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Comparison of Extraglycemic effects of Dapagliflozin and Empagliflozin

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ABSTRACT

Objective: To compare extra glycaemic effects of dapagliflozin and empagliflozin in Type 2 Diabetes mellitus.
Study Design: Quasi-experimental study.
Place and Duration of Study: Pharmacology Department, Army Medical College, in collaboration with Endocrine Department, Pak Emirate Military Hospital, Rawalpindi Pakistan, from Sep 2021 to Jan 2022.
Methodology: One hundred and twenty diabetic patients were recruited strictly according to inclusion and exclusion criteria. They were randomly alienated into two groups (A & B) by lottery method and were prescribed oral dapagliflozin and empagliflozin 10 mg/day each for four weeks, respectively. Serum uric acid, erythropoietin levels, and weight were recorded on day 0 and after four weeks of treatment.
Results: There were statistically significant differences in weight (p-value=0.004) and erythropoietin levels (p-value=0.027). However, an inconsequential variance was observed in serum uric acid levels Uric Acid (p-value=0.365) between the two groups after four weeks of treatment with dapagliflozin and empagliflozin.
Conclusions: Dapagliflozin and empagliflozin have significantly improved weight, erythropoietin and serum uric acid levels. Moreover, Dapagliflozin is superior to Empagliflozin in improving weight and erythropoietin levels and has almost equivalent efficacy in improving uric acid levels in T2DM patients.

Keywords: Dapagliflozin; Empagliflozin; SGLT2 inhibitors; Type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus is related to high mortality and morbidity due to micro and macrovascular complications.[1] People with diabetes are at a greater risk of developing cardiovascular disease (CVD), the leading cause of mortality and illness.[2,3] Diabetic nephropathy, which can damage one or both kidneys throughout a patient's lifetime, affects forty per cent of the population with diabetes at some point in their lives. [4]

Sodium-glucose transporter-2 (SGLT2) inhibitors are a more recent class of oral anti-hyperglycemic medicines licenced for treating diabetes mellitus.[5] Since SGLT2 inhibitors block sodium-dependent glucose transporter-2, which is present in the early proximal renal tubule, their use leads to glycosuria. SGLT2 inhibitors reduce body weight by the excretion of between 60 and 80 grams of glucose daily, equivalent to around 220 to 320 calories.[6] Patients treated with SGLT2 inhibitors often have an average weight loss of two to four kilogrammes. This mass loss was consistent regardless of whether SGLT2 inhibitors were prescribed as monotherapy or combined with other medicines that lowered glucose levels.[7] According to the findings of dual-energy x-ray absorption spectroscopy, Dapagliflozin was responsible for a reduction in fat mass that contributed around sixty to seventy per cent of the overall reduction in body weight.

Several studies found no connection between the consumption of iron or the morphology of red blood cells and the early rise in erythropoietin levels. These studies indicated that erythropoietin levels tended to rise early. All of the clinical trials conducted with SGLT2i showed an upsurge in haematocrit due to faster erythropoiesis due to higher levels of erythropoietin.[8,9]

Currently, SGLT2i are indicated in patients whose first-line antidiabetic medicines have failed to control plasma glucose levels.[10] Dapagliflozin and empagliflozin are rising due to their promising efficacy in glycemic and extra-glycemic effects. The current study evaluated the extra glycemic effects of the two leading drugs of this group in type 2 diabetic patients. Though much research has been done to explore such effects, studies have yet to be conducted in local settings.

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METHODOLOGY

The quasi-experimental study has been conducted at the Department of Pharmacology, Army Medical College, Rawalpindi, in collaboration with the Department of Endocrinology, Pak Emirates Military Hospital (PEMH), Rawalpindi Pakistan from September 2021 to January 2022 after the approval of the Ethics Review Committee (ERC/ID/149). The sample size was calculated by the WHO calculator.[11]

Inclusion Criteria: Patients of diabetes, aged 18-55 years, of either gender, diagnosed with T2DM for at least six months and having HBA1c ≥8.0 presenting to the Outpatient Department, were included in the study after informed consent.

Exclusion Criteria: Patients diagnosed with T1DM or steroid-induced DM, gestational diabetes and patients already on urate-reducing therapy were excluded from the study.

Sixty-three adult females and fifty-seven adult males were randomly selected by nonprobability consecutive sampling from the Outpatient Department of the hospital. The patients were divided into Group-A (Dapagliflozin Group n=60) and Group-B (Empagliflozin Group n=60) by lottery. Patients in both groups (A and B) were prescribed once daily dapagliflozin 10 mg and empagliflozin 10 mg orally for four consecutive weeks.

Five millilitres of blood sample was obtained from the patients using an aseptic venepuncture technique for the baseline levels of the serum erythropoietin and uric acid. Body mass index was also calculated. The previous tests were repeated after four weeks of treatment, and all the results were noted down for comparison.

Statistical Package for the Social Sciences (SPSS) 26 was utilised to analyse the data. The chi-square test was carried out to analyse categorical data, whereas an independent t-test was utilised to analyse the continuous variables. The paired t-test was utilised to examine the differences in weight, uric acid, and erythropoietin levels. The *p*-value of ≤0.05 was considered significant.

RESULTS

Out of 120 patients, 63(52.5%) participants were females, whereas 57(47.5%) were male, with a mean age of 40±10 years. Sixty patients (50.0%) enrolled in this study were obese (BMI >30). The mean weight and uric acid levels were significantly reduced (*p*-value <0.001), and erythropoietin levels were meaningfully increased (*p*-value <0.001) in both groups after four weeks of treatment with dapagliflozin and empagliflozin respectively. Table-I compares mean differences in baseline weight, uric acid, and erythropoietin levels. After four weeks of treatment for Group-A, Table-II shows the same parameters in Group-B. There was a significant statistical difference in study outcomes between the two groups. Follow-up weight between both groups was compared and found to have a significant statistical difference (*p*-value =0.004). Similarly, a statistically significant difference (*p*-value =0.027) was observed when follow-up values of Erythropoietin were compared between both groups. However, the Uric Acid levels after four weeks of treatment were statistically insignificant (*p*-value =0.365) within both groups, as shown in Table-III.

Table-I: Mean Differences in Baseline and Follow up of Weight, Uric Acid and Erythropoietin Level in Group-A (n=60)

Variable	Mean±SD	*p*-value
Baseline weight	87.54±13.37 kg	<0.001
Follow up weight	83.31±12.33kg	
Baseline Uric Acid	302.95±103.56 mg/24 hr	<0.001
Follow up Uric Acid	230.20±83.34 mg/24 hr	
Baseline Erythropoietin	43.03±60.62 mU/mL	<0.001
Follow up Erythropoietin	58.92±80.24 mU/mL	

Table-II: Mean Differences in Baseline and Follow up of Weight, Uric Acid and Erythropoietin Level of Group-B (n=60)

Variable	Mean±SD	*p*-value
Baseline Weight	79.97±9.83kg	<0.001
Follow up Weight	77.31±9.78kg	
Baseline Uric Acid	329.08±86.54 mg/24 hr	<0.001
Follow up Uric Acid	243.51±76.39 mg/24 hr	
Baseline Erythropoietin	21.67±22.56 mU/mL	<0.001
Follow up Erythropoietin	33.46±36.20 mU/mL	

Table-III: Mean Differences in Weight, Uric Acid and Erythropoietin Level of Group A and B after Four Weeks (n=120)

Variables	Group-A (n=60)	Group-B (n=60)	*p*-value
Follow up Weight	83.31±12.33kg	77.31±9.78kg	0.004
Follow up Uric Acid	230.24±83.34 mg/24 hr	243.51±76.39 mg/24 hr	0.365
Follow up Erythropoietin	58.92±80.24 mU/mL	33.46±36.20 mU/mL	0.027

DISCUSSION

The present study evaluated the extra glycemic effects of Dapagliflozin in contrast to Empagliflozin among T2DM patients. The outcomes of our research have elucidated that both drugs have promising beneficial effects beyond glycemic control in DM

patients. Nevertheless, Dapagliflozin, compared with Empagliflozin, produced noteworthy betterment in body weight and serum erythropoietin levels and showed almost equivalent effects on plasma uric acid levels.We have observed statistically significant weight loss by dapagliflozin and empagliflozin. Similar effects on body weight were shown by Neeland *et al.*, who concluded that empagliflozin meaningfully decreased weight in 3 months of treatment.[12] This was supported by another study of almost three years duration, in which Dapagliflozin reduced body weight and HbA1c.[13] Both of these researches compared the effects on weight with a placebo, whereas we compared the two most commonly used SGLT2 inhibitors. Hussain *et al*. demonstrated that empagliflozin lead to more significant weight reduction as compared to dapagliflozin after 12 weeks of treatment.[14] These findings are contrary to our results, possibly due to the longer treatment duration and larger cohort size in contrast to the current study.

According to reports, the use of SGLT2 inhibitors has been associated with a reduction in uric acid levels.[15] Yuan *et al*. revealed that dapagliflozin 10mg daily could shrink the serum uric acid levels to near normal like healthy individuals within one week.[16] Likewise, our results confirm these findings, and both the SGLT2 inhibitors effectively decreased the plasma uric acid levels after four weeks. However, there was no remarkable difference in lowering the serum uric acid among the Dapagliflozin and empagliflozin.

Our results have demonstrated the positive impact of Dapagliflozin and empagliflozin in raising the erythropoietin levels after four weeks in hyperglycaemic patients. Furthermore, dapagliflozin showed a more promising impression on red cell synthesis hormone levels than empagliflozin.[17] This enhanced the erythropoietin-producing ability of SGLT inhibitors has also been exhibited in a prospective, open-label, single-arm study conducted by Maruyama and colleagues.[18] in which Canagliflozin 100mg/day orally was given for three months. Their results showed amplified erythropoiesis due to increased biosynthesis of erythropoietic growth factor. However, our study was superior to theirs for a more significant sample size and the existence of a comparator group.

The exact mechanism of amplification of Erythropoietin by SGLT2 inhibitors is yet to be elucidated; it is believed that these second-line antidiabetic drugs might decrease tubulointerstitial oxygen demand by improving the proximal convoluted tubule's burden hence facilitating the erythropoietin synthesis. The production of hypoxia-inducible factors, triggered by more significant oxygen-consuming sodium reabsorption to the distal tubules, is a possible mechanism for increased erythropoietin levels mediated by SGLT2 inhibitors. In addition, a rise in erythropoietin-induced haematocrit may improve cardiac performance by directly enhancing myocardial and systemic tissue oxygenation.

CONCLUSION

In conclusion, as per our findings, both antidiabetic drugs have produced promising extra glycemic effects that go beyond the glycemic control, and Dapagliflozin has shown noteworthy betterment in body weight and serum erythropoietin levels in comparison with Empagliflozin and both drugs have almost equivalent effects on plasma uric acid concentration in T2DM patients.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HA & MN: Data acquisition, data analysis, drafting the manuscript, approval of the final version to be published.

BA & SA: Data interpretation, critical review, concept, study design, approval of the final version to be published.

KF & FAS: Critical review, data acquisition, drafting the manuscript , approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Riaz S, Nisar S, Anwer W, Palwa AR, Saeed F, Hussain M,et al. Effect of patient understanding of diabetes self-care on glycemic control, a hospital based cross sectional analytical study. Pak Armed Forces Med J 2022; 72(3): 758-62. https://doi.org/10.51253/pafmj.v72i3.4471
2. Ali M, Mahmood F, Mudassar S, Mustafa ZU, Uddin MA, Nishat M, et al. Diabetes Mellitus Type 2 Associated Alterations in the Regulation of Blood Sugar, Kidney Function and Oxidative Stress. Pak J Med Health Sci 2022; 16(02): 226-227. https://doi.org/10.53350/pjmhs22162226
3. Cefalu WT, Berg EG, Saraco M, Petersen MP, Robinson S. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. Diabetes Care 2019; 42: S13-S28.
4. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010; 375(9733):2215-2222. https;//doi: 10.1016/S0140-6736(10)jurnal-publishid60484-9.
5. Bonora BM, Avogaro A, Fadini GP. Extraglycemic Effects of SGLT2 Inhibitors: A Review of the Evidence. Diabetes Metab Syndr Obes 2020; 13(1): 161-174. https://doi: 10.2147/DMSO 012155.S233538.

6. Fadini GP, Bonora BM, Zatti G, Vitturi N, Iori E, Marescotti MC, et al. Effects of the SGLT2 inhibitor dapagliflozin on HDL cholesterol, particle size, and cholesterol efflux capacity in patients with type 2 diabetes: a randomized placebo-controlled trial. Cardiovasc Diabetol 2017; 16(1): 42. https://doi: 10.1186/s12933-017-0529-3.
7. Scholtes RA, Muskiet MH, van Baar MJ, Hesp AC, Greasley PJ, Karlsson C, et al. Natriuretic effect of two weeks of dapagliflozin treatment in patients with type 2 diabetes and preserved kidney function during standardized sodium intake: results of the DAPASALT trial. Diabetes Care 2021; 44(2): 440-7. https://doi.org/10.2337/dc20-2604
8. Díaz-Rodríguez E, Agra RM, Fernández ÁL, Adrio B, García-Caballero T, González-Juanatey JR, et al. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. Cardiovasc Res 2018; 114(2): 336-346. https://doi: 10.1093/cvr/cvx186.
9. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi J, Nakanishi T, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos 2014; 35(7): 391-404. https://doi: 10.1002/bdd.1909.
10. Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, et al. Effect of Empagliflozin on Erythropoietin Levels, Iron Stores, and Red Blood Cell Morphology in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease. Circulation 2020; 141(8): 704-707. https://doi: 10.1161/Circulationaha.119.044235.
11. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 2017; 60(2): 215-225. https://doi: 10.1007/s00125-016-4157-3.
12. Neeland IJ, McGuire DK, Chilton R, Crowe S, Lund SS, Woerle HJ, et al. Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus. Diab Vasc Dis Res 2016; 13(2): 119-126. https://doi: 10.1177/1479164115616901.
13. Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, et al. Sugg J, Parikh S. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab 2014; 16(2): 159-169. https://doi: 10.1111/dom.12189.
14. Hussain M, Atif M, Babar M, Akhtar L. Comparison of efficacy and safety profile of empagliflozin versus dapagliflozin as add on therapy in type 2 diabetic patients. J Ayub Med Coll 2021; 33(4): 593-597.
15. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes Obes Metab 2018; 20(2): 458-462. https://doi: 10.1111/dom.13101.
16. Yuan T, Liu S, Dong Y, Fu Y, Tang Y, Zhao W, et al. Effects of dapagliflozin on serum and urinary uric acid levels in patients with type 2 diabetes: a prospective pilot trial. Diabetol Metab Syndr 2020; 12: 92. https://doi: 10.1186/s13098-020-00600-9.
17. Suijk DLS, van Baar MJB, van Bommel EJM, Iqbal Z, Krebber MM, Vallon V, et al. SGLT2 Inhibition and uric acid excretion in patients with type 2 diabetes and normal kidney function. Clin J Am Soc Nephrol 2022; 17(5): 663-671. https://doi: 10.2215/CJN.11480821.
18. Maruyama T, Takashima H, Oguma H, Nakamura Y, Ohno M. Canagliflozin Improves Erythropoiesis in Diabetes Patients with Anemia of Chronic Kidney Disease. Diabetes Technol Ther 2019; 21(12): 713-720. https://doi: 10.1089/dia.2019.0212.

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