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Original Research Paper

Dapagliflozin A Solution to Prevent Heart Failure in Patients with Type 2 Diabetes

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ABSTRACT:

Introduction: Heart failure (HF) is a major cause of morbidity and mortality worldwide and one of the most common reasons for hospitalization. Diabetes mellitus (DM) is a common metabolic disease characterized by chronic hyperglycemia, affecting approximately 10% of the population worldwide. Sodium-glucose cotransporter 2 inhibitors (SGLT2) are a new class of oral hypoglycemic drugs that inhibit renal glucose reabsorption. Treatment with SGLT2 inhibitors has beneficial effects on several atherogenic risk factors in patients with type 2 diabetes. **Aim of the work**: To investigate the effects of dapagliflozin on diabetes control and prevention of atherogenic risk factors. **Materials and Methods**: This was a randomized controlled trial conducted from January 2021 to January 2022 at the Cardiology Department of Tobruk Medical Center in Libya. A total of 308 men and women with diabetes between the ages of 25 and 72 participated in the study. Patients provided written informed consent before participating in the study. After obtaining consent, we began the investigation. The patients were then randomly divided into two groups. Group 1 (n = 154) received dapagliflozin 5 mg orally daily in the morning. Group 2 (n = 154), the group taking regular medicine without dapagliflozin (control group); Serum glucose levels, serum uric acid levels, blood pressure and body weight were estimated monthly during the study. **Results**: Details of the 308 patients selected for analysis are as follows. The mean age of group 1 patients was 56.5 years (range 41–72 years), and the mean age of group 2 patients was 38.5 years (range 25–52 years). Pre-study mean serum glucose levels were 197 mg/dL in group 1 and 203 mg/dL in group 2. Pre-study mean serum uric acid levels were 6.3 mg/dL in group 1 and 6.7 mg/dL in group 2. There are statistically significant associations between dapagliflozin efficacy and gender, blood sugar levels, uric acid levels, blood pressure, weight, and heart disease complications. **Conclusion**: SGLT2 inhibitors effectively protect against major cardiovascular events, especially in type 2 diabetic patients with a history of atherosclerotic cardiovascular disease or progressive renal disease.

Keywords: Dapagliflozin, Diabetes Mellitus, Heart Failure.

INTRODUCTION:

Heart failure (HF) is a major cause of morbidity and mortality worldwide and one of the most common reasons for hospitalization. The estimated lifetime risk of developing heart failure is approximately 20% [1]. Heart failure is often associated with comorbidities such as diabetes, arterial hypertension, and atrial fibrillation. Based on the ejection fraction of heart failure patients, heart failure can be classified into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) [2]. Diabetes mellitus (DM) is a common metabolic disease characterized by chronic hyperglycemia, affecting approximately 10% of the population worldwide. Its prevalence is expected to increase in the coming years [3]. Cardiovascular disease remains the main cause of morbidity and mortality in the diabetic population, and is estimated to be two to four times more common in diabetic patients than in non-diabetic patients [4,5]. The prevalence of heart failure due to diabetes is twice as high in men and five times as high in diabetic women as in age-matched non-diabetics. Furthermore, older

patients with type 2 diabetes have a 1.3 times higher risk of developing heart failure than non-diabetic patients of the same age [6,7]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of oral drugs that increase urinary glucose loss and cause osmotic diuresis in patients with and without diabetes by inhibiting glucose reabsorption from the kidneys. It is a hypoglycemic drug. Administration of SGLT2 inhibitors results in urinary loss of 60–100 g of glucose per day, resulting in a negative energy balance and major changes in energy metabolism throughout the body [1,7]. Treatment with SGLT2 inhibitors in patients with type 2 diabetes significantly reduces plasma glucose and insulin concentrations, which are associated with significant improvements in both insulin resistance and insulin secretion [8-11]. Furthermore, SGLT2 inhibitors increase glucagon secretion by directly stimulating pancreatic A cells [12]. As a result, hepatic triglyceride synthesis, hepatic fat deposition, serum triglyceride concentrations are reduced, and hepatic ketone body production is increased [5-7, 11]. Additionally, greater urinary sugar losses increase uric acid excretion, resulting in lower serum uric acid concentrations [13]. Therefore, treatment with SGLT2 inhibitors has beneficial effects on several atherogenic risk factors in patients with type 2 diabetes. SGLT2 inhibitors also have hemodynamic effects. It increases urinary water excretion and sodium loss, leading to a decrease in body weight and systolic and diastolic blood pressure [14-19]. Due to the increasing prevalence of heart failure in patients with type 2 diabetes, we are investigating the effects of dapagliflozin on diabetes control and prevention of atherogenic risk factors.

Patients, Materials and Methods:

This was a randomized controlled trial conducted from January 2021 to January 2022 at the Cardiology Department of Tobruk Medical Center in Libya. A total of 308 men and women with diabetes between the ages of 25 and 72 participated in the study. patients provided written informed consent before participating in the study. After obtaining consent, we began the investigation. Then, patients were randomly assigned to two groups. Group 1 (n = 154) received dapagliflozin 5 mg orally daily in the morning. Group 2 (n = 154), the group taking regular medicine without dapagliflozin (control group); serum glucose levels, serum uric acid levels, blood pressure, and body weight were estimated monthly during the study.

Statistical Analysis:

The data collected were coded, entered and analyzed using SPSS version 22 (Statistical Package for the Social Sciences).

Descriptive statistics were performed by frequency and percentage for categorical variables and in the form of mean and standard deviation (mean ± SD) for numerical variables.

Appropriate statistical significance test was used [Chi-square test ($\chi 2$) for categorical data].

P values less than or equal to 0.05 were considered statistically significant.

RESULTS:

Details of the 308 patients selected for analysis are as follows. The mean age of group 1 patients was 56.5 years (range 41–72 years), and the mean age of group 2 patients was 38.5 years (range 25–52 years). Pre-study mean serum glucose levels were 197 mg/dL in group 1 and 203 mg/dL in group 2. Pre-study mean serum uric acid levels were 6.3 mg/dL in group 1 and 6.7 mg/dL in group 2. (table 1).

Variables	Group 1 (Mean)	Group 2 (Mean)
Age (years)	56.5	38.5
Pre-study glucose mg/dl	197	203
Pre- study uric acid mg/dl	6.3	6.7

Table (1): Mean age and pre-study serum glucose and uric acid levels in Group 1 and Group 2.

Relation of Dapagliflozin effects with respect to gender, serum glucose level, serum uric acid level, blood pressure, body weight and complicated by cardiac diseases in Group 1 and Group 2 is presented in table 2.

Variables	Group 1 (n:154)	Group 2 (n:154)	*Chi*-square test
	Use of Dapagliflozin	Not use of Dapagliflozin	
Gender			
Male (183 cases)	79	104	*P*=0.00372*
Female (125 cases)	75	50	
Serum glucose level			
Improved (172 cases)	132	40	*P*=0.00001*
Not (136 cases)	22	114	
Serum uric acid level			
Improved (194 cases)	143	51	*P*=0.00001*
Not (114 cases)	11	103	
Blood pressure			
Decreased (203 cases)	146	57	*P*=0.00001*
Not (105 cases)	8	97	
Body weight			
Decreased (166 cases)	132	34	*P*=0.00001*
Not (142 cases)	22	120	
Complicated by cardiac diseases			
Yes (145 cases)	20	125	*P*=0.00001*
No (163 cases)	134	29	

***p*-value <0.05 was considered statistically significant.**

Table 2: The relationship between the effects of dapagliflozin and gender, blood sugar level, uric acid level, blood pressure, weight, and complications of heart disease

DISCUSSION:

First, we investigated the effect of dapagliflozin on glycemic control in untreated T2DM patients. After 24 weeks of intervention, dapagliflozin 1, 2.5, and 5 mg once daily reduced HbA1c by 0.68%, 0.72%, and 0.82%, respectively [8].

The recently published Dapagliflozin and Prevention of Heart Failure Adverse Events (DAPA-HF) study showed that the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin reduced the risk of hospitalization due to worsening heart failure. Heart failure with reduced ejection fraction (HFrEF) [9]. Although SGLT2 inhibitors were developed as a hypoglycemic treatment for patients with type 2 diabetes, approximately half of DAPA-HF patients did not have type 2 diabetes [10,11]. Recently, many studies have shown that SGLT2 inhibitors improve ventricular diastolic function and microvascular and macrovascular perfusion in heart failure diabetic patients. A prospective multicenter study in type 2 diabetic patients with stable HF was conducted, in which dapagliflozin 5 mg/day was administered to patients with HFpEF (69%) and HFrEF+HF patients with intermediate EF (31%). It was administered for several months. This indicates that in response to dapagliflozin treatment, the ratio of mitral inflow E to mitral e` annular velocity (E/e`) significantly decreases from 9.3 to 8.5 cm/s ($P < 0.02$). demonstrated [12]. Although this was an observational follow-up study without a control group, the results suggest that SGLT2 inhibitors may be beneficial in treating left ventricular diastolic dysfunction in diabetes.

Another study [13] showed that empagliflozin significantly reduced diastolic tension without affecting contractile function. This was studied in vitro using ventricular trabeculae isolated from patients with end-systolic heart failure. Furthermore, empagliflozin had the beneficial effect of reducing passive myofilament stiffness by increasing the phosphorylation of myofilament regulatory proteins. Obesity is an independent risk factor for cardiovascular events [14]. Inhibiting SGLT2 increases urinary glucose excretion. It has been estimated that with a diuresis of 400 ml/day, 75 g of glucose per day (approximately 300 kcal/day) is lost in the urine [15]. Data from previous clinical trials indicate that the total weight loss with these drugs is 2–3 kg [15]. Weight loss is observed in the first few weeks of treatment, reaches a plateau after 6 months, and persists for a long time [16].

It is well known that lower arterial blood pressure (BP) is associated with reduced cardiovascular morbidity and mortality in DM patients [17]. In the EMPAREG OUTCOME study, SGLT2i was successful in reducing both systolic and diastolic blood pressure without increasing heart rate [18]. These results have been replicated in several studies, and two meta-analyses have demonstrated the beneficial effects of herSGLT2i on blood pressure. Specifically, SGLT2i reduces systolic blood pressure by 2.46 mmHg and diastolic blood pressure by 1.46 mmHg, while simultaneously reducing 24-hour ambulatory systolic and diastolic blood pressure by 3.76 mmHg and 1.83 mmHg, respectively [19,20].

Dyslipidemia is a common comorbidity of T2DM and increases cardiovascular morbidity and mortality [21]. A meta-analysis of 34 RCTs showed that SGLT2i administration increased HDL-C (mean difference 1.93 mg/dL), decreased LDL-C (mean difference 3.5 mg/dL), and serum triglycerides (mean difference 7.8 mg/dL) [22]. Additionally, treatment with dapagliflozin increased LDL-C levels, which were associated with greater buoyancy and were less atherogenic [23].

CONCLUSION:

In conclusion, SGLT2 inhibitors effectively protect against major cardiovascular events, especially in type 2 diabetic patients with a history of atherosclerotic cardiovascular disease or progressive renal disease

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