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The glycemic control and side effects of Empagliflozin on patients with type II diabetes mellitus in tertiary care Hospital.

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Abstract

Background: Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia associated with disturbances of carbohydrate, fat and protein metabolism due to absolute or relative deficiency in insulin secretion and/or action. The burden of it is increased globally especially middle- or low-income countries. Different oral anti-diabetic medicines including older regimen to novel medicine like empagliflozin are used for the treatment of different types of diabetes. This study was aimed to study the effects of empagliflozin on patients with type II diabetes mellitus in tertiary care Hospital, Nepal. **Methods:** A hospital based prospective follow up study with purposive sampling was carried out for a period of six months from July to December 2022. A representative sample of more than 110 from prescriptions of T2DM patients aged between 20 to 60 years were observed for demographic details (age, sex, body weight, body height, body mass index (BMI) etc.), Hb1AC level, fasting plasma glucose (FPG), postprandial plasma glucose (after 2 hours) (PPG), blood pressure (SBP and DBP), adverse effects and an interview was conducted with Endocrinologist as well as patients who receive empagliflozin for first time and data were analyzed by using applicable statistical tolls. **Results:** A total of 215 patients were prescribed empagliflozin 10mg tablet out of which only 110 patients came for the follow up at 6 months. Hence, 110 respondents completed the study with in the study period (n=110). Out of 110 patients, 56 (50.9%) were male and 54(49.1%) were female. The majority of patients belonged to the age group 51-60 years 55(50%) with mean age of 48.89±8.81 years. The mean diabetic duration was 7 years. After 6 months of empagliflozin therapy there was significantly reduction in weight, BMI, blood pressure, anthropometric values (HbA1c, FPG, and PPG) with some suspected side effects were also observed. **Conclusion:** Thus, the main aim of this research was to study the effects of empagliflozin on patients with type II diabetes mellitus in tertiary care Hospital, Nepal. The outcomes of this research will be used as the reference for the preparation of diabetes treatment guidelines, regimens and related policies in the future.

Key words: Empagliflozin, Glycemic Control, Follow up study, Type II diabetes mellitus, Side effects.

Introduction

Diabetes mellitus is defined as a chronic metabolic disorder characterized by chronic hyperglycemia associated with disturbances of carbohydrate, fat and protein metabolism due to absolute or relative deficiency in insulin secretion. and its action. The prevalence of type 2 diabetes mellitus (T2DM) has rapidly increased in Nepal which was 8.5 to 10.5% with age group 20-79 years in 2021.[1] At first in 2014, the Food and drug administration (FDA) approved Empagliflozin belongs to class Sodium–glucose cotransporter-2 (SGLT2) inhibitor as a food supplement to diet and exercise to improve glucose control in T2DM patients but till to date it has multiple therapeutic outcomes from glycemic control to improvement in cardiac parameters, renal parameters and lipid profile as well. Generally, it is used as monotherapy or in combination

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with other hypoglycemic agents at a dose of 10mg to 25mg orally. Empagliflozin improves glucose control by elevating renal glucose excretion by suppressing SGLT2 function in the kidneys.[2] Empagliflozin decreases the fasting and postprandial plasma glucose levels. It also reduces the body weight of obese T2DM patients via secondary caloric loss due to urinary glucose excretion.[3] Empagliflozin exhibits positive results on blood pressure when given to hypertensive patients. The mechanism behind this may be depletion in water content through urine. Thus, there is reduction in blood pressure of the patient.[4]

The issue of non-communicable diseases (NCDS) is major health problem worldwide. Among them diabetes has reached at alarming level including Nepal. Approximately half billion of people are living with diabetes globally.[5] According to the findings it is confirmed that diabetes is the fastest growing disease and become health emergency in running century. The prevalence of diabetes is high especially under developed and developing countries.[6] Oral and parenteral therapy along with nutritional therapy, physical activity and mental well being are main key stones of the treatment protocol used widely.[7]The existing oral hypoglycemic agents are insufficient in covering the management of DM along with drug related adverse effects. Although empagliflozin has wide therapeutic outcomes but it causes some adverse effects in some patients. According to the data generated by different studies, the major side effects observed are hypoglycemia, genital mycosis, urinary tract infection, diabetic ketoacidosis etc.[8] So, this study was carried out with aim to study the glycemic control and side effects of Empagliflozin on T2DM patients with related co-morbidity in Nepalese context.

Methods

It was hospital based prospective follow up study with purposive sampling was carried out in the Endocrinology Department of NAMS-Bir Hospital, Kathmandu Nepal for a period of six months from July to December 2022. A representative sample of more than 110 patients aged between 20 to 60 years and diagnosed with uncontrolled T2DM with related co-morbidity who received Empagliflozin 10mg without changing existing anti-diabetic therapy for the first time (for 180 consecutive days or more) were included in the study whereas patients with frequent UTI and terminally ill CKD, DKA patients were excluded from the study. After six months of Empagliflozin therapy (at the follow up) were assessed for changes in basic clinical and biochemical parameters. The data regarding clinical and biochemical parameters were collected from the same patient. Any adverse effects related to the empagliflozin therapy during the study period were also taken into account and managed as per protocol. Once the adverse effects were noted in patients, the drug was stopped and the patient was advised for follow up and patients were managed other existing oral and parenteral ant-diabetic drugs.

Patient's demographics like age, sex, and diabetic duration were collected by reviewing the patient's prescription. Height and body weight were measured with the participants wearing light clothing and no footwear. The patients' body mass index (BMI) was calculated by obtaining their body weight in kilograms and dividing it by the square of their height in meters. Blood pressure was measured using aneroid sphygmomanometer, with the cuff placed on the right arm of the patient. Blood and urine samples were used for analyzing biochemical and metabolic

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ORIGINAL ARTICLE   OPEN ACCESS

parameters in certified pathology laboratory of NAMS, Bir Hospital. The laboratory serum measurements included glycated hemoglobin (HbA1C), fasting plasma glucose (FPG), postprandial 2-hour plasma glucose (PPG-2), as well as urine sample were measured by using standard techniques and instruments. Data were collected using semi-structured questionnaire containing proforma. Shapiro-Wilk test was run to check the normal distribution of data. The continuous data were expressed as mean± standard deviation (SD), median Interquartile rank (IQR) and categorical data were expressed as number (%). In case of the continuous variables, paired t-test/ Wilcoxon Signed rank test was applied as appropriate to see the changes in baseline data to final follow up data. The data entry and analysis were done with the help of SPSS version 24 (Statistical Package for Social Sciences) (IBM version -24) for further analysis. A p-value of <0.05 was considered statistically significant. Ethical approval was obtained from the institutional review board (IRB) of National Academy of Medical Sciences (NAMS) Bir Hospital (Approval number: 1546-078/079). Informed written consent was obtained from the patients and their care takers.

Results:

A total of 215 patients were prescribed empagliflozin 10mg tablet out of which only 110 patients came for the follow up at 6 months. Hence, 110 respondents completed the study with in the study period (n=110). Out of 110 patients, 56(50.9%) were male and 54(49.1%) were female. The majority of patients belonged to the age group 51-60 years 55(50%) with mean age of 48.89±8.81 years. The mean diabetic duration was 7 years.

Variables	Category	N (%)
Gender	Male	56(50.9)
	Female	54(49.1)
Age Groups(years)	Under 40	27(24.5)
	41-50	28(25.5)
	51-60	55(50.0)
Total		110(100)

Journal of Diabetes and Endocrinology Association of Nepal

ORIGINAL ARTICLE

Table 1: Demographic profile of the patients

Change in basic clinical parameters after Empagliflozin therapy

Parameters	Pre-Treatment (Baseline)	Post-Treatment (After 6 months)	Mean Value Difference	P- (P<0.05)
Weight (kg)	66.60±10.30	63.95±10.34	2.64	0.000*
BMI (kg/m^2)	25.80±3.30	24.75±3.28	1.06	0.000*
SBP (mmHg)	125.00±9.77	119.50±11.02	5.50	0.000*
DBP (mmHg)	81.64±4.65	77.55±4.92	4.09	0.000*

Table 2: Change in Basic clinical parameters after Empagliflozin therapy

Effect of empagliflozin on weight after pre and post treatment

Because, the data was normally distributed, a paired t-test was run and the outcome indicated that post treatment mean weight was (63.95±10.34) kg was statistically lower than pre weight (66.60±10.30) kg, t= 20.842 (p=0.000) as presented in table 2.

Effect of empagliflozin on BMI after pre and post treatment

Because, the data was normally distributed, a paired t-test was run and the outcome indicated that post treatment mean BMI was (24.75±3.28) kg/m2 was statistically lower than pre-BMI (25.80±3.30) kg/m2, t= 18.71 (p=0.000) as presented in table 2.

Effect of empagliflozin on systolic blood pressure after pre and post treatment

Because, the data was skewed for both the variables, a Wilcoxon Signed rank test was run and the output indicated that post SBP (119.50± 11.02 mmHg) was statistically lower than pre SBP 125.00 ± 9.77mmHg), Z= -8.40. (P=0.000).

Effect of empagliflozin on diastolic blood pressure after pre and post treatment

Because the data was skewed for both the variables, a Wilcoxon signed rank test was run and the output indicated that post DBP (77.55 ± 4.92 mmHg) was statistically lower than pre DBP (81.64± 4.65 mmHg), Z= -7.25. P=0.000.

Change in biochemical parameters after Empagliflozin therapy
Table 3: Change in biochemical parameters after empagliflozin therapy

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ORIGINAL ARTICLE   OPEN ACCESS

Parameters	Pre-Treatment (Baseline)	Post-Treatment (After 6 months)	Mean Difference	P-Value (P<0.05)
HbA1C	9.14±1.16	8.28±1.00	0.86	0.000*
FPG	179.88±41.41	130.60±28.52	49.28	0.000*
PPG	284.36±45.29	228.19±34.25	56.16	0.000*

Effect of empagliflozin on HbA1C after pre and post treatment

The pre-treatment (baseline) and post treatment (after 6 months) mean Hb1AC of the patients was 9.14±1.16 and 8.28±1.00 % respectively. The mean reduction of Hb1AC level of patients was 0.86%, Z= -9.07. (P=0.00) which was statistically significant.

Effect of empagliflozin on Fasting plasma glucose after pre and post treatment

The pre-treatment (baseline) fasting plasma glucose (FPG) was 179.88 ± 41.41 and the posttreatment (after 6 months) FPG was 130.60 ± 28.52 mg/dl, respectively with a mean difference of 49.28, Z=-9.11) which was statistically significant.

Effect of empagliflozin on Post prandial plasma glucose (2 Hour) after pre and post treatment

Likewise, the mean difference (56.16mg/dl) in post prandial plasma glucose (PPG) after 2 hour indicated that post PPG (228.19 ±34.25mg/dl) was statistically lower than pre-PPG (284.36 ±45.29mg/dl), Z= -9.11. (P=0.000).

Adverse effects of empagliflozin

Table 5 shows that out of 110 patients 82 (74.5%) patients developed adverse effects of empagliflozin 10mg. The most commonly observed side effect was urinary tract infection (UTI) (23.6%) followed by genital mycosis (16.4%), others (25.5%), hypoglycemia (6.4%), dyslipidemia (1.8%) and prepuce gangrene (0.9%).

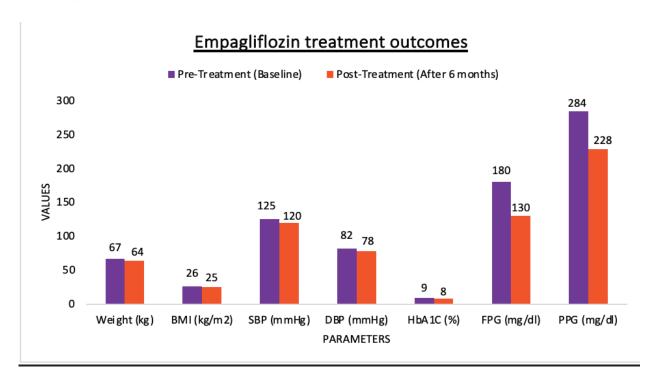**Table 4: Suspected Adverse effects of empagliflozin**

Adverse Effects	Frequency	Percentage
Urinary Tract Infection (UTI)	26	23.6
Genital Mycosis	18	16.4
Dyslipidemia	2	1.8
Hypoglycemia	7	6.4
Prepuce Gangrene	1	0.9
Others*	28	25.5
No Adverse Events	28	25.5
Total Adverse Events	82	74.5

* Others (headache, diarrhea, nausea, abdominal pain, joint pain)

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ORIGINAL ARTICLE   OPEN ACCESS

Summary of results

DISCUSSIONS

Socio-demographic characteristics of the patient

The demographic details of our study revealed that mean age of participants was 48.89±8.81 years. They were prescribed Empagliflozin 10mg tablet for uncontrolled type 2 diabetes mellitus including co-morbidity like cardiac, liver and hyperlipidemia. A similar finding was noted in a study conducted by Pokharel et al. in NAMS Bir hospital, Nepal showed that the average age of patients was 47.23±10 years[9]. Out of 110 patients, 50.9% were male patients and rests were female. This correlates with similar findings observed by Joshi et al. in Nepal where there was out of 111 patients, 53.15% (n = 59) were female and 46.8% (n = 52) were male10.

Comparisons of basic clinical parameters:

In the present study we found that there is significant weight loss in patients, the mean reduction in weight was 2.64 (P=0.000.) The study conducted by different scholars[11,12,9] (Neeland et al., 2016, Pokharel et al., 2021, Joshi et al., 2020) has also shown a significant weight loss (p=0.000) and another study has also elicited similar findings. The mechanism behind significant weight loss after empagliflozin therapy is urinary caloric loss and potential compensatory hyperphagia without a significant change in resting metabolic rate (RMR).[13]

In our study, there was a significant change (P=0.000) in both SBP and DBP, where the mean difference between SBP and DBP was 5.50 mmHg and 4.09 mmHg respectively. This finding is supported by study conducted by Lee L et. al.,[14] where there was significant

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Journal of Diabetes and Endocrinology Association of Nepal

ORIGINAL ARTICLE

OPEN ACCESS

change in SBP (P=0.006) whereas there was no significant change in DBP (P=0.115). Another study conducted by Chilton R. et al., (2015) and Zanchi A et al., (2022) [15,4] revealed that there was reduction in both SBP and DBP within 1 month in which empagliflozin 10 mg decreased 24-h systolic (SBP) and diastolic (DBP) BP significantly by -5± 7 mmHg (p < 0.001) and -2± 6 mmHg (p = 0.03). The exact mechanism by which empagliflozin lowers blood pressure is unknown, but studies have suggested that it could be the effect of weight loss and reduction in arterial stiffness.

Here, the BMI of T2DM patients after treatment was found to be significantly reduced that is the mean change was 1.06kg/m2 (P=0.000). The similar study conducted by Cho YK et al., (2019)12 revealed significant reduction in mean BMI 0.6kg/m2 (P=0.001).

Comparison of biochemical parameters after empagliflozin therapy:

In our study, HbA1c level was significantly reduced from baseline by 9.14±1.16 and 8.28±1.0. The mean reduction in HbA1c was 0.86% (P<0.000). This finding is supported by the research data by Gupta A et al., (2021)[16] showed that the HbA1c level was significantly reduced from baseline by 1.5±1.2% (P<.001).

There was a significant decrease in FBS, and PPBS in the present study; the mean differences were 49.28, and 56.16 respectively (p=0.000). A similar study by Cho YK et al., (2019)[12] also showed a significant drop in FBS, and PPBS (p<0.001).

Adverse effects of Empagliflozin

In our study, adverse events were observed in 74.5% of patients, but there were no serious effects. Various studies have reported adverse events from 60% to 80%.[19,20] The variation in population size and sample size leads to variation in development of adverse effects of empagliflozin. The most common side effect was urinary tract infection UTI (23.6%). A similar finding was demonstrated in another study Shiba Tetal., (2017).[20] The risk of UTI is due to excessive glycosuria. Genital mycosis and prepuce gangrene were noted in 16.4% and 0.9% of patients, which is slightly higher than the other findings Chacko J et al., (2021).[19] Hypoglycemia developed in 6.4% of patients in our study. When side effects were observed, the empagliflozin was discontinued and these were managed by standard protocol. This information is supported by the study Pokharel A et al., (2021)[9]. Other adverse effects in our study were diarrhea, abdominal pain, joint pain and headache. The results were comparable to other studies like. [8,11]

Conclusion

The present study revealed that Empagliflozin shows benefits in basic clinical parameters like reducing weight, BMI, blood pressure as well as improvement in biochemical and metabolic parameters like HbA1C, Fasting glucose level, postprandial glucose level. In contrast to this empagliflozin causes some suspected side effects like urinary tract infections, genital mycotic infections, hypoglycemia etc. during therapy. Hence, proper counselling is always advised to all the patients concerning side effects of the drug. So, long-term randomized type study will be needed to know the actual safety and efficacy of the empagliflozin.

In conclusion, Empagliflozin could be used as an effective treatment modality for T2DM patients with /without related co-morbidities.

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Journal of Diabetes and Endocrinology Association of Nepal

ORIGINAL ARTICLE   **OPEN ACCESS**

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ORIGINAL ARTICLE   OPEN ACCESS

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