Safety and Efficacy of adding Dapagliflozin to Furosemide in Type 2 Diabetic Patients with Decompensated Heart Failure and Reduced Ejection Fraction

Ayman Ibrahim
Aswan University
Ramadan Ghaleb
Aswan University
Hossam Mansour
Aswan University
Amr Hanafy
Aswan University
Naggeh M. Mahmoud
Aswan University
M Abdelfatah Elsharef
Aswan University
Mohamed Kamal Salama
Aswan University
Saud M. Elsaughier
Aswan University
Lobna Abdel-Wahid
Assiut University
Mona Embarek Mohamed
Assiut University
Ahmed Khair Ibrahim (ahmed.khair@yahoo.com)
Assiut University Faculty of Medicine https://orcid.org/0000-0002-2286-7188
Ahmed Abdel-Galeel
Assiut University

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Abstract

Background: Heart failure is the most common cause of hospitalization in elderly patients. It is likely that many of the mechanisms that contribute to reductions in systolic and diastolic function seen in diabetic patients also place them at an increased risk of heart failure. Diuretic therapy, especially loop diuretics, is the usual way of managing congestion, particularly in volume-overloaded patients. Little is known about the beneficial effect of dapagliflozin when added to loop diuretics in managing patients with decompensated heart failure.

Aim: To assess the effect of addition of dapagliflozin to furosemide in managing decompensated patient with heart failure and reduced left ventricular ejection fraction.

Patients and methods: The study included 100 type 2 diabetic patients who were admitted with decompensated heart failure. The study population was randomly divided into two arms. Serum electrolytes and kidney functions were followed up during hospital stay.

Results: With dapagliflozin, there was statistically significant difference between the two groups regarding the change in body weight and body mass index. Also, the diuresis parameters including urine output, total fluid loss, and fluid balance showed statistically significant difference in favor the use of dapagliflozin with no significant change in serum potassium or kidney functions. There was significant improvement in patient-reported dyspnea score with the use of dapagliflozin.

Conclusions: Dapagliflozin may provide a new drug option in the treatment of heart failure especially among vulnerable group as diabetics. It has no remarkable effects on serum potassium level and kidney functions.

Background

Heart failure (HF) was considered to be one of the most common causes of hospitalization in elderly patients [1]. Diuretic therapy, especially loop diuretics, is the 1st line of treatment of congestion, especially in volume-overloaded patients [2]. Although furosemide is the most common oral loop diuretic, patients with resistance may advantage from second-generation oral loop diuretics (i.e. bumetanide and torsemide). These may be more effective, due to their higher oral bioavailability and potency [3]. Previous randomized clinical trials have shown that potassium-sparing diuretics were able to reduce both hospitalizations and mortality in patients with chronic HF. However, in patients with acute decompensated HF, they yielded less effective results [4]. Moreover, resistance to diuretics is frequently reported in HF patients [3]. Elimination of excessive fluid is usually achieved by a combination of salt restriction and loop diuretics, but in some cases, congestion persists despite adequate diuretic therapy [5].

It was found that mechanisms responsible for reductions of systolic and diastolic functions present in diabetic patients might increase the risk of HF [6, 7]. Epidemiological studies have shown that HF incidence was double to quadruple fold higher in people with diabetes compared to those without

diabetes [8–9]. A recent analysis of more than 10,000 patients with diabetes treated with dipeptidyl peptidase-4 (DPP-4) inhibitors or sulfonylurea as added on to metformin reported that DPP-4 inhibitors was associated with a lower risk for mortality and major cardiac adverse events compared with sulfonylureas with no difference in hospitalization [10]. Nevertheless, others found that sulfonylurea was correlated with increased HF risk when compared with metformin in a retrospective cohort study [11].

In type 2 diabetic patients with atherosclerotic cardiovascular disease (ASCVD) experiencing myocardial infarction, sitagliptin did not improve the subsequent risk of cardiovascular mortality or HF hospitalization, contrary to the expectations derived from pre-clinical animal models [12]. An unexpected finding of the SAVOR-TIMI 53 trial was that the incidence of hospitalization for HF was higher in patients who received saxagliptin compared with the placebo group [13].

In EMPA-REG OUTCOME, type 2 diabetic patients with high risk of CVD (cardiovascular disease) who received empagliflozin added to the standard care showed significant risk reduction of primary outcome event (i.e. CV (cardiovascular) mortality, non-fatal MI (myocardial infarction), or non-fatal stroke) compared with those randomized to receive placebo [14]. In particular, the CV benefit was driven by substantial and early effects of empagliflozin on CV deaths and hospitalization for HF, in addition to reduction in all-cause mortality [15].

Volume contraction, a result of natriuresis and diuresis, has been hypothesized to play a major role in sodium-glucose co-transporter-2 (SGLT2) inhibitor-associated CV benefits [16]. In an EMPA-REG OUTCOME data analysis, hemoconcentration was identified as the most important mediator for reduction in CV death, with approximately half of the CV benefit attributed to increase in hematocrit [16]. Likewise, when comparing dapagliflozin to hydrochlorothiazide in patients with type 2 diabetes, SGLT-2 inhibitor treatment led to a reduction in plasma volume and increase in erythrocyte mass, an effect that was not observed with the diuretic [17].

In HF patients with reduced ejection fraction (EF), those treated with dapagliflozin had lower risk of worsening HF or CV mortality than those received placebo, regardless of the presence or absence of diabetes [18]. The combination of empagliflozin and loop diuretics seems to have synergistic effects on diuresis, without inducing renin-angiotensin-aldosterone system (RAAS) activation. Additionally, it resulted in significant increase in both urinary sodium concentration, and peak oxygen consumption [19].

It has been contemplated that SGLPT-2 inhibitors (i.e. empagliflozin/dapagliflozin) reduced the incidence of HF hospitalization and patients with type 2 diabetes mellitus (DM) were not an exception [20]. Nonetheless, the beneficial effect of dapagliflozin was not clear when added to loop diuretics in treating decompensated HF patients with and its subsequent effects on blood glucose, renal function and electrolyte levels.

The current study aimed at assessing the adjusted effect of adding dapagliflozin to furosemide in managing decompensated HF patient and reduced left ventricular EF. Also, to assess the subsequent effects on blood sugar level, kidney function and serum electrolytes.

Methodology

Patients and Methods

The study included 100 DM patients (type 2) who were admitted to Aswan university hospital, cardiac care unit and Assiut University Heart Hospital, critical care unit with decompensated HF. Sample size calculation was carried out using G*Power 3 software. A calculated minimum sample of 94 patients with type 2 DM and HF (46 -Group A- and 46 -Group B-) was needed to detect an effect size of 0.3 in the change in weight and body mass index (BMI), with an error probability of 0.05 and 80% power on a two-tailed test. The sample was raised to include 100 patients.

Inclusion criteria were age more than 18 years, type 2 diabetic patients, with history of chronic HF, had indication for admission to cardiac care unit (decompensated HF). The patients were included as they had at least one symptom (respiratory discomfort or orthopnea) and one clinical sign (pedal edema, engorged jugular vein, or pulmonary congestion), the patients already were on furosemide for at least 1 month before admission plus other conventional anti-failure treatment, had left ventricular ejection fraction (LVEF) ≤ 40% and there is no prespecified inclusion criterion with respect to HF etiology.

The patients were excluded if they had any of the followings: other causes of fluid overload different from HF, marked hyponatremia: sodium level below 125 mmol/l, unstable patients: acute coronary syndrome, cardiogenic shock, patients requiring positive inotropic agents or renal dialysis, pregnancy or breast-feeding period, advanced hepatic disease, advanced kidney disease with glomerular filtration rate (GFR) less than 45 mL/min/1.73 m² and patients with diabetic ketoacidosis.

The study population was randomly divided into two groups: **Group I (study arm)**: included 50 patient who received dapagliflozin alone or plus insulin (when needed) for control of blood glucose levels and furosemide plus conventional anti-failure measures. **Group II (control arm)**: included 50 patients who received insulin for control of blood sugar and furosemide plus other anti-failure measures.

(A) Group I (Study arm): The patients received:

a. **Furosemide**: It was administered at doses sufficient to achieve optimal volume status and relieve congestion without inducing an excessively rapid reduction in intravascular volume. Furosemide was given intravenously either by continuous infusion or boluses.
b. **Anti-failure treatment**: Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, mineralocorticoid receptor antagonists, ivabradine or others were individualized according to the patient condition.
c. **Dapagliflozin**: It was given in a dose of 10 mg once daily.
d. **Insulin**: Insulin therapy was initiated if blood glucose level is ≥ 180 mg/dL (10 mmol/L) after initiation of dapagliflozin treatment. Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended. Subcutaneous regular insulin every 6 h_s was used according to blood glucose level [21].

(B) Group II (Control arm): The patients received:

a. **Furosemide**: as in study arm.
b. **Anti-failure treatment**: as in study arm.
c. **Insulin**: as in study arm.

All the patients underwent:

1- Continuous monitoring: Oxygen saturation and blood pressure monitoring.

2- Electrocardiogram (ECG) on admission and daily.

3- Complete echocardiographic assessment.

4- Laboratory assessment: including complete blood count, blood urea, serum creatinine, blood sugar, electrolytes, complete liver function tests on admission.

5- Follow up lab. assessment: including blood sugar and urea, serum creatinine, sodium (Na^+) and potassium (K^+) were measured daily along the whole days of admission.

Follow up parameters:

* **Diuresis parameters**:

- Total urine output: 24-hour diuresis was quantified from admission till discharge and recorded in liters.
- Total fluid intake was calculated for patients and recorded in liters.
- Fluid balance was defined as the difference between total fluid intake and total urine output in liters.
- Fluid loss/diuretic: This relates the total urine output to the amount of administered furosemide in ml/mg.
- Fluid balance/diuretic: This relates the change in fluid balance to the amount of administered furosemide in ml/mg.
- Daily dose of furosemide and total dose of furosemide along whole hospital stay in mg were reported.

* **Changes in body weight measurements**: The body weight difference between admission and discharge was recorded in Kg. Also, the percentage of weight loss related to the initial body weight was reported. BMI and percentage of its change were recorded as well.

*** Dose of insulin**

The total dose of insulin used during the admission in order to control the blood sugar level was reported for both study arms in international units (IU).

* **Renal function**: It was determined every 24 hours (during hospitalization) from admission till discharge. Renal function was assessed with the serum creatinine level. A worsening renal function is defined as an increase ≥ 0.3 mg/dL in the serum creatinine level compared with the value on admission [22, 23].

* **Electrolyte levels**: Serum sodium and potassium were assessed every 24 hours (during hospitalization) from admission till discharge.

* **Patient-reported dyspnea**: Patient-reported dyspnea was assessed every 24 hours (during hospitalization) from admission till discharge.

Patient-reported dyspnea was assessed with the use five-point Likert scale (5PLS), a psychometric instrument for the measurement and grading of dyspnea [24–26]. Many authors had validated this score and recommended its use assess patients with acute decompensated HF [27, 28].

The scale includes the absence of dyspnea (a score of 1), mild shortness of breath (a score of 2), moderate shortness of breath (a score of 3), severe shortness of breath (a score of 4) and the worst possible shortness of breath (a score of 5). All patients filled out the 5PLS without any interference after a brief explanation provided by a nurse.

Statistical analysis:

Data were verified, coded by the researcher, and analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics: Means, standard deviations, and percentages were calculated. Test of significances: Chi square test was used to compare the difference in distribution of frequencies among different groups while for repeated measure (on admission vs, on discharge); McNemar's test was used. Student t-test analysis was carried out to compare the means of dichotomous data that follow the normal distribution. For repeated measure (on admission vs, on discharge); paired sample t-test was used. A significant p value was considered when it is equal or less than 0.05.

Results

This multi-center randomized clinical trial was conducted in the Cardiovascular Medicine Department, Assiut University Heart Hospital, Assiut University and Cardiology Department, Aswan University Hospital, Aswan University during the period from April 2020 to June 2020. This study involved 100 DM type 2 patients admitted with decompensated HF. The study cohort was randomly assigned to one of the two treatment modalities; 50 patients received dapagliflozin plus insulin (if needed) and furosemide plus conventional anti-HF measures (Study Group) and 50 patients received insulin plus furosemide and conventional anti-failure measures (Control group).

Table (1) showed the baseline characteristics of the study population.

ble 1: Baseline characteristics of the studied population

Parameter	Control Group (n=50)	Study Group (n=50)	P-value
Age in years (mean ± SD)	60.64 ± 9.9	62.02 ± 8.8	0.462*
Sex, male (%)	26 (52%)	28 (56%)	0.688**
Hypertensive (%)	31 (62%)	28 (56%)	0.542**
Duration of DM in years (mean ± SD)	13.04 ± 1.2	13.34 ± 1.1	0.875*
Weight/kg on admission (mean ± SD)	82.07 ± 9.1	80.56 ± 6.2	0.334*
BMI on admission (mean ± SD)	28.23 ± 3.3	27.78 ± 2.3	0.436*
Dyspnea on admission			
• Severe	11 (22%)	8 (16%)	0.444**
• Very Severe	39 (78%)	42 (84%)	
Serum creatinine on admission (mean ± SD)	1.40 ± 0.3	1.32 ± 0.2	0.126*
Serum Na on admission in mEq/L (mean ± SD)	137.64 ± 3.9	136.76 ± 3.6	0.241*
Serum K on admission in mEq/L (mean ± SD)	4.27 ± 0.6	4.18 ± 0.6	0.427*
RBS (mean ± SD)	272.16 ± 77.6	263.26 ± 83.1	0.583*
HbA1c (mean ± SD)	9.09 ± 2.1	8.61 ± 1.2	0.176*

* Independent t-test test was used to compare the mean difference between groups

** Chi-square test was used to compare proportions between groups

*** Follow up parameters**:

(1) Diuresis parameters: Although the difference in fluid intake between the two groups was statistically insignificant, the amount of urine output was higher in the study versus control groups (p<0.001). Patients of the study group had higher fluid loss/diuretics (34.8±2.2) compared to controls (19.5±1.2). Moreover, fluid balance/diuretics was significantly lower for the study (-21) compared with control (-10) group (p<0.01). The mean total dose of furosemide and furosemide dose/day were significantly lower for the study compared with control group (p<0.01), table (2).

Table 2: Change associated with diuresis in the studied population

Parameter	Control Group (n=50)	Study Group (n=50)	P-value*
Urine output in liters (mean ± SD)	14.43 ± 0.7	18.46 ± 0.5	< 0.001*
Fluid intake in liters (mean ± SD)	7.01 ± 0.3	7.52 ± 0.2	0.139*
Total fluid balance in liters (mean ± SD)	-7.42 ± 0.7	-11.33 ± 0.4	< 0.001*
Fluid loss/diuretics in ml/mg liters (mean ± SD)	19.49 ± 1.2	34.75 ± 2.2	< 0.001*
Fluid balance/diuretics ml/mg liters (mean ± SD)	-9.87 ± 0.6	-20.86 ± 1.0	< 0.001*
Furosemide use			
• Total dose	855.00 ± 74.8	597.60 ± 34.4	0.002*
• Dose/day	170.78 ± 9.7	126.07 ± 4.3	< 0.001*

* Independent t-test test was used to compare the mean difference between groups

(2) Change in body weight measurements: Both groups showed no significant difference regarding mean values of weight and BMI on admission. On the other hand, on discharge, mean weight and BMI were lower in the study (76.5 kg and 26.4) compared with control (79.6 kg, 27.4) group (p=0.004 and 0.074, respectively). The percent change for both measures was significantly higher (p<0.001) for the study group (5%) compared with controls (3.4%) table (3) and Figure (1).

ble 3: Change in the BMI of the studied population

Parameter	Control Group (n=50)	Study Group (n=50)	P-value*
Weight in Kg (mean ± SD)			
• On admission	82.07 ± 9.1	80.56 ± 6.2	0.334*
• On discharge	79.63 ± 8.9	76.51 ± 6.0	0.046*
P-value**	< 0.001	< 0.001	
Weight % change (mean ± SD)	- 3.41 ± 0.2	- 4.96 ± 0.2	< 0.001*
BMI (mean ± SD)			
• On admission	28.23 ± 3.3	27.78 ± 2.3	0.436*
• On discharge	27.38 ± 3.1	26.39 ± 2.2	0.074*
P-value**	< 0.001	< 0.001	
BMI % change	-3.41 ± 0.2	-4.97 ± 0.2	< 0.001*

* Independent t-test test was used to compare the mean difference between groups

** Paired t-test test was used to compare the mean difference between groups

(3) Dose of insulin: The total dose of insulin was significantly lower for the study (29.6±9.5 IU) compared with control (44.0±13.3 IU) group (p<0.01).

(4) Change in renal function and serum electrolytes: Both groups showed no significant difference regarding mean level of serum creatinine on admission. On the other hand, on discharge, mean level of serum creatinine was lower in the study (1.4 mg/dl) compared with control (1.5 mg/dl) group (p=0.009). Significant increase in serum creatinine for both groups was observed on discharge (p<0.01).

Likewise, both groups showed no significant difference regarding mean potassium level on admission. Contrarily, mean level of serum potassium was higher in the study (4.1 mEq/L) compared with control (3.8 mEq/L) group (p=0.003).

On the other hand, serum sodium level was comparable between the two study arms regarding on admission and on discharge levels. However, overall, there was statistically significant reduction in serum sodium for both groups on discharge (p < 0.001), table (4).

ble 4: Change in renal function and serum electrolytes of the studied population.

Parameter	Control Group (n=50)	Study Group (n=50)	P-value*
Serum creatinine level in mg/dL (mean ± SD)			
• On admission	1.40 ± 0.3	1.32 ± 0.2	0.126*
• On discharge	1.53 ± 0.3	1.39 ± 0.2	0.009*
P-value**	< 0.001	0.003	
Serum creatinine level % change	12.34 ± 2.9	8.76 ± 2.5	0.349*
Serum sodium level in mEq/L (mean ± SD)			
• On admission	137.64 ± 3.9	136.76 ± 3.6	0.24*
• On discharge	131.52 ± 3.2	131.96 ± 2.7	0.46*
P-value**	< 0.001	< 0.001	
S. Na^+ Level % change	4.42 ± 2.0	3.48 ± 1.7	0.01*
Serum potassium level in mEq/L (mean ± SD)			
• On admission	4.27 ± 0.6	4.18 ± 0.6	0.427*
• On discharge	3.83 ± 0.5	4.11 ± 0.4	0.003*
P-value**	< 0.001	0.005	
S. K^+ Level % change	9.82 ± 0.9	1.37 ± 0.7	< 0.001*

* Independent t-test test was used to compare the mean difference between groups

** Paired t-test test was used to compare the mean difference between groups

(5) Patient-reported dyspnea: At baseline, in both groups about one-fifth (22% vs. 16%) of patients had severe dysnea and the other four-fifth had very severe grades (78% vs. 84%) (p=0.444). On discharge, the study group had better improvement (about one third had no dyspnea (34%), about one half had mild grade and only 16% had moderate grade) compared to control group (about 16%had no dyspnea, 44% had mild and 40% had moderate grade of dyspea) (p<0.002). Overall, significant improvement was observed on discharge for both groups (p<0.001), Figure (2).

(6) Other outcomes: There was no statistically significant difference between the two study arms regarding mortality during hospitalization, one case in each arm. Also, there was no statistically significant difference between the two arms regarding the duration of hospital stay, 4.92 ± 1.5 days for the control group versus 4.64 ± 1.0 days for the study group, p value 0.27.

Discussion

Type 2 diabetes mellitus (T2DM) was associated with increased incidence of congestive heart failure (CHF) [29,30]. Loop diuretics are the corner stone of treatment for patients with acute decompensated heart failure (ADHF) and fluid overload [31]. However, many patients show a poor response, with up to 50% considered diuretic resistant [31]. Prolonged administration of loop diuretics increases Na^+ reabsorption at the distal nephron segments, thereby limiting Na^+ loss [33,34]. This “diuretic braking

phenomenon" [35] definitely leaves many patients with CHF with an expanded blood volume that predicts adverse outcomes [36].

In high doses, diuretics activate the RAAS and may promote HF progression [37,38]. Furthermore, excess diuretics causes plasma volume contraction, worsens renal function and leads to various electrolyte disturbances including hypokalemia, hypomagnesemia, hypocalcemia, hyponatremia and hyperuricemia [39–41]. While mineralocorticoid receptor antagonists (MRAs) have mild diuretic effects and improve prognosis in HF with reduced EF [42], hyperkalemia and worsening renal function are common side effects of these drugs [43].

Although originally developed as glucose-lowering medications for patients with T2DM, SGLT-2 inhibitors have improved event-free survival in patients with chronic HF, regardless the degree of hyperglycemia or diabetic status [14,44]. SGLT-2 inhibitors increase urinary excretion of glucose and sodium and appear to produce a durable reduction in blood volume [17,45]. SGLT-2 accounts for a portion of proximal Na^+ reabsorption [46,47]. Its inhibition causes an osmotic diuresis that can enhance Na^+ excretion [48]. However, unlike traditional diuretics, their action involves limited activation of the neurohormonal system and insignificant change in electrolyte profile of the patient [49].

Reports from the EMPA-REG OUTCOME and the Canagliflozin Cardiovascular Assessment Study (CANVAS) showed that SGLT-2 inhibitors were effective for medium- and long-term inhibition of major adverse cardiovascular events and the progression of renal dysfunction [14,50]. In the placebo-controlled Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial, dapagliflozin reduced the risk of HF hospitalization and mortality, and improved symptoms, in more than 4500 patients with heart failure and reduced ejection fraction (HFrEF) [16,51].

Therefore, SGLT-2 inhibitors may be a good option in patients with T2DM and CHF, the interaction between SGLT-2 inhibitors and furosemide needs a well randomized prospective study. An augmented natriuresis with one diuretic when added to the other would indicate a synergetic effect, such as has been shown with loop diuretics and thiazides [34]. This study tested the hypothesis that there would be a favored interactions between these 2 classes of drugs (dapagliflozin and furosemide) in patients with T2DM and acutely decompensated HF and to our knowledge this is the first prospective randomized controlled trial to test the effect of both agents when given together in patients with HF.

Petrie et al. in 2020 evaluated the effects of dapagliflozin in patients with HFrEF with and without diabetes, where 10 mg once-daily of dapagliflozin or placebo were added to the recommended therapy. They concluded that dapagliflozin significantly reduced the risk of worsening HF or CV death independently of diabetes status [52].

The diuretic actions of SGLT-2 inhibitors presumably play an important role in cardioprotection, as shown in the EMPA-REG OUTCOME study and the CANVAS program. SGLT-2 inhibitors have acutely caused an increase in urinary sodium excretion in non-diabetic [53] and diabetic rats [54,55].Our study showed that addition of dapagliflozin to furosemide actually improved all studied diuresis parameters including urine

output, total fluid balance as well as fluid balance/diuretic dose. In a small randomized, placebo-controlled, double-blind trial, involving 75 subjects with T2DM, dapagliflozin has been shown to reduce plasma volume in a similar way to thiazide diuretics, but dapagliflozin has a more enduring diuretic effect than other diuretics [17].

In 2018, Wilcox et al. concluded that first-dose Na^+ excretion with bumetanide and dapagliflozin is not additive, but the weekly administration of one diuretic enhances the initial Na^+ excretion with the other. Thus, there was significant 2-way adaptive natriuretic synergy. This resulted in a greater Na^+ excretion during the second week when both diuretics were given together. Prior diuretic administration was required to evoke this synergistic natriuretic interaction [56]. If we assume that this postulation was correct, this would explain the rapid and good response for combined therapy with both dapagliflozin and furosemide in our enrolled patients as one of our prerequisites to include patients was that the patient should be already on furosemide for at least 1 month before admission.

Our results reported a statistically significant reduction in serum sodium for both study arms. However, the percentage reduction in serum sodium was significant for the control arm (4.4% for control group versus 3.5% for the study group, p value 0.01). The control group received relatively large doses of furosemide (mean total furosemide dose was 855 mg in control group versus 597 mg in study group). Despite that the study reported an obvious improvement in all studied diuresis parameters, we didn't notice any deleterious effects of dapagliflozin on serum potassium. The use of dapagliflozin wasn't associated with hypokalemia or worsening renal function as observed with diuretics alone. The hypothesis that the use of dapagliflozin acutely reduced the dose of needed furosemide hence limiting its associated side effects including hypokalemia and renal troubles. In agreement with our results, the retrospective analysis done by Griffin et al. (2020) showed that therapy with an SGLT-2 inhibitor was associated with improved urine output and weight loss after therapy. These effects were observed without increase of loop diuretic or thiazide therapy, and the resultant diuretic efficiency was markedly improved as daily urine output improved during Day 1 ($P = 0.002$), Day 2 ($P = 0.02$), and Day 3 ($P = 0.02$) compared with the 24 hours prior to treatment. They also detected no adverse outcomes, including deterioration of renal function, change in blood pressure or electrolytes, or genitourinary infections while on therapy [57]. Regarding safety of using dapagliflozin in patients with HF, our results go hand in hand with DAPA-HF findings which revealed that the beneficial effects of dapagliflozin was not associated with any adverse events on renal function. [16]. Cahn et al. also confirmed that SGLT-2 inhibitors do not increase risk for acute kidney injury compared with DPP-4 inhibitors among patients with T2DM [58].

With concordance with our results concerning change in potassium level, Yavin et al. found that dapagliflozin did not appear to increase serum potassium levels in patients with T2DM, including patients at a higher risk of hyperkalemia, such as those with moderate renal impairment or treated with angiotensin converting enzymes (ACE) inhibitors, angiotensin II receptor blockers (ARBs) or potassium-sparing diuretics [20]. Although, Wilcox et al. agreed with our results as they showed that there were no clinically significant changes in serum sodium, or creatinine concentrations. They found that dapagliflozin induced hypokalemia with bumetanide. Serum potassium was unchanged by dapagliflozin

alone but was reduced 7% by bumetanide alone and 12% by the combination, reflecting increases in renal K^+ excretion. They explained the greater K^+ excretion and hypokalemia with combined therapy as a consequence of hyperaldosteronism because there were high levels of plasma renin activity [56].

In our study, the use of dapagliflozin has reduced the mean total dose of required furosemide by approximately one third (mean total furosemide dose was 855 mg in control group versus 597 mg in study group). A similar pattern of observations was obtained by Kambara et al. who concluded that the use of SGLT-2 inhibitors (empagliflozin and canagliflozin) was safe and effective in DM patients who required inpatient treatment for acute HF. Early initiation of SGLT-2 inhibitor therapy after the onset of acute HF reduced the doses of loop diuretics (to approximately one third), leading to greater prevention of acute kidney injury [59]. It is noteworthy that his study was retrospective, not randomized and the sample size was relatively small, included only 31 patients (12 patients in SGLT-2 inhibitor group and 19 patients in the conventional treatment group). No patients of them received dapagliflozin as nine patients (75%) received empagliflozin and three patients (25%) received canagliflozin [59].

As the addition of dapagliflozin ensured more diuresis, our study detected a statistically significant difference regarding the percentage of change in the body weight (3.4 Kg for control arm versus 5 Kg for the study arm; p value 0.001). The effects of empagliflozin on cardiorespiratory fitness in patients with T2DM and HFrEF were studied by Carbone et al. Empagliflozin reduced body weight (−1.7 kg; P = 0.031) but did not change peak oxygen consumption. However, patients using loop diuretics (n=9) demonstrated an improvement, whereas those without loop diuretics (n=6) experienced a decrease in peak oxygen consumption and peak oxygen consumption changes correlated with the baseline daily dose of diuretics (R = +0.83; P < .001) [19]. The most important finding would be that the use of empagliflozin in HFrEF patients not treated with loop diuretics may be less beneficial and this could greatly influence the final therapeutic outcome [19].

In our study, the use of dapagliflozin was associated with dyspnea improvement, that was more pronounced than that associated with diuretic alone. Dyspnea improvement in HF patients is mostly attributed to reduction in plasma volume that can be carried out effectively by diuretics especially loop diuretic. However, to achieve a good reduction of plasma volume, we may be forced to use high doses of diuretics and this is mostly associated with side effects such electrolyte imbalance. This electrolyte imbalance can cause muscle fatigue especially the respiratory muscles, hence the continued sense of dyspnea. This could be the case in the control arm of our study where we used large doses of furosemide. On the other hand, in the study arm, the reduction of plasma volume was achieved by the synergistic effect of using dapagliflozin and furosemide in relatively lower doses than the control arm, so less side effects, less muscle fatigue and less dyspnea. Incongruency with our findings, in 2020, Damman et al. found that in patients with acute HF, treatment with empagliflozin had no effect on change in visual analogue scale, dyspnea score, diuretic response, N-terminal pro-natriuretic peptide (NT-pro BNP), and length of hospital stay, but was safe, increased urinary output and reduced endpoint of worsening HF, re-hospitalization for HF or death at 60 days [60].

Limitations

Despite meaningful effects which were extrapolated from our study with respect to the synergetic effect of adding dapagliflozin to furosemide in patients with ADHF. It was difficult to clarify whether there was a remarkable interaction with other anti-failure drugs or not. Second limitation was that the only loop diuretic which was used in our study is furosemide so further researches are clearly required to ascertain such synergetic effect with other loop diuretics. Also, further studies designing dapagliflozin and furosemide as long-term treatment for HF patients are needed for better assessment of this combination therapy for such patients.

Conclusions

Dapagliflozin is a relatively newly introduced anti-diabetic drug. However, it demonstrates outstanding diuretic effects that put it among the lines of treatment of HF in DM patients. Its use potentiates the action of loop diuretics and lowers their dose. It has a non-remarkable effect on serum potassium and renal function.

List Of Abbreviations

HF: Heart Failure

DPP-4: Dipeptidyl peptidase-4

ASCVD: Atherosclerotic cardiovascular disease

SAVOR-TIMI 53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM-TIMI-53

EMPA-REG OUTCOME: The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) OUTCOME trial

CVD: Cardiovascular Disease.

CV: Cardiovascular

MI: Myocardial Infarction.

SGLT2: Sodium-glucose co-transporter-2

EF: Ejection fraction

RAAS: Renin-angiotensin-aldosterone system

DM: Diabetes mellitus

BMI: Body mass index

LVEF: Left ventricular ejection fraction

GFR: Glomerular filtration rate

ECG: Electrocardiogram

Na^+: Sodium

K^+: Potassium

5PLS: Five-point Likert scale

T2DM: Type 2 diabetes mellitus

CHF: Congestive heart failure

ADHF: Acute decompensated heart failure

MRAs: Mineralocorticoid receptor antagonists

CANVAS: Canagliflozin Cardiovascular Assessment Study

DAPA-HF: Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure

HFrEF: Heart failure with reduced ejection fraction

ACE: Angiotensin converting enzyme

ARBs: Angiotensin II receptor blockers

NT-pro BNP: N-terminal pro-natriuretic peptide

Declarations

* The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Assiut University, 18th March 2020.

* A written informed consent was taken from every participant.

* The institutional written consent of involves a consent for publication of the processed obtained data without any names or private data of the participants.

* All data of the study is available upon request. Data generated or analyzed during this study are included in this published article.

* All authors declare no financial or non-financial conflict of interests.

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Authors' Contribution

AI: concept, design, literature search, clinical studies, experimental studies manuscript preparation, editing and review

RG, HM, AH, NM, ME, SE, and MM: definition of intellectual content, literature search and manuscript review, clinical studies, experimental studies, data acquisition

LA: clinical studies, experimental studies, data acquisition

AI: data analysis, statistical analysis, manuscript preparation, editing and review

AA: concept, design, literature search, clinical studies, experimental studies manuscript preparation, editing and review

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Figures

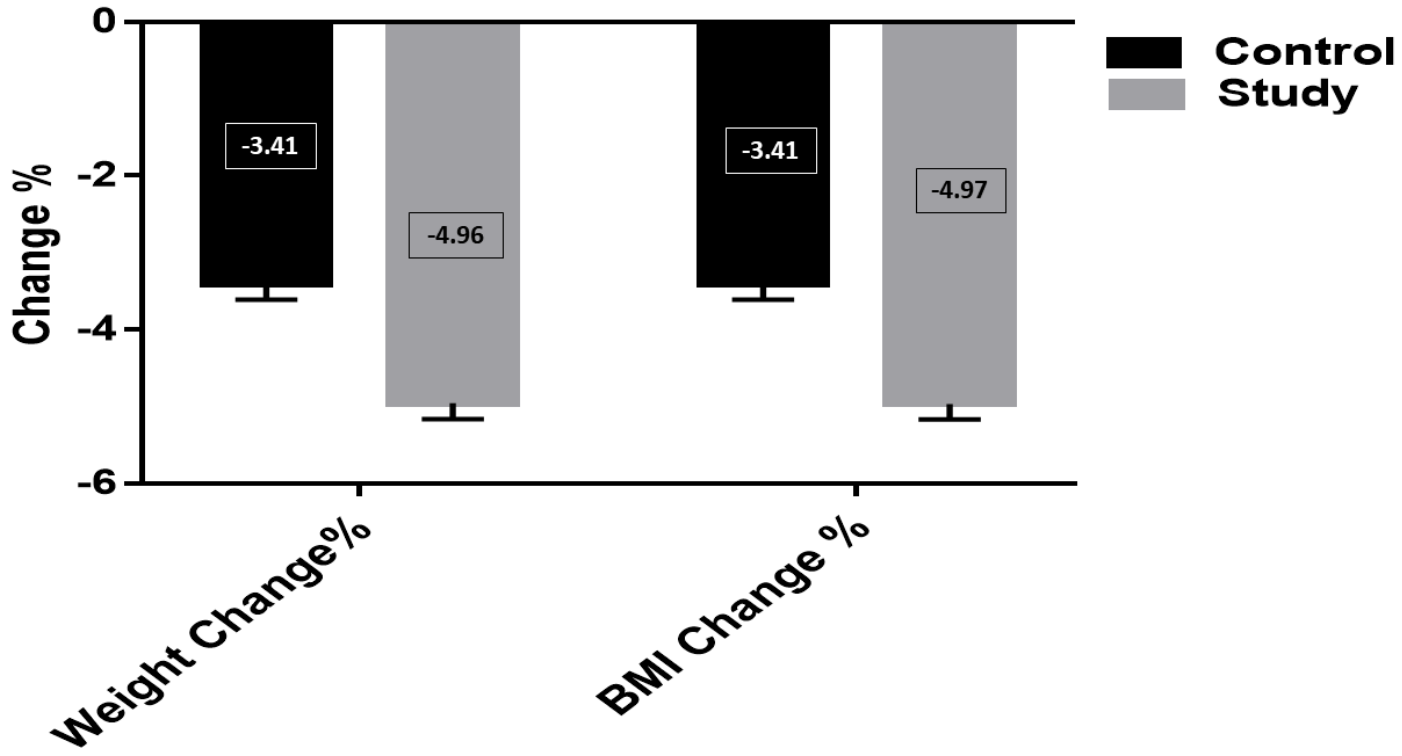
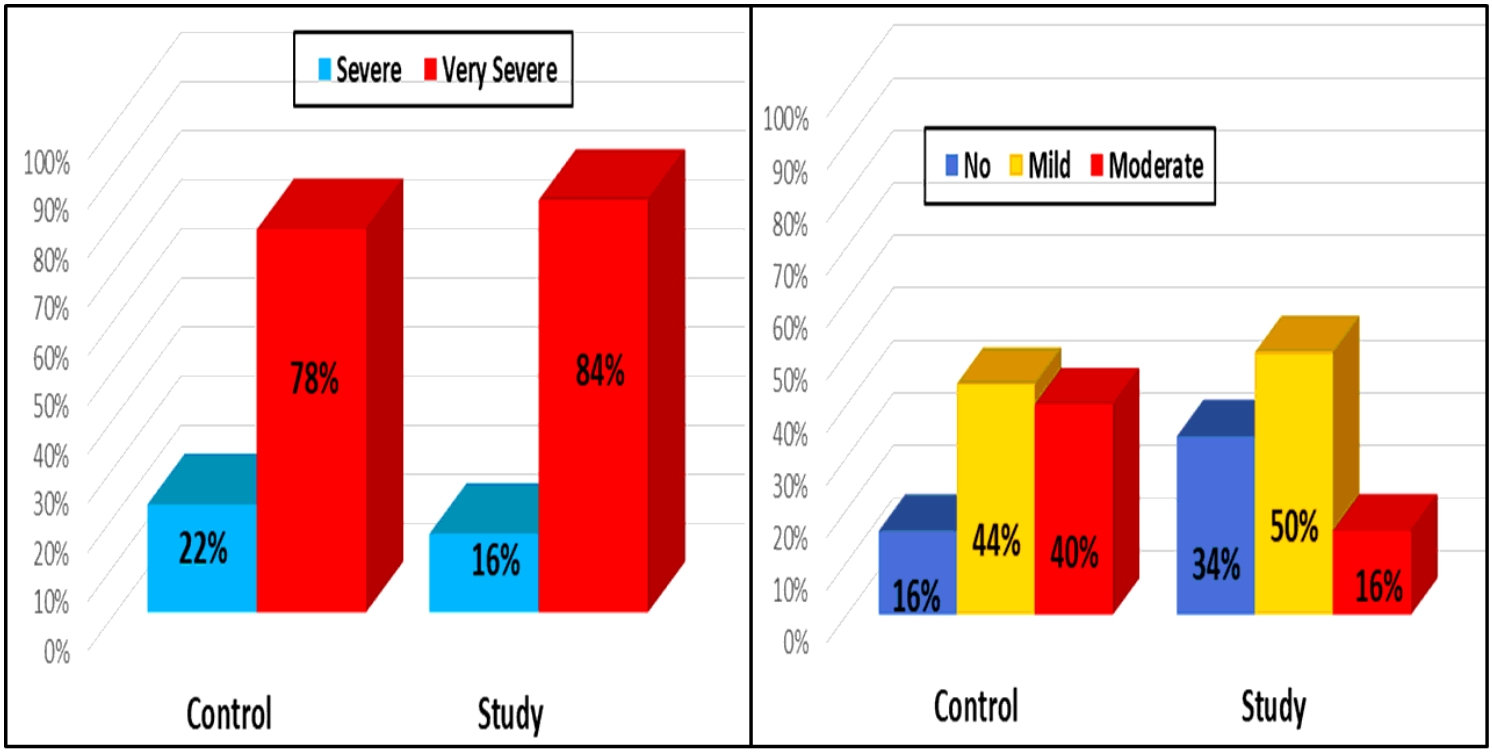


Figure 1

Mean Percent Change in Patients' Weight and BMI On Discharge



Grades of Dyspnea on Admission **Grades of Dyspnea on Discharge**

Figure 2

Change in the Dyspnea Grades on Admission vs. on Discharge