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Original Article

Efficacy and Safety of Dapagliflozin in Treatment Naive or Treatment Experienced Type 2 Diabetes Mellitus Patients from South Punjab, Pakistan

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Abstract

Objective: To gather clinical data regarding weight reduction, glycemic control and safety of dapagliflozin oral tablets in Type 2 Diabetes Mellitus patients from South Punjab, Pakistan.

Methods: This prospective clinical trial was conducted at Department of Medicine, Bahawal Victoria Hospital, Bahawalpur from July 2019 to June 2020. A total of 400 patients of genders aged above 18 years, BMI > 25 and having type-2 diabetes mellitus were enrolled. Patients losing planned follow ups were excluded from the final analysis. Dapagliflozin as 5mg or 10mg was prescribed. Patients were asked to follow up after every 2 weeks up till 24 weeks. Change in weight, HbA1c, FBS, RBS and blood pressure was recorded during the follow ups.

Results: Out of a total of 400 patients enrolled, 238 (59.5%) were female. Overall, mean age was 48.06+10.38 years. Mean baseline body weight was noted to 78.81±15.67 kg. Mean HbA1c (%) was recorded to be 9.14+2.12. Statistically significantly reduction in body weight was noted at 4 weeks, 12 weeks and 24 weeks when compared to baseline values ($p<0.05$). Statistically significant reduction in HbA1c levels were recorded among study participants at 12th week (change in HbA1c=0.42+0.75, $p=0.0022$) and 24th weeks (change in HbA1c=0.85+0.67, $p<0.0001$). In terms of side effects, hypoglycemia was reported in 12 (3.0%) patients, polyuria 10 (2.5%), urinary tract infection 5 (1.3%) and genital infection 4 (1.0%) patients.

Conclusion: Dapagliflozin was found to have good efficacy in terms of body weight reduction and improvement in glycemic control among patients with T2DM. Overall, safety profile of dapagliflozin was good.

Keywords: Efficacy, safety, dapagliflozin, HbA1c, body weight.

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Introduction

Pakistan is ranked 4th globally in terms of percentage of population with diabetes mellitus (DM) as the prevalence of DM is around 26% in Pakistan.[1] Appropriate management options are required to manage this large proportion of population aiming timely prevention of diabetes linked microvascular and macrovascular complications.[2]

Dapagliflozin is known to be a selective "sodium-glucose cotransporter type-2 inhibitor (iSGLT2)" that blocks glucose resorption in the proximal tubule of the kidneys which increase urinary glucose excretion that helps in reduction of blood glucose levels.[3,4] Dapagliflozin has been licensed in Pakistan since 2017 for the management of type-2 diabetes mellitus (T2DM).[5,6] Systemic review conducted by Baker WL et al described Dapagliflozin to result in reduction in systolic blood pressure by 4 to 5 mmHg while it also resulted in reduction in 1.7 kg weight loss as well.[7] Other researchers have found Dapagliflozin to raise high-density lipoprotein cholesterol (HDL-c) as 1.8-4.4%[8] while it has been observed to result in reducing triglyceride concentration by 2.4-6.2%.[9] Researchers are currently evaluating roles of Dapagliflozin among patients having pre-diabetes and other types of diabetes.[9,10]

There is scarcity of local data about the safety and effectiveness of Dapagliflozin. As Pakistani population have differences in genetic, demographic, cultural and lifestyle characteristics when compared to other parts of the world, it is vital to find out the role of Dapagliflozin in our local population. The present study was conducted to gather clinical data regarding weight reduction, glycemic control and safety of Dapagliflozin oral tablets in T2DM patients from South Punjab, Pakistan.

Methods

This prospective clinical trial was conducted at Department of Medicine, Bahawal Victoria Hospital, Bahawalpur from July 2019 to June 2020. Approval from Institutional Ethical Committee was taken for this study. Written consent was sought from all study participants.

Sample size was calculated by clincalc.com for 0.752 anticipated mean of outcome (i.e. reduction in HbA1c) by use of study drug using 0.77±0.11 HbA1c reduction from published clinical study.[11] Sample size calculated was 312 at 0.05 α, using 80% power. By equating dropout rate 22.1% from previous study for the calculated sample size, the final adjusted sample size would be n = 400 using dropout rate equation as: Dropout Rate, N = n / (1- (z/100)), where N= final adjusted sample size, n= calculated sample size and Z%= dropout rate. So, finalized adjusted sample size was 400.

A total of 400 patients of genders aged above 18 years having type-2 diabetes mellitus were enrolled. All patients had BMI above 25 kg/m^2. All patients did not have any known hypersensitive to Dapagliflozin or any of its ingredients. Patients having type-I diabetes, or those with complaints of urinary tract infections, genital infections, or eGFR < 60 mL/min/1.73 m^2, having end stage renal disease or going through dialysis were were excluded. All pregnant females or those patients who had suspected ketoacidosis were also excluded from this study. Patients losing planned follow ups were excluded from the final analysis.

Demographic data of all patients like gender, age, weight, height, disease related information, blood pressure, comorbid conditions, number of concomitant medications and number of anti-hyperglycemic agents were noted. Baseline HbA1c, fasting blood sugar (FBS) and random blood sugar (RBS) levels were also recorded. Dapagliflozin prescribed as 5mg or 10mg was also noted. Patients whose blood sugar levels were not controlled on 5 mg in 2 weeks were given 10 mg once daily. Patients were asked to follow up after every 2 weeks up till 24 weeks. Change in weight, HbA1c, FBS, RBS and blood pressure was recorded during the follow ups.

Data was analyzed using SPSS version 26.0. Qualitative variables like gender area of residence and past history were represented as frequency and percentages. Quantitative variables like age, weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), number of comorbidities, concomitant medications, anti-hyperglycemic agents, RBS, FBS and HbA1c were calculated as mean and standard deviation. Paired sample t-test was employed to compare data between baseline and follow ups considering p value less than or equal to 0.05 as significant.

Results

Out of a total of 400 patients enrolled, 238 (59.5%) were female. Overall, mean age was 48.06+10.38 years. There were 352 (88.0%) patients with known history of T2DM whereas 48 (12.0%) were newly diagnosed cases of T2DM. In known T2DM patients, mean duration of T2DM was noted to be 4.51+2.1 years. Mean baseline body weight was noted to 78.81 ± 15.67 kg. Mean HbA1c (%) was recorded to be 9.14+2.12. Table 1 is showing baseline characteristics of all 400 patients enrolled for this study.

Table 1: *Baseline Characteristics of Patients (n=400)*

Characteristics		Number (%) / Mean±SD
Gender	Male	162 (40.5%)
	Female	238 (59.5%)
Age in Years		48.06±10.38
Area of Residence	Urban	148 (37.0%)
	Rural	252 (63.0%)
Past History	Type II Diabetes	352 (88.0%)
	Smoking	29 (7.3%)
	Hematologic Disease	12 (3.0%)
	Steroid Intake	35 (8.8%)
	Hypertension	270 (67.5%)
	Cancer	1 (0.3%)
Number of Comorbidities		2.06±1.38
Number of Concomitant Medications		5.41±2.63
Number of Antihyperglycemic Medications		2.11±1.02
Weight in kg		78.81±15.67
Height in feet		4.88±1.54
FBS in mg/dl		241.99±85.27
RBS in mg/dl		267.58±74.46
HbA1c (%)		9.14±2.12
Dapagliflozin Dose	**5mg**	92 (23.0%)
	10mg	308 (77.0%)

Table 2 is showing comparison of body weight at baseline and during various follow ups among study participants. Statistically significantly reduction in body weight was noted at 4 weeks, 12 weeks and 24 weeks when compared to baseline values (p<0.05).

Table 2: *Weight of the Patients at Various Follow Ups*

Follow up Interval	Weight (Mean±SD)	P-value
Baseline (n=400)	78.81±15.67	0.4781
2nd Week (n=372)	78.03±14.80	
Baseline (n=400)	78.81±15.67	0.0369
4th Week (n=347)	76.51±14.18	
Baseline (n=400)	78.81±15.67	0.0048
12th Week (n=320)	75.40±16.60	
Baseline (n=400)	78.81±15.67	0.0147
24th Week (n=268)	76.0±12.71	

Table 3 is highlighting comparison of HbA1c levels between baseline and 12th week and 24th week. Statistically significant reduction in HbA1c levels were recorded among study participants at 12th week (change in HbA1c=0.42+0.75, p=0.0022) and 24th weeks (change in HbA1c=0.85+0.67, p<0.0001). By the end of study period, there were 58 (21.6%) patients who achieved HbA1c < 7%.

Table 3: *HbA1c (%) of the patients at various follow ups*

Follow up Interval	HbA1c% (Mean±SD)	P-value
Baseline (n=400)	9.14±2.12	0.0022
12th Week (n=320)	8.72±1.37	
Baseline (n=400)	9.14±2.12	<0.0001
24th Week (n=268)	8.29±1.45	

Mean fasting blood sugar at baseline was noted to be 221.99+85.27 at baseline while it was found to be 154.50+24.36 at the end of the study period (24th week) (p=<0.0001). Mean random blood sugar was noted to be 267.58+74.46 mg/dl at baseline while it was found to be 189.42+38.77 at the end of the study period (24th week) (p=<0.0001). Mean systolic blood pressure was noted to be 142.24+21.47 mmHg at baseline while it was found to be 138.50+16.47 mmHg at the end of the study period (24th week) (p=0.0160). Mean diastolic blood pressure was noted to be 92.14+7.14 mmHg at baseline while it was found to be 90.40+5.48 at the end of the study period (24th week) (p=0.0008).

In terms of side effects, hypoglycemia was reported in 12 (3.0%) patients, polyuria 10 (2.5%), urinary tract infection 5 (1.3%) and genital infection 4 (1.0%) while remaining patients did not report any side effects. Five (1.3%) patients reported with foot ulcer within 4 weeks after starting the treatment and treatment was stopped in all those patients. There were 9 (2.3%) patients who left the dapagliflozin treatment due to no benefits.

Discussion

Present study is the 1st one from South Punjab, Pakistan that evaluated effectiveness and safety and of dapagliflozin in T2DM patients. We noted significant reduction in body weight, HbA1c, FBS, RBS, SBP and DBP in our study participants. It is also worth noting that 21.6% of patients achieved HbA1c < 7% after initiating dapagliflozin.

In this study, we found mean reduction of 2.30+1.49 kg body weight at 4th week (p=0.0369), 3.41+1.93 kg at 12th week (p=0.0048) and 2.81+3.96 kg at 24th week (p=0.0147). Our results are quite consistent with a previous local study conducted by Kamin M et al from Islamabad who evaluated effectiveness of dapagliflozin in terms of body weight reduction and found dapagliflozin to result in 1.95+3.03 kg exact body weight reduction after 24 weeks of treatment in T2DM patients.[12] List JF et al also noted dapagliflozin treatment to enhance hyperglycemia and assist weight loss among patients having T2DM by inducing controlled glucosuria with urinary loss of approximately 200-300 kcal/day.[13] Some researchers evaluating older patients with T2DM having concomitant cardiovascular disease have found dapagliflozin to improve glycemic control and well as weight reduction.[14,15]

In the present work, statistically significant reduction in HbA1c levels were recorded among study participants at 12th week (change in HbA1c=0.42+0.75, p= 0.0022) and 24th weeks (change in HbA1c= 0.85+0.67, p<0.0001). Past data endorse dapagliflozin to result in reduction in HbA1c levels which are quite similar to other oral anti-hyperglycemic medications but dapagliflozin has additional advantages in terms of beneficial effects on T2DM related comorbid conditions like cardiovascular diseases.[16,17] Some studies have also evaluated possible role of dapagliflozin in raising risk of cardiovascular risk in T2DM patient and found no associated risks involved.[18,19]

In the present study, no serious side effects were recorded among study participants as hypoglycemia, polyuria and urinary tract infection were the most common side effects reported in 3.0%, 2.5% and1.3% patients respectively. Past studies have reported occurrence of hypoglycemia in about 4% cases using oral dapagliflozin and our findings are consistent with the past data.[12,20] It is important to note that no major side effects or hypoglycemic episodes were noted in the

present study participants. Five (1.3%) patients reported with foot ulcer within 4 weeks after starting the treatment and treatment was stopped in all those patients. We are not sure that the relation between occurrence of diabetic foot ulcer after starting dapagliflozin is casual or not. We are living in high temperature area and many patients are working in the field. In future studies we may be considering high risk patients for diabetic foot.

The present study had some limitations as well. We were unable to evaluate the impact of concomitant anti-hyperglycemic agents on the outcomes measured in this study. Also, we did not analyze the decrease or increase in insulin dosage among patients who were suing insulin. Patients missing out on follow ups could have influenced the outcome as some of them are believed to have lost due to lack in efficacy of the treatment so their inclusion could have further strengthen the authenticity of the outcome data.

Conclusion

Dapagliflozin was found to have good efficacy in terms of body weight reduction and improvement in glycemic control among patients with T2DM. Overall, safety profile of dapagliflozin was good.

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Conflict of Interest

None

Funding Source

None

References

1. Basit A, Fawwad A, Qureshi H, Shera AS. Prevalence of diabetes, pre-diabetes and associated risk factors: second National Diabetes Survey of Pakistan (NDSP), 2016-2017. BMJ Open. 2018;8(8): e020961.
2. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of Diabetes 2017. J Diabetes Res. 2018; https://doi.org/10.1155/2018/3086167.
3. Oral EA. Closing the knowledge gap on cardiovascular disease in type 2 diabetes: the EMPAREG outcome trial and beyond. Drugs Context. 2016;5: doi: 10.7573/dic.212299.
4. Singh JSS, Fathi A, Vickneson K, Mordi I, Mohan M, Houston JG, et al. Research into the effect of SGLT2 inhibition on left ventricular remodelling in patients with heart failure and diabetes mellitus (REFORM) trial rationale and design. Cardiovasc Diabetol. 2016; 15(1):97.
5. United States Food and Drug Administration: Highlights of prescribing information for Farxiga (dapagliflozin) tablets. [Updated 2019, cited April 2021]. Available from website. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202293s015lbl.pdf]
6. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, doubleblind, placebo-controlled 102-week trial. BMC Med. 2013;11(1):43.
7. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014;8(4):262–75.e9.
8. Jayawardene D, Ward GM, O'Neal DN, Theverkalam G, MacIsaac AI, MacIsaac RJ. New treatments for type 2 diabetes: cardiovascular protection beyond glucose lowering? Heart Lung Circ. 2014;23(11): 997– 1008.
9. Faerch K, Amadid H, Nielsen LB, Ried-Larsen M, Karstoft K, Persson F, et al. Protocol for a randomised controlled trial of the effect of dapagliflozin, metformin and exercise on glycaemic variability, body composition and cardiovascular risk in prediabetes (the PRE-D Trial). BMJ Open. 2017;7(5):e013802.
10. Ferreira-Hermosillo A, Molina-Ayala MA, Molina-Guerrero D, Garrido-Mendoza AP, Ramírez-Rentería C, Mendoza-Zubieta V, et al. Efficacy of the treatment with dapagliflozin and metformin compared to metformin monotherapy for weight loss in patients with class III obesity: a randomized controlled trial. Trials. 2020;21(1):186.
11. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010;33(10):2217-24.
12. Kamin M, Ishtiaq O, Raashid K, Wahab MU, Khan SA, Raja U. The outcomes of dapagliflozin use in real-life clinical settings in endocrinology clinics of Islamabad, Pakistan. Cureus. 2020;12(6):e8565.
13. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009; 32: 650–7.
14. Leiter LA, Cefalu WT, de Bruin TW, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc. 2014;62:1252–1262.
15. Kosiborod M, Gause-Nilsson I, Xu J, Sonesson C, Johnsson E. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and concomitant heart failure. J Diabetes Complications. 2017;31(7): 1215–21.

16. Sanz-Serra P, Pedro-Botet J, Flores-Le Roux JA, Benaiges D, Chillaron JJ, et al. Dapagliflozin: beyond glycemic control in the treatment of type 2 diabetes mellitus. Clínica E Investigación En Arteriosclerosis. 2015;27(4):205–11.

17. Weber MA, Mansfield TA, Alessi F, Iqbal N, Parikh S, Ptaszynska A. Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin-angiotensin system blockade. Blood Press. 2016; 25(2): 93-103.

18. Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. Cardiovasc Diabetol. 2016;15(1):37.

19. Toulis KA, Willis BH, Marshall T, Kumarendran B, Gokhale K, Ghosh S, et al. All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in the health improvement network database. J Clin Endocrinol Metab. 2017;102(5):1719–25.

20. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35(7):1473-8.