Original Article

Comparative Analysis for Reduction in $A1_c$ in Dapagliflozin Versus Glimepiride Monotherapy in Non-Obese Type 2 Diabetic Patients

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ABSTRACT

Objective: To compare the efficacy and safety profile of dapagliflozin and glimepiride in type 2 diabetic non-obese patients.

Study Design: Randomized controlled trial study.

Place and Duration of Study: This study was conducted at the National Medical Center, Karachi from June 2019-December 2019.

Materials and Methods: A total of 200 diabetic patients had body mass index ≥ 28- ≤29.9 Kg/m^2, body fat percentage ≥ 21- ≤31 in female, and ≥ 14 - ≤ 24 in male, baseline fasting blood sugar ≥ 126 mg/dL and glycated haemoglobin between ≥ 7.5 - ≤10% were recruited in the study. All the eligible patients were divided into two groups: dapagliflozin 10 mg and glimepiride 04 mg. The endpoint assessment included change of fasting plasma glucose (FPG), A_{1c}, liver function test, renal function test, lipid profile and urinalysis. The analysis of the data performed by using statistical package of social sciences (SPSS) version 25.

Results: Both combination therapy led significant reductions in FPG and $A1_c$ levels as compared with baseline at 12^{th} week. The monotherapy of dapagliflozin comparatively improve more level of $A1_c$ at short time than other intervention. Both of these therapies were shown safe levels of lipid profile, liver function test, renal function test and urinalysis among groups. None of the incidence of hypoglycemia, and urinary and genital tract infection were reported during the entire period of the study.

Conclusion: The treatment with dapagliflozin or glimepiride was generally well tolerated and effective for the improvement of glycemia in T2D patients. Dapagliflozin monotherapy with metformin relatively more effective in reducing FPG and $A1_c$ even in short time.

Key Words: Dapagliflozin, Glycemia, Glimepride, Obese, Type 2 diabetes mellitus

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INTRODUCTION

The foremost cause of increased type 2 diabetes mellitus (T2DM) prevalence is the epidemic of obesity in both developing and un-developing countries.[1] Whereas many T2DM patients of European and, more particularly, Asian countries have normal body weight.[2] The earlier study has found disproportionally decrease levels of insulin secretion and reduced insulin resistance in non-obese T2DM compared to obese T2DM patients.[3] In Pakistan, Sindh had high incidence level, i.e., 19.25%, followed by Punjab (18.52%), Baluchistan (15.25%), and Khyber Pakhtunkhwa (13.98%)[4], and the incidence ratio became worst gradually. The diversity of diabetic probability among countries and even in regions may be due to a neglected focus on identifying specifically obese and non-obese T2DM prevalence, as globally, the diverse probability of obesity exists in diabetic patients.

Earlier studies define metformin has equal potency in non-obese as obese. Previously, reduced $A1_c$ levels in the obese and non-obese group observed. However, reduced dose of metformin needed to improve $A1_c$ in normal weight diabetic participants without producing an effect in BMI during the entire observational period.[5] Another study found similar A1c levels among metformin-treated groups based on BMI. Moreover, the duration of successful improvement in glycemia

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followed by metformin in normal and overweight diabetic participants and their frequency of progressing diabetes-associated impairments duration was not inferior compared to diabetic obese subjects.[6] However, bodyweight estimation by using BMI in these earlier reported studies may be inadequate to categorize patients according to "leanness." Instead, the degree of adiposity reflects the amount of adipose tissue in total body mass and the degree of central obesity (abdominal). [(7)] Besides, most of the other anti-diabetic drugs are associated with serious clinical events. Hence, the identification of effective and tolerable option that improves glycemia in non-obese patients.

Among numerous conventional anti-diabetic agents with diverse mechanisms of action, the efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and sulphonylureas are well-documented. SGLT-2i acts via reabsorbing glucose from glomerular filtrate, and sulphonylureas acts as insulin secretagogues.[8,9] The earlier study found decrease in $A1_c$ in the treatment-naive obese diabetic patients followed by taking treatment of SGLT-2i and sulphonylureas as monotherapy or combination therapy.[10-12] However, the comparative analysis of efficacy and toleberity between dapagliflozin and glimepiride monotherapy in non-obese diabetic participants was a neglected area.

Besides, the population of Pakistan is diverse according to their body weight, genotype, demography, and culture than the population of Western countries.[13-14]. These modifications lead effect in the clinical response of the effective anti-diabetic drug among non-obese patients. Therefore, the present study aims to compare safety and efficacy of dapagliflozin and glimepiride monotherapy efficacy to control glycemia in newly diagnosed non-obese diabetic patients.

MATERIALS AND METHODS

This 12-week randomized control trial was conducted in 200 diabetic patients at the National medical center, Karachi, Pakistan during June-2019 to Dec-2019. An Ethical Research Committee (ERC) of Bahria University approved the study protocol, and all enrolled diabetic participants gave written, informed consent.

Patients with $A1_c$ between ≥7.0% - ≤ 10.0 % were divided randomly into two groups; group A: dapagliflozin and group B: glimepiride. The patients' age was between 45-55 years, body mass index ≥ 28-≤29.9 Kg/m^2, body fat percentage ≥ 21- ≤31 in female, and ≥ 14 - ≤ 24 in male, and had normal liver function test, renal function test, lipid profile, and white blood cell counts (WBC). Treatment with oral antidiabetic drugs within 12-weeks before enrollment was not allowed. All the participants had a liver impairment, type 1 diabetes (T1DM), congestive heart failure, cancer, terminal illness, > 270 mg/dL of FPG, < 50 mL/min of creatinine clearance level, < 40% of left ventricular ejection fraction and ≥170 mmHg of systolic blood pressure or ≥110 of diastolic blood pressure were excluded from current randomized control trial.

The population size of diabetic patients was estimated *via* OpenEpi, Version 3. Group A patients were given a fixed dose of 10 mg of dapagliflozin, whereas group B was given 04 mg of glimepiride throughout the 12-weeks of treatment. All subjects were restricted to take a sugary meal.

The primary endpoints were change in $A1_c$ and FPG from baseline to week 12. Key secondary endpoints were changed in liver function test, [serum glutamic pyruvic transaminase (SGPT; IU/L), serum glutamic-oxaloacetic transaminase (SGOT; IU/dL), alkaline phosphate, bilirubin (mg/dL)], lipid profile [high-density lipoprotein-cholesterol (HDL-c; mg/dL), low-density lipoprotein –cholesterol (LDL-c; mg/dL), triglyceride (TG; mg/dL), and cholesterol (CHO; mg/dL)], renal function test [urea (mg/dL), creatinine (mg/dL)], blood pressure [diastolic and systolic blood pressure (MM/Hg)], body mass index (kg/m^2), body fat mass (%) and hypoglycemic events from baseline to week 12. The hypoglycemic events were categories based on FPG levels and diabetic symptoms such as ≤ 70, ≤ 54, ≤ 50, ≤ 70 with asymptomatic hypoglycaemic episode, and > 70 mg/dL with another hypoglycaemic event.

All continuous variables were represented in mean ± St. Dev (standard deviation). The significant clinical difference between before and after treatment were estimated by applying parametric t-test and paired t-test. P-values < 0.05 were considered significant in the present randomized control trial. The statistical analysis was conducted through the IBM statistical package of social sciences (SPSS) version 25.

RESULTS

The analysis for the efficacy and safety of dapagliflozin and glimepride was conducted in 200 newly diagnosed diabetic patients. Among them, 48% were male, and rest of the non-obese diabetic patients were female. As per ADA guidelines, metformin is the first-line therapy to control glycated hemoglobin (hemoglobin A1c) below or around 7% and subsequently prevent the development of secondary complications of T2D. But, it was recommended for obese diabetic patients, and studies suggested significant role in non-obese patients based on BMI and limit to show mean percent body fat in patients. [(5-7)] Therefore, subjects were divided into two groups equally based on pharmacotherapy; group A: dapagliflozin, group B: glimepiride. The baseline characteristics (included age, BMI, body fat percentage, A_{1c}, FBG, blood pressure, RFT, LFT, lipid profile, and urinalysis) were similar between both groups at week-0. None of the patients rejected to receive respective therapy entire study period.

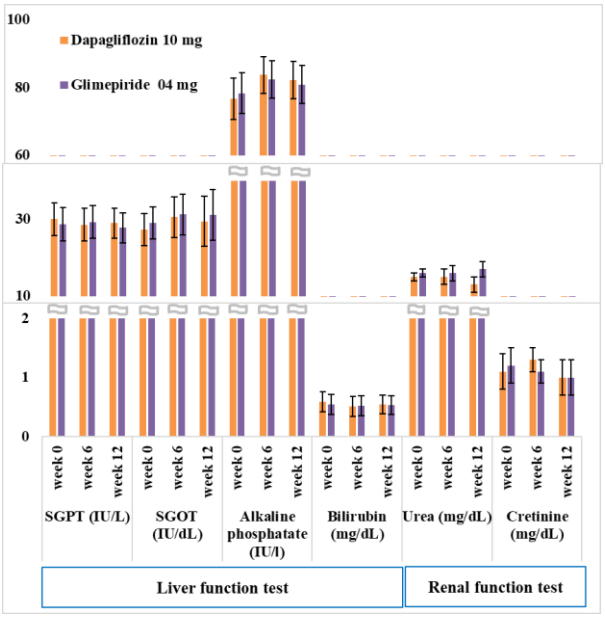

Figure No.1: Liver and renal function test in T2D patients followed by monotherapy.

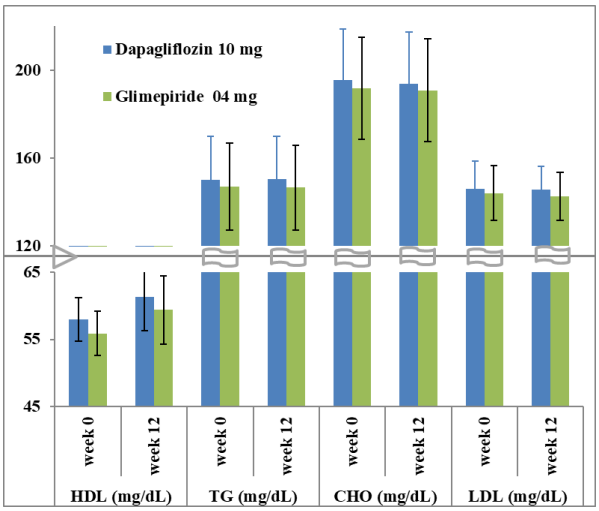

Figure No. 2: Lipid profile in T2D patients followed by monotherapy.

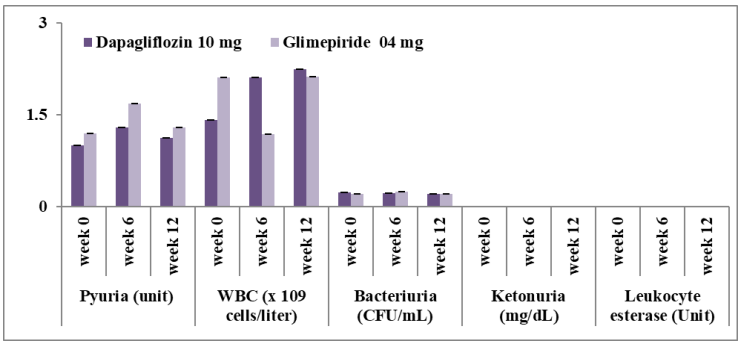

Figure No.3: Urinalysis in T2D patients followed by monotherapy.

First, to achieve the aim, it was identified whether dapagliflozin/glimepride decline hyperglycemia in diabetic patients. Hence, paired t-test was applied to estimate the statistical differences in the levels of FPG and $A1_c$ of diabetic patients followed by receiving treatment. The results revealed significantly reduced levels of FPG after 6 weeks (dapagliflozin: 147.13 ± 12.14; glimepiride: 166.14±13.4 mg/dL) of interventions in both groups compared to baseline (dapagliflozin: 189.78±41.22; glimepiride: 185.41±3.52 mg/dL ; P: 0.083). Moreover, at the 12th-week follow-up, FBG and $A1_c$ reduced significantly in these two groups compared with the baseline values by showing P-value < 0.05 (FBG: dapagliflozin: 105.64±11.52; glimepiride: 128.42±10.52%; P : 0.03 ; $A1_c$). However, dapagliflozin group produced comparatively more reduction in FPG and $A1_c$ than glimepiride and even almost maintained almost euglycemia in patients. Moreover, diabetic patients in group A were more improve glycemia in a shorter time, i.e., the 6th week, than another invention.

The mean BMI (Kg/m^2) was in group A at 0-week 32±2.43, at 6th week 32±1.82 and at 12th week 30±3.02. The mean BMI was in group B at 0-week 32±2.41, at 6th week 32±3.21 and at 12th week 32±2.45. There was no significant difference found among different groups. At 0-week 0.071, at 6th-week and at 12th-week 0.08.

The mean value of percent body fat (%) was in group A males at 0-week 23±1, at 6th week 24±2 and at 12th week 23±3.The mean percent body fat was in group B males at at 0-week 23±2, at 6th week 23±1 and at 12th week 23±3. There was no significant difference found among different groups. At 0-week 0.81, at 6th-week 0.72 and at 12th-week 0.90.

The mean value of percent body fat (%) was in group A females at 0-week 28±2, at 6th week 27±1 and at 12th week 28±4.The mean percent body fat was in group B females at at 0-week 27±1, at 6th week 28±3 and at 12th week 28±3. There was no significant difference found among different groups. At 0-week 0.87, at 6th-week 0.62 and at 12th-week 0.88.

The mean value of systolic blood pressure (SBP; mm/Hg; Mean ± St.Dev)) was in group A at 0-week

130±11.22, at 6th week 131±11.20 and at 12th week 127±12.14.The mean systolic blood pressure was in group B at 0-week 135±6.03, at 6th week 132±13.52 and at 12th week 133±4.12. There was no significant difference found among different groups. At 0-week 0.052, at 6th-week 0.064 and at 12th-week 0.073.

The mean value of diastolic blood pressure (DBP; mm/Hg; Mean ± St.Dev)) was in group A at 0-week 92±1.52, at 6th week 92 ±1.62 and at 12th week 90±4.12.The mean diastolic blood pressure was in group B at 0-week 94±6.32, at 6th week 95±3.31 and at 12th week 95±3.64. There was no significant difference found among different groups. At 0-week 0.075, at 6th-week 0.062 and at 12th-week 0.082.

The frequency of glucosuria (%) was measured in both groups. At 0-week , 99% mild, 0 % moderate and severe in group A. At 0-week , 98% mild, 2 % moderate, and 0% severe in group B. There was no significant difference among group at week 0 by showing p value > 0.05.

The frequency of glycosuria (%) was measured in both groups. At 6-week, 14% mild, 87 % moderate and 7% severe in group A. At 6-week, 97% mild, 3 % moderate, and 0% severe in group B. There was significant difference among group at week 6 by showing p value < 0.01.

The frequency of glycosuria (%) was measured in both groups. At 12-week, 0% mild, 8 % moderate and 91% severe in group A. At 12-week, 99% mild, 1 % moderate, and 0% severe in group B. There was significant difference among group at week 12 by showing p value < 0.001.

Followed by the identification of efficacy levels among the groups, the safety profile was evaluated. No clinically significant severe hypoglycaemic events or other serious adverse events were observed in either group. The levels of LFT, RFT, lipid profile, and urinalysis were found similar between the dapagliflozin and glimepiride groups. Of note, diabetic subjects of group A exhibited insignificant weight loss and decreased blood pressure compared to another group at week 12 (Figure 1,2,and 3).

DISCUSSION

This randomized control trial demonstrates SGLT-2i and sulphonyl urea with dapagliflozin and glimepride, respectively, can significantly maintain glycemia followed by instigating pharmacotherapy. The increased prevalence of diabetes is particularly due to epidemic of obesity in developing and un-developing countries. Whereas many diabetic patients of European and, Asian countries are non-obese, and earlier studies recommended metformin for obese diabetic patients, however recent studies found similar outcomes in obsess and non-obese patients but the identification of obesity was based on BMI, not percent body fat i.e., comparatively more recommended scale. Therefore, the present study was conducted to identify the efficacy and safety of dapagliflozin and glimepiride in non-obese diabetic population of Pakistan.

Patients treated with dapagliflozin showed a more reduced mean level of FPG and $A1_c$ than patients who received glimepiride. Previously, many clinical trials have shown improvement in glycemic profile followed by the treatment with combination of metformin with various other antidiabetic agents that differ in mechanisms. [15], but they had an adverse effect and based on obese individuals. The decrease in $A1_c$ found in the treatment-naive obese followed by dapagliflozin-monotherapy and combination therapy. [10] The study of Nauck MA et al. compared dapagliflozin- metformin vs. glipizide- metformin combination in obese diabetic patients and observed high glycemic stability, increase weight reduction, decreased blood pressure, and low hypoglycemic events but frequent incidence of genital and urinary tract infections in the dapagliflozin-metformin combination group.[11] Moreover, the comparative analysis between canagliflozin-metformin, SGLT-2i, and glimepiride- metformin found more A1c reduction in obese patients of canagliflozin group than glimepiride group.[14] The findings of present study showed that dapagliflozin-metformin group produced comparatively more reduction in FPG and $A1_c$ than glimepiride monotherapy and even almost maintained almost euglycemia in non-obese diabetic patients without producing adverse effect. Moreover, diabetic patients in group A were more improve glycemia in a shorter time, i.e., the 6th week, than another invention (Table 1).

Dapagliflozin acts unique mode of action and consequently provides a different therapeutic profile. In the current randomized study, the rate of hypoglycaemic events was not found in both treatment groups. Dapagliflozin improves glycemia by preventing SGLT-2 from eliminating glucose in urination. Subsequently, excess level of glucose removes from the body directly instead of metabolized in tissues. The unique mechanism of dapagliflozin improves more glycemia as compare to other treatment. The glimepiride increases the production of insulin in pancreatic beta cells to accelerate the glucose regulation and subsequently prevent hyperglycemia.

Followed by identifying the efficacy of the invention, safety of these combination therapies were evaluated. T2D patients are more susceptible to developed liver dysfunction, cardiovascular impairment, and renal failure due to drug-mediated toxicity. The liver function is determined in the current study as drug toxicity likely to produce acute or chronic liver impairment instigated by cytochrome P450 action. Our findings revealed that both of the intervention showed similar and normal levels of liver enzymes and bilirubin, and thus likely present that these did impaired physiological regulations (Figure 1).

The renal function and urinalysis followed by the treatments was normal in both groups to suggest that these interventions are non-toxic and retain physiological mechanism of the kidney (Figure 1 & 3). Previous studies reported glucosuria is due to the inhibition of SGLT2, which is linked with the development of urinary tract or genital infection.[16, 17] These findings are inconsistent with present study, as none of the incidences of these infections is observed in the co-administration of dapagliflozin. Another previous study elucidated the safety of dapagliflozin-metformin and found mild or moderate in the intensity of vulvovaginitis and balanitis, which were resolved easily with self-treatment or taking conventional drugs, and hardly withdrawal from the clinical trials.

Moreover, the lipid profile was identified and found similar HDL levels, LDL, CHO, and triglycerides b groups (Figure 2). In contrast, significant LDL and triglycerides levels were found in previous studies by using dapagliflozin as compared to placebo group.[18] The increased invention period likely to produce significant advantage for lipid levels.

The incidence of hypertension and obesity is high in T2DM of the Southeast Asian region of Pakistan. Studies suggested that dapagliflozin is a promising therapeutic approach to halt the increased ratio. [19, 20] Compared with glimepride, an insignificant mean drop of blood pressure was found in patients treated with dapagliflozin. The increased period of study might produce significant improvement in blood pressure.

The major assesses of this randomized clinical trial is the comparison dapagliflozin and glimepiride to improve glycemia in non-obese T2DM patients. As far as our knowledge, this study first compares the effect of two frequently prescribed inventions in non-obese diabetic patients as first-line therapy. The determination of efficacy in FBS was performed in two intervals followed by the intervention to more assured with hemoglobin A1c. Moreover, the safety of combinations were carefully identified in hepatic functions, urinary tract, and cardiovascular system at different intervals (6th and 12th- week) to prevent the onset of secondary diabetic complications. Whereas, the current study is limited to provide the effect of invention in long-term glycemic efficacy and safety profile on liver and heart physiology and heart, moreover this study is restricted in a limited dose of drug.

CONCLUSION

Dapagliflozin and glimepiride monotherapy improves glycemia, and both interventions are well tolerated for patients with type 2 diabetes. The dapagliflozin is superior to glimepiride in reducing FPG and $A1_c$ levels in non-obese diabetic patients.

Author's Contribution:

Concept & Design of Study:	Muhammad Kamran Yousuf
Drafting:	Mehr Fatima, M.Sajid Abbas Jaffri
Data Analysis:	Sadaf Haris, Khalid Mustafa, Shahid Mustafa Memon
Revisiting Critically:	Muhammad Kamran Yousuf, Mehr Fatima
Final Approval of version:	Muhammad Kamran Yousuf

Conflict of Interest: The study has no conflict of interest to declare by any author.

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