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Possible Beneficial Effect of Dapagliflozin in Improvement of Dyspnea Scale (VAS and SA-NYHA Class) in Patients with Acute Decompensated Heart Failure (ADHF)

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Abstract*—Heart failure (HF) is a condition in which the heart is unable to pump enough blood to meet the body's needs. Diuretics are the mainstay of acute heart failure therapy, especially intravenous loop diuretics. In this study, IV.furosemide (120mg/day) plus 10mg dapagliflozin tablet were used daily. The aim of the present study is to observe the Possible beneficial effect of dapagliflozin in the improvement of dyspnea scale (VAS and SA-NYHA Class) in patients with ADHF. Between October 2023 and April 2024, a study was conducted at AL- Nasiriyah Heart Center, in the coronary care unit (CCU), in Thi-Qar Province, southern of Iraq . One hundred subjects, both male and female were enrolled in the study after describing the study's goals, gauging patient satisfaction, and getting informed consent from the subjects. 100 enrolled patients were divided into two groups: The control group (Group A) involved (50 patients), given IV.furosemide (120mg/day) and the studied group (Group B) involved (50 patients), given IV. furosemide (120 mg/day) plus 10mg dapagliflozin tablet daily. Then, it was the assessment of symptoms of dyspnea by Visual Analog Scale and SA-NYHA class. It was found that dyspnea scales (VAS and SA-NYHA Class) for patients in both groups (A and B) at hospital admission were significantly improved after subsequent days of admission. There was a significant reduction in the dyspnea scale (VAS & SA-NYHA) of patients on 4th day of hospital admission as compared to the day of admission in both groups (A & B). Conversely, there was no statistically significant difference in the dyspnea scale (VAS & SA-NYHA) of patients at hospital admission between groups (A & B). However, dyspnea scale (VAS & SA-NYHA) of patients during 4th day of admission of group B was significantly lower compared with patients in group A during 4th day of admission. The present study has reported a positive effect of dapagliflozin in reducing dyspnea in patients with ADHF.

Keywords— Dapagliflozin, Acute Decompensated Heart Failure, Dyspnea Scale, Visual Analog Scale, Self-Assigned New York Heart Association.

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major risk factor for heart failure (HF), and both conditions have been increasing in prevalence globally over time, largely due to population aging. This dual epidemic of T2DM and HF highlights the need for effective treatments to manage the expected increase in HF burden, particularly among patients with T2DM [1].

Heart failure (HF) is a condition in which the heart is unable to pump enough blood to meet the body's needs. This is most commonly due to reduced cardiac output (CO) due to impaired cardiac function. While low-output HF refers to the typical form, high-output HF involves a disproportion between the body's increased metabolic demands and a heart that is generally functioning normally [2].

Heart failure can cause various symptoms, including shortness of breath, especially during physical activity, and fatigue. Respiratory symptoms, such as shortness of breath when lying flat (orthopnea|), sudden shortness of breath at night (paroxysmal nocturnal dyspnea), rapid breathing, and coughing. Fluid retention symptoms, such as fluid buildup in the lungs (pulmonary congestion) and swelling in the extremities (edema) [3]. Heart failure (HF) is a significant concern among elderly individuals with cardiovascular diseases [4]. Globally, around 64 million people are affected by HF, a number expected to rise as life expectancy increases. The risk of developing HF rises with age, with rates of 28.5% for women and 33% for men aged over 55. The prognosis for HF is poor, with over 50% 5-year mortality for chronic HF. In Europe and North America, a 40-year-old man has about a one in five chance of developing heart failure in his lifetime [5]. The primary risk factors include coronary heart disease, high blood pressure, diabetes, and a family history of heart disease, atherosclerotic cardiovascular disease, smoking, obesity, chronic pulmonary diseases, inflammation or chronic infection, metabolic diseases, treatment with cardiotoxic agents or alcohol abuse [6]. Causes of diminished contractility that result in systolic dysfunction include a reduction in muscle mass (such as from a myocardial infarction), dilated cardiomyopathies, and ventricular hypertrophy, all of which are forms of heart failure.

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Ventricular hypertrophy can be caused by: Pressure overload (such as high blood pressure, aortic valve stenosis, or pulmonic valve stenosis) and volume overload (such as valvular regurgitation, shunts, or high-output states) [7]. Factors contributing to diastolic dysfunction, resulting in restriction in the ventricular filling, increased ventricular stiffness, ventricular hypertrophy, infiltrative myocardial diseases, myocardial ischemia, myocardial infarction, mitral or tricuspid valve stenosis , and pericardial diseases (such as pericarditis or pericardial tamponade) [8]. In the neurohormonal model of HF, an initial event like an acute MI leads to decreased cardiac output, transforming HF into a systemic disease driven by neurohormones. Factors contributing to chronic heart failure: Neurohormones (such as angiotensin II, norepinephrine, aldosterone, natriuretic peptides, arginine vasopressin, proinflammatory cytokines, and endothelin-1) [9].

Various factors can trigger acute decompensation, including poor dietary choices, inadequate adjustment of heart failure medications, myocardial ischemia or heart attack, arrhythmias (both tachycardia and bradycardia), infections, anemia, introduction of medications that exacerbate heart failure symptoms (such as certain calcium channel blockers and beta-blockers, thiazolidinediones,[10] antiarrhythmic agents, and NSAIDs antibodies), alcohol consumption, pregnancy, worsening hypertension, and acute valvular insufficiency [11]. Diuretics are the mainstay of acute heart failure therapy, especially intravenous loop diuretics. Dyspnea (shortness of breath) is the most common symptom in patients who are hospitalized for AHF. It is a major stress factor for patients. Although dyspnea is not a symptom that is specific to AHF, its severity can vary over time [12,13].

The severity of dyspnea varies between patients and physicians, making it a subjective concept [14]. Although limited research has devised scales specifically for measuring dyspnea severity in acute heart failure (AHF), visual analog scales (VAS) and Self-Assigned New York Heart Association (SA-NYHA) classifications have often been employed to assess dyspnea in recently hospitalized patients [15]. This study aims to evaluate the potential beneficial impact of dapagliflozin on dyspnea severity, as measured by VAS and SA-NYHA, in patients with acute decompensated heart failure (ADHF).

II. Materials and Methods

Between October 2023 and April 2024, a study was conducted at AL- Nasiriyah Heart Center, in the coronary care unit (CCU), in Thi-Qar province southern Iraq. One hundred subjects, both male and female, were enrolled in the study after describing the study's goals, gauging patient satisfaction, and getting informed consent from the subjects. Prospective Interventional study was done in AL-Nasiriyah Heart Center.

The study enrolled 118 of type II diabetic patients who were admitted to cardiac care unit for hypervolemic acute decompensated heart failure (ADHF) with evidence of congestion, and had left ventricular ejection fraction (LVEF) of 40% or below. All patients were diagnosed by a specialist cardiologist based on the European Society of Cardiology (ESC); eighteen patients were excluded due to not meeting inclusion criteria. 100 enrolled patients were divided into two group: Control group ((Group A)) involved 50 patients given IV.furosemide (120mg/day), and the studied group ((Group B)) involved (50patients), given IV.furosemide (120mg/day) plus 10mg dapagliflozin tablet daily. Urinary Sodium Excretion: 2 ml of urine was taken from all participants after 6 hours from admission to measure urinary sodium excretion by Cobas c 311 analyzer [16]. Urine Output: (24 hours urine output for the first 24hours after admission measured in milliliters/day.

a) Inclusion criteria

The study enrolled patients aged 18 years and older who were hospitalized within 24 hours for hypervolemic acute decompensated heart failure ((with evidence of congestion)), whose planned treatment was intravenous administration of loop diuretics. Patients were included in the study if they met the following criteria: At least one symptom of heart failure (respiratory discomfort or orthopnea). At least one clinical sign of heart failure (peripheral edema, engorged jugular vein, 2.27 Kg weight gain, or pulmonary congestion on chest x-ray). An estimated glomerular filtration rate (eGFR) of no less than 30 ml/min/1.73m², was determined using the Modification of Diet in Renal Disease (MDRD) formula, and history of type II diabetes.

b) Exclusion criteria.

Type 1 diabetes mellitus, cardiogenic shock, patients undergoing continuous ambulant peritoneal dialysis/patients on hemodialysis, unstable patients, acute coronary syndrome, and chronic obstructive pulmonary disease (COPD), patients requiring mechanical ventilation use of intravenous inotropes or vasopressors, renal dialysis. Dyspnea is primarily due to non-cardiac causes. Scheduled or recent percutaneous or surgical coronary intervention within 30 days. Patients already hospitalized for AHF triggered by an acute myocardial infarction or pulmonary embolism)). Signs of ketoacidosis and/or hyperosmolar hyperglycemic syndrome in pregnant or nursing (lactating) women, heart failure due to drug toxicity, severe kidney disease with a glomerular filtration rate (GFR) below 30 ml/min/1.73 m², child-Pugh class C liver failure, and severe valvular heart disease.

c) Evaluation of Symptoms of Dyspnea Using the Visual Analog Scale (VAS): Patient Global Assessment (PGA) and Dyspnea

Patients were instructed to self-assess their overall well-being and level of dyspnea using the visual analog scale method. For the patient global assessment, they indicated their overall well-being on a vertical 10-centimeter line, with the top labeled as "best you have ever felt" and the bottom as "worst you have ever felt." For dyspnea, the top label was "I am not breathless at all" and the bottom was "I am as breathless as I have ever been." The VAS scores were quantified on a scale from 0 to 100 by measuring A perspective distance in millimeters from the bottom of the line. Patients self-assessed both PGA and dyspnea at admission, and then again at 24, 48, 72, and 96 hours [17].

The SA-NYHA CLASS: ((SA-NYHA))

The New York Heart Association (NYHA) classification is the widely adopted system for describing the effects of heart failure on a patient's daily life. Initially developed in 1928 and later updated, this classification divides heart failure patients into 4 categories (I, II, III, and IV), with higher classes signifying more severe symptoms, greater limitations in physical activity, and poorer health status. Clinicians determine the NYHA class based on their indirect assessment of patients' reported symptoms, medical histories, and clinical test results related to cardiac structure and function [18]. Patients were asked to self-assign to one of the four Self-Assigned NYHA (SA-NYHA) classes. If patients could not do so, usually due to poor health or cognitive function, this inability was noted, and assistance was provided by either a researcher or a caregiver/relative. The questionnaire used for this self-assessment is structured with SA-NYHA Class I at the top and Class IV at the bottom [19].

d) Statistical Analysis

The results of the experiment were presented as mean ± standard deviations, or mean ± SD. T- test was employed to compare parameters among the several groups under analysis. $P < 0.05$ indicated statistical significance for the P values. The correlation between the various parameters in each patient group was tested using the person correlation coefficient (r). Receiver operating characteristic (ROC) curve analysis was also employed

III. Results and Discussion

Table (1) showed (SpO_2 , HR , blood pressure, and EF) of all participants in both groups A and B . There was no significant difference in SpO_2 at admission between patients in groups A and B while, there was significant (P=0.003) elevation in SpO_2 during 4th day of admission for groups A & B compared with at admission (group A: 91.21±2.50 vs, 87.86±3.96; group B: 94.82±2.62 vs, 87.68±2.84). At the same time, 40% of patients in group B had $SpO_2 > 95$ during the 4th day of admission, which was significantly higher (p-0.007) compared to patients in group A (14%). At admission (HR) was (102.68 ±6.86, 104.30±8.72) in both groups A &B respectively. There was significant (P-0.000) reduction in HR of patients on the 4th day of admission in both groups (A & B) as compared to their values at hospital admission (group A: 87.58±6.05 vs, 102.68 ±6.86 ; group B: 82.64±4.42 vs, 104.30±8.72). Additionally, the HR of patients in group B during 4th day of hospital admission was significantly (P=0.028) lower compared to patients during 4th day of admission in group A ((82.64±4.42 vs, 87.58±6.05)). Regarding blood pressure there was significant (P=0.041) reduction in SBP and DBP of group B patients during 4th day compared to their values at hospital admission. In the same mannar, patients in group A showed significant reduction in SBP and DBP on 4th day of admission compared with their values at admission.

In patients with well-managed diabetes, the diuretic and natriuretic effects brought about by SGLT2 inhibitors are less prominent due to decreased glycosuria when compared to patients with poorly managed diabetes. Nonetheless, studies have demonstrated that the blood pressure-lowering effect of SGLT2 inhibitors remains consistent in individuals with type 2 diabetes and chronic kidney disease, although the impact on glycaemia control is less significant [20]. This implies that the reduction in blood pressure is not directly dependent on glycosuria, which is the primary mechanism of action for SGLT2 inhibitors. This indicates that other mechanisms must be contributing to the observed decrease in systolic blood pressure, both in the short and long term. Consequently, it can be inferred that in patients with well-controlled diabetes, natriuresis is not a major factor in the blood pressure-lowering effect of dapagliflozin, either initially or over time. There is a reduction in angiotensinogen and angiotensin II levels, which is consistent with the suppression of a strong vasoconstrictor system and may assist in arterial vasodilation, leading to lower systolic blood pressure. Furthermore, angiotensinogen may influence adiposity and liver fat [21], which could contribute to weight loss, reduced visceral fat, and lowered hepatic fat, outcomes frequently observed with this treatment. In this study, while systolic blood pressure showed a tendency to decrease and heart rate significantly dropped in the SGLT2 inhibitor group, typically, heart rate would rise due to reduced high-pressure receptor loading in baroreceptors located in the aortic arch and carotid arteries. This unexpected observation could be explained by a potential resetting of the baroreflex induced by SGLT2 inhibitors [22].

Table (2) showed that dyspnea scales (Visual Analog Scale and Self-Assigned New York Heart Association) for patients in both groups A and B at hospital admission were significantly improved after subsequent days of admission. There was a significant reduction in the dyspnea scale (VAS and SA-NYHA) of patients 4th day of hospital admission as compared to the day of admission in both groups A & B. On the other hand, no significant difference was observed in dyspnea scale (VAS and SA-NYHA) of patients at hospital admission between groups A and B. However, dyspnea scale (VAS and SA-NYHA) of patients during 4th day of admission of group B was significantly lower compared with patients in group A during 4th day of admission.

Table (3) showed significant difference in 24 hours urine output and urinary sodium excretion after 6 hours from admission between both groups A & B patients. It was found patient in group B showed significantly higher (P=0.013) 24 hours urine output compared to group A patients. In the same mannar group B patient had significantly higher (P=0.004) urinary sodium excretion compared with group A patients. The administration of SGLT2 inhibitors alongside loop diuretics resulted in a significant increase in urinary sodium excretion and urine volume. In this study, group B exhibited a notably higher urinary sodium excretion than group A. SGLT2 inhibitors act on a different target site than loop diuretics and thiazides, inhibiting the co-transport of glucose and sodium from the proximal tubule lumen to the bloodstream.

In 2020, Petrie et al. evaluated the effects of dapagliflozin in patients with HFrEF with and without diabetes, where 10 mg of dapagliflozin or a placebo was added to the recommended therapy once daily. They concluded that dapagliflozin significantly reduced the risk of worsening HF or CV death independently of diabetes status [22]. 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 and diabetic rats [23].

Table (1): Some clinical features of participants at hospital admission and during the 4th day of admission.

Parameters		Group A	Group B	P-value
SpO_2 (Mean ±SD)	At admission	87.86±3.96	87.68±2.84	0.086
	At 4th day	91.21±2.50	94.82±2.62	0.007*a
	P-value	0.003*	0.007*	
Heart rate (beat/minute) Mean±SD	At admission	102.68±6.86	104.30±8.72	0.079
	At 4th day	87.58±6.05	82.64±4.42	0.028*a
	P-value	0.037*	0.000 *	
SBP Mean±SD	At admission	141.20±26.48	151.53 ±18.95	0.007*a
	At 4th day	125.18±15.16	131.18±15.58	0.068
	P-value	0.029*	0.041*	
DBP Mean±SD	At admission	76.71±8.80	76.79 ± 8.49	0.081
	At 4th day	72.00±5.79	73.59±6.38	0.104
	P-value	0.005 *	0.041*	
EF Mean ±SD	At admission	36.56±4.45	32.27±3.56	0.004

Table (2): Assessment of dyspnea of participants at hospital admission and during 4th day of admission

Parameters		Group A	Group B	P-value
VAS Scale	At admission	90.40	91.30	0.005
	2nd day	71.30	63.44	0.009
	3rd day	39.10	31.40	0.001
	4th day	15.20	11.00	0.34
	p-value	0.004	0.001	
SA-NYHA	At admission	3.96	3.90	0.045
	2nd day	3.17	2.98	0.011
	3rd day	1.90	1.84	0.48
	4th day	1.18	1.12	0.059
	P-value	0.008	0.006	

Table (3): Assessment of urine output (U.O.P) and urinary sodium excretion(UNa excretion) of participant

	Group A (Mean ±SD)	Group B (Mean ±SD)	P-value
U.O.P (ml)	2893.00±320.39	4113.8±304.20	0.013
U_{Na} excretion (ml)	104.58±15.35	115.76±12.46	0.004

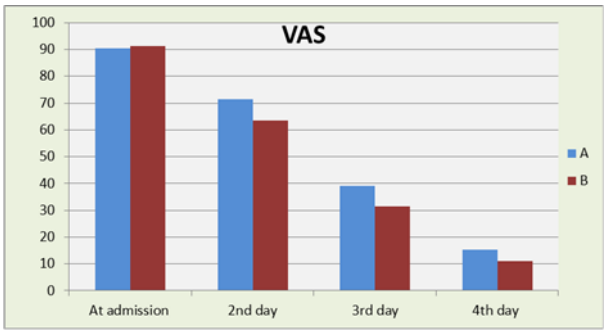

Fig.1Visual analog scale.

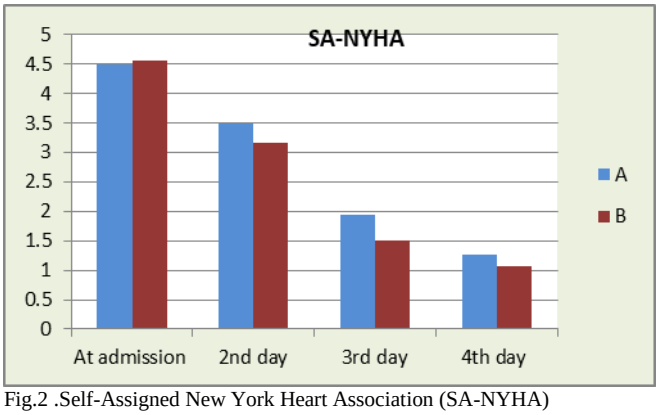

Fig.2 .Self-Assigned New York Heart Association (SA-NYHA)

IV. Conclusions

Initiation of dapagliflozin early during ADHF hospitalization among patients with diabetes may facilitate both decongestion and optimization of chronic HF medical therapies. The study shows that dapagliflozin reduces HHF in a broad spectrum of T2DM patients admitted with ADHF.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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