International Journal of Research and Review
Vol.7; Issue: 12; December 2020
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Observational Study to Evaluate Effectiveness of Adding Empagliflozin to Uncontrolled Type 2 Diabetes Patients Who Were Uncontrolled On Metformin Rather Than Up Titrating the Metformin Dose

Khwaja Ahtesham Ahmad

Department of Medicine, Jamia Tibbiya Deoband, Saharanpur (U.P.)

ABSTRACT

Aim: The main objective of this prospective observational study to evaluate effectiveness of adding empagliflozin to uncontrolled type 2 diabetes patients who were uncontrolled on metformin rather than up titrating the metformin dose.

Material & Method: This was a prospective observational study conducted among 90 patients who had qualified as per the inclusion and exclusion criteria. After inclusion patients were divided into two groups one group 10 mg Empagliflozin OD were added with 1000 mg metformin OD (N=45) and in other group metformin were up titrated to 2000 mg OD (N=45) as this is considered as maximum tolerable dose of metformin.

Result: There was a significant weight reduction in Empa + Met group which was as high as 1 kg over 24 weeks' time frame. Despite on adequate anti-hypertensive management in both the group further statistically significant reduction in both SBP and DBP were observed in Empa+Met group (10.2±3.5 mmHg and 7.2±2.6, respectively) which was not with Met group. There were a further statistically significant reduction in total cholesterol; triglyceride and LDL Cholesterol despite the group were on optimal dosage of lipid lowering therapy.

Conclusion: Empagliflozin 10 mg is a potent glucose lowering agent and should be added to patients who were initially uncontrolled with metformin monotherapy rather than up titrating metformin dose. Empagliflozin offer better pleotropic benefits when added as second line therapy to metformin.

Keywords: Empagliflozin, uncontrolled type 2 diabetes patients, metformin

INTRODUCTION

Diabetes, a slowly growing epidemic, is becoming a growing burden to the nation's health and economy [1]. Efforts to curb the complications as well as limit the disease by intense management was met with several challenges earlier, including metabolic side effects, fatal complications and sometime raised overall mortality [2-5].

Diabetes and its complications are one of the leading causes of mortality and morbidity all over the world. As the disease and its complications are becoming rampant, a stringent management plan is essential [6]. A 1% increase in the glycated hemoglobin (HbA1c) level is associated with can increase of 18% in the risk of cardiovascular (CV) events. Apart from that, can increase of 12-14% in the risk of death and can increase of 37% in the risk of retinopathy or renal failure is also noted, implying a definite need to keep blood sugar in check [6,7].

Glycemic control has always been a delicately balanced act. The patients not only needs to maintain a euglycemic state but also should be educated enough to make or revise decision strategies, volitional control and the sense to avoid hypo and hyperglycemia. Metformin is a biguanide drug, currently recommended as the first line of therapy in most patients with type 2

diabetes [8-10]. Its advantages include low risk of hypoglycemia, modest weight loss and low cost. The sodium glucose cotransporter 2 (SGLT2) inhibitors reduce hyperglycemia by inhibiting the SGLT2 transporter found on the proximal convoluted tubule of the nephron [11-14]. This leads to loss of a significant proportion of the filtered glucose by means of glycosuria. Recently, duel inhibitors have been developed, that inhibit not only SGLT2, but also SGLT1, which is responsible for glucose absorption [15].

The main objective of this prospective observational study to evaluate effectiveness of adding empagliflozin to uncontrolled type 2 diabetes patients who were uncontrolled on metformin rather than up titrating the metformin dose.

METHODS AND MATERIALS

This was a prospective observational study conducted among 90 patients who had qualified as per the inclusion and exclusion criteria. Initially 108 patients were identified but 18 patients were excluded from the study as 13 were lost in follow-up and 5 were irregular in follow up checkup. The main inclusion criteria were type 2 diabetes patients who were ≥ 18 years of age and HbA1c >7%, were on metformin monotherapy 1000 mg and ready to give informed consent. Patients who were having documented micro and macro vascular complications, pregnant or lactating women, patients with impaired liver function were excluded from the study.

After inclusion patients were divided into two groups one group 10 mg Empagliflozin OD were added with 1000 mg metformin OD (N=45) and in other group metformin were up titrated to 2000 mg OD (N=45) as this is considered as maximum tolerable dose of metformin. Demographic details like age, gender, duration of diabetes, weight, BMI and other medication detailed were collected through a predesigned proforma. Blood pressure was measured at baseline and during each follow-up by a clinic manual BP measurement instrument (AccuSure Mercury Sphygmomanometer). Serological test like FBS, PPBS, HbA1c, lipid profile (total cholesterol, triglyceride, LDL cholesterol and HDL cholesterol), blood urea and serum creatinine were evaluated at baseline and in each follow up.

Microsoft excel sheet were used to collect the data thereafter with help of SPSS 22.0 data were analysed. A descriptive bivariate analysis was performed; for the chi-squared distribution, significance was assumed to be <0.05.

RESULT

Demographic details were listed in table 1. It was observed that the demographic characters were almost similar in both the groups. A good percentage of patients in both the group were having similar co morbidity like hypertension and dyslipidemia. Maximum numbers of patients in both the group were on anti-hypertensive and lipid lowering drugs.

Table 1: Demographic characteristic of the participants in both group

Characteristics	Empa + Met Gr (N=45)	Met Gr (N=45)	P Value
Age (Years)	52.8±7.2	53.2±6.9	0.671
Gender (M/F)	23/22	21/24	0.945
Duration of Diabetes (Years)	2.1±1.3	2.3±0.8	0.037
BMI (Kg/m2)	30.4 ±5.3	30.5 ±5.0	0.742
Weight (Kg)	83.8 ±19.8	83.0 ±19.1	0.385
SBP (mmHg)	128.4 ± 15.8	127.0 ±13.7	0.583
DBP (mmHg)	79.3 ± 9.4	78.5 ± 8.1	0.491
No of patients on hypertension medication (N%)	31 (69%)	28 (62%)	0.854
No of patients on lipid lowering drugs (N%)	38 (84.4%)	37 (82.2%)	0.985

Table 2 demonstrates the changes in parameters under study over 24 weeks' time frame in both the groups. There was a significant weight reduction in Empa + Met group which was as high as 1 kg over 24 weeks' time frame. Despite on adequate

anti-hypertensive management in both the group further statistically significant reduction in both SBP and DBP were observed in Empa+Met group (10.2±3.5 mmHg and 7.2±2.6, respectively) which was not with Met group.

Table 2: Changes in parameters among two studied group from baseline to 24th week

Parameters	Empa + Met Gr (N=45)		Met Gr N=45)		P Value
	Baseline	*24th Week*	*Baseline*	*24th Week*	
Weight (Kg)	83.8 ±19.8	82.3 ±9.8	83.0 ±19.1	82.6 ±18.8	0.001
FBS (mg/dl)	161.27±18.27	121.86±15.25	159.46±21.75	128.46±19.33	0.001
PPBS (mg/dl)	244.65±39.34	184.79±28.56	238.5±29.71	196.83±31.43	0.001
HbA1c (%)	8.66±0.87	7.50±0.56	8.42±0.98	7.7±0.89	0.001
SBP (mmHg)	128.4 ± 15.8	118.2 ± 9.3	127.0 ±13.7	125.7 ± 9.3	0.001
DBP (mmHg)	79.3 ± 9.4	72.1 ± 6.7	78.5 ± 8.1	77.1 ± 9.2	0.001
T. Cholesterol (mg/dl)	193.76±37.94	176.83±31.26	190.66±47.89	177.23±42.64	0.001
S. Triglycerides (mg/dl)	173.53±31.12	159.36±25.55	166.5±45.85	155.5±40.80	0.005
LDL Cholesterol (mg/dl)	131.32±28.21	119.41±25.55	130.28±27.78	122.42±24.62	0.005
HDL Cholesterol (mg/dl)	41.52±9.36	42.05±6.22	42.34±9.67	42.95±7.88	0.142
Blood Urea	29.4±5.04	26.96±4.18	29.56±5.41	28.06±4.09	0.3079
S. Creatinine	0.91±0.05	0.88±0.04	0.92±0.08	0.87±0.06	0.5826

Empa + Met group has demonstrated a higher impact on lipid profile as compare to metformin group which listed in table 2. There were a further statistically significant reduction in total cholesterol, triglyceride and LDL Cholesterol despite the group were on optimal dosage of lipid lowering therapy.

Reduction in HbA1c (Figure 1) and FBG and PPG (figure 2) is demonstrated in details bellow.

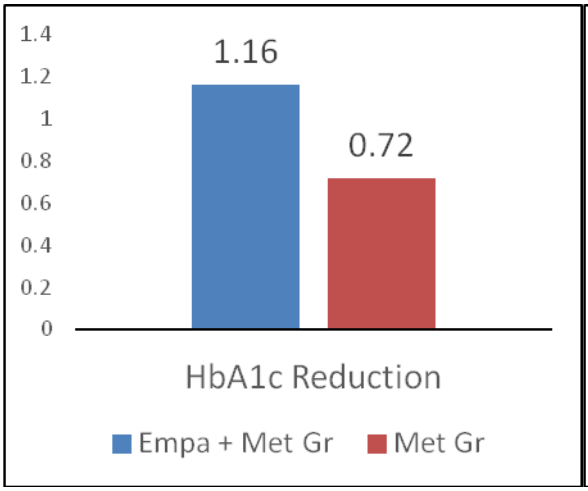

Figure 1:HbA1c Reduction over 24 weeks in two groups

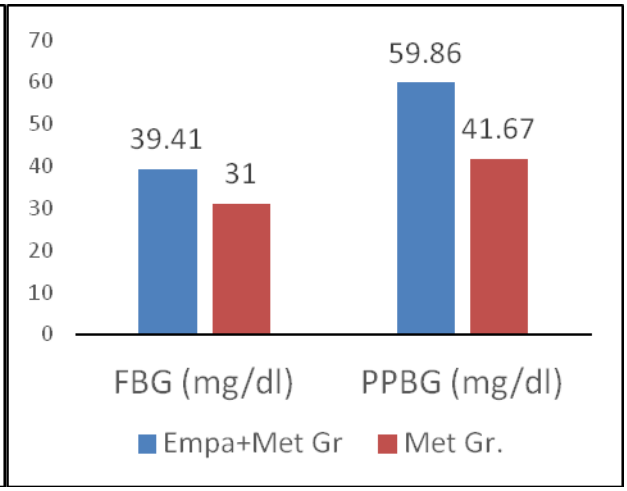

Figure 2:FBG and PPBG reduction in both the group after 24 weeks

DISCUSSION

The role of metformin in the treatment of type 2 diabetes is already well established. Its multitude of actions and good safety profile has made it the most prescribed oral anti diabetic drug. Recent literature and ongoing studies of its benefits on a wide variety of risk factors and complications of diabetes (such as lipid profile, body weight, cardiovascular risk, antiaging and antineoplastic) are providing promising results. The potential of this safe and simple drug to shape the future of diabetes should not be underestimate [16,17].

Sodium glues transporter 2 (SGLT2) inhibitors act by reducing renal glucose reabsorption and lowering blood glucose through glycosuria. EMPAREG OUTCOME and CANVAS programs are two post marketing CV outcome studies with the SGLT2 inhibitors empagliflozin and canagliflozin, respectively which showed significant improvements in the 3 point MACE with these agents [18-20].

The effect of empagliflozin was found with the EMPAREG OUTCOME study which randomized 7,200 T2DM patients with CV disease, A dose of 10 mg

to 25 mg /day empagliflozin or placebo was administration and the patients were followed for 3.1 years. More than 75% treatment of the CV risk of patients in EMPAREG OUTCOME trial included the following received statin, more than 95% received antihypertensive therapy and about 90% received anticoagulant/antiplatelet drugs [20]. Though, empagliflozin did not affect the onset of nonfatal MI and stroke, it seemed to significantly reduce hospitalization for heart failure [22]. Rapid divergent rates of the MACE, mortality and heart failure hospitalization between the empagliflozin and placebo groups was a notable feature of this trial, recorded within the first 6 months after randomization.

Current study has addressed very pertinent clinical question that whether should clinician up titrate the monotherapy or add second therapy. It this study it was clear that adding empagliflozin to metformin monotherapy not only help the patients to achieve better glycemic control than compare to high dose titration but also offer better pleotropic benefits like reduction in weight, BMI, blood pressure and lipid profile. Despite on adequate anti-hypertensive management in both the group further statistically significant reduction in both SBP and DBP were observed in Empa+Met group (10.2±3.5 mmHg and 7.2±2.6, respectively) which was not with Met group. There were a further statistically significant reduction in total cholesterol; triglyceride and LDL Cholesterol despite the group were on optimal dosage of lipid lowering therapy.

CONCLUSION

Empagliflozin 10 mg is a potent glucose lowering agent and should be added to patients who were initially uncontrolled with metformin monotherapy rather than up titrating metformin dose. Empagliflozin offer better pleotropic benefits when added as second line therapy to metformin. The use of SGLT2i is a novel approach to glycemic control and is accompanied by multiple demonstrable cardio-metabolic and renal benefits beyond its glucose-lowering effect.

REFERENCES

1. Tabish SA. Is Diabetes Becoming the Biggest Epidemic of the Twenty-first Century?. *Int J Health Sci (Qassim)*. 2007;1(2):V-VIII.
2. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. *Metabolism*. 2011;60(1):1-23. doi:10.1016/j.metabol.2010.09.010
3. De Fronzo RA. Lilly lecture 1987. The triumvirate: beta cell, muscle, liver. A collusion responsible for NIDDM. Diabetes. 1988;37:667–87.
4. Herman WH, Young MA, Waifo GU, et al. the Diabetes Preventions Program Research Group Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care. 2007;30:2453–7.
5. Bergenstal RM, Kendall DM, Franz MJ, et al. Management of type 2 diabetes: a systematic approach to meeting the standards of care. II: oral agents, insulin, and management of complications. In: DeGroot LJ, Jameson JL, editors. Endocrinology. 4. Philadelphia: WB: Saunders Co.; 2001. pp. 821–35.
6. Shrivastava SR, Shrivastava PS, Ramasamy J. Role of self-care in management of diabetes mellitus. *J Diabetes Metab Disord*. 2013;12(1):14. Published 2013 Mar 5. doi:10.1186/2251-6581-12-14
7. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. *BMJ Open*. 2017; 7(7):e015949. Published 2017 Jul 31. doi:10.1136/bmjopen-2017-015949
8. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-1585. doi:10.1007/s00125-017-4342-z
9. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med. 2002; 137:25–33. doi: 10.7326/0003-4819-137-1-200207020-00009.

10. Howlett HCS, Bailey CJ. Discovery of metformin. In: Bailey CJ, Campbell IW, Chan JCN, Davidson JA, Howlett HCS, Ritz P, editors. Metformin—the gold standard. Chichester: Wiley; 2007. pp. 11–16.
11. Katsiki N, Mikhailidis DP, Theodorakis MJ. Sodium-glucose Cotransporter 2 Inhibitors (SGLT2i): Their Role in Cardiometabolic Risk Management. Curr Pharm Des. 2017;23(10):1522-1532.
12. Pradhan A, Vohra S, Vishwakarma P, Sethi R. Review on sodium-glucose cotransporter 2 inhibitor (SGLT2i) in diabetes mellitus and heart failure. *J Family Med Prim Care*. 2019;8(6):1855-1862. doi:10.4103/jfmpc.jfmpc_232_19
13. Tanaka A, Node K. J. Emerging roles of sodium-glucose cotransporter 2 inhibitors in cardiology. Cardiol. 2017;69:501–507.
14. Suga T, Kikuchi O, Kobayashi M, Matsui S, Yokota-Hashimoto H, Wada E, Kohno D, Sasaki T, Takeuchi K, Kakizaki S, Yamada M, Kitamura T. SGLT1 in pancreatic α cells regulates glucagon secretion in mice, possibly explaining the distinct effects of SGLT2 inhibitors on plasma glucagon levels. Mol Metab. 2019 Jan;19:1-12. doi: 10.1016/j.molmet.2018.10.009. Epub 2018 Oct 27.
15. Rehman SU, Rahman F. Evidence-Based Clinical Review on Cardiovascular Benefits of SGLT2 (Sodium-Glucose Co-Transporter Type 2) Inhibitors in Type 2 Diabetes Mellitus. *Cureus*. 2020;12(8):e9655. Published 2020 Aug 11. doi:10.7759/cureus.9655
16. Lv Z, Guo Y. Metformin and Its Benefits for Various Diseases. *Front Endocrinol (Lausanne)*. 2020;11:191. Published 2020 Apr 16. doi:10.3389/fendo.2020.00191
17. Wang YW, He SJ, Feng X, et al. Metformin: a review of its potential indications. *Drug Des Devel Ther*. 2017;11:2421-2429. Published 2017 Aug 22. doi:10.2147/DDDT.S141675
18. Kluger AY, Tecson KM, Barbin CM, Lee AY, Lerma EV, Rosol ZP, Rangaswami J, Lepor NE, Cobble ME, McCullough PA. Cardiorenal Outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME Trials: A Systematic Review. Rev Cardiovasc Med. 2018 Jun 30;19(2):41-49.
19. Kluger AY, Tecson KM, Lee AY, Lerma EV, Rangaswami J, Lepor NE, Cobble ME, McCullough PA. Class effects of SGLT2 inhibitors on cardiorenal outcomes. Cardiovasc Diabetol. 2019 Aug 5;18(1):99.
20. Rastogi A, Bhansali A. SGLT2 Inhibitors Through the Windows of EMPA-REG and CANVAS Trials: A Review. *Diabetes Ther*. 2017;8(6):1245-1251. doi:10.1007/s13300-017-0320-1
21. Scheen AJ. L'ETUDE CLINIQUE DU MOIS EMPA-REG OUTCOME: L'empagliflozine réduit la mortalité chez le patient diabétique de type 2 à haut risque cardiovasculaire [EMPA-REG OUTCOME: Empagliflozin reduces mortality in patients with type 2 diabetes at high cardiovascular risk]. Rev Med Liege. 2015 Nov;70(11): 583-9. French.

How to cite this article: Ahmad KA. Observational study to evaluate effectiveness of adding empagliflozin to uncontrolled type 2 diabetes patients who were uncontrolled on metformin rather than up titrating the metformin dose. International Journal of Research and Review. 2020; 7(12): 371-375.

******