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Effects of the Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor Empagliflozin Added to Metformin in Patients with Type 2 Diabetes

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a chronic progressive disease characterized by a progressive decline in pancreatic beta-cell function and insulin resistance. Multiple blood glucose-lowering agents targeting the main pathogenic mechanisms of insulin deficiency and insulin resistance are available for the management of type 2 diabetes. However, many patients do not achieve or maintain recommended blood glucose targets even with combination therapies, which are often delayed. Therefore, this study aimed to observe the effects of Empagliflozin as an add-on to Metformin in patients with type 2 diabetes. ***Methods:*** This was a retrospective observational study and was conducted in the Department of Medicine, Popular Medical College Hospital, Dhaka, Bangladesh during the period from January 2023 to December 2023. In our study, we included 255 type 2 diabetes mellitus patients who came to receive treatment at the outdoor department of medicine of our hospital. The patients were divided into three groups- Group A (Patients who received the combination of Empagliflozin 10 mg and Metformin 1000 mg), Group B (Patients who received Empagliflozin 10 mg), and Group C (Patients who received Metformin 1000 mg). ***Result:*** We found the mean age was 55.8 ± 11.3 years. Most of our patients were male (60%). Among our patients, the majority (57.25%) of them had HbA1c of 8% to 9%. Most patients (60%) got < 8% HbA1c level in Empagliflozin 10 mg combined with metformin 1000 mg group at the end of our study. The majority (9.41%) of patients in the Empagliflozin 10 mg group had >9% HbA1c level compared to other groups. Dizziness, dyspepsia, diarrhea, nasopharyngitis, hyperglycemia, and hypoglycemia were the most common adverse events. ***Conclusion:*** The findings of the study showed that in people with Type 2 diabetes and insufficient glycaemic control, 52 weeks' treatment with empagliflozin 10 mg as an add-on to metformin 1000 mg resulted in sustained and clinically substantial decreases in HbA1c, body weight,FPG, systolic and diastolic blood pressure.

Keywords: Effects, Sodium-glucose cotransporter 2 (SGLT2), Empagliflozin, Metformin, T2DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease characterized by a progressive decline in pancreatic beta-cell function and insulin resistance [1]. Multiple blood glucose-lowering agents targeting the main pathogenic mechanisms of insulin deficiency and insulin resistance are available for the management of type 2 diabetes [2]. However, despite combination medications, which are frequently delayed, many patients are unable to reach or maintain prescribed blood glucose levels [3,4]. But many anti-diabetic agents (sulphonylurea, thiazolidinedione, and insulin) and their treatment success can be limited by adverse events (AEs) and medication side effects such as hypoglycaemia or weight gain, which are counter-productive effects and hamper adherence to treatment [5].

For individuals with type 2 diabetes who have not achieved or are unlikely to achieve glycemic control by lifestyle changes, metformin is advised as first-line medication [6]. Metformin mainly acts by reducing hepatic glucose production through inhibition of gluconeogenesis and may increase glucose uptake in peripheral tissue [7,8]. Although initially effective, metformin alone frequently fails to maintain glycemic control as type 2 diabetes progresses [6,9]. After two years of metformin monotherapy, 40-50% of patients fail to meet treatment goals, which rises to 70% after three years and 90% after nine years [10-12]. When glycemic control can no longer be maintained with monotherapy, additional therapies are required, but several of the agents used as second-line treatment are associated with tolerability issues, such as gastrointestinal side effects, hypoglycemia, and weight gain [13]. There is, therefore, a need for new agents that are effective and well-tolerated and can be added to metformin therapy that can further improve glycaemic control in type 2 diabetes.

It is increasingly recognized that the kidney can play an important role in controlling plasma glucose levels. Renal reabsorption of glucose is mediated by sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2), both located in the brush border membrane, with SGLT2 responsible for the vast majority of renal glucose reabsorption in the proximal tubule [14,15]. Initial preclinical studies with phlorizin, a potent non-selective SGLT inhibitor, showed that blocking these transporters promotes glucose excretion in the urine resulting in significant reductions in plasma glucose. These results prompted the development of selective SGLT2 inhibitors, which target this specific glucose transporter for antidiabetic treatment [16]. Furthermore, SGLT2 inhibitors can lower body weight by increasing urine glucose excretion, which means calorie reduction [16].

In 2014, the European Union (EU) and the United States approved empagliflozin (EMPA), a powerful and highly specific inhibitor of sodium-glucose co-transporter 2 (SGLT2), for the treatment of type 2 diabetes [17,18]. Empagliflozin lowers the plasma glucose concentration by inhibiting renal glucose reabsorption and increasing urinary glucose excretion [19]. As the mechanism is independent of insulin, Empagliflozin is associated with a low risk of hypoglycemia [20].

The drug selection of combination therapy for patients with T2DM must balance glucose-lowering efficacy, side-effect profiles, the anticipation of additional benefits, costs, drug-drug interactions, and patient compliance. There are potential benefits of Empagliflozin as an add-on to Metformin. First, Empagliflozin shows excellent pharmacokinetic characteristics: good oral bioavailability, a rather long elimination half-life (10–19 h) allowing once-daily administration, and a negligible risk of drug-drug interactions [21,22]. Second, SGLT2 inhibitor leads to a reduction in tissue glucose disposal and a rise in endogenous glucose production (EGP) [23,24]. Metformin enhances the glucose-lowering actions of SGLT2 inhibitors by restraining EGP, which may provide long-term improvement of glycaemic control [25]. Given the complementary mechanisms of Empagliflozin and Metformin, this combination may offer a promising treatment strategy for T2DM [26].

Therefore, we conducted this study intending to observe the effects of Empagliflozin as an add-on to Metformin in patients with type 2 diabetes mellitus.

METHODOLOGY & MATERIALS

This was a retrospective observational study and was conducted in the Department of Medicine, Popular Medical College Hospital, Dhaka, Bangladesh during the period from January, 2023 to December 2023. In our study, we included 255 type 2 diabetes mellitus patients who came to receive treatment at the outdoor department of medicine of our hospital. The patients were divided into three groups- Group A (Patients who received the combination of Empagliflozin 10 mg and Metformin 1000 mg), Group B (Patients who received Empagliflozin 10 mg), and Group C (Patients who received Metformin 1000 mg).

These are the following criteria to be eligible for enrollment as our study participants: a) Patients aged more than 18 years; b)Patients with type 2 diabetes mellitus; c) Patients with BMI $\leq$ 45 kg/m^2 ; d) Patients with HbA1c $\geq$7%; e) Patients who were willing to participate were included in the study And a) Patients with uncontrolled hyperglycemia; b) Patients with Coagulopathy or received anticoagulant; c) Patients with previous surgical history; d) Patients with known allergy/hypersensitivity to study medicine; e) Patients with any history of chronic illness (e.g., renal or pancreatic diseases, ischemic heart disease etc.) were excluded from our study.

In the current study, the patients received a combination of Empagliflozin 10 mg & Metformin 1000 mg twice a day, Empagliflozin 10 mg once a day, and Metformin 1000 mg twice a day. They received medications for 12 weeks. After receiving our prescribed medicine, our patients were re-examined after the 12th week, 24th week, and 52 weeks.

Statistical Analysis: All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. The differences between groups were analyzed by chi-square (X^2) test, fisher's exact test. A p-value <0.05 was considered as significant. Statistical analysis was performed by using SPSS 23 (Statistical Package for Social Sciences) for Windows version 10. The study was approved by the

Ethical Review Committee of Popular Medical College Hospital, Dhaka, Bangladesh.

RESULTS

Table 1: Baseline characteristics of our study subjects

Baseline	N=255	P (%)	P-value
Mean age (years)	55.8 ± 11.3		0.486
Gender			
Male	**153**	**60.00**	
Female	**102**	**40.00**	
HbA1c, (%)			
<8%	**75**	**29.41**	
8% to 9%	144	**56.47**	
>9%	36	**14.12**	
Time since diagnosis of type 2 diabetes*			
<1 year	**31**	**12.16**	
1–5 years	97	**38.04**	
6–10 years	73	**28.63**	
>10 years	54	**21.18**	
DM duration (years)	6.81±4.34		0.421
Body weight (kg)	76.84±18.24		0.074
Waist circumference (cm)	98.67±11.24		0.235
BMI (kg/m^2)	29.67±6.24		0.614
Heart Rate (per minute)	76.0 ± 11.9		0.474
Systolic blood pressure (mm Hg)	155.24 ± 20.78		0.641
Diastolic blood pressure (mm Hg)	95.94 ± 11.69		0.162
Mean FPG (mg/dl)	170.45 ± 43.10		0.015
Comorbidities			
Hypertension	**118**	**46.27**	
Dyslipidemia	54	**21.18**	
COPD	32	**12.55**	
Asthma	45	**17.65**	

Table 1 shows the baseline characteristics of our patients. We found the mean age was 55.8 ± 11.3 years. Most of our patients were male (60%) compared to female (40%). Among our patients, 57.25% had HbA1c of 8% to 9%. The mean DM duration was 6.81±4.34 years. The mean body weight was 76.84±18.24 kg, BMI was 29.67±6.24 kg/m^2, and heart rate was 76.0 ± 11.9 beats /min. The mean FPG was 170.45 ± 43.10 mg/dl. As comorbidity, we found HTN (46.27%) and dyslipidemia (21.18%) in our patients.

Table 2: Distribution of our study patients by efficacy variables

Efficacy variables	Time point	Empagliflozin 10 mg + metformin 1000 mg b.i.d.(N=85)	Empagliflozin 10 mg q.d. (N=85)	Metformin 1000 mg b.i.d. (N=85)	P-value
HbA1c (%)	At baseline	7.1 ± 1.8	7.0 ± 1.2	7.1 ± 1.4	
	At 12th week	6.7 ± 0.6	6.8 ± 0.7	6.7 ± 0.6	0.034
	At 24th week	6.0 ± 1.2	6.2 ± 1.7	6.1 ± 1.2	
	At 52nd week	5.7 ± 0.1	5.9 ± 0.4	5.7 ± 0.7	
Body weight(kg)	At baseline	76.85±18.24	77.84±16.84	76.47±18.64	
	At 12th week	74.77±14.34	76.87±12.24	75.84±13.24	0.674
	At 24th week	72.05±12.84	73.34±13.04	73.47±12.54	
	At 52nd week	64.67±10.44	66.47±12.24	65.84±11.37	
FPG (mg/dl)	At baseline	170.45 ± 43.10	171.45 ± 47.34	170.84 ± 42.07	
	At 12th week	168.87 ± 38.08	170.25 ± 37.10	169.45 ± 39.85	0.021
	At 24th week	160.45 ± 33.41	161.45 ± 37.34	160.44 ± 38.07	
	At 52nd week	155.67 ± 31.02	157.56 ± 32.10	157.45 ± 30.58	
SBP (mmHg)	At baseline	155.24 ± 20.75	154.04 ± 21.58	155.02 ± 20.48	
	At 12th week	154.0 ± 10.2	153.0 ± 10.4	152.5 ± 11.1	0.051
	At 24th week	153.2 ± 7.4	153.0 ± 8.4	151.0 ± 10.4	
	At 52nd week	147.0 ± 7.0	149.0 ± 8.1	147.0 ± 8.4	
DBP (mmHg)	At baseline	95.4 ± 11.7	95.94 ± 11.69	95.94 ± 11.69	
	At 12th week	96.1 ± 8.8	96.7 ± 8.1	96.7 ± 6.1	0.042
	At 24th week	95.4 ± 6.8	95.1 ± 7.2	95.6 ± 7.1	
	At 52nd week	94.1 ± 2.9	94.7 ± 3.8	94.7 ± 4.1	

DBP = diastolic blood pressure; SBP = systolic blood pressure

Table 2 shows the efficacy variables of our patients. In the 52nd week, the mean HbA1c reduced significantly in group A compared to groups B and C. Body weight decreased in all groups, but the differences were insignificant. In the 52nd week, FPG significantly decreased in Group A than in Groups B & C. SBP and DBP decreased from their baseline in all groups with a significant value of 0.051 & 0.042 respectively.

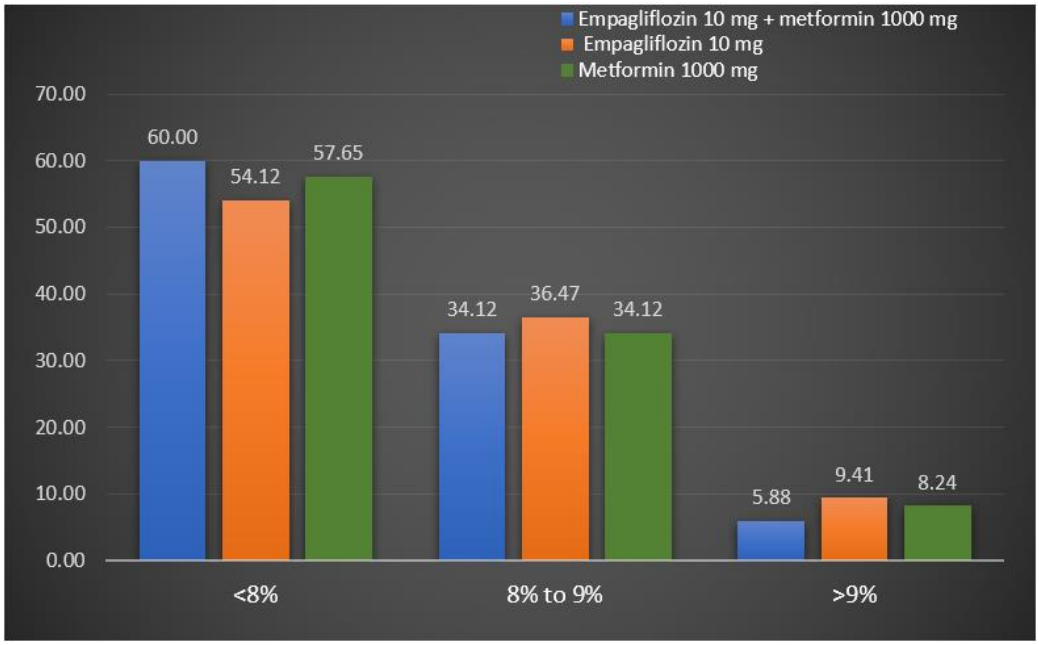

Figure 1: Distribution of our study patients by HbA1c at the end of our study

Figure 1 describes the HbA1c level at the end of our study period. Most patients (60%) got < 8% HbA1c level in Empagliflozin 10 mg combined with metformin 1000 mg group. The majority (9.41%) of patients in the Empagliflozin 10 mg group had >9% HbA1c level compared to other groups.

Table 3: Distribution of our patients by adverse events

Adverse events	Group A Em + M	Group B EM	Group C M
Dizziness	12(14.12%)	18(21.18%)	16(18.82%)
Dyspepsia	4(4.71%)	8(9.41%)	3(3.53%)
Diarrhea	11(12.94%)	17(20%)	15(17.65%)
Nasopharyngitis	8(9.41%)	11(12.94%)	6(7.06%)
Hyperglycaemia	4 (4.71%)	7(8.24%)	9(10.59%)
Hypoglycaemia	3(3.53%)	8(9.41%)	5(5.88%)
Urinary tract infection	0	2(2.35%)	1 (1.18%)
Upper respiratory tract infection	0	2(2.35%)	1 (1.18%)
Genital infection	3 (4.29%)	4(4.71%)	4(4.7%)
Dyslipidaemia	11 (12.94%)	0	10 (1.43%)
Hypertension	2(2.35%)	11 (12.94%)	9(10.59%)
Back pain	4(4.71%)	3 (4.29%)	8(9.41%)
Number of adverse events			
One adverse event	12 (14.12%)	17 (20%)	19(22.35%)
More than one adverse event	7(8.24%)	8(9.41%)	9(10.59%)
Severe adverse events	4(4.71%)	7(8.24%)	6(7.06%)

Table 3 shows the adverse events of our patients. The majority of patients had dizziness in Group B (21.18%) than in Group C (18.82%) & Group A (14.12%). Followed by diarrhea of 12.94% in Group A, 20% in Group B, and 17.65% in Group C. Hyperglycemia was mostly present in Group C while hypoglycemia was mostly present in Group B. In Group A, 4 severe adverse events were found, and in Group B, 7 severe events were found while in Group C, 6 cases were found.

DISCUSSION

Higher levels of hyperglycemia in type 2 diabetes patients are associated with an increased risk of vascular events, with each 1% increase in glycosylated hemoglobin (HbA1c) resulting in a 38% increase in

mortality [27]. In those with type 1 diabetes, intensive diabetes treatment has been shown to reduce the risk of clinical cardiovascular events such as myocardial infarction, stroke, and cardiac death. The link between therapeutic HbA1c reduction and mortality risk in type 2 diabetes is not well established, but good glycemic control undoubtedly lowers the risk of microvascular outcomes such as retinopathy, neuropathy, and nephropathy, with potential long-term effects on cardiovascular outcomes such as myocardial infarction [28-30]. Cardiovascular (CV) outcome trials in individuals with type 2 diabetes (T2D) have shown that sodium-glucose co-transporter-2 (SGLT2) inhibitors improve CV and heart failure (HF) outcomes and progression of kidney disease in those with established CV disease as well as those at high CV or renal risk [31,32].

Despite advancements in knowledge and the effects of different medications on CV and HF outcomes, in particular, a considerable fraction of T2DM patients still have poorly controlled blood pressure, body weight, and glycaemic control, with a large proportion not meeting treatment targets as advised by professional societies [33-35]. Individualization of therapy is now a widely recommended strategy in the management of patients with T2D. A better understanding of the clinical efficacy of specific glucose-lowering drugs across phenotypical characteristics of key cardiometabolic factors will help clinicians to better tailor therapy, while potentially helping patients achieve their treatment goals. This is especially significant when talking about the effectiveness of other glucose-lowering medications as metformin's backup therapy. It's also vital to consider patient preferences when choosing a therapy, as treatment inertia is a common occurrence throughout T2D management [36-38].

In this 52-week study, empagliflozin doses of 10 mg BID administered as add-on therapy to metformin 1000 mg resulted in significant decreases in HbA1c, FPG, and body weight compared with other groups in metformin and empagliflozin treated patients with type 2 diabetes with relatively mild hyperglycemia at baseline. The largest decreases were seen in the 10 mg empagliflozin combined with the 1000 mg metformin group. These findings contradict another study, which found that 12 weeks' treatment with empagliflozin monotherapy resulted in similar reductions in HbA1c, FPG, and body weight versus placebo in patients with type 2 diabetes [39]. Reductions in HbA1c, FPG, and body weight relative to placebo were also consistent with those reported from 12-week studies with other SGLT2 inhibitors [40-42]. SGLT2 inhibitors have the potential to lower body weight, which makes them potentially valuable drugs to combine with other antidiabetic therapy to lower blood glucose levels even further, aid in weight loss, or lessen any weight gain that may result from improved glycaemic control [39, 43,44]. Caloric loss through urinary glucose excretion may be an important contributor to this effect [44].

The specific effect of empagliflozin on blood pressure is being evaluated in several phase III trials, as well as in a dedicated blood pressure study (NCT01370005), as the present study was not powered to investigate this endpoint. Overall, empagliflozin was well tolerated, with no major difference in adverse events across treatment groups. As expected, owing to its insulin-independent mechanism of action, hypoglycaemia has been reported very rarely in people taking empagliflozin [39].

The majority of patients had dizziness in Group empagliflozin (21.18%) than in Group metformin (18.82%) & Group empagliflozin combined with metformin (14.12%). Followed by diarrhea of 12.94% in the Empagliflozin/Metformin group, 20% in the Empagliflozin Group, and 17.65% in the Metformin Group. Hyperglycemia was mostly present in the Metformin Group while hypoglycemia was mostly present in the Empagliflozin Group. There were also some common adverse events like UTI, respiratory infection, and genital infection.

The incidence of UTIs was similar in the empagliflozin, and metformin groups in this study, but there was a small increase in genital infections in the empagliflozin groups. Increases in genital infections and UTIs have also been documented in clinical studies with other SGLT2 inhibitors. [40,41, 45,46] Interestingly, compared with other reports on SGLT2 inhibitors, the genital infections in this study appear to have a lower frequency in all groups and were balanced between male and female patients.

In the current study, Group Empagliflozin/Metformin had 4 severe adverse events, and Empagliflozin Group had 7 severe events while Metformin Group had 6 cases. There were no deaths in our study patients. The results of this study show that empagliflozin added to metformin therapy improved glycaemic control, resulted in weight loss, and was well tolerated except for increased genital infections, and dyslipidemia in patients with type 2 diabetes.

Limitations of the study

Our study was a single-center study. Patients with severe adverse events were withdrawn due to our short study period. After evaluating these patients, we follow up with them for only one year, and after that, we do not know any other possible interference that may happen in the long term with these patients.

CONCLUSION AND RECOMMENDATIONS

The study's conclusions demonstrated that 52 weeks of treatment with empagliflozin 10 mg as an adjuvant to metformin 1000 mg resulted in sustained and clinically substantial decreases in body weight, systolic

and diastolic blood pressure, and HbA1c in individuals with Type 2 diabetes with inadequate glycaemic control. The present study also found that Empagliflozin/ Metformin (10/1000) mg was more effective at decreasing fasting plasma glucose than Empagliflozin 10 mg or Metformin 1000 mg alone. There were no unexpected or unusual safety concerns found with Empagliflozin/ Metformin combo therapy. Empagliflozin/ Metformin (10/1000) mg had more long-term effects than Empagliflozin 10 mg or Metformin 1000 mg among patients with type 2 diabetes mellitus. So further study with a prospective study design including a larger sample size needs to be done to validate and evaluate our findings.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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