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Original Article

Efficacy of Empagliflozin as Add-on Therapy in Patients with Uncontrolled Type 2 Diabetes Mellitus

Mita Rani Joysoual,[1] Shahin Ara,[2] Md. Nazmul Haque,[3] Rita Ghosh,[4] Tamanna Afroze,[5] Saqib Salah Aufi [6]

Abstract

Background: Metformin is recommended as first-line pharmacotherapy for patients with type 2 Diabetes Mellitus (T2DM) who fail to achieve glycemic control through lifestyle modification. Metformin initially lowers blood glucose, but as diabetes progresses, it alone frequently fails to maintain glycemic control, and additional therapies are required. Empagliflozin is a potent and selective sodium-glucose co-transporter 2 (SGLT2) inhibitor that is effective in reducing blood sugar levels as monotherapy or add-on to existing therapy with significant improvements in glycemic control and weight.

Materials & Methods: This quasi-experimental study was conducted in the Department of Pharmacology and Therapeutics in collaboration with Rajshahi Diabetic Association General Hospital, Rajshahi, for one year from January 2021 to December 2021 on 50 uncontrolled T2DM patients (glycosylated hemoglobin, HbA1c > 7.0 to ≤ 10.5%) for more than 12 weeks. The investigating drug, empagliflozin 10 mg (1 tablet) as a once-daily dose, was added to the ongoing treatment of each patient as 3rd line treatment and was followed up at 6 and 12 weeks.

Results: The mean FBS at baseline was 10.8 mmol/L, which declined to 8.5 mmol/L at six weeks and then to 7.2 mmol/L after 12 weeks of intervention with Empagliflozin as add-on therapy in patients with uncontrolled T2DM. The overall reduction of FBS from baseline to 12 weeks of intervention was statistically significant ($p < 0.001$). Simultaneously the mean HbA1c also reduced from 9.4% to 7.7% after six weeks and to 7.1% after 12 weeks of intervention ($p < 0.001$). The mean systolic and diastolic blood pressures decreased from 129 mmHg to below 120 mmHg ($p < 0.001$) and 82.3 mmHg to below 80 mmHg ($p = 0.029$), respectively, after three months of intervention.

Conclusion: Empagliflozin as add-on therapy responded well in patients with uncontrolled T2DM (previously treated with metformin combined with either sulfonylurea or DPP-4 inhibitors and/or supplemented by insulin) in achieving glycemic control.

Keywords: Type 2 Diabetes Mellitus, add-on therapy, glycemic control.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder caused by carbohydrate, fat, and protein metabolism disturbances due to defects in insulin secretion, insulin action, or both resulting in chronic hyperglycemia. Chronic hyperglycemia of diabetes leads to damage or dysfunction of

[1] Lecturer, Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh.
[2] Professor & Head, Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh.
[3] Lecturer, Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh.
[4] Lecturer, Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, Bangladesh.
[5] Assistant Professor, Department of Microbiology, Udayan Dental College, Rajshahi, Bangladesh.
[6] Medical Officer, Rajshahi Diabetic Association General Hospital, Rajshahi, Bangladesh.

various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] Diabetes mellitus is a leading cause of death and disability worldwide.[2,3] The magnitude of DM in Bangladesh is increasing alarmingly. Its global prevalence was about 8% in 2011 and is predicted to rise to 10% by 2030.[4] Prevalence of DM in our country is about 8.4 million or 10% of the total population.[5]

Diabetes mellitus is an incurable disease but can be controlled by dietary modification (dietary control and regular physical exercise) and with or without anti-diabetic medicine.[6] Uncontrolled diabetes may lead to several complications like coronary heart disease, stroke, chronic kidney disease, diabetic retinopathy, erectile dysfunction, neuropathy, gangrene, and gastroparesis.[5] Approximately half or more of patients with T2DM do not obtain a glycosylated hemoglobin (HbA1c) level lower than 7%.[6]

The therapeutic goals of T2DM are to achieve and maintain glycemic targets, mitigate hypoglycemia, and reduce the development of complications that lead to morbidity and mortality, especially cardiovascular disease.[7,8] As T2DM progresses, with loss of β-cell function and increased insulin resistance, the use of agents utilizing pathways dependent on insulin becomes increasingly difficult. The majority of patients fail to achieve their target control of HbA1c, with the failure rate being approximately 63%.[7,8,9]

In addition, steady increases in weight are observed in patients with T2DM.[10,11] Thus, there is still a great unmet need for effective and well-tolerated anti-diabetic agents that can be used in combination with existing treatments to improve glycemic control in patients with T2DM without the risk of hypoglycemia and weight gain. Maintaining intensive glucose control early in the disease process may lead to legacy benefits that persist beyond the period of treatment. Therefore, when metformin fails to achieve glycemic control, an add-on combination therapy with two oral hypoglycaemic agents may be beneficial.[12] When these combinations also fail, insulin is given to achieve glycemic control. But even then, some T2DM may continually show resistance, and an even more potent additional anti-diabetic agent is required to bring glycemic control. Thus, the continuous efforts in developing novel treatment modalities led to the introduction of new medications in the past ten years, such as glucagon-like peptide one agonist, DPP-4 inhibitors, SGLT2 inhibitors, etc.

Empagliflozin has been approved to treat T2DM insufficiently controlled by diet and exercise and other first and second-line anti-diabetic agents. By inhibiting SGLT2, a protein involved in glucose reabsorption by the kidneys, empagliflozin lowers blood glucose levels. Instead of being reabsorbed into the bloodstream by blocking SGLT2, empagliflozin removes glucose through urine. Numerous clinical studies have shown the effectiveness of Empagliflozin, but the recent reports of bone fractures and lower limb amputations (LLAs), which are the two types of serious side effects associated with another drug in this class, have triggered a review of the risk associated with taking SGLT2 inhibitors. The objective of this study was, therefore, to observe the clinical outcomes of empagliflozin 10 mg as a once-daily dose over 12 weeks when added as a third-line oral hypoglycemic agent in patients with uncontrolled diabetes.

Materials and Methods

This was a quasi-experimental study at the Department of Pharmacology and Therapeutics, Rajshahi Medical College, Rajshahi, from January 2021 to December 2021 to observe the clinical outcomes of empagliflozin 10 mg as once daily dose over 12 weeks when added as third line oral hypoglycemic agent in patients with uncontrolled diabetes. Adults with inadequately controlled T2DM patients (HbA1c > 7.0 to ≤ 10.5%) despite diet, physical exercise, and a stable glucose-lowering treatment (treated with metformin combined with either sulfonylurea or DPP-4 inhibitors and/or insulin therapy) for more than 12 weeks were the study population. A systematic random sampling technique was employed to enroll the required number of patients with defined eligibility criteria. Consulting with the supervisor and reviewing the previously published literature

researcher developed the research instrument for the study. Having obtained ethical clearance from the Institutional Review Board (IRB) of Rajshahi Medical College and informed consent from the patients (based on predefined eligibility criteria), a total of 50 uncontrolled adult type 2 diabetic patients were included in the study. The primary outcome measure was a change in HbA1c from baseline to end-point of the study (12 weeks), while the secondary outcome measures were changes in fasting blood sugar, BMI, systolic and diastolic blood pressures from baseline to 3 months. The proportion of patients who achieved HbA1c levels lower than 7% after 12 weeks of treatment was also assessed. Seven patients dropped out at the second follow-up from the first follow-up. All efforts were made to collect data accurately. The test statistics used to analyze the data were descriptive statistics, Paired sample t-Test, and Repeated Measure ANOVA statistics. All statistical analysis was done by SPSS (version 24) for Windows. The level of significance was set at 0.05, and a p-value < 0.05 was considered significant.

Results

Table I. Distribution of patients according to age (n = 50)

Demographic characteristics	Frequency	Percentage
Age (years)		
31- 40	11	22.0
41-50	14	28.0
51-60	15	30.0
> 60	10	20.0

*****Mean age = 51.6 ± 10.4 yrs; range = (31 – 70) yrs.

Most (30%) of the patients belonged to the age group of 51-60 years, less than 3/10th (28%) were age group of 41-50 years, more than 1/5th (22%) were 31-40 age group and 1/5th (20%) were > 60 years. The mean age of the respondents was 51.6±10.4 years (Table-I).

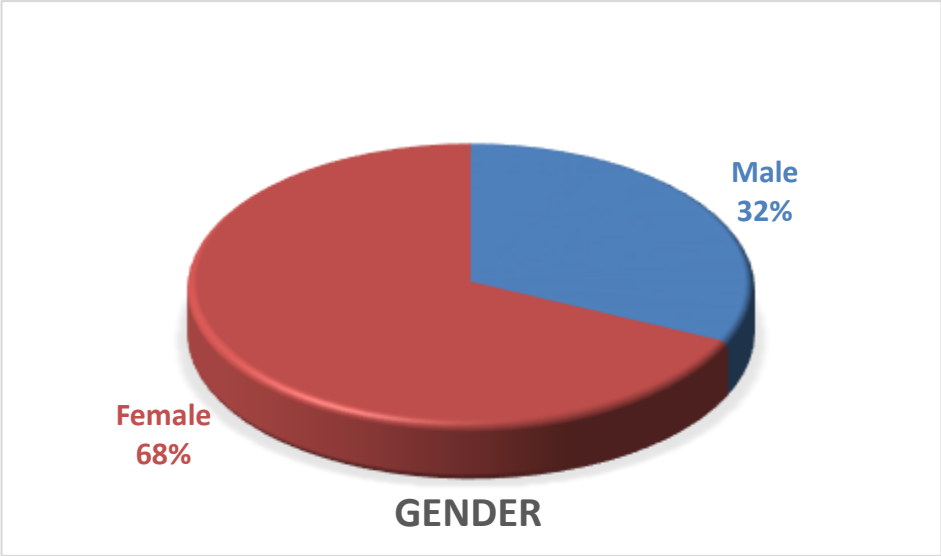

Figure I: Gender distribution of the patients (n=50)

Over two-thirds (68%) of the patients were female, and 32% were male, giving a female-to-male ratio of roughly 2:1 (Figure 1).

Table II: Distribution of patients by their BMI (n = 50).

BMI (kg/m^2)	Frequency	Percentage
<18.5 (Underweight)	1	2.0
18.5 to 24.9 (Normal)	7	14.0
25.0 to 29.9 (Overweight)	23	46.0
30.0 to 39.9 (Obese)	19	38.0

Nearly half (46%) of the patients were overweight, 38% were obese,14% had normal BMI, and only the remaining 2% were underweight (Table II).

Table III: Distribution of patients based on duration of diabetes (n = 50).

Duration of diabetes since first diagnosis (years)	Frequency	Percentage
< 5	15	30.0
5 to 10	14	28.0
11 to 15	12	24.0
16 to 20	5	10.0
> 20	4	8.0

*****Mean duration = 9.1 ± 6.4 yrs; range = (1 – 22) yrs.

About one-third (30%) of the patients had diabetes of < 5 years' duration, 28% had 5-10 years, 24% had 11-15 years, 10% had 16-20 years, and 8% had > 20 years duration with mean duration of diabetes being 9.1 ± 6.4 years (range:1 – 22) years (Table III).

Table IV: Distribution of patients by their medications received (n = 50).

Medications received	Frequency	Percentage
Metformin + sulfonylureas	14	28%
Metformin + sulfonylureas + insulin	1	2%
Metformin + DPP4 inhibitor	8	16%
Metformin + DPP4 inhibitor + insulin	16	32%
Metformin + insulin	5	10%
Metformin + sulfonylureas + DPP4 inhibitor	6	12%

The study patients invariably received metformin. The most commonly prescribed combined anti-diabetic medication was Metformin+DPP4 inhibitor+Insulin (32%), followed by Metformin+Sulfonylureas (28%),

Metformin+DPP4 inhibitor (16%), Metformin+Sulfonylureas+DPP4 inhibitor (12%), Metformin+Insulin (10%) and Metformin+Sulfonylureas+Insulin (2%) (Table IV).

Table V: Monitoring of fasting blood sugar at different time intervals (n=43).

Time of evaluation	Level of FBS (mmol/L)	F, P-value[#]
At baseline	10.8 ± 2.9	
At six weeks	8.5 ± 1.4	1726.7, <0.001
At 12 weeks	7.2 ± 1.1	

(NB- Out of 50 patients, 43 were considered here)

Data were analyzed using **Repeated Measure ANOVA statistics** and were presented as **mean ± SD**.

The mean FBS at baseline was 10.8 mmol/L which decreased to 8.5 mmol/L at six weeks and then to 7.2 mmol/L at 12 weeks after administration of Empagliflozin. So, the overall reduction of FBS from baseline to 12 weeks after the intervention was statistically significant ($p < 0.001$) (Table V).

Table VI: Monitoring of HbA1c at a different time interval (n=43).

HbA1c (%)		F, P-value[#]
At baseline	9.4 ± 1.1	
At six weeks	7.7 ± 0.7	6765.4, <0.001
At 12 weeks	7.1 ± 0.7	

(NB- Out of 50 patients, 43 were considered here)

Data were analyzed using **Repeated Measure ANOVA statistics** and were presented as **mean ± SD**.

The mean HbA1c at baseline was 9.4% which significantly reduced to 7.7% after six weeks and to 7.1% after 12 weeks of intervention ($p < 0.001$) (Table VI).

Table VII: Changes in blood pressure before and after intervention (n=43)

Blood pressure	Level of evaluation		p-value[#]
	At baseline	At 12 weeks of intervention	
Systolic Blood Pressure (mmHg)	128.8 ± 13.4	119.2 ± 8.7	< 0.001
Diastolic Blood Pressure (mmHg)	82.3 ± 9.7	79.8 ± 5.4	0.029

(NB- Out of 50 patients, 43 were considered here)

Data were analyzed using paired-sample t-test and were presented as mean ± SD.

The mean systolic blood pressure at baseline was 129 mmHg which reduced to below 120 mmHg after 12 weeks of intervention ($p < 0.001$). Likewise, the mean diastolic blood pressure at baseline was 82.3 mmHg which decreased significantly to 79.8 mmHg at the end-point of the study ($p = 0.029$) (Table VII).

Discussion

Type 2 diabetes mellitus (T2DM) is a chronic disease that is multifactorial and manifested by progressive β-cell failure. Due to the progressive nature of the disease, most patients with T2DM will ultimately require multiple antidiabetes drugs to maintain glycemic control. The present study was conducted to observe the efficacy of Empagliflozin as an add-on therapy in patients with uncontrolled T2DM (previously treated with metformin combined with either sulfonylurea or DPP-4 inhibitors and/or supplemented by insulin).

The present study demonstrated that the mean FBS at baseline was 10.8 mmol/L which decreased steadily to 8.5 mmol/L at six weeks and then to 7.2 mmol/L after 12 weeks of intervention with Empagliflozin as add-on therapy in patients with uncontrolled T2DM (previously treated with metformin combined with either sulfonylureas or DPP-4 inhibitors and/or supplemented by insulin). The overall reduction of FBS from baseline to 12 weeks of intervention is statistically significant ($p < 0.001$), which was in line with the study of Puli and Vanjari and Søfteland and associates.[13,14]

Puli and Vanjari,[13] in a prospective study in India, demonstrated that the mean change of FBS from baseline to 12 weeks was 26 mg/dl. Søfteland and associates [14] evaluated the efficacy and safety of empagliflozin as add-on therapy in inadequately controlled type 2 diabetic patients under treatment of linagliptin and metformin and found that fasting blood sugar (FBS) and weight was significantly reduced in both empagliflozin groups versus placebo ($p<0.001$ for all comparisons). empagliflozin was not associated with a higher rate of hypoglycemia (low blood sugar) versus placebo, except in patients also treated with insulin and/or sulfonylurea.

But that value was not consistent with the study done by Zhong et al.,[15] established that empagliflozin as an add-on to metformin is well-tolerated and provides additional benefits beyond glucose-lowering, such as weight loss and blood pressure reduction.

In the current study, the mean HbA1c significantly reduced from 9.4% at baseline to 7.7% after six weeks and to 7.1% after 12 weeks of intervention ($p < 0.001$) with empagliflozin. These findings were in accordance with studies done by Puli and Vanjari, Søfteland and associates, Zhong et al., & Kovacs and associates.[13,14,15,16]

A prospective study conducted by Puli and Vanjari [13] demonstrated that the addition of empagliflozin to metformin and sulfonylurea therapy for 12 weeks caused a 0.87% reduction in HbA1c. Søfteland and associates [14] evaluated the efficacy and safety of empagliflozin as add-on therapy in inadequately controlled type 2 diabetic patients under treatment of linagliptin and metformin and concluded that at week 24, empagliflozin significantly reduced HbA1c compared to placebo; the adjusted mean differences in the change from baseline with empagliflozin 10 and 25 mg in comparison to placebo were 0.79% and 0.70% respectively (both $p < 0.001$). Zhong et al.,[15] assessed the efficacy and safety of empagliflozin as an add-on to metformin in patients with type 2 diabetes mellitus (T2DM) and demonstrated that compared with a placebo, two different doses of empagliflozin significantly reduced glycated hemoglobin [10 mg: $p < 0.001$; 25 mg: $p < 0.001$]. Compared with active comparators (two sitagliptin, one linagliptin, and one glimepiride), 10 mg of empagliflozin provided a similar reduction in HbA1c ($p = 0.13$), while 25 mg of Empagliflozin provided a significantly greater reduction in HbA1c ($p = 0.0005$). Kovacs and associates,[16] showed that empagliflozin 10 mg or 25 mg as add-on therapy to pioglitazone with or without metformin for 76 weeks was well-tolerated and led to sustained reductions in HbA1c and weight compared with placebo in patients with T2DM.

Our study found that the mean systolic and diastolic blood pressures decreased from 129 mmHg to below 120 mmHg ($p < 0.001$) and 82.3 mmHg to below 80 mmHg ($p = 0.029$), respectively, after three months of intervention. Our findings were in good agreement with Puli and Vanjari & Zhong et al.[13,15] Puli and Vanjari,[13] in a prospective study demonstrated that at 24

hours, empagliflozin significantly reduced blood pressure with mean change in SBP and DBP were 4.147 and 1.526 mmHg respectively.

Conclusion

This study concludes that empagliflozin as an add-on therapy responded well in patients with uncontrolled T2DM (previously treated with metformin combined with either sulfonylurea or DPP-4 inhibitors and/or supplemented by insulin) in achieving glycemic control. The FBS and HbA1c both reduced significantly to almost normal levels after 12 weeks of intervention with empagliflozin. The additional benefit (reduction of blood pressure) may be an added advantage for many diabetic patients with concurrent hypertension.

Conflict of interest: None declared

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All correspondence to
Dr. Mita Rani Joysoual
Lecturer
Department of Pharmacology and Therapeutics
Rajshahi Medical College, Rajshahi
E-mail: mita.joysoual@gmail.com