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Efficacy and safety of Dapagliflozin and Glimepiride in combination with Metformin: Randomized clinical trial

Muhammad Kamran Yousuf, Khalid Mustafa Memon, M. Sajid Abbas Jaffri, Mehar Fatima, Mamoora Arslaan, Shizma Junejo

ABSTRACT:

Objective: To identify the effective treatment option between dapagliflozin-metformin and glimepiride-metformin combination in patients with type 2 diabetes who were inadequately controlled with metformin monotherapy.

Study design and setting: The present study is randomized, conducted for 12 weeks at the National Medical center, Karachi, Pakistan.

Methodology: The patients were divided into 2 treatment groups; group A was given dapagliflozin-metformin combination, while group B was given glimepiride-metformin combination. The efficacy endpoint of groups was estimated by hemoglobin A1c and fasting blood glucose levels at 0-, 6- and 12-week. While, safety endpoints were identified by analyzing liver function tests, lipid profile tests, renal function test, and urine analysis. The significant difference of data was analyzed by using statistical package of social sciences (SPSS) version 25. The parametric t-test and paired t-test were performed and considered p-value = 0.05 as statistical significant.

Results: Baseline demographics, clinical features of diabetes, levels of liver enzymes, liver function test, renal function test, lipid profile, and urinalysis of randomized patients were similar in both treatment groups by showing p = 0.05. Followed by the initiation of the respective treatment, the baseline change of mean FBG and hemoglobin A1c levels with dapagliflozin-metformin combination was shown significantly reduce more compared to glimepiride-metformin combination (p = 0.05).

Conclusion: Dapagliflozin-metformin combination therapy was superior and well-tolerated to regulate glycemic control as compare to glimepiride-metformin combination.

Keywords: Type 2 diabetes mellitus, glimepiride, dapagliflozin, fasting blood glucose, glycated hemoglobin

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INTRODUCTION

Diabetes mellitus is a chronic metabolic condition defined by insulin resistance that prevents glucose uptake into the cells and ultimately causes hyperglycemia over a prolonged period. Currently, around 463 million people live with diabetes and produce drastic effect on health of individuals of all ages.[1] Therefore, the focus of attention of medical practitioners and researchers is to highlight the agents that control the blood sugar level of type 2 diabetes (T2D) patients and having a decreased probability of causing hypoglycemia and weight loss. According to the American Diabetes Association (ADA) recommendation, metformin is the first-line treatment prescribed in T2D that requires maintaining glycated hemoglobin (hemoglobin A1c) below or around 7%. However, modifications in treatment are strictly needed if the target to maintain hemoglobin A1c is not achieved at maximal tolerated dose over the use of 3 to 6 months. This modification involves the addition of a second oral anti-diabetic drug or initiation of subcutaneous administration of basal insulin.[2] Many FDA-approved therapies control blood sugar levels,[3] but the elucidation of safety and efficacy profile between dapagliflozin-metformin

and glimepiride-metformin combination in patients with type 2 diabetes was unfocused.

Many studies have compared the safety and efficacy profile of sulfonylurea-metformin and SGLT-2 inhibitor-metformin in patients with type 2 diabetes inadequately controlled with metformin. Nauck MA and colleagues compared dapagliflozin *vs.* glipizide (sulfonylurea) in combination with metformin over 2 years. They found greater glycemic stability, weight loss, reduced systolic blood pressure, and low hypoglycemia but frequent genital and urinary tract infections in dapagliflozin-metformin compared with other combinations.[4] Cefalu WT and Del Prato S colleagues study the same combination for 54 weeks and 4 years, respectively, and found consistent results.[5,6] Moreover, Ridderstråle M and colleagues study canagliflozin (SGLT-2 inhibitor) *vs.* glimepiride (sulfonylurea) in combination with metformin and revealed the greater reduction of HbA1c level in canagliflozin group than glimepiride.[7] And Nauck MA and colleagues study empagliflozin-metformin *vs.* glimepiride-metformin and found empagliflozin effective and a well-tolerated option.[8] However, the comparation of dapagliflozin-metformin *vs.* glimepiride-metformin combination was a neglected area.

The clinical studies reveal that glimepiride exhibits a lower association with hypoglycemia and increase weight.[9] Furthermore, it is safer to prescribe in T2D patients suffering from cardiovascular disease (CVDs). It does not produce an effect in the ischemic preconditioning, which is defined as an adaptive physiological mechanism in response to an ischemic event. This eventually delays cardiac infarction and prevents cardiac tissue injury.[10] On the other hand, SGLT-2 inhibitors are also the possible option for the treatment of diabetes and produce a definitive role in the management of diabetes-mediated heart failure. Remarkably, dapagliflozin is the latest generation of anti-diabetic drug and the first FDA-approved regimen for treating heart failure compared with other SGLT-2 inhibitors.[11] The number of studies has highlighted its more prominent role over other SGLT-2 inhibitors to cardiac safety and considered it for opening future floodgates by repurposing from anti-glycemic drugs to anti-heart failure medicine[12,13].

Taken all together, both of these drugs are promising add-on pharmacotherapies, but the selection of effective therapy between these two is a neglected area. Therefore, the present study aimed to study the efficacy and safety profile of dapagliflozin-metformin *vs.* glimepiride-metformin in type 2 diabetes patients given maximum tolerated dose of metformin monotherapy. To the best of our knowledge, this comparative analysis was not investigated before.

METHODOLOGY:

The present study is a randomized control trial conducted for 12 weeks at the National medical center, Karachi, Pakistan. A total of 200 diabetic patients were enlisted in which 190 patients were randomly enrolled according to inclusion criteria and completed the study successfully. The patients were assigned numbers from 1 to 190, and then they were randomly selected using a Google random number generator to be part of either group A or group B. A total of 95 patients were selected for each group. A double-blind method was used to ensure that neither the patients nor the researchers assessing the outcomes were aware of the assigned groups. The patients of group A were taken a fixed dose of 10 mg of dapagliflozin with 500 mg of metformin orally, while the patients of group B were taken 4 mg of glimepiride with 500 mg of metformin orally thrice a day throughout the 12-weeks of treatment. They were strictly restricted to a sugary diet in their meal. Initially, the approval of protocol was obtained by Ethical Research Committee (ERC) of Bahria University, and the written informed consent taken from all the enrolled participants.

The inclusion criteria were based on normal baseline levels of LFT, RFT, lipid profile, and white blood cell count (WBC). The fasting blood glucose (FBG) levels of all recruited participants were = 126 mg/dL, and hemoglobin A1c levels were >7-10%, followed by 1500 mg/day metformin monotherapy last 3 to 6 months. The exclusion criteria were based on hypertension, decompensated or acute congestive heart failure, estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, left ventricular ejection fraction (LEVF) less than 40%, liver impairment, terminal illness, or cancer.

The sample size for the frequency of population was calculated by using the OpenEpi, Version 3. [14] The efficacy endpoints of groups were estimated by quantifying glycated hemoglobin (Hemoglobin A1c) and FBG levels at 0-, 6- and 12-week of treatment. Safety endpoints were identified by analysing levels of LFT, RFT, lipid profile, urinalysis, and hypoglycemic events.

The hypoglycaemic events were divided into five definitions as per the glucose level and symptoms; (i) FBG level = 70 mg/ dL, (ii) FBG level = 54 mg/Dl, (iii) FBG level = 50 mg/dL, (iv) FBG level = 70 mg/dL but an asymptomatic hypoglycaemic event, and (5) FBG level > 70 mg/dL but with another hypoglycaemic episode.

The statistical significance of data was analyzed using the IBM statistical package of social sciences (SPSS) version 25. All quantitative parameters such as FBG, hemoglobin A1c, liver enzymes, bilirubin, lipid profile, blood pressure, and body mass index (BMI) were presented in mean ± standard deviation (SD). The parametric t-test and paired t-test were performed to estimate the significant clinical difference between pre and post findings. P-values less than 0.05 were considered significant in the study.

RESULTS:

All participants in this study were between the age group of 45-55 years. Baseline demographics and clinical diabetes

characteristics of randomized patients were the same in both treatment groups. All patients were Asian and belonged to Karachi, Pakistan, in which a total of 50% were male, and 50% were female. At baseline, the mean age and BMI were 56± 4 years, 31±2.15 kg/m2, respectively. All enrolled patients were previously taking metformin monotherapy of =1500 mg, once or twice in 24-hours from the last 3 to 6 months, and had insignificant FBG and haemoglobin A1c levels between groups at week-0 shown in table 1. Furthermore, the lipid profile, LFT, RFT, and urinalysis levels were similar in both groups, as depicted in Figures 1,2, 4 and 4, and table 3.

The baseline change of mean FBG at 6-week of treatment with dapagliflozin- metformin and glimepiride-metformin combination were shown 137.02±12.30 and 146.23±12.54 levels, and at 12-weeks of treatment were shown 101.40±16.85 and 121.89±9.22 mg/dL levels, respectively. Whereas, mean of baseline hemoglobin A1c at 0-week with dapagliflozin- metformin and glimepiride-metformin combinations were 7.83±0.54 and 8.21±0.45 %, respectively and, at the end of the study (at 12-week) this were 6.91±0.74 and 7.91±0.49 %, respectively. The change in glycemic levels was significantly greater (*P*= < 0.001) in group A compared to group B at 6- and 12-week, thereby demonstrating the superiority of dapagliflozin-metformin over another treatment regimen. A slightly more shift in FBG levels was achieved, followed by the first 6 weeks of dapagliflozin-metformin combination. The glimepiride-metformin combination treatment showed increased reduction at week-12, as shown in Table 1.

Table 1: Glycemic profile at intervals of 0-, 6- and 12-week in treatment regimens

	Dapagliflozin-Metformin (Mean±SD)	Glimepiride-Metformin (Mean±SD)	Mean Difference	P-Value
FBG (mg/dL)				
At Week 0	184.05±14.82	178.19±9.04	5.86	0.067[S]
At Week 6	137.02±12.30	146.23±12.54	-9.210	0.000 [S]
At Week 12	101.40±16.85	121.89±9.22	-20.49	0.000[S]
HbA1c (%)				
At Week 0	7.83±0.54	8.21±0.45	-0.377	0.075[S]
At Week 12	6.91±0.74	7.91±0.49	-1.000	0.000[S]

FBG: Fasting blood glucose, HbA1c: haemoglobin A1c, SD: standard deviation; [S]: statistical significant

Table 2: Blood pressure and body mass index at intervals of 0-, 6- and 12-week in both treatment regimens

	Group A (Mean±SD)	Group B (Mean±SD)	Mean Difference	P-Value
SBP				
At Week 0	184±14.82	178±9.04	5.86	0.052
At Week 6	137±12.30	146±12.54	-9.210	0.064
At Week 12	101±16.85	121±9.22	-20.49	0.073
DBP				
At Week 0	95±0.25	98±0.12	-0.377	0.075
At Week 6	93 ±0.73	97±0.37	-1.000	0.062
At Week 12	92±0.89	98±0.69	-1.000	0.082
BMI				
At Week 0	31±2.15	31±2.15	-0.377	0.071
At Week 6	30±1.82	31±1.06	-1.000	0.052
At Week 12	30±6.12	30±9.15	-0.200	0.08

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, [S]: statistical significant

The safety and tolerability profiles in treatment arms were identified. The analysis was shown that patients did not significantly experience adverse hypoglycemia in both groups during the entire study period of 12-week. No clinically meaningful lipid profile changes were observed between the dapagliflozin-metformin combination group and the glimepiride-metformin group at 12-week by showing p-value >0.05, as depicted in figure 1. Furthermore, insignificant LFT and RFT changes were found in the dapagliflozin-metformin combination group at 6- and at 12-week compared to the glimepiride-metformin combination group (Figure 2 and 3).

Furthermore, urinalysis of A group and B group at 6- and 12-week were similar (Figure 4 and Table 3). In group A, an increased concentration of ketone was found in one patient. Whereas the patient continued the prescribed study regimen. None of the profound adverse effects was observed in both groups.

DISCUSSION:

The present study compared the efficacy and safety profile of dapagliflozin-metformin with the glimepiride-metformin combination is used glycaemic control in type 2 diabetes patients of Karachi, Pakistan. Dapagliflozin-metformin combination was lead to superior improvements in glycaemic management than other treatment regimens followed by 12-week treatment. Previously, many studies have compared the safety and efficacy profile of sulfonylurea-metformin and SGLT-2 inhibitor-metformin in patients with type 2 diabetes who are inadequately controlled with metformin, [4-8]. But none of them reported glimepiride-metformin and dapagliflozin-metformin combination.

Table 3: Glycosuria at 0 week, 6 week and 12 week in treatment regimens

		Mild (n = %)	Moderate (n = %)	Severe (n = %)
Group A	At Week 0	97 (97)	3 (3)	0 (0)
	At Week 6	12 (12)	82 (82)	6 (6)
	At week 12	2 (2)	9 (9)	89 (89)
Group B	At Week 0	96 (96)	3 (3)	1 (1)
	At Week 6	98 (98)	2 (2)	0 (0)
	At week 12	99	1	0

Figure 1: Lipid Profile at week 0, 6 and 12 in both treatment groups.

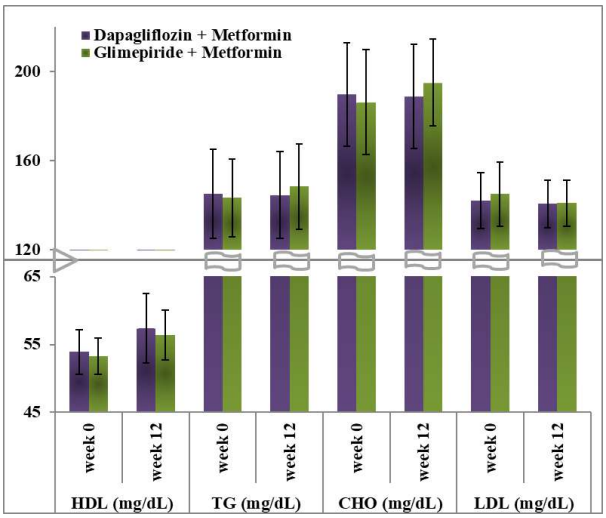
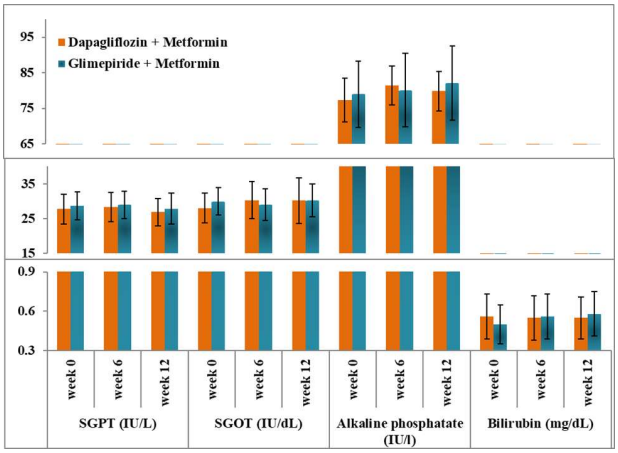


Figure 2: Liver function test at week 0, 6 and 12 in both treatment groups



The glycemic control analysis showed decreased FBS and hemoglobin A1c levels from baseline to week 12, and superiority was met for dapagliflozin-metformin compared with the glimepiride-metformin combination. No statistically significant differences between groups were found for lipid profile, LFT, RFT, urinalysis, and hypoglycaemic events during the complete study. Dapagliflozin-metformin therapy reduced baseline FBS level to a greater extent than glimepiride-metformin combination therapy at week 6. But, both treatment regimens were well tolerated. The findings of glycemic control of dapagliflozin-metformin combination are similar to previously reported study of Bailey CJ and colleagues. They enrolled 546 patients for 102 weeks and given them 2.5 to 5 and 10 mg of dapagliflozin monotherapy. Their results were shown changes from baseline HbA1c from all the treatment doses.Moreover, all dapagliflozin groups sustained decline in baseline FBG levels and weight without producing prominent hypoglycemia. In contrast,

Figure 3: Renal function test at week 0, 6 and 12 in both treatment groups

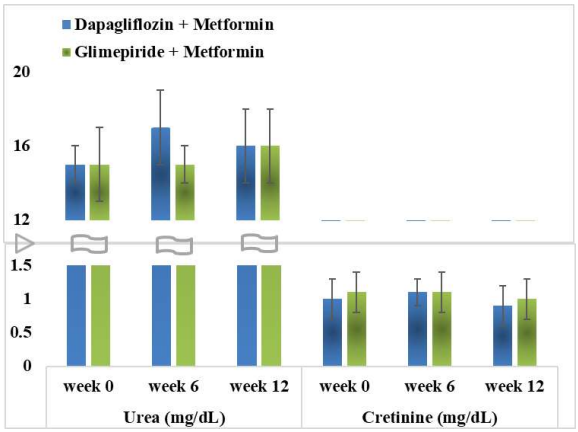
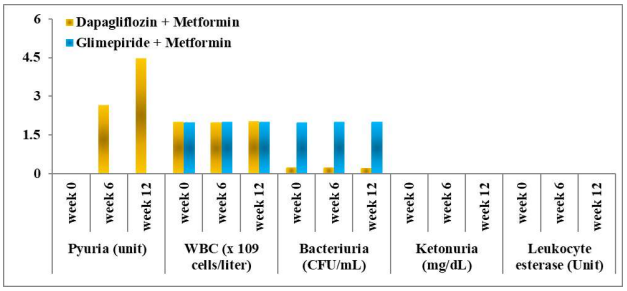


Figure 4: Urinalysis at week 0, 6 and 12 in both treatment groups



some patients experienced genital infections . Another study conducted by Rosenstock J and colleagues is also consistent with our findings. They identified a significant decrease in HbA1c levels in SAXA+DAPA+MET, SAXA+MET, and DAPA+MET combinations. Whereas less than 1% of Urinary and genital infections found in patients receiving SAXA+DAPA+MET combination and hypoglycemia was infrequent, with no episodes of major hypoglycemia. Besides, our results were in accordance with previously reported comparison study of dapagliflozin and many other SGLT-2 inhibitors with sulphonylureas.[4-8]

Dapagliflozin-metformin combination was insignificantly decreased BMI, compared with other therapy which insignificantly increases weight during treatment. Furthermore, the dapagliflozin-metformin combination reduced systolic blood pressure insignificantly. Sjöström CD et al. and Yamout H et al. in their study highlighted the similar effect, and another investigation was concluded that these effects possibly due to the natriuretic, osmotic, and weight-decreasing property of SGLT-2 inhibitors.[17-20] The insignificant findings in the present study may be due to the short period of treatment, and the long-term study will define it more clearly. The earlier study conducted by and colleagues emphasized the importance of control blood pressure in T2DM patients; they analyzed data of 10 mg dapagliflozin as monotherapy and combination therapy and highlighted that increase in blood pressure is greatly associated with

decreased risk of micro-and macro-vascular diabetic impairments, including cardiovascular disease (CVDs).[21]

This study revealed the combination therapy of dapagliflozin-metformin was well tolerated compared to previous studies that reported mild or moderate intensity of urinary tract and tract genital infections in patients who were taking dapagliflozin.[22,23] Numerous hypotheses have been proposed for the underlying mechanism of infection, but the simplest being is the production of glycosuria mediated by SGLT-2 inhibitor.[24]

The preliminary study was shown the transient reductions of lipid profile by SGLT-2 inhibitors, but the present study revealed that patients receiving dapagliflozin-metformin combination experienced insignificantly reduced cholesterol, LDL, and TG than patients receiving the glimepiride-metformin combination; this may be due to the short duration of treatment. Furthermore, the study criteria for withdrawal because of the high lipid profile were strict and modified the treatment if TG, CHO, and LDL-c level were not reversed within 1-week of biochemical analysis. Earlier findings have revealed the reversible effect of SGLT-2 inhibitors on lipid profile and suggested its association with decreased risk of CVDs.[11,12,17]

In the present study, mild hypoglycaemic events occurred in 1 patient out who was given glimepiride-metformin combination. There were substantially no events found in patients taking dapagliflozin-metformin variety. These findings are in line with the previous study of Nauck MA and colleagues.[24] The increase in induction of hypoglycemia is the critical adverse effect of glimepiride-metformin combination therapy, which is greatly associated with various life-threatening complications. Around six times increase mortality rate has been observed attributed to hypoglycemia-mediated impairments, acute neurocognitive dysfunction, retinal cell death, cerebrovascular disease, vision loss, and myocardial infarction. Moreover, it compromises the life quality by producing insomnia, inactiveness in the workplace, and decrease interest in recreational activities (exercise and travel). The clinical spectrum of glimepiride-metformin increases the burden of hypoglycaemia.[25] While none of the hypoglycaemic episodes is the imperative advantage to select dapagliflozin-metformin combination therapy for the treatment of inadequate glycemia. Taken all together, the practical disadvantage of dapagliflozin-metformin combination regimen was not found relative to the glimepiride-metformin combination, which needs constant glucose monitoring and careful titration to maintain good glycemic control.

A key strength of this study is the comparison between dapagliflozin-metformin and glimepiride-metformin combinations for the treatment of glycemia in poorly controlled T2DM patients. This is the first study regarding the comparative effect of these two frequently prescribed medicines to the best of our knowledge. Efficacy of present pharmacological treatment for FBS and hemoglobin A1c were performed. The drug groups' safety profile was closely observed in hepatic functions, urinary tract, and cardiovascular system at intervals of 6th and 12th- week. While possible limitations of the current study include the failure to monitor the long-term efficacy and safety profile of study treatments on liver and heart physiology and heart and restricted population size.

The study included 190 participants, which is a reasonable sample size, but increasing the sample size could improve the generalizability of the findings. Furthermore, the study's results highlight the significance of using the dapagliflozin-metformin combination, which resulted in better improvements in managing blood sugar levels compared to other treatment regimens. Conducting a multi-centre study would allow for a more diverse population to be included and would provide valuable insights on this topic.

CONCLUSION:

In conclusion, dapagliflozin-metformin therapy was superior to the glimepiride-metformin combination in terms of reductions in FBS and hemoglobin A1c levels. This combination produced benefits to control BMI, improved blood pressure, well-tolerated safety profile and was substantially ineffective in producing hypoglycaemic episodes. All of these findings are emphasized for the selection of dapagliflozin-metformin combination therapy in T2DM patients. The long-term follow-up study will define the comparation and safety profile and efficacy among diabetic patients more clearly.

Authors Contribution:
Muhammad Kamran Yousuf: Substantial contribtion to conception and ddesign, acquisition of data analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. Final approval of the version to be published
Khalid Mustafa Memon: Acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published
M. Sajid Abbas Jaffri: Acquisition of data, revising it critically for important intellectual content, final approval of the version to be published
Mehar Fatima: Drafting the article, final approval of the version to be published
Mamoora Arslaan: Drafting the article, final approval of the version to be published
Shizma Junejo: Analysis and interpretation of data, final approval of the version to be published

REFERENCES

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice. 2019;157:107843. DOI: 10.1016/j.diabres.2019.107843

2. Kim J, Park S, Kim H, Je NK. National trends in metformin-based combination therapy of oral hypoglycaemic agents for type 2 diabetes mellitus. European journal of clinical pharmacology. 2019 ;75:1723-30. DOI: 10.1007/s00228-019-02751-9

3. Dahlén AD, Dashi G, Maslov I, Attwood MM, Jonsson J, Trukhan V, Schiöth HB. Trends in antidiabetic drug discovery: FDA approved drugs, new drugs in clinical trials and global sales. Frontiers in Pharmacology. 2022 ;12:807548. DOI: 10.3389/fphar.2021.807548

4. Nauck MA, Del Prato S, Durán-García S, Rohwedder K, Langkilde AM, Sugg J, et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes, obesity & metabolism. 2020;16(11):1111-20. DOI: 10.1111/dom.12327

5. Nauck MA, Del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2019;34(9):2015-22. DOI: 10.2337/dc11-0606

6. Del Prato S, Nauck M, Durán-Garcia S, Maffei L, Rohwedder K, Theuerkauf A, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes, obesity & metabolism. 2015;176:581-90. DOI: 10.1111/dom.12459

7. Sezai A, Tanaka A, Imai T, Kida K, Sekino H, Murohara T, Sata M, Suzuki N, Node K; CANDLE Trial Investigators. Comparing the Effects of Canagliflozin vs. Glimepiride by Body Mass Index in Patients with Type 2 Diabetes and Chronic Heart Failure: A Subanalysis of the CANDLE Trial. Biomedicines. 2022 Jul 9;10(7):1656. doi: 10.3390/ biomedi cines100 71656. PMID: 35884961

8. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. The lancet Diabetes & endocrinology. 2018;2(9):691-700.doi.org/10.1111/dom.13457

9. Riddle MC. A Verdict for Glimepiride: Effective and Not Guilty of Cardiovascular Harm. Diabetes Care. 2019;42(12): 2161-3.

10. Trerattanavong K, Tadi P. Glimepiride. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC.; 2020.

11. Melillo G. FDA approves dapagliflozin to treat heart failure, breaking new ground in SGLT2 competition. American Journal of Managed Care. 2020;1.

12. Raj GM, Wyawahare M. Dapagliflozin for heart failure: is it a class effect?. Future cardiology. 2021 ;17(2):355-61. DOI: 10.2217/fca-2020-0087

13. Shao S-C, Chang K-C, Hung M-J, Yang N-I, Chan Y-Y, Chen H-Y, et al. Comparative risk evaluation for cardiovascular events associated with dapagliflozin vs. empagliflozin in real-world type 2 diabetes patients: a multi-institutional cohort study. Cardiovascular Diabetology. 2019;18(1):120. doi.org/ 10.1186/s12933-019-0919-9

14. Mosleh H, Alenezi M. Prevalence and factors of anxiety and depression in chronic kidney disease patients undergoing hemodialysis: A cross-sectional single-center study in Saudi Arabia. Cureus. 2020;12(1). DOI: 10.7759/cureus.6668

15. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC medicine. 2013;11:43. doi: 10.1186/1741-7015-11-43

16. Rosenstock J, Perl S, Johnsson E, García-Sánchez R, Jacob S. Triple therapy with low-dose dapagliflozin plus saxagliptin versus dual therapy with each monocomponent, all added to metformin, in uncontrolled type 2 diabetes. Diabetes Obes Metab. 2019 Sep;21;9;2152-2162. doi: 10.1111/dom.13795.

17. Sjöström CD, Johansson P, Ptaszynska A, List J, Johnsson E. Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes. Diabetes & vascular disease research. 2015;12(5):352-8. DOI: 10.1177/ 147916411 5585298

18. Yamout H, Perkovic V, Davies M, Woo V, de Zeeuw D, Mayer C, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes and stage 3 nephropathy. American journal of nephrology. 2014;40(1):64-74. DOI: 10.1159/000364909

19. 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. doi: 10.2337/dc20-2604

20. Sjöström CD, Hashemi M, Sugg J, Ptaszynska A, Johnsson E. Dapagliflozin-induced weight loss affects 24-week glycated haemoglobin and blood pressure levels. Diabetes, obesity & metabolism. 2015;17(8):809-12. DOI: 10.1177/ 1479164115 585298

21. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood Pressure Lowering in Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA. 2015;313;6;603–615. doi:10.1001/jama.2014.18574

22. Vilsbøll T, Ekholm E, Johnsson E, et al. Efficacy and safety of dapagliflozin plus saxagliptin versus insulin glargine over 52 weeks as add-on to metformin with or without sulphonylurea in patients with type 2 diabetes: A randomized, parallel-design, open-label, Phase 3 trial. Diabetes Obes Metab. 2020; 22: 957–968. https://doi.org/10.1111/dom.13981

23. Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, et al. Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes. Diabetes Care. 2015;38(11) :2009-17. DOI: 10.2337/dc15-0779

24. Fadini GP, Bonora BM, Mayur S, Rigato M, Avogaro A. Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors. 2018;20(3):740-4. DOI: 10.1111/dom. 13130

25. Gopal CDSM, Rathi S, Tyagi S. Clinical profile of hypoglycemia in emergency department of tertiary care hospital: A single center study. International Journal of Advanced Research in Medicine 2021; 3(1): 340-343.DOI: 10.22271/27069567. 2021.v3.i1f.162