Efficacy and Safety of Empagliflozin in Patients with Type 2 Diabetes Mellitus in Adequately Controlled on Triple Drug Therapy

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Abstract
Objective: *Empagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, has been associated with HbA1c reduction and weight loss in a broad range of patients with type 2 diabetes mellitus (T2DM). This analysis evaluated changes in HbA1c and body weight in patients who were inadequately responding to maximum dose of three oral hypoglycemic agents and reluctant to take insulin therapy.*

Methods: *In this open label interventional single arm study, patients aged 18 to 65 years (N=100) received Empagliflozin 10mg for in addition to an ongoing triple drug oral hypoglycemic agents (OHA) regimen for a period of 12 weeks.*

The said population was inadequately responding to maximum dose of three oral hypoglycemic agents and was reluctant to take insulin therapy. Percent change from baseline in HbA1c and body weight was evaluated in the study.

Results: *Empagliflozin 10mg additional dose above a triple OH provided significant HbA1c reduction by 1.4% and weight reduction by 1.5 kg over 12 weeks from baseline. Empagliflozin was generally well tolerated, with 2.54% of the patient population reporting Urinary tract infection (UTI) who were withdrawn from study and given appropriate treatment.*

Conclusions: *Empagliflozin 10 mg (One tablet) administered to patients in addition to the inadequately controlled triple drug OHs who were reluctant for an insulin therapy provided a significant reduction in HbAlc and body weight over 12 weeks. Empagliflozin a SGLT 2 inhibitor is a promising new drug in patients with T2DM in patients who are inadequately controlled on triple therapy and are reluctant to insulin therapy.*

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease that develops as a result of defective insulin secretion and is frequently associated with obesity-related insulin resistance l Glucose-lowering agents are regularly implemented to manage hyperglycemia when lifestyle modifications (eg,diet and exercise) are insufficient. The disease progression leads to treatment intensification with combination therapy, and ultimately insulin therapy is often initiated which again may be inadequate in managing hyperglycemia in some patients.' Some oral hypoglycaemic agents (OHs) are associated with weight gain (e.g. sulfonylurea, insulin, thiazolidinediones, glinides), which can make it difficult for patients with T2DM to achieve and maintain weight loss.?

Empagliflozin is a novel oral antidiabetic agent belonging to the class of sodium-glucose co-transporter 2 (SGLT2) inhibitors provides glycemic control along with clinically meaningful weight loss, in a broad range of patients with T2DM who were on various background OHAs.? This analysis evaluated changes in HbA1c and body weight in patients who were

inadequately responding to maximum dose of three oral hypoglycemic agents and reluctant to take insulin therapy.

Materials & Methods

Type of Study: Randomized control trial.

Place of Study: Study conducted in the department of General Medicine, Katihar medical College & Hospital.

Study Period: December 2019 to May 2021.

Sample size: A total 100 patients of type 2 diabetes mellitus was taken from the department of General Medicine, Katihar medical college & Hospital, who were on triple drug oral hypoglycaemic agent regimen not adequately controlled and reluctant to take insulin. All these patients were put on empagliflozin 10 mg in addition to ongoing triple drug (Metformin, Voglibose, glimepiride) oral hypoglycaemic agent for a period of 12 weeks and percentage changes from baseline in blood sugar level HbA1c lvel, body weight was evaluated.

Inclusion Criteria

- Patients of both sex (Male & Female) on maximum dose of three OHAs inadequate response was included.
- Patients between age 18 – 65 years who were inadequately controlled on triple drug therapy was taken for this study.
- Patients fulfilling the eligibility criteria at first visit was screened for fasting and post prandial blood glucose, HbA1c, body weight, and renal profile.

Exclusion Criteria

- Newly diagnosed cases of type 2 diabetes mellitus.
- Type 1 diabetes mellitus.
- Gestational diabetes.
- Patients with eGFR value<60 ml/ min/1.73 meter square.
- Patients with recurrent UTI and patient with history of diabetic ketoacidosis or other comorbid cardiac, hepatic and renal diseases.

Ethical Consideration: All issues including ethical issues of the protocol were evaluated by the Institutional Review Board and have been approved.

Methodology

The patients were evaluated as per the standard protocol specially concentrating on-

- Age
- Gender
- Duration of diabetes
- H/O pain, numbness, paraesthesias, numbness, weakness, ataxias along with duration
- H/O hypertension, CAD, nephropathy, retinopathy
- Physical examination(including height, weight and BMI)

Baseline routine investigations

- FBS, PPBS, (GOD POD Method).
- HbA1C (HPLC Method).
- Urea (GLDH Method)
- Creatinin (Jaffe Method)
- Lipid Profile (Total Cholesterol, HDL, LDL, VLDL, Triglycerides)
- ACR

The duration of triple therapy and dosage history was determined for each patient by review of their medical record, and these dosages was confirmed verbally by the patients. Use of other anti-diabetic agents was also being recorded.

Capillary blood glucose, hypoglycemic episodes, and adverse events were documented by the patient via diary cards or were recorded by the study

investigator when mentioned by the patient. A physical examination to identify signs of peripheral edema was performed at baseline and final visit or at patient discontinuation.

At the time of a hypoglycemic episode, patients were instructed to measure glucose and document the date, start and end time, time of last meal, blood glucose level, and whether assistance was needed.

Statistical Analysis

Data was analyzed using Statistical Package for Social Sciences, version 23 (SPSS). Results for continuous variables are presented U t test as mean ± standard deviation, whereas results for categorical variables are presented as number (percentage).The level $P < 0.05$ was considered as the cutoff value or significance.

Result

Among 100 patients recruited, 97 patients completed the study(97%), 3 were withdrawn due to ADR (3% and there was 1 drop out (1%). After 12 weeks of study, 46mg/dl reduction fasting was observed from baseline (Figure 1), 157 mg/dl reduction in PP was observed from baseline (Figure 2) ,1.44% reduction in HbAlc was observed from baseline (Figure 3) and 1.5 kg reduction in body weight was recorded (Figure 4), P value= 0.001. 3 out of 100patients (3%) reported UTI and were withdrawn from study. All the three patients were female and treatment for UTI was provided as required.

Discussion

In our study consisting of total of 100 patients with type 2 diabetes were recruited from the department of General Medicine at Katihar Medical College and Hospital, who were on a triple medication oral hypoglycaemic agent regimen that was not sufficiently controlling their blood sugar and were unwilling to use insulin. For a period of 12 weeks, all of these patients were given empagliflozin 10 mg in addition to their ongoing triple medication (Metformin, Voglibose, glimepiride) oral hypoglycaemic agent, and percentage changes in blood sugar level HbA1c , fasting ,pp level, as well

as body weight, were assessed.

In this study we have found maximum number of study participant belong in 51- 60 years of age group, i.e. 24%. 18% cases belong to 30-40 years of age group, 22%, 16% & 20% participant are belongs to 41-50, 61-70 & >70 years of age groups respectively. The Mean SD value is 55.710±14.53. Study conducted by MAZHAR HUSSAIN AND ASIM ELAHI on comparison of efficacy and safety profile of SGLT2 inhibitors as Add-on therapy in patients with Type 2 Diabetes found the similar mean age range was 52.5± 15.6 years supporting my work.

Another study conducted by Ian J Neeland, Darren k. Mcguire on efficacy and safety of titrated SGLT2 inhibitors in patients with T2DM Inadequately controlled on metformin and sitagliptin found , the mean age 60.3 supporting my work.

In my study Male cases were predominantly high than female, 56% hmale cases and 44% female cases. M& F ratio was 1: 0.78.

MAZHAR HUSSAIN AND ASIM ELAHI conducted study on comparison of efficacy and safety profile of SGLT2 inhibitors as Add-on therapy in patients with Type 2 Diabetes found the similar sex distribution with 60% male and 40% female cases.

Ian J Neeland, Darren k. Mcguire conducted study on efficacy and safety of titrated SGLT2 inhibitors in patients with T2DM Inadequately controlled on metformin and sitagliptin found 62% were male and 38% female supporting my work.

Anthropometric Measurement of the study population shows that the Mean & SD value of Height, weight, & BMI were 163.27±10.0, 65.93±6.36 & 24.36±2.56 respectively. On the other hand mean weight was also reduced after treatment. The baseline mean value of weight is 64.93±6.36, after treatment 62.42±6.20 respectively. P value >0.05.

Study conducted by MAZHAR HUSSAIN AND ASIM ELAHI found, the Mean & weight and BMI were 93.5±18.4 and 28.5±4.9 respectively .

Another study conducted by Ian J Neeland, Darren

k. Mcguire found the Mean& SD value of BMI & weight were 28.6±5.5 & 78.8±18.8 respectively supports my study.

In this study, Clinical History of study participant 46% patients have family history of diabetes mellitus, 4% patients have smoking habits, 85% patients ad mix diet habit, 12 % had Hypertension, family history of CKD-1 % and most of the patients belongs to urban area i.e. 68 % & the mean & SD value of duration of the diabetes is 4.650±1.95 .

The baseline characteristics of our study found the Mean & SD value of Urea 40.80±6.28, Creatinine 1.25 ±0.22, ACR 34.30±4.70 & BUN 19.04±2.94 respectively. We have found reduction in value of Urea from baseline with treatment after 12 weeks of follow-up. Mean & SD value of urea was 40.80±6.28 reduced to 27.72±4.40. respectively, p value was <0.001. And creatinine value was also reducing from baseline with treatment after 12 weeks, but it was not significant. P value was 0.381.

Work done by Seigo sugjyama on Renoprotective effects of additional SGLT2 inhibitor therapy in patients with T2DM with chronic kidney disease found the mean value of eGFR and S. creatinine after 1 year of SGLT2 inhibitor therapy was 41.0 ml/min/1.73 m2 and 1.7 mg/dl for create with no significant difference compared with baseline. Similar results found by Francesco Giorgino work done on Renoprotection with SGLT2 inhibitors in T2DM over a spectrum of cardiovascular and renal risk the renoprotective effects of SGLT2 inhibitors were seen across all levels of baseline eGFR, although the largest benefits were apparent in patients with preserved renal function at baseline with no significant changes in S. creatinine and eGFR .

The baseline characteristics of our study found the minimum range of Total Cholesterol was 145 & maximum is 315. Mean & SD value shows 214.63±34.80. The minimum range of Triglyceride was 103 & maximum was 455. Mean & SD value shown 277.640±80.90. The minimum range of HDL was 30.0 & maximum was 56.0 Mean & SD

value shows 39.04±6.46. The minimum range of LDL was 63.0 & maximum is 190.0 Mean & SD value shows 120.06±25.57. We have found significant different of lipid profile parameters between baseline and treatment after 12 weeks of follow-up. P value was <0.05. When blood glucose management is optimised, the likelihood of hypoglycemic episodes may rise, especially when paired with sulfonylureas or other hypoglycemic medicines.[152-154] However, no severe hypoglycemia episodes or the need for help were discovered throughout this investigation. Finally, the effects of empagliflozin on HDL cholesterol and, to a lesser extent, LDL cholesterol are consistent with previous SGLT2 inhibitor trials. [155,156] The aetiology of these alterations is unclear, as is their clinical importance, but they have no effect on the atherogenic LDL/HDL cholesterol index.

Work done by Zsolt Szekeres on the effects of SGLT2 inhibitors on lipid metabolism found they decrease lipid accumulation in visceral fat, regulate the serum lipoprotein levels ,beneficially change the ratio of LDL particles along with increasing HDL level.

MAZHAR HUSSAIN AND ASIM ELAHI conducted study on comparison of efficacy and safety profile of SGLT2 inhibitors as Add-on therapy in patients with Type 2 Diabetes also found reduction in lipid profile supporting my work.

The baseline characteristics of our study found, the minimum range of Sugar (F) have 124.0 mg/dl and maximum is 195.0 mg/dl, the mean & SD value 146.760±16.38. The minimum range of BS (PP) have 202.0mg/dl & maximum range have 365.0 mg/dl. Mean & SD value of BSPP is 282.240±41.14. The mean & SD value of HbA1c -7.568±0.74.

We have found statistically significant different between the groups, Baseline and Treatment after 12 weeks of follow-up of sugar (F). Mean and SD value was 146.760±16.38 & 99.91±5.58, respectively, p value was <0.0001. & Baseline and Treatment after 12 weeks of follow-up of sugar

(PP). Mean & SD value was 282.240±41.14 & 125.86±10.95, respectively, p value was <0.0001. We have found statistically highly significant different between baseline and treatment after 2 weeks of follow-up of HbA1c, and reduce concentration of HbA1c. p Value was <0.0001.

Study conducted by Mazhar Hussain on comparison of efficacy and safety profile of SGLT2 inhibitors as Add-on therapy in patients with Type 2 Diabetes found patient receiving empagliflozin with significant reduction in fasting blood sugar by mean of 88.5±38.7 mg/dl with reduction in hba1c by mean of 2.1%±1.1%.

Another study conducted by H.W. Rodbard on efficacy and safety of titrated SGLT2 inhibitors in patients with T2DM Inadequately controlled on metformin and sitagliptin found reduction in fasting blood sugar was 29.8 mg/dl with reduction in HbA1c by mean of 1.

The fact that this was a post-hoc analysis is one of the study's flaws. Furthermore, the findings are only applicable to individuals who have the same characteristics as the patients in the clinical trials on which the study is based. It would be interesting to investigate the impact of adding empagliflozin to the therapy of people with T2DM who have less constraints. It's also worth noting that the trials only lasted 24 weeks, so extrapolating the duration of the results described may be difficult. On the other hand, the huge sample size of this study lends credibility to its findings.

In most patients with T2DM, failure of metformin monotherapy[157] necessitates advancement to treatment with two or even three drugs[158], which may result in an increased risk of hypoglycemia or weight gain, depending on the agent used.[159] This post hoc analysis based on three Phase III studies shows that empagliflozin, in combination with other oral glucose-lowering drugs, effectively decreases HbA1c levels in patients with T2DM previously treated with monotherapy or triple therapy who have an inadequate blood glucose control. Treatment with empagliflozin was also associated to decreased body weight and blood pressure, and showed a good safety and tolerability profile. These data support empagliflozin as an adequate therapeutic option for second or third-line treatment of T2DM. In their analysis, treatment with empagliflozin decreased SBP and DBP were also decreased as compared to placebo. These findings are consistent with those previously reported with SGLT2 inhibitors.[144,145]

References

1. Melmed, Shlomo; Polonsky, Kenneth S.; Larsen, P. Reed; Kronenberg, Henry M., eds. (2019). *Williams textbook of endocrinology* (12th ed.). Philadelphia: Elsevier/Saunders. pp. 1371–1435.

2. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators) (October 2016).

3. Gardner, David G.; Shoback, Dolores, eds. "Pancreatic hormones & diabetes mellitus". *Greenspan's basic & clinical endocrinology* (9th ed.). New York: McGraw-Hill Medical. 2011;17.

4. *National Institute of Diabetes and Digestive and Kidney Diseases*. June 2014. Archived from the original on 2 February 2016. Retrieved 10 February 2016.

5. "Diabetes Fact sheet N°312". *World Health Organization*. August 2011. Archived from the original on 26 August 2013. Retrieved 2012-01-09.

6. Ripsin CM, Kang H, Urban RJ (January 2009). "Management of blood glucose in type 2 diabetes mellitus". *American Family Physician*. 79 (1): 29–36.

7. Inzucchi SE, Bergenstal RM, Buse JB, et al,.; American Diabetes Association (ADA), ; European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes

(EASD). Diabetes Care 2012;35: 1364–1379.

8. Diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379.

9. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589.

10. Medivizor "Is empagliflozin better than glimepiride?" in Diabetes mellitus on Aug 5, 2018.

11. A.S. Dabhi, N.R. Bhatt, M.J. Shah Voglibose: An Alpha Glucosidase Inhibitor J. Clin. Diagn. Res., 7 (2013), pp. 3023-3027.

12. Therapy in Type 2 Diabetes, Diabetes. Care. 39 (2016) S137–S145.

13. Diabetes and vascular disease research 2016 vol.13(2) 119-126

14. Diabetes, obesity and metabolism 18. 812-819 2016.

15. J Clin med research 2019 11(4) 267-274

16. Giorgino et al. cardiovascular diabetology 2020,19:196.