Original Article

Dapagliflozin in the management of type 2 diabetes mellitus: a real-life experience in Bangladesh

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ABSTRACT

Background: *Dapagliflozin, a selective renal sodium-glucose cotransporter-2 inhibitor (SGLT2i), lowers plasma glucose by increasing urinary excretion of glucose. This study evaluated the efficacy and safety of dapagliflozin as add on therapy for a selected group of Bangladeshi type 2 diabetic patients.*

Methods: *This was a 24-week, open-label, prospective, real-life study including type 2 diabetic patients with glycated hemoglobin (HbA1c) 7.0–10% (N =53). Study subjects were selectively assigned to dapagliflozin 5 mg once-daily in the morning along with ongoing oral anti-diabetic drug (OAD). The primary end point was to see the safety (adverse events) and efficacy (reduction of fasting and post-prandial blood glucose, HbA1c) of dapagliflozin.*

Results: *Mean HbA1c changes from baseline to week 24 was – 1.15 ± 0.82 % (P = 0.000) and weight reduction was – 2.49 ± 0.32 kg from base line (P=0.000). Among total study subjects, 6 (11.3 %) had developed urinary tract infection (UTI). There were no major episodes of hypoglycemia or renal function deterioration.*

Conclusion: *Dapagliflozin showed significant reduction of HbA1c as add on therapy. The low incidence of hypoglycemia and UTI make dapagliflozin as an acceptable addition to existing treatment option for type 2 diabetes in Bangladeshi population.*

Key words: *dapagliflozin, glycemic control, sodium-glucose cotransporter-2 inhibitor, type 2 diabetes mellitus.*

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by insulin secretary defects, insulin resistance and a progressive loss of â-cell function, which causes an increase in plasma glucose.[1] Type 2 diabetes mellitus (T2DM) is the commonest type of diabetes, comprising about 90% of the diabetes cases around the world and over 90% of them are either overweight or obese.[2] Hyperglycaemia is associated with microvascular and macrovascular complications in people with diabetes, the incidence and severity of these complications can be reduced by early and sustained glycaemic control.[3]

Diabetes prevalence shows a continuous increasing trend in South Asia. Although well-established treatment modalities exist for T2DM management, they are limited by their side effect profile.[4] Bangladesh is one of the 6 countries of the IDF SEA region and had 8.4 million patients with diabetes and projected to have 10.4 million in 2045. The overall glycemic control is not satisfactory here.[2]

The principal goal of effective treatment of T2DM is to reduce blood glucose.[5] T2DM is characterized by systemic dysregulation of metabolism and is strongly associated with obesity.[6] Glucose-lowering agents that reduce body weight are preferable to those that have no effect on or increase it. Cardiovascular diseases, for which obesity is a major risk factor, are estimated to cause 40% of all deaths attributed to T2DM.[7]

At present, there are different kinds of anti-diabetic agents utilizing different mechanisms to lower blood glucose level in patients with T2DM inadequately controlled by diet and exercise. However, most of them are dependent on insulin secretion or function, it is usually insufficient to achieve or maintain glycaemic goals with the progression of diabetes and progressive

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loss of â-cell function. Treatment for T2DM requires new mechanisms of action and synergistic drugs.[8]

In recent years, sodium glucose co-trasnsporter-2 inhibitors (SGLT2i) had been added in these line and showed promise. SGLT2i block the SGLT2 recepter of proximal renal tubule, reducing glucose and sodium reabsorption and increasing glycosuria and fluid loss.

Dapagliflozin is a new SGLT2i indicated alongside for improving glycaemic control in adults with T2DM licensed in Europe in 2012[9] and the USA in 2014.[10] In randomized control ledtrials(RCTs)[11-18], dapagliflozin was found to improve glycaemic control, with mean difference in HbA1c of~5.5 mmol/mol (0.52%) vs control groups.[19-20] It has been reported that with dapagliflozin, the primary safety endpoint of non-inferiority for major adverse cardiovascular events was met and that, there was a significant reduction in one of two primary efficacy cardiovascular (CVD) end points.[21,9] There are few case reports detailing the development of (often euglycemic) diabetic ketoacidosis (DKA) following initiation of SGLT2i therapy, with increased dis proportional signaling in both European Medicines Agency (EMA) and FDA pharmaco vigilance data bases.[23,24] It is unclear whether this is a true drug effect. Dapagliflozin is licensed for those between 18 and 75years of age, with an eGFRe"60 ml/min/1.73m2 and not receiving pioglitazone or loop diuretics.

In this study, it was aimed to determine whether the effects of dapagliflozin on HbA1c, fasting (F) and post-prandial blood sugar is achievable or not. Second, we aimed to analyze the adverse events with dapagliflozin.

METHODS

This was an open-label, prospective study, carried out in outdoor consultations by the investigators in their respective practice setups from January to December 2019. The purpose and procedure of the study was discussed and informed consent was taken from patients. Information about the patient was recorded in the structured data collection sheet. Total 53 patients were enrolled in the study. All the patients were non-pregnant adult with T2DM, having HbA1c 7%-10%, e-GFR > 60 ml/min with no history of any diabetic emergency, chronic liver disease, recent UTI and history of previous use of SGLT2i. All the patients were evaluated for F, post meal (ABF), HbA1c, lipid profile, S. creatinine, e-GFR, ALT, Urine RME and urine for ketone body in initial visit (Visit 1) and two separate consultations on three months interval (visit 2 after 3 months and visit 3 after 6 months of initial visit). Dapagliflozin (5mg) once daily was added to all patients with their ongoing anti-diabetic regimens. Dose adjustment of anti-diabetic regimens and continuation of dapagliflozin were independently decided by concerned investigator. Urine culture was done in patients having pus cell in urine and patients having reports suggestive of UTI were excluded from the study. Data were analyzed by computer with the help of Statistical Package for the Social Sciences (SPSS) version 20.0 by using appropriate statistical tool like student 's' 't' test. Statistical significance was set at a P value <0.05 level.

RESULTS

During the study period, a total 53 patients including 32(60.4 %) females were enrolled. Dapagliflozin 5 mg was added in every patient; out of them, 6 (11.3 %) patients developed UTI during the study period. Base line characteristics of the study subjects are shown in Table I. At the end of the study, 27.65 % patients achieved HbA1c< 7 % and mean HbA1cwas 7.38±0.86 %, HbA1c reduction at 24 weeks - 1.15±0.82 % from baseline which was statistically significant (P = 0.000).

Table I Baseline demographic characteristics of the study population (N = 53)

Characteristics	Results
Mean age (years)	47.3± 11.4
Male : Female	1:1.52
Duration of DM (years)	6.7 ± 7
Hypertension present (%)	43.4
Systolic BP (mm of Hg)	131 ± 14.1
Diastolic BP (mm of Hg)	80.5±7.7
Weight (kg)	71.3 ± 14.3
BMI (kg/m^2)	28.1±4.7
Anti diabetic regimen	
Metformin monotherapy (%)	18.9
Metformin with OAD (%)	22.6
Metformin with Insulin (%)	26.4
Sulphonylureamonotherapy (%)	13.2
Insulin (%)	18.9
Mean Fasting (mmol/L)	9.5±1.7
Mean PPG (mmol)	14.1±2.5
Mean HbA1c (%)	8.6±1.2
Mean e-GFR (ml/min/1.73 m2)	76.8±19.5
Mean Creatinine (micromole/L)	85.3±14.4
Mean ALT(U/L)	39.8±11.9
Mean Chol (mg/dl)	198.1±39.5
Mean HDL (mg/dl)	33.6±7.6
Mean LDL (mg/dl)	111.6±34.7
Mean TG (mg/dl)	233.8±179.8
Mean Urinary Pus cell (HPF)	2.02±1.5

Table II Comparison of different clinical and biochemical parameters among the patients on dapagliflozin (N = 47)

Parameter	Baseline	Final visit	P value
Fasting (mmol/)	9.4±1.6	7.8±1.3	0.000
ABF (mmol/L)	14.1±2.6	9.9±1.7	0.000
HbA1c (%)	8.5±1.2	7.4±0.9	0.000
Creatinine (umol/l)	85.2±14.2	84.29±14.8	0.620
e-GFR (ml/min)	76.6±19.4	74.9±23.3	0.564
Chol (mg/dl)	193.8±38.6	184.9±32.3	0.000
HDL (mg/dl)	33.3±7.1	33.6±6.9	0.476
LDL (mg/dl)	108.5±33.6	97.1±27.2	0.000
TG (mg/dl)	237.9±190.2	185.1±59.6	0.016
ALT (mg/dl)	40.4±12.2	38.1±10.3	0.025
Na (mmol/L)	138.3±3.1	136.4±1.9	0.002
Urinary Pus cell (HPF)	2.2 ±1.5	2.5±1.6	0.255
Weight (kg)	71.9±14.9	69.3±14.1	0.000
BMI (kg/m^2)	28.5±4.5	27.5±4.3	0.000

Reductions in F, ABF were apparent and were statistically significant at week 24 (Table II). Mean body weight decreased – 2.49±0.32 kg, reductions from base line and was statistically significant (Table II). HbA1c and body weight changes were significant in three follow up visits at baseline 3rd month and 6th months (Figures 1 & 2 respectively).

Treatment with dapagliflozin did not result in any significant changes from baseline in serum ALT, HDL,TG and no relevant changes in any renal function parameter including serum creatinine, e-GFR or increasing the number of urinary pus cells. Significant (P = 0.002) reduction of serum sodium was observed but not in the level of requiring hospital admission.

Adverse events are summarized in Table III. There was no death or major episodes of hypoglycemia in this study. Among the total study subjects, 6 patients (11%) developed UTI and genital infection and required to discontinue dapagliflozin. There was no ketonuria in any study subject in fasting urine samples.

Table III Adverse events during study period (N = 53)

Adverse events	N (%)
UTI	6 (11%)
Major hypoglycemia	-
Ketonuria	-

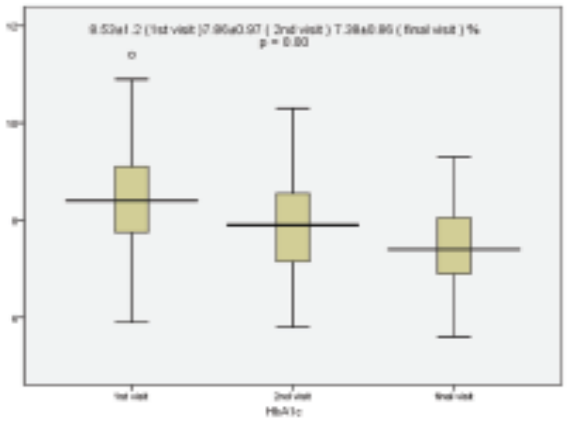

Figure 1 HbA1c among study subjects (N =47) in three visits at baseline 3rd month and 6th month follow up

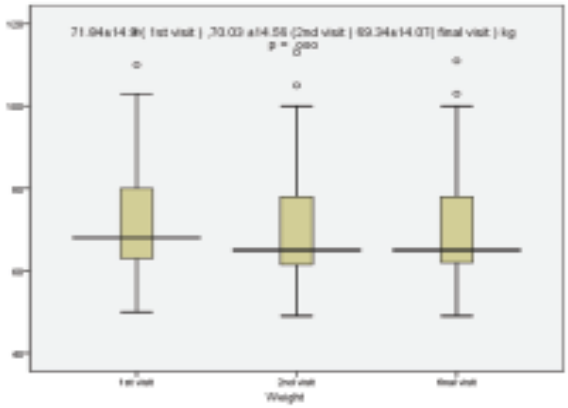

Figure 2 Weight changes among study subjects (N =47) in three visits at baseline 3rd month and 6th month follow up

DISCUSSION

The efficacy and safety findings of dapagliflozin observed in this study are similar to those in other studies of SGLT2i treatment as monotherapy in non-Asian populations. In a Phase III study of dapagliflozin as monotherapy in treatment-naive patients enrolled from the United States, Canada, Mexico and Russia, mean HbA1c reductions from baseline at week 24 were 0.23% with placebo, 0.77% with dapagliflozin 5 mg and 0.89% with dapagliflozin 10 mg, with no major hypoglycemic episodes.[25] In the current study of Bangladeshi patients with T2DM and inadequate glycemic control with diet, exercise and other OAD, dapagliflozin achieved the primary end point of statistically significant mean reductions in F, ABF and HbA1c at 6 months.

In this 6 months study, the mean weight reductions was 2.7 kg and BMI (kg /m^2) reduction was -0.99. This observation for dapagliflozin in the current study are similar to the mean weight loss observed in the study of dapagliflozin in the Western population, which was 2.83 kg However, the baseline patient characteristics in the current study are typical of an Asian population,[25-28] with mean weight and BMI lower than observations from comparable, non-Asian patients with T2DM.[25,29] A study of dapagliflozin comparing healthy Chinese vs non-Chinese subjects has also demonstrated similar efficacy.[30] A study by Bolinder et al [31] showed reduction of total body fat mass (both visceral and subcutaneous adipose tissue) and thus reducing total body weight among dapagliflozin users. Relief of glucotoxicity, improved â-cell function and increase in mean insulin sensitivity was observed in another study which was consistent with weight loss.[32]

Considering the adverse event of dapagliflozin, 6 patients (11%) had developed UTI and were excluded from the current study as the drug was discontinued. Other side effects like ketonuria, hypoglycemia was absent among this current study population. Among diabetic population, the relative risk of genital infections and UTIs is increased as a whole which may be explained by inadequate glycemic control, changes in immune function or presence of glycosuria. There are few studies, where data shows increase the incidence of genital infections among SGLT2i users; but the relationship to UTI with drug use is uncertain and requires additional long-term studies to confirm this issue.[33]

No adverse events regarding deterioration of renal function were reported in this study and there was no evidence of an adverse impact on renal function as evidenced by no significant change in S. creatinine or e-GFR throughout the study period. In this current study, reductions from baseline in mean blood pressure were observed, without an increase in the incidence of orthostatic hypotension, dehydration or hypovolemia.

Numerically higher rates of dyslipidemia with dapagliflozin versus placebo have been reported, with small elevations in total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol and reductions in triglycerides .[34] Contrarily, the present study revealed significant improvement of LDL, total cholesterol, triglyceride and also ALT at the end of study period from the baseline. From the current study it is evident that the newer drug dapagliflozin was well tolerated and significantly lowered HbA1c, F and body weight in patients with T2DM with minimal adverse events. Patients with T2DM have a higher risk of genital infection, treatment with dapagliflozin increases urine glucose excretion and increases the risk of genitourinary infections. The results of this current study still need more large-sample, long-course and randomized controlled trials to evaluate and establish the result. The limitation of the study was that the sample size was small and follow up period was short to comment largely.

Conclusion

This study reveals that dapagliflozin as add on therapy had significant achievement of glycemic control and weight reduction without significant increase in UTI or ketonuria among Bangladeshi population.

Authors' contribution: MFA was the principal investigator and did data analysis and result interpretation. FA contributed in writing, compiling and overall review of the manuscript. MFA and FA contributed equally to the research and manuscript preparation. SMS, SS, MI contributed in writing and editing the manuscript. All authors read and approved the final manuscript for submission.

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