, BLOOD PRESSURE & GLYCEMIC PARAMETERS IN T2DM PATIENTS: A REAL-WORLD EXPERIENCE IN INDIAN PATIENTS

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ABSTRACT **Aim:** Retrospective, Observational Study to evaluate effect Dapagliflozin on body weight, Blood Pressure & Glycemic parameters in T2DM Patients: A real-world experience in Indian patients. **Method:** A retrospective observational study was conducted from November 2021 to May 2022, where prescriptions generated during the period of May 2022 to October 2022 were studied retrospectively and overall prescriptions generated for 145 patients were analyzed after obtaining approval from institutional ethics committee. Both male and female patients between 18 to 60years of age, having type 2 diabetes mellitus who received dapagliflozin as routine clinical practice in management of T2DM during this period were included in the study. Patients with type 1 DM, gestational DM, receiving insulin therapy, having known allergy to the drug, patients with known significant renal and hepatic diseases and prescriptions with illegible hand writing were excluded from the observations. Data collected from past medical records from Healthplix EMR software. Primary endpoint was mean change in weight from baseline to weeks 12 and 24 weeks. Secondary endpoints were change in blood pressure, and glycaemic parameters Fasting Plasma Glucose (FPG), Post Prandial Plasma Glucose (PPPG) and HbA1c from baseline to weeks 12 & 24. **Results:** Paired t test was applied to obtain the results comparing the observations from the baseline to 12 weeks and 24 weeks**.** Significant reduction in body weight at the end of 12 and 24 weeks of Dapagliflozin therapy was –3.069 and -5.911 kg respectively from the baseline of 81.531 kg (p value p-value is .000024). At the end of 12 and 24 weeks of addition of Dapagliflozin, significant reduction in systolic blood pressure was seen i.e. -3.8843 and -6.00 mm of Hg respectively from base line of 139.441 mm of Hg(p-value is < .00001.) and reduction in diastolic blood pressure was -2mm of Hg and -4 mm of Hg respectively from base line 88.3931mm of Hg (p-value < .00001) which was significant. Significant reduction in HbA1c i.e -4.21 % (p-value is .000294) seen at the end of 24 weeks from baseline after adding Dapagliflozin on existing treatment. Reduction in FPG &PPPG seen at 12 & 24 weeks were -30.98 (p-value < .00001), -56.11(p-value < .00001) respectively for F PG and -40.39 (p-value < .00001), -69.95 (p-value < .00001) respectively for PPPG seen which is significant from baseline after adding Dapagliflozin on existing treatment. **Conclusion:** Dapagliflozin was found to be effective in reducing body weight and blood pressure when added to the patients who were already on anti-diabetic medications. It effectively showed reduction in body weight at the end of 12 and 24 weeks. Significant reduction in systolic& diastolic blood pressure seen with dapagliflozin. Significant reduction in glucose parameters like HbA1c, FBG and PPG also seen at the end of 24 weeks.

KEYWORDS : Dapagliflozin, Diabetes mellitus, HbA1c, Weight and Blood Pressure

INTRODUCTION

Out of metabolic diseases, Diabetes is major disease which occurs due to deficiency in insulin secretion or insulin action or both and is characterized by persistent elevation of blood glucose. As per International Diabetes Federation (IDF) Diabetes Atlas 2021, around 537 million adults (20-79 years of age) are suffering from diabetes. By year 2030, number of people living with diabetes is projected to rise to 643 million. India is major contributor for global burden of diabetes. As per IDF Diabetes Atlas 2021, number of people with diabetes in India were 74.2 million.[1] According to World Health Organization (WHO), diabetes resulted in 1.6 million deaths across the globe, thereby accounting 9th leading cause of death globally.[2] Treatment of diabetes involves use of different types of insulin, biguanides, sulfonylureas, non-sulfonylureas insulin secretagogues, thiazolidinediones, Alpha glucosidase inhibitors, dipeptidyl peptidase inhibitors (DPP4i), and sodium-glucose cotransporter type 2 inhibitors (SGLT2i).[3]

SGLT2i are promising and latest drugs class among all orally active antidiabetic drugs. Due to their novel mode of action, they are now considered as most upcoming and promising therapy for diabetes[4]. First SGLT2is approved in 2013 were canagliflozin and dapagliflozin. In 2014, empagliflozin was approved by US FDA and then ertugliflozin was approved in 2017. After metformin and incretin based therapies (DPP4i), SGLT2 inhibitors are second largest orally given antidiabetic drugs with evidence from randomized controlled trials and metanalysis for cardiovascular and renovascular safety in addition to control of parameters of hypaerglycemia[3-4].

These drugs inhibit sodium glucose co-transporter 2 in kidneys and thereby reduce glucose and sodium reabsorption in proximal convoluted tubule (PCT). This leads to excretion of glucose from urine, natriuresis and osmotic diuresis[4]. As a result of this, SGLT2i exhibit different pharmacological benefits such as reduction in HbA1c, weight reduction, and reduction in both systolic and diastolic blood pressure[5]. Not only this, SGLT2 inhibitors showed cardio-renal benefits such as reduction of three-point major adverse cardiovascular effects (3P MACE), cardiovascular death (CV Death), hospitalization due to heart failure (HHF), and kidney outcomes[4] but also has shown good glycemic control.

Considering beneficial effects of SGLT2i, different guidelines such as American Association of Clinical Endocrinology (AACE) 2020[6]; 2021 American Diabetes Association (ADA) standards of Care[7]; 2019 European Society of Cardiology (ESC)[8] and Research Society for scientific studies in diabetes in India also recommend SGLT2i as promising treatment option for diabetes, and cardiovascular disease.

Dapagliflozin is one of the landmark molecules among SGLT2i class. On January 2014, it was first approved by United States Food and Drug Administration (US FDA) for treatment of type 2 diabetes mellitus (T2DM). On October 2019, it was approved by US FDA for reduction of risk of HHF in patients with T2DM. After this, it got approval for treatment of heart failure with reduced ejection fraction (HFrEF) and treatment of chronic kidney disease in the patients at risk of progression with T2DM on May 2020 and April 2021 respectively[4,9]. Currently Dapagliflozins approved in more than 40 countries across the globe including European Union (EU), Australia and United States of America.

Dapagliflozin has been extensively studied in different clinical trial programs. Different large-scale clinical trials (including landmark cardio-renal trials such as DECLARE-TIMI 58[10], DAPA-HF[11], and DAPA-CKD[12]) have demonstrated efficacy of dapagliflozin in diabetes, cardiovascular, and renovascular disease. Recent DAPA RWE Spanish multicenter study demonstrated that Dapagliflozin showed significant reduction in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), weight, and blood pressure (BP) along with increase in estimated glomerular filtration rate (eGFR)[13]. In April 2022, post hoc analysis of DAPA-CKD trial demonstrated efficacy and safety of dapagliflozin across wide types of KDIGO (Kidney Disease: Improving Global Outcomes) risk categories[14]. Additionally, post hoc analysis of DAPA HF trial demonstrated that irrespective of fatality status, dapagliflozin improved worsening of heart failure or cardiovascular death[15].

Considering the upcoming utility of Dapagliflozin, it was thought to assess effect of Dapagliflozin(10mg) on body weight, blood pressure and glycemic parameters of patients with T2DM who were prescribed Dapagliflozin with other oral hypoglycemic agents as routine clinical practice in real world scenario.

METHODS:

A retrospective observational study was conducted in Department of pharmacology, MGM Medical College Aurangabad Maharashtra State, India from May 2022 to October 2022, after receiving approval from Institutional Ethics Committee. Data is collected from OPD electronic data base of software.

Inclusion And Exclusion Criteria :

Patients of either gender between 18 to 60 years of age and having type 2 diabetes mellitus and were taking dapagliflozin 10 mg as routine glucose lowering therapy along with other oral antidiabetic medications in management of T2DM during this period. Patients having Type I diabetes, gestational diabetes, on insulin therapy, known allergic to study drug were excluded. Prescriptions with illegible hand writing were also excluded.

In the current retrospective study 145 prescriptions generated for dapagliflozin 10 mg for Type II diabetic patients along with other glucose lowering therapy during the period of May 2022 to October 2022 were included in the study and were considered for analysis.

Endpoints Of The Study

Primary endpoint of study was mean change in weight from baseline to 12 weeks and 24 weeks.

Secondary endpoints of study were change in systolic and diastolic blood pressure, glycaemic parameters (FPG, PPG, and HbA1c) from baseline to weeks 12 & 24.

Data Analysis

Mean values were calculated for body weight, glycemic parameters (FPG, PPG and HbA1c) and blood pressure for baseline, 12 weeks and 24 week periods. Standard deviation and p values were calculated. Paired t test was applied to obtain the results comparing the observations from the baseline to 12 weeks and 24 weeks**.**

RESULTS:

Baseline characteristics of T2DM patients in this study are highlighted in table 1.

Table 1: Baseline Parameters Of T2DM Patients In The Study

Parameter	Baseline (SD)
Mean Glycated hemoglobin (HbA1c) (%)	12.2766 (10.7767)
Mean Fasting plasma glucose (FPG) (mg/dl)	198.4207 (26.9778)
Mean Post prandial glucose (PPG) (mg/dl)	345.3655 (63.5739)
Mean Body Weight (kg)	81.531 (13.9324)
Systolic Blood pressure (mmHg)	139.4414 (5.5225)
Diastolic Blood pressure (mmHg)	88.3931 (5.3713)

Changes In Body Weight:

Significant reduction in body weight at the end of 12 and 24 weeks of Dapagliflozin therapy was– 3.069 and -5.911 kg respectively from the baseline of 81.531 kg (p-value=0.000024). **Table 2** shows results of the study.

Table 2: Changes In Body Weight After Treatment Of Dapgalifozin

Changes in Body Weight				
Time Period	Mean (kg)	SD	P Value	Difference from Baseline
Baseline	81.531	13.9324	-	0.0
12 weeks	78.4621	13.6468	The p-value is 0.000024. The result is significant at p <0.05.	-3.069
24 weeks	75.6207	13.8655	The p-value is <0.00001. The result is significant at p <0.05.	-5.911

Results are shown graphically as follows:

Figure 1: Changes In Body Weight Due To Dapagliflozin Treatment

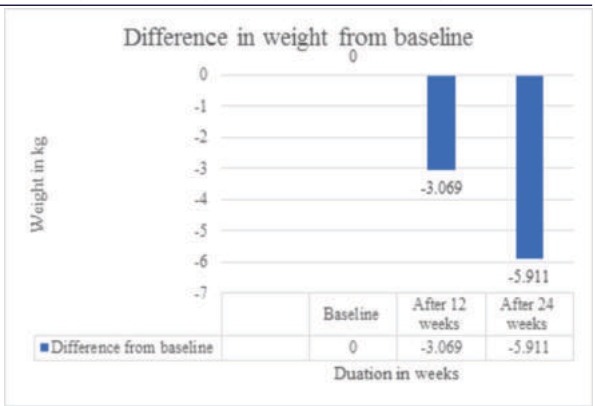

Figure 2: Difference In Body Weight From Baseline Due To Dapagliflozin Treatment

Effect Of Dapagliflozin On Glycemic Parameters:

Significant reduction in HbA1c i.e. -4.21 % (p-value is .000294) seen at the end of 24 weeks from baseline after adding Dapagliflozin on existing treatment. Table 3 highlights the results from study.

Table 3: Reduction Of HbA1c Due To Dapagliflozin

Changes in HbA1c				
Time Period	Mean (%)	SD	P Value	Difference from Baseline
Baseline	12.2766	10.7767	-	0.0
12 weeks	9.9521	10.9523	The p-value is 0.65114. The result is not significant at p <0.05.	-2.32
24 weeks	8.0662	0.7106	The p-value is <0.000294. The result is significant at p <0.05.	-4.21

Results are shown graphically as follows:

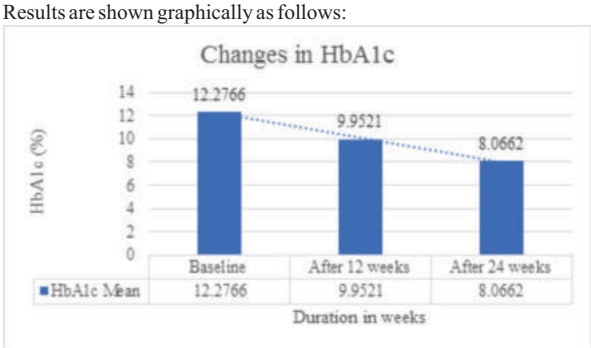

Figure 3: Changes In HbA1c Due To Dapagliflozin Treatment

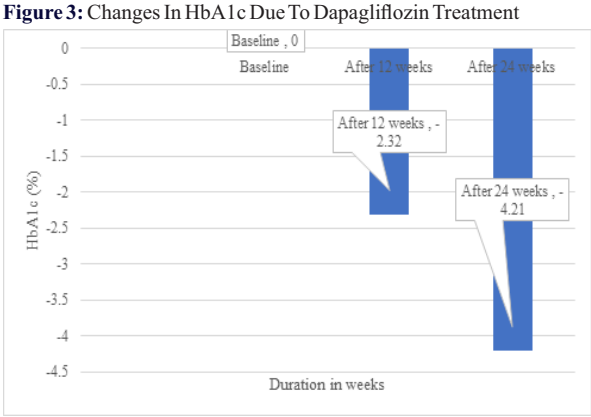

Figure 4: Difference In HbA1c After Dapagliflozin Treatment

Reduction in FPG & PPG seen at 12 & 24 weeks were -30.98 (p-value = <0.00001), -56.11 (p-value =<0.00001) for FPG and -40.39 (p-value < .00001), -69.95 (p-value = <0 .00001) for PPG seen which is significant from baseline after adding Dapagliflozin on existing treatment. Table 4 and 5 highlights results of the study.

Table 4: Changes In Fasting Plasma Glucose (FPG) Due To Dapagliflozin Treatment

Changes in FPG				
Time Period	**Mean (mg/dl)**	**SD**	**P Value**	**Difference from Baseline**
Baseline	198.4207	26.9778	-	0.0
12 weeks	167.4897	30.4058	The p-value is <0.00001. The result issignificant at p <0.05.	-30.98
24 weeks	142.3103	35.5755	The p-value is <0.00001. The result issignificant at p <0.05.	-56.11

Table 5: Changes In Post Prandial Glucose (PPG) Due To Dapagliflozin Treatment

Changes in PPG				
Time Period	**Mean (mg/dl)**	**SD**	**P Value**	**Difference from Baseline**
Baseline	345.3655	63.5739	-	0.0
12 weeks	304.9793	63.5195	The p-value is <0.00001. The result issignificant at p <0.05.	-40.39
24 weeks	275.4138	61.1458	The p-value is <0.00001. The result issignificant at p <0.05.	-69.95

Figure 5 shows the results of the study in graphical manner.

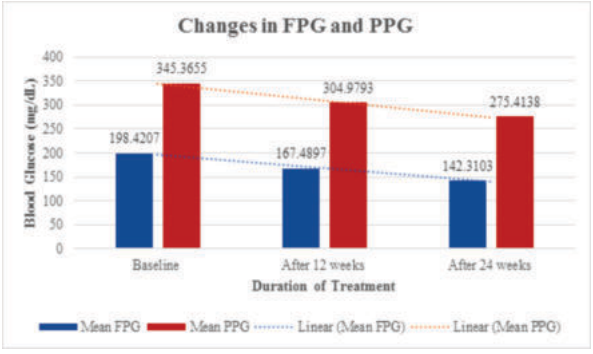

Figure 5: Changes in FPG and PPG after Dapagliflozin treatment

Figure 6 shows results of difference in FPG and PPG:

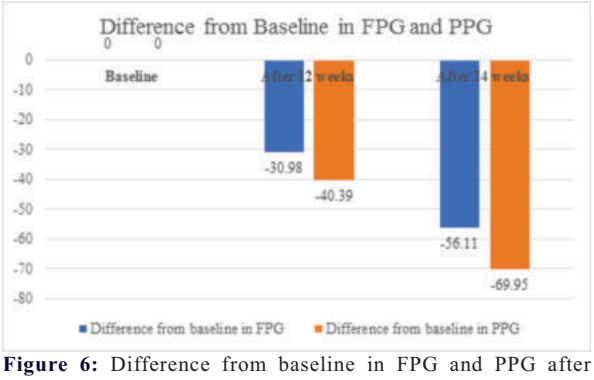

Figure 6: Difference from baseline in FPG and PPG after Dapagliflozin treatment

Effect On Blood Pressure (systolic and diastolic):

At the end of 12 and 24 weeks of addition of Dapagliflozin, significant reduction in systolic blood pressure were seen i.e. -3.8843 and -6.00 mm of Hg respectively from base line of 139.441 mm of Hg (p-value =<0.00001.) and reduction in Diastolic blood pressure were -2mm of Hg and -4 mm of Hg respectively from base line 88.3931mm of Hg (p-value = <0.00001) which was significant. Table 6 and 7 highlights results of the study.

Table 6: Changes In Systolic Blood Pressure After Dapagliflozin Treatment

Changes in Systolic Blood pressure				
Time Period	**Mean (mmHg)**	**SD**	**P Value**	**Difference from Baseline**
Baseline	139.4414	5.5255	-	0.0
12 weeks	135.5517	5.5975	The p-value is <0.00001. The result issignificant at p <0.05.	-3.889
24 weeks	133.4414	5.5225	The p-value is <0.00001. The result issignificant at p <0.05.	-6

Table 7: Changes In Diastolic Blood Pressure After Dapagliflozin Treatment

Changes in Diastolic Blood pressure				
Time Period	**Mean (mmHg)**	**SD**	**P Value**	**Difference from Baseline**
Baseline	87.9655	5.3713	-	0.0
12 weeks	85.9655	5.2477	The p-value is <0.00001. The result issignificant at p <0.05.	-2.0
24 weeks	83.9655	5.3318	The p-value is <0.00001. The result issignificant at p <0.05.	-4.0

Figure 7 and 8 showed the effect of Dapagliflozin on blood pressure in graphical manner.

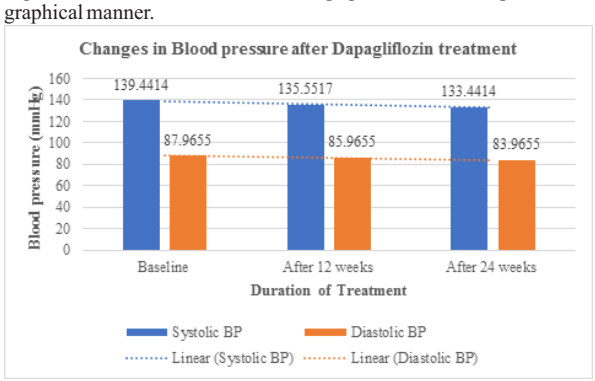

Figure 7: Changes In Blood Pressure After Dapagliflozin Treatment

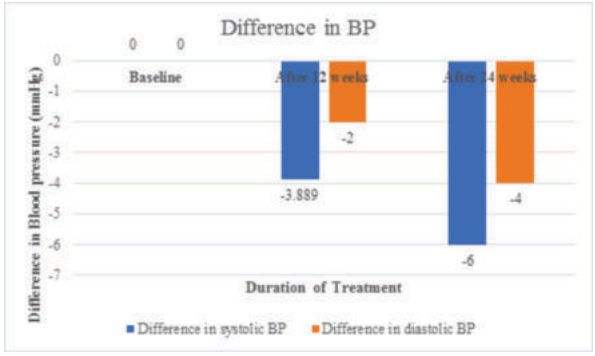

Figure 8: Difference In Blood Pressure After Dapagliflozin

DISCUSSION:

In the present retrospective, observational study, effectiveness of dapagliflozin was analyzed in total 145 patients who received Dapagliflozin in routine clinical management of type 2 diabetes mellitus, showing utility of Dapagliflozin in reducing body weight, glycemic parameters such as HbA1c, FPG, and PPG; and blood pressure (systolic and diastolic blood pressure) after duration of 24 weeks in state of Maharashtra, India.

In our study, at baseline, mean age was 50 years, and all patients were clinically known cases of type 2 diabetes mellitus. Mean body weight was 81.5 kg, mean HbA1c was 12.27 mg/dL, mean FPG was 198.42 mg/dL, and mean PPG was 345.36 mg/dL. Patients were having already diagnosed hypertension with mean values of 139.44 mmHg (systolic blood pressure) and 88.39 mmHg (diastolic blood pressure). Baseline values data indicates that results of DECLARE-TIMI 58 study can be applied to this study[10]. DECLARE TIMI[10] included ~60% of patients who had no previous cardiovascular disease whereas EMPA-REG[16], and CANVAS[17] studies had <1% and ~34% population with no previous cardiovascular disease respectively.

It is usual scenario that obesity and predominantly visceral/abdominal obesity are related with diabetes, insulin resistance, metabolic syndrome, and increased cardiovascular risk. Antidiabetic drugs such

as sulfonylureas, thiazolidinediones and insulin have weight gain as one of the important side effects. Whereas, metformin and DPP-4 inhibitors are weight neutral. GLP-1 agonists such as exenatide, liraglutide, and semaglutide are associated with weight loss. Weight loss has been a positive secondary outcome that has been consistently demonstrated in the Phase III studies of all available SGLT2 inhibitors[10,16,17].

Osmotic diuretic effect of treatment may be attributed to initial weight loss for SGLT2 inhibitors. However, sustained weight loss over the subsequent weeks is a consequence of caloric loss due to glycosuria. The glucose excreted in the urine is usually equal to net loss of 200–300 cal per day. Earlier studies have demonstrated that Dapagliflozin not only causes reduction in total body weight but also showed reduction of waist circumference (−1.52 cm) when compared to placebo[18].

The reductions in total body weight, fat mass, and waist circumference occurred in the context of sustained and significant glycosuria. Reduction in total body weight was due to loss in fat mass, and not loss of fluid or lean mass. It also demonstrated an initial rapid decline in weight over the first week, followed by a more gradual decline that had not plateaued at 24 weeks. This, coupled with a partial rebound in weight after discontinuation, suggests that diuresis may contribute to the initial weight loss, and loss in total body fat is predominant after this[18].

In our study, we observed significant reduction in body weight from baseline at the end of 12 weeks and 24 weeks which is -3.069 kg and -5.911 kg respectively. This finding is in accordance with findings of DECLARE-TIMI 58 and Spanish RWE studies. In the DECLARE TIMI 58 study, mean reduction in weight was 1.8 kg indicating capability of Dapagliflozin in reducing body weight[10]. Not only this, study done in Spanish patients (Spanish RWE study) showed 2.9 kg reduction in body weight due Dapagliflozin treatment within 6 months[13]. These findings are also supported by study from Bailey CJ et al in phase III randomized trial of 102 weeks wherein > 2.2 kg weight reduction was observed[19].

In DECLARE TIMI 58, mean reduction in HbA1c was 0.42% and in Spanish RWE study, it was 1.6%[10,13]. Studies by Bailey CJ et al.[5,19]also showed reduction in HbA1c of about 0.8%. Real world study results of our study showed reduction in HbA1c of 2.32% at the end of 12 weeks and 4.21% at the end of 24 weeks indicates glucose lowering ability of Dapagliflozin. The extent of reduction of body weight and HbA1c from our results was found to be higher as that of observed in earlier studies. This difference could be attributed to real world setting of the study.

Not only this, reduction in FPG levels (difference from baseline) was found to be -30.98 mg/dl at the end of 12 weeks and -56.11 mg/dl at the end of 24 weeks. Also, reduction in PPG levels was found to be (difference from baseline) -40.39 mg/dl at the end of 12 weeks and 69.95 mg/dl at the end of 24 weeks. Reduction of blood glucose levels (both FPG and PPG) can be attributed to the sodium glucose co-transporter (SGLT2) inhibition due to Dapagliflozin. This reduction in blood glucose levels is result of strong potency of 1200 times inhibition of SGLT2 by Dapagliflozin[4].

It has been observed that hypertension is most commonly found in patients of diabetes[20]. According to study from Kakabovet al[21], prevalence of hypertension in diabetic patients is 60.2%. In meta-analysis, it was found that SGLT2i reduced both systolic and diastolic blood pressure in diabetic patients by 3.76 mmHg and 1.83 mmHg respectively. Mechanisms of blood pressure reduction include enhancement of natriuresis, which in turn increases sodium excretion and lowers blood pressure due to SGLT2 inhibition effects[22]. Results of our study are in accordance with findings of earlier studies. It was found that at the end of 12 and 24 weeks, Dapagliflozin lowered systolic blood pressure by 3.8843 mmHg and 6.00 mmHg respectively from baseline and reduced diastolic blood pressure by 2 mmHg and 4 mmHg respectively from baseline.

Despite of promising results of the study, current study has some limitations. Being a retrospective observational study, no control group was available which reduces generalization of results of this study. However, this study was done in real world scenario providing effectiveness of Dapagliflozin in reducing body weight, glycemic parameters (FPG, PPG, and HbA1c), and blood pressure and also indicated safety of clinical use of Dapagliflozin in diabetic patients.

CONCLUSION

In clinical practice, after 24 weeks of treatment, Dapagliflozin was found to be effective in reducing body weight, glycemic parameters (FPG, PPG and HbA1c), and blood pressure (systolic and diastolic) when added to the patients who were already on anti-diabetic medications. Therefore, Dapagliflozin can be considered as a promising option for comprehensive management of patients with Type 2 diabetes mellitus.

Conflict Of Interest

Authors state that they do not have any conflicts of interest to declare.

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