Original Article

Comparative Analysis of Metformin and its Combination with Dapagliflozin in Type 2 Diabetes: Randomized Control Trial

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ABSTRACT

Objective: The current clinical trial compared the effects of metformin monotherapy and dapagliflozin plus metformin combination in diabetic patients. The secondary objectives included estimating the effects of these regimens on safety and tolerability.

Study Design: Randomized clinical trial study

Place and Duration of Study: This study was conducted at the National Medical Center, Karachi, Pakistan from January – June 2020.

Materials and Methods: A total of 200 patients were recruited, had baseline FPG ≥ 126 mg/dL, and glycated hemoglobin A1c (HbA1c) ≥ 7.5- ≤10%. All the participants were divided into two groups: metformin (group A) and dapagliflozin plus metformin combination (group B). The study's primary endpoint was FBG and HbA(1c), and secondary included change in lipid profile, liver function test, renal function test, and urinalysis.

Results: The primary endpoints for combination therapy led to significantly greater reductions in FBG and HbA(1c) than metformin monotherapy. The change in FPG levels at week 12 in groups A and B were 184.05±14.82 vs. 101.40±16.85; $p < 0.0001$. The HbA(1c) change at week 12 in groups A and B was 7.83±0.54 vs. 6.91±0.74; $p < 0.0001$. Insignificant findings were observed for lipid profile, liver function test, renal function test, and urinalysis among both groups at the entire study.

Conclusion: This is the first randomized clinical trial in diabetic patients of Pakistan treated with and dapagliflozin-metformin combination. Combination therapy was generally well-tolerated and effective in reducing HbA(1c) and FPG relatively metformin monotherapy after initiation of therapy.

Key Words: β cell dysfunction, Dapagliflozin, hemoglobin A1c, Metformin, Type 2 diabetes mellitus

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INTRODUCTION

Pakistan is still listed as the top 10th country in the world for having high prevalence of people, i.e., 19.4 million with type 2 diabetes mellitus as per the estimates of the international diabetic federation[1] and this has been gradually increasing at an alarming level.

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Hence, this emerged as the focus of Pakistani researchers' attention in identifying effective therapeutic agents to control uncontrolled glycemia in diabetes. European Association for The Study of Diabetes and American Diabetes Association is deemed to use metformin as the cornerstone in native diabetic patients due to its clinical superiorities[2]. Nevertheless, many studies have revealed its limited response due to its gastrointestinal side effects in the Pakistani population[3].

The failure in the therapeutic intervention of metformin to maintain long-term glycaemic control in diabetic patients of Pakistan increases the need to identify the benefits and risk factors of different antidiabetic agents as monotherapy and combination therapy. Study of Harrower AD and team has shown an effective response by adding sulphonylureas in the regimen[4]. However, these regimens vary mechanistically. They employ an insulin-dependent intracellular cascade; subsequently, the reduction in effectiveness is observed due to b-cell dysfunction and insulin resistance, thus elevated disease progression. Moreover, the step-wise modification of strategy is inadequate for late-

diagnosed patients or experiencing severe hyperglycaemic events. For them, combination therapy with differing mechanisms has great importance as it produces a benefit to increase therapeutic response in the management of T2D.

One of the potential combination strategies involves metformin and sodium-glucose cotransporter-2 inhibitors (SGLT-2), in which one of them employs an insulin-dependent cascade while the other does not[5]. One potentially advantageous SGLT-2 regimen, dapagliflozin, was effective as add-on therapy to metformin in real-life clinical settings of the different genetical populations[6,7]. In Pakistan, it was first licensed to use in 2017[8]. The Pakistani population is genetically, demographically, and culturally diverse, and their lifestyle interventions are changed compared to the Western population[9-12], and with these changes, clinical response of the dapagliflozin-metformin combination is unknown. Therefore, the present clinical randomized trial aims to compare the efficacy of metformin and its combination with dapagliflozin to control diabetes in Pakistani patients. Moreover, the safety of these regimens was evaluated to prevent drug-induced complications.

MATERIALS AND METHODS

Clinical study design: The current randomized clinical trial was 12-week, conducted at the National medical center, Karachi, Pakistan. A total of 200 diabetic patients were recruited in the study who had uncontrolled glycemia with metformin; 190 were successfully completed. They were divided into two groups based on their treatment regimens. In the group A, patients was taken metformin 1500 mg, whereas the group B patients were given dapagliflozin 10 mg plus metformin 500 mg. The clinical trial was conducted after approval by the Ethical Research Committee (ERC) of Bahria University, Karachi, Pakistan. All diabetic patients provided informed consent.

Patients: All the diabetic patients were aged 45–55 years, had fasting plasma glucose (FPG) ≥ 126 mg/dL, hemoglobin A1c [HbA(1c)] >7-10%, and uncontrolled diabetes by restricted diet, regular exercise, and metformin monotherapy 1500 mg. Patients were excluded if their serum creatinine > 123.76 lmol ⁄ l; urine albumin to creatinine ratio (ACR) > 1800 mg ⁄ g; creatine kinase > 3 x ULN; glomerular filtration rate (GFR) < 45 ml/min/1.73 m^2; serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN); left ventricular ejection fraction (LEVF) < 40%; history of recurrent genitourinary tract infections, diabetes insipidus; cardiovascular event; and suffering with other than diabetes.

Endpoints and assessments: The sample size calculation of the diabetic population was estimated using OpenEpi, Version 3. The primary efficacy endpoint, i.e., FBG and glycated hemoglobin (hemoglobin A1c) levels, were estimated at different intervals (FPG: baseline, week 6, and week 12; HbA(1c): baseline, and week 12). The study's key secondary endpoints were lipid profile, liver function test, renal function test, and urinalysis. The change in lipid profile levels, i.e., high-density lipoprotein, cholesterol, triglyceride, and low-density lipoprotein, were estimated at baseline and week 12. Whereas, liver function test (serum glutamic pyruvic transaminase, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, and bilirubin), renal function test, and (urea, creatinine) urinalysis (pyuria, white blood cell count, bacteria, ketonuria, leukocyte, and glucosuria) were quantified at baseline, week 6, and week 12. Moreover, the BMI and blood pressure difference with both treatment regimens were also observed for statistical significance.

All continuous variables were represented in mean ± SDev (standard deviation). The significant difference among the group was identified by applying student t-test and paired t-test. The analysis was carried out by using IBM statistical package of social sciences (SPSS) version 25 and taking P-values < 0.05 as significant.

RESULTS

The current randomized clinical trial enrolled 190 diabetic patients from Karachi, Pakistan. Of these patients, 50 % were men, and 50 % were women between the age of 45-55 years. At baseline, their mean BMI was 31±2.15 kg/m^2. All the patients had mean FBS level > 126 mg/dL and mean HbA(1c) level was ≥ 7 - ≤ 10 %. All the patients were initially being treated with metformin monotherapy. Table 1 depicts baseline and changes in mean characteristics of patients.

The primary objective of this study was to identify the efficacy of metformin vs. dapagliflozin-metformin combination in diabetic patients of Karachi. Followed by given respective treatment regimens, FBS and HbA(1c) levels were estimated. The results revealed that group A significantly increased concentrations of FBG at 1st follow-up (6th week) than group B (group A: FPG 144.23±12.54; group B: FPG 137.02±12.30 mg/dL; p<0.001). Consistently, significantly less control in FBG and HbA(1c) level was observed in group A relatively group B at 12th week (group A: FPG 122.89±9.22, HbA(1c) 7.51±0.49; group B: FPG 101.40±16.85 mg/dL, HbA(1c) 7.83±0.54 %; p<0.001). (Table 1).

The safety and tolerability were identified by measuring lipid profile, RFT, LFT, and urinalysis. Statistically insignificant changes in lipid profile were found between groups at the end of the study (12-week) by showing p-value >0.05, as represented in figure 1. Furthermore, no clinically significant levels of LFT and RFT and urinalysis were observed at 6th week and 12th week between both groups, as shown in Figures 1, 2, and 3. Furthermore, BMI, systolic blood pressure, and diastolic blood pressure were found similar in both groups and follow-ups. The mean change in characteristics at 1st and 2nd follow-up is presented in Table 1.

Table No.1: Mean changes in body mass index, systolic and diastolic blood pressure, glycemic profile, and glycosuria at 0-, 6- and 12-week followed by given metformin monotherapy and metformin-dapagliflozin combination therapy.

		Dapagliflozin-Metformin	Mean Difference	P-Value
Body mass index (BMI; kg/m^2, Mean±SDev)				
At Week 0	31±2.15	31±2.15		0.071
At Week 6	30±1.82	30±1.82		0.052
At Week 12	30±6.12	30±6.12		0.08
Systolic blood pressure (SBP; mm/Hg; Mean±SDev)				
At Week 0	130±9.04	134±14.82		0.052
At Week 6	123±11.34	137±12.30		0.064
At Week 12	134±8.12	131±16.85		0.073
Diastolic blood pressure (DBP; mm/Hg; Mean±SDev)				
At Week 0	95±0.22	95±0.25		0.075
At Week 6	93±0.24	93 ±0.73		0.062
At Week 12	97±0.57	92±0.89		0.082
Fasting plasma glucose (FPG; mg/dL; Mean±SDev)				
At Week 0	188. ±9.04	184. ±14.82		>0.05
At Week 6	144. ±12.54	137.±12.30		0.000^S
At Week 12	122. ±9.22	101. ±16.85		0.000 ^{S}
Glycated haemoglobin (HbA1c: %;Mean±SDev)				
At Week 0	7.91±0.45	7.83±0.54		>0.05
At Week 12	7.51±0.49	6.91±0.74		0.000 ^{S}
Glycosuria (n)				
At Week 0 Mild Moderate Severe	 98 2 0	 97 3 0		 <0.05
At Week 6 Mild Moderate Severe	 97 2 1	 12 86 6		 <0.01
At Week 12 Mild Moderate Severe	 98 2 0	 2 9 89		 <0.001

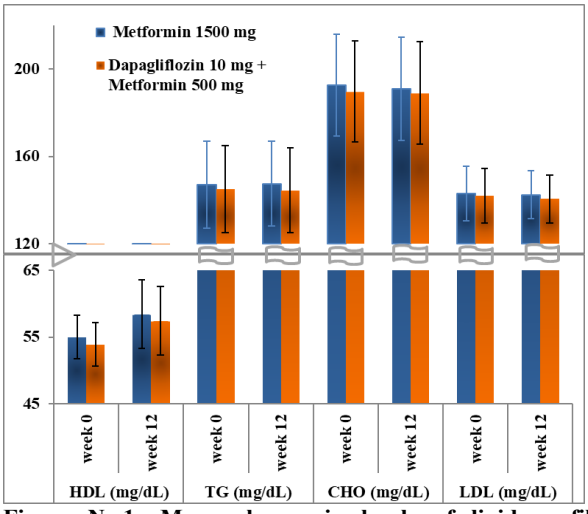

Figure No.1: Mean change in levels of lipid profile followed by given metformin monotherapy and metformin-dapagliflozin combination therapy.

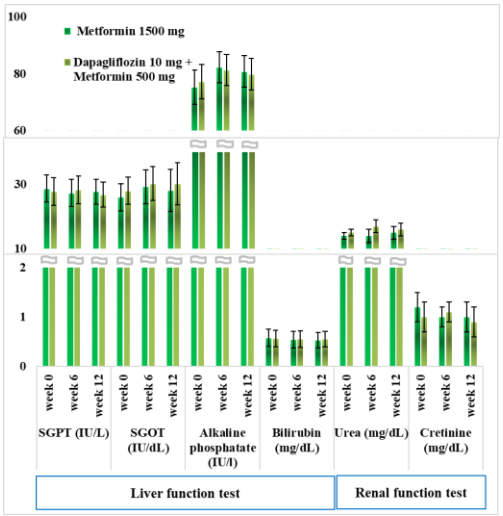

Figure No.2: Mean change in liver and renal function test in group A and B.

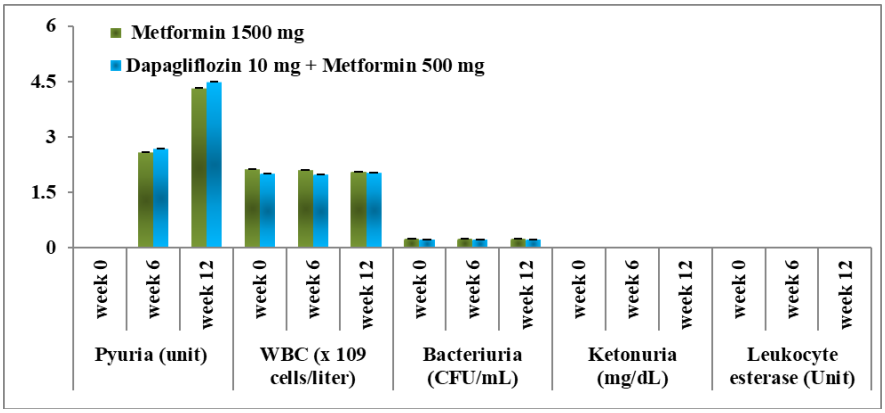

Figure No.3: Urinalysis followed by given treatment regimens.

DISCUSSION

The alarmingly increase incidence of diabetes needed the prompt identification of effective treatment. In general, as per the recommendation of the European Association for The Study of Diabetes and American Diabetes Association, the physicians of Pakistan routinely prescribed metformin monotherapy as pharmacotherapy of T2D[2]. However, a number of studies have been mentioned its decrease effectiveness of controlling glycemia in native patients. This elevates hyperglycemia which leads to various pathological impairments. The combination therapy is recommended by the American Association of Clinical Endocrinologists (AACE) in patients with HbA(1c) >8.5%. But, successful management of T2D in the population is a challenge. In Pakistan, the novel SGLT-2 inhibitor, dapagliflozin, was first licensed to use in 2017[8]. Previously several studies have been published on its potency and safety. But the focus on its effect in the patients of Pakistan was needed. Many studies have been found the diversity in the genetics, demography, culture, and lifestyle intervention of Pakistan's population compared to the Western population[9-12]. The alarmingly increase in the incidence and the diversity of population characteristics emerge the necessity of identifying the efficacy and safety of dapagliflozin-metformin and its comparison with first-line therapy, metformin. Therefore, a total of 200 patients were enrolled in the study and randomly assigned to receive metformin (group A) or dapagliflozin (10 mg) plus metformin (group B). As far as our knowledge, this is the first study which address the dapagliflozin combination in the population of Pakistan.

Our study revealed that both of these interventions effectively decrease levels of HbA(1c) and FBG in the Pakistani diabetic population. But comparatively, the proportion of achieving a greater decrease in FBG and HbA(1c) was significantly more in combination therapy than metformin monotherapy. Our findings are in line with the phase III trial conducted for 24-week in the population of northern Europe (Sweden)[13]. Another phase III trial covers the diabetic population of many north and south American areas and found −0.67%, −0.70%, and −0.84% mean changes in HbA(1c) by receiving 2.5, 5, and 10 mg monotherapy of dapagliflozin[14]. In the present study, we found a greater % change in HbA(1c) level, as this may due to the addition of metformin which may boost glycemic control. Furthermore, the age criteria recruited in our study was limited with may produce more potential outcomes as compared to their study, which was 18-77 years.

Besides the control effect of the combination, another most important challenge is to control or prevent the onset of comorbidity or drug-induced toxicity. Older age T2D patients are vulnerable to liver impairment, cardiovascular disease, and renal dysfunction. Drug-induced injury to the liver can mimic acute or chronic liver ailment triggered by cytochrome P450 action. This activation breaks drugs into reactive metabolites to bind with the protein moiety of unsaturated fatty acids, induce lipid peroxidation and subsequently impair calcium homeostasis. These events lead to death. Therefore, in the present study, the effect of both interventions on liver function tests was identified. As far as our knowledge, this is the first study that analysis the liver function in diabetic patients without co-morbidities. The results revealed similar findings between groups.

Besides, the safety of interventions was estimated at the different intervals of the study in both Pakistani diabetic patients. In South East Asian region of Pakistan, hypertension and obesity are prevalent comorbidities with T2DM, and SGLT-2 inhibitors, including dapagliflozin, are suggested as advantageous agents to prevent them potentially in multifold[15-18]. But in the present study, the reduction in BMI, systolic blood pressure, diastolic blood pressure were not found in any group during the entire study. The possible reason is that these studies are based on long-term, and thus, they found significant control of glycemia and maintained blood pressure and weight.

Identifying its effect on kidney function is vital before its use, as many previous studies suggested discontinuing it if the level of estimated glomerular filtration rate (eGFR) remains persistently less than 60 mL/min/ 1.73 m2. Other studies have shown genital or urinary tract infections, nasopharyngitis, diarrhea, back pain, and constipation as the most common adverse reactions of dapagliflozin. Urogenital infections were reported more frequently in diabetic patients of Europe, North America, South America, and Southern Africa followed by receiving dapagliflozin- metformin combination. But in the present study, urea and creatinine levels were observed normal, and no side effects were reported respected to the urogenital area. This may due to the short time duration of the study. Thus, this can be suggested that both of these interventions were not toxicants and retain the mechanism of kidney-specific detoxification, excretion, and homeostasis of body and are unable to produce a modification in tubular cell toxicity, crystal nephropathy, glomerular hemodynamics, inflammation, thrombotic microangiopathy and rhabdomyolysis in the population of Pakistan.

Next, the drug-mediated toxicity of heart is one of the major adverse effects. Therefore, the lipid profile was identified, followed by the intervention, and found similar HDL levels, LDL, CHO, and triglycerides among diabetic groups. Whereas, clinically significant findings of plasma lipids was observed by using dapagliflozin in LDL (4.8–0.9%), and triglycerides (−8.0% to 2.9%) levels as compared to placebo group[19]. The short duration of the current study may prevent significant findings.

Moreover, the hypoglycemic or hyperglycemic events were not observed during the entire study. Similarly, previous studies have found a similar observation in diabetic population of Europe (UK) and America receiving dapagliflozin monotherapy. Overall, the SGLT- 2 inhibitors have been shown to lower susceptibility of hypoglycemia than other oral antidiabetic drugs and insulin because of their insulin-independent mechanism of action. But, it is recommended to monitor the diabetic patients for the risk of hypoglycemia and make adjustments in doses of SGLT-2 inhibitors, including dapagliflozin. The religious and cultural practices of prolonged fasting (e.g., Ramadan) in Pakistan may elevate the risk of hypoglycemia in population.

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A key strength of this study is the comparison of first-line medication, metformin, with dapagliflozin-metformin combination for the treatment of glycemia in diabetic patients of Pakistan. Best of our knowledge, this is the first study that compares these two frequently prescribed medicines in the population of Pakistan. The efficacy of both therapeutic interventions for FBS and HbA(1c) were performed at intervals 0 and 12^{th} weeks of the study. The safety profile in both groups to liver functions, renal functions, cardiovascular dynamics, urinary and genital tract, and monitored closely. The possible limitations of the present study are the failure to observe the long-term potential and tolerability level on liver, kidney, and heart physiology, and the population size of the study is limited.

CONCLUSION

Metformin monotherapy and its combination with dapagliflozin improve glycaemic control, and both are well-tolerated pharmacotherapy for the treatment of type 2 diabetes. The dapagliflozin- metformin therapy inferior to reduced greater HbA(1c) and FBG levels compared to metformin monotherapy in diabetic patients of Pakistan. None of the interventions elevates the incidence of cardiovascular disorder, liver toxicity, renal impairment, and urinary tract and genital infections. Dapagliflozin-metformin therapy can be an alternative selection to reduce the obtain optimal glycemia without producing major side effects in the diabetic population of Pakistan.

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Author's Contribution:

Concept & Design of Study:	Muhammad Kamran Yousuf
Drafting:	Mehar Fatima, Sadaf Haris
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Revisiting Critically:	Muhammad Kamran Yousuf, Mehar 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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