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Effect of dapagliflozin on serum N-terminal fragment-proB-type natriuretic peptide level in patient with acute decompensated heart failure

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Aim. HF is a complex clinical syndrome that manifests with symptoms such as dyspnea (shortness of breath) and fatigue. It can arise from various conditions that impact ventricular filling (diastolic dysfunction) or myocardial contractility (systolic dysfunction). Additionally, clinical signs like pulmonary rales, peripheral edema, or distended jugular veins may be present. The aim of the present study was to observe the possible effect of dapagliflozin on serum NT-proBNP level in ADHF and its relationship with weight.

Material and methods. Between October 2023 and April 2024, a study was conducted at AL-Nassiriyah Heart Center, in the coronary care unit (CCU), in Thi-Qar city southern of Iraq. One hundred subjects both males and females were enrolled in 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: Control group (Group A) involved (50 patients), given intravenous (iv) furosemide (120 mg/day) and Studied group (Group B) involved (50 patients), given iv furosemide (120 mg/day) plus 10 mg dapagliflozin tablet daily.

Results. It was found a significant reduction in body weight and BMI of patients during 4th day of hospital admission compared with days of admission in both groups (A&B). However, body weight and BMI of group B patients during 4th day of hospital admission were significantly lower compared to 4th day of admission in group A. Serum NT-proBNP during 4th day of admission in group B patients during 4th day of admission were significantly lower compared to group A patients during 4th day of admission. It was found that dapagliflozin, compared with control, reduced NT-proBNP levels in patients with HFrEF.

Conclusion. Dapagliflozin reduced the risk of worsening HF events and cardiovascular death, and improved symptoms, across the spectrum of baseline NT-proBNP levels. Also, it was confirmed the strong association between higher NT-proBNP levels and worse outcomes in HFrEF. Because body weight and NT-proBNP were decreased at 4th day of drug treatment, fluid loss must have been induced at the same time. The present study has reported a positive effect of dapagliflozin to reduce level of NT-proBNP and weight in patient with ADHF.

Keywords: dapagliflozin, acute decompensated heart failure, pro-BNP, weight.

Relationships and Activities: none.

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Влияние дапаглифлозина на уровень сывороточного N-концевого промозгового натрийуретического пептида у пациента с острой декомпенсированной сердечной недостаточностью

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Цель. Сердечная недостаточность (СН) — это сложный клинический синдром, проявляющийся такими симптомами, как одышка и утомляемость. Его причиной развития могут быть различные состояния, которые влияют на наполнение желудочков (диастолическая дисфункция) или сократимость миокарда (систолическая дисфункция). Кроме того, могут присутствовать такие клинические признаки, как хрипы в легких, периферические отеки или расширение яремных вен. Целью настоящего исследования была оценка влияния дапаглифлозина на уровень сывороточного N-концевого промозгового натрийуретического пептида (NT-proBNP) при острой декомпенсированной СН (ОДСН) и его связь с массой тела.

Материал и методы. Исследование проводилось в период с октября 2023г по апрель 2024г на базе кардиологического центра Эн-Насирии (Ди-Кар, Ирак) в условиях отделения коронарной терапии. 100 пациентов, как мужчин, так и женщин, были включены в исследование после описания целей исследования, оценки удовлетворенности пациентов и получения информированного согласия. 100 пациентов, включенных в исследование, были разделены

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на две группы: контрольная группа (группа А) — 50 пациентов, которым вводили внутривенно фуросемид (120 мг/сут.), и исследуемая группа (группа В) — 50 пациентов, которые получали фуросемид внутривенно (120 мг/сут.) в сочетании с дапаглифлозином внутрь (10 мг) ежедневно.

Результаты. Было обнаружено значительное снижение массы тела и индекса массы тела (ИМТ) пациентов на 4-й день госпитализации по сравнению с днем поступления в обеих группах (А и В). Однако масса тела и ИМТ пациентов группы В на 4-й день госпитализации были значительно ниже по сравнению с 4-м днем госпитализации в группе А. На 4-й день госпитализации уровень NT-proBNP в сыворотке крови у пациентов группы В был значительно ниже по сравнению с пациентами группы А. Было обнаружено, что дапаглифлозин, по сравнению с контрольной группой, снижал уровень NT-proBNP у пациентов с СН с низкой фракцией выброса (СНнФВ).

Заключение. Дапаглифлозин снижал риск событий, ассоциированных с СН, и риск сердечно-сосудистой смерти, а также улучшал симптомы по всему спектру исходных уровней NT-proBNP. Также была подтверждена сильная ассоциация между более высокими уровнями NT-proBNP и худшими исходами при СНнФВ. Поскольку масса тела и NT-proBNP снижались на 4-й день терапии, потеря жидкости происходила в то же время. Настоящее исследование показало положительный эффект дапаглифлозина на снижение уровня NT-proBNP и веса у пациентов с ОДСН.

Ключевые слова: дапаглифлозин, острая декомпенсированная сердечная недостаточность, pro-BNP, масса тела.

Отношения и деятельность: нет.

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ABP — Amyloid-β Peptides, ACE Inhibition — Angiotensin-Converting Enzyme Inhibitors, ADHF — Acute Decompensated Heart Failure, ANP — Atrial Natriuretic Peptide, AT1 Receptor Antagonist — Angiotensin II Type 1 Receptor, BNP — Brain Natriuretic Peptide, Cat. No. — catalogue number, CCU — Coronary Care Unit, CD — Standard Deviation, cGMP — cyclic Guanosine Mono Phosphate, CNP — C-Type Natriuretic Peptide, DBP — Diastolic Blood Pressure, DNP — Dendroaspis Natriuretic Peptide, EF — Ejection Fraction, ESC — European Society of Cardiology, GFR — Glomerular Filtration Rate, Group A — iv Furosemide, Group B — iv Furosemide plus dapagliflozin, HF — Heart Failure, HFpEF — Heart Failure with Normal or Preserved Left Ventricular Ejection Fraction, HFrEF — Heart Failure with Reduced Ejection Fraction, HR — Heart Rate, iv — intravenous, Kg — kilogram, LV — Left Ventricle, LVEF — Left Ventricle Ejection Fraction, mg/dL — milligram per deciliter, NEP — Neutral Endopeptidase, NPR-A — Natriuretic Peptide Receptors A, NPR-B — Natriuretic Peptide Receptors B, NPR-C — Natriuretic Peptide Receptors C, NT-proBNP — N-terminal-natriuretic propeptide, pg/ml — picograms per milliliter, r — Correlation Coefficient, SpO_2 — Oxygen Saturation, SBP — Systolic Blood Pressure, UPT — Up-converting Phosphor Technology, vs — versus, % — Percentage.

Ключевые моменты

Что известно о предмете исследования?

- Начало приема дапаглифлозина на ранней стадии госпитализации с острой декомпенсированной сердечной недостаточностью (ОДСН) у пациентов с диабетом может способствовать как снятию отечности, так и оптимизации медикаментозной терапии хронической сердечной недостаточности (ХСН). Исследование показывает, что дапаглифлозин снижает ХСН у широкого спектра пациентов с сахарным диабетом 2 типа (СД2), поступивших с ОДСН.

Что добавляют результаты исследования?

- Это исследование пришло к выводу о значительном снижении массы тела, одышки и увеличении SpO_2 на 4-й день сочетанного применения фуросемида внутривенно и дапаглифлозина внутрь против только фуросемида внутривенно.
- Это исследование показало эффективность препаратов по снижению уровня NT-proBNP на 4-й день госпитализации.
- Исследование показало повышение уровня мочевины и креатинина на 4-й день госпитализации.

Key messages

What is already known about the subject?

- Initiation of dapagliflozin early in the course of an acute decompensated heart failure (ADHF) hospitalization among patients with diabetes may facilitate both decongestion and optimization of chronic heart failure (HF) medical therapies. The study shows that dapagliflozin reduces HF in broad spectrum of type 2 diabetes mellitus (T2DM) patients admitted with ADHF.

What might this study add?

- This study concluded a significant reduction in body weight, dyspnea scale, and increase in the SpO_2 at 4^{th} day of admission of intravenous (iv) Furosemide plus dapagliflozin and iv Furosemide only.
- This study showed the effectiveness of drugs on reduction of N-terminal fragment of brain natriuretic propeptide (NT-proBNP) level at 4^{th} day of admission.
- The study demonstrated increase urea and creatinine levels at 4^{th} day of admission.

Introduction

Heart failure (HF) is a complex clinical syndrome that manifests with symptoms such as dyspnea (shortness of breath) and fatigue. It can arise from various conditions that impact ventricular filling (diastolic dysfunction) or myocardial contractility (systolic dysfunction). Additionally, clinical signs like pulmonary rales, peripheral edema, or distended jugular veins may be present [1].

Acute decompensated heart failure (ADHF) is a potentially life-threatening condition characterized by worsening of HF symptoms, necessitating urgent evaluation and escalation of treatment, often requiring hospital admission [2].

Additional respiratory symptoms may consist of orthopnea, paroxysmal nocturnal dyspnea, rapid breathing, and coughing [3]. Fluid retention can cause pulmonary congestion and swelling in the extremities. Other non-specific symptoms may involve weakness, nocturia, hemoptysis, abdominal discomfort, loss of appetite, nausea, bloating, fluid accumulation in the abdomen (ascites), altered mental status, and weight gain [4]. Weakness, fatigue, and bluish discoloration of the skin result from reduced cardiac output and compromised tissue blood flow. Incomplete emptying of the left ventricle can lead to pulmonary congestion [5], causing breathlessness, a cough, crackling sounds in the lungs, fluid accumulation around the lungs (pleural effusions), and low blood oxygen levels.

These symptoms worsen when lying down [6], with orthopnea often measured by the number of pillows needed for comfort. Enlarged heart size and abnormal pulsations on the chest may be observed on a chest X-ray, along with an S3 gallop rhythm indicating poor heart function [7]. Tachycardia (rapid heart rate) is driven by increased sympathetic activity, while weight gain and edema result from fluid retention due to reduced kidney function. Nocturia is increased urination at night due to improved kidney function when lying down [8]. Physical examinations may reveal crackles in the lungs, rapid heartbeat, swelling in the legs, distended neck veins, liver enlargement, and signs of fluid backup in the liver [9].

Natriuretic peptide system, used to diagnosis heart failure, composed of five similar peptides: atrial natriuretic peptide (ANP), urodilatin (a variant of ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP) [10]. ANP, a 28-amino acid hormone, is primarily produced in the cardiac atria, while BNP, a 32-amino acid peptide initially found in the brain, is mainly produced in the cardiac ventricles. Both ANP and BNP are released in response to increased cardiac wall tension, with various factors like neurohormones and physiological factors contributing to their regulation [11]. BNP and NT-proBNP are considered the gold standard biomarkers in the diagnosis and prognosis of HF and may play a role in HF management. Natriuretic peptides should be measured in all patients with symptoms suggestive of HF, to facilitate early diagnosis and risk stratification. For chronic HF, natriuretic peptides are reasonable surrogates for intracardiac volumes and filling pressures but should always be used in conjunction with clinical information [12, 13]. BNP is produced by the ventricles in an inactive form which undergoes enzymatic cleavage to proBNP and further broken down to active BNP and inactive NT-proBNP. Compared with BNP, NT-proBNP is a more stable marker of intravascular congestion and left ventricular dysfunction due to its longer half-life (BNP: 20 min; NT-proBNP: 90 min) and its plasma concentrations are unaffected by neprilysin inhibition with sacubitril [12].

CNP is primarily located in blood vessels. Natriuretic peptides stimulate cyclic guanosine monophosphate (cGMP) production by binding to natriuretic peptide receptors A (NPR-A) and B (NPR-B), leading to natriuresis, vasorelaxation, and other effects [12, 13].

The natriuretic peptides are broken down through NPR-C-mediated internalization followed by lysosomal degradation and enzymatic degradation by neutral endopeptidase (NEP), which is expressed in various tissues. NEP is found in tissues such as the endothelium, muscle cells, kidney tubules, and nerve cells [14]. NEP also plays a crucial role in clearing amyloid peptides in the brain, particularly amyloid-beta peptides (Aβ), linked to Alzheimer's disease[1]. NEP inhibition to preserve natriuretic peptides was explored for heart failure therapy. While omapatrilat showed no added benefit over ACE inhibition alone, a combined AT1 receptor antagonist and neprilysin inhibitor (valsartan/sacubitril, LCZ696) demonstrated positive outcomes for heart failure patients [15].

This study aimed to determine the effect of dapagliflozin on serum NT-proBNP level in ADHF and its relationship with weight.

Material and methods

Study design and setting. A prospective Interventional study was done in AL-Nassiriyah Heart Center between October 2023 and April 2024, a study was conducted at AL-Nassiriyah Heart Center, in the coronary care unit (CCU), in Thi-Qar city southern of Iraq. One hundred subjects both males and females were enrolled in study after describing the study's goals, gauging patient satisfaction, and getting informed consent from the subjects.

Inclusion criteria

1. Study enrolled patients aged ⩾18 years who were hospitalized within 24 hours for hypervolemic acute decompensated HF (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 HF (respiratory discomfort or orthopnea); At least one clinical sign of HF (peripheral edema, engorged jugular vein, 5-pound weight gain, or pulmonary congestion on chest x-ray or lung ultrasound).
2. An estimated glomerular filtration rate (eGFR) of no <30 ml/min/1.73 m^2, determined using the Modification of Diet in Renal Disease (MDRD) formula.
3. History of type II diabetes.

Exclusion criteria

1. Type 1 diabetes mellitus.
2. Cardiogenic shock.
3. Patients undergoing continuous ambulant peritoneal dialysis/patients on hemodialysis.

[1] Fagerheim S. Natriuretic peptides as therapeutic agents: Project thesis. Candidate no.: 2144. https://www.duo.uio.no/handle/10852/68262 (23 June 2019).

4. Unstable patients; acute coronary syndrome, chronic obstructive pulmonary disease (COPD), patients requiring mechanical ventilation; use of intravenous inotropes or vasopressors.

5. Dyspnea primarily due to non-cardiac causes.

6. Scheduled or recent percutaneous or surgical coronary intervention within 30 days (patients already hospitalized for ADHF triggered by an acute myocardial infarction or pulmonary embolism).

7. Signs of ketoacidosis and/or hyperosmolar hyperglycemic syndrome.

8. Pregnant or nursing (lactating) women.

9. HF due to drug toxicity.

10. Severe kidney disease with a glomerular filtration rate (GFR) below 30 ml/min/1.73 m^2.

11. Child-Pugh class C liver failure.

12. Severe valvular heart disease.

Participants and studied groups. Study enrolled (118) (type II) diabetic patients who were admitted to cardiac care unit for hypervolemic ADHF with evidence of congestion, had left ventricular ejection fraction (LVEF) 40% or below. All patients were diagnosis by a specialist cardiologist based on the European Society of Cardiology (ESC), 18 patients were excluded because they didn't meet inclusion criteria. 100 enrolled patients were divided into two group:

• Control group (Group A) involved (50patients), given iv furosemide (120 mg/day).

• Studied group (Group B) involved (50patients), given iv furosemide (120 mg/day) plus 10 mg dapagliflozin tablet daily.

Blood samples (5 ml each) were collected from each subject at admission and at 4th day from admission using gel tube, were centrifuged to obtain serum. Then serum refrigerated at -40 ºC for further using to determine serum NT-proBNP and other biochemical parameters.

Determination of serum NT-proBNP. The kit (Hotgen Biotech Company, Tangpu (Beijing) Technology Co., Ltd, China) employs a combination of Up-converting Phosphor Technology (UPT) with sandwich immunochromatography. The reaction zone (T band) on the NC membrane of the test cassette is coated with NT-proBNP antibody while the control zone (C band) is coated with goat anti mouse antibody. When diluted sample containing NT-proBNP is added to the sample cavity on the test cassette, capillary effect causes the fluid to flow to the other end. During the migration, NT-proBNP in the sample first binds to NT-proBNP antibody coated on the Up-Converting Phosphor (UCP) nanoparticles, then binds to the NT-proBNP antibody immobilized on the T line, forming antibody-antigen-antibody-UCP complex, and the rest UCP nanoparticles flows forward and binds to the goat anti-mouse antibody on the C line, forming secondary antibody-antibody-UCP complex. UCP particles emit visible light when excited by infrared source. The intensity of the emission from the UCP particles at the T line and C line are measured simultaneously and the ratio (T/C) of the emission intensity is proportional to the NT-proBNP concentration in the sample. NT-proBNP concentration is automatically calculated by reference to a calibration curve stored in the UPT system and displayed on the screen of the instrument. The procedure done according to company manufacture directions. The kit used was Cardiac Rapid Test Kit (Beijing Hotgen Biotech Co., Ltd, China; Cat. No. C2880709).

Determination of Serum Potassium. Sodium tetra phenyl boron reacts with potassium ions in a protein free alkaline medium to produce a turbid suspension of potassium tetra phenyl boron. The amount of turbidity produced is proportional to the potassium concentration. The kit used was Randox Potassium (Colorimetric & UV) kit (Randox, France; Cat. No. PT3852).

Determination of Serum Sodium. The present method is based on reaction of sodium with a selective chromogen producing a chromophore whose absorbance varies directly as the concentration of sodium in the test specimen. The kit used was Randox Sodium (Enzymatic) kit (Randox, France; Cat. No. NA3851).

Determination of Urinary Sodium Excretion. Sodium was measured using ion-selective electrodes utilizing an indirect (diluted) method where urine samples are automatically diluted at 1:46 ratio (standard range) or 1:31 (under range) using ISE diluent. The electrodes of (Sodium) have a membrane with an open liquid junction that is ion-selective. The reference electrode uses the same design of the ion-electrode and it is exclusively used as a reference for every measurement. The difference of all voltages between the reference electrode and any ion-selective electrode is a measure for the concentration of individual ion. For every test, the voltages of both ISE internal standard and diluted sample solution is measured for type of ion (Sodium). The resulting voltages are converted into operator readable results. The kit used was ISE SODIUM ELECTR. cobas c 111 system kit (Roche, Germany; Cat. No. 04838084001).

Determination of serum Urea. Urea in serum is hydrolysed to ammonia in the presence of urease. The ammonia is then measured photometrically by Berthelot's reaction. The kit used was Randox Urea (Kinetic) kit (Randox, France; Cat. No. UR446).

Determination of serum Creatinine. Creatinine in alkaline solution reacts with picric acid to form a colored complex. The amount of the complex formed is directly proportional to the creatinine concentration. The kit used was Randox Jaffe Creatinine Assay kit (Randox, France; Cat. No. CR510).

Basic medications and therapy included: Piozex (Furosemide) Ampule 20 mg/2 ml (Pioneer) and Exorena (Dapagliflozin) Film-Coated Caplet 10 mg (Sama-Alfayhaa/Basrah-Iraq). Other included: Anti-Lipid: Atorvastatin tablet 40 mg 1×1, ACEI: Lisinopril tablet 10 mg 1×1, Beta blockers: Bisoprolol tablet 5 mg 1×1, Anticoagulant: Heparin vial 1cc ×4, Antiplatelet: Aspirin tablet 100 mg 1×1 and Plavix tablet 75 mg 1×1, in addition to Lansoprazole capsule 30 mg 1×2, Aldactone tablet 25 mg, Cordarone tablet 200 mg 1×1 and Oral antidiabetic (Amaryl 4 mg 1×1, Glucophage 500 mg 1×2, Diamicron 60 mg 1×1, Meligamet tablet 50/1000 mg 1×1).

Ethical approval. A research proposal explaining the goal of the study and data collection methods was presented to the university committee in accordance with the standards of the division of graduate studies in the College of Pharmacy/University of Basrah. The present study's proposal was approved and sent to ThiQar Health Department's Committee. The mentioned center's ethical approval committee gave their approval (EC57 at 01/06/2023).

Statistical Analysis. The statistical analysis was done using SPSS v 23 the results were expressed as mean ± standard deviation (mean ± SD). Data expressed as n (%) compared by using analyzed Chi-square analysis. It was used t-test to compare study groups. Pearson's correlation was applied to determine the relationship among the present study parameters. P-values ($p<0.05$) were considered statistically significant.

Table 1

Demographic characteristics of participants

Parameters	Group A, n (%)	Group B, n (%)	p-value
Sex			
Male	24 (48)	26 (52)	0.321
Female	26 (52)	24 (48)	
Age Distribution (years)			
20-29 years	5 (10)	3 (6)	0.004
30-39 years	7 (14)	5 (10)	
40-49 years	8 (16)	8 (16)	
50-59 years	8 (16)	11 (22)	
60-69 years	9 (18)	10 (20)	
>70 years	13 (26)	13 (26)	
Mean±SD	60.04±15.01	59.12±15.59	0.138
Range	20-82	20-82	
Smoker			
Smoker	15 (30)	18 (36)	0.005
Nonsmoker	35 (70)	32 (64)	
Duration of disease			
1-5 years	38 (76)	40 (80)	0.006
6-10 years	12 (24)	10 (20)	

Note: The p-value is statistically significant at the 0.05 level; Data denoted as Mean±Standard Deviation.

Table 2

Assessment of body weight and body mass index of participants

Parameters		Group A	Group B	p-value
Wight (Kg) (Mean±SD)	At admission	81.40±12.13	81.56±9.56	0.092
	At 4th day	79.56±12.07	78.58±4.17	0.032*^{a}
	P-value	0.008*	0.029*	
BMI (Kg/m^2) (Mean±SD)	At admission	29.08±4.45	29.58±4.54	0.067
	At 4th day	28.42±4.47	27.29±3.21	0.026*^{a}
	P-value	0.004*	0.006*	

Note: The p-value is statistically significant at the 0.05 level; * — significant compared at admission to group at 4th day; *^{a} — significant compared A to B admission to hospital; Data denoted as Mean±Standard Deviation; BMI — Body mass index; Kg — Kilogram; Kg/m^2 — Kilogram per square meter.

Table 3

Assessment of serum NT-proBNP concentration of participants

		Group A	Group B	p-value
proBNP (pg/ml) (Mean±SD)	At admission	5907.32±1400.00	6448.00±1686.00	0.083
	At 4th day	3758.00±924.18	3360.00±1172.00	0.004*^{a}
	P-value	0.007*	0.002*	

Note: The p-value is statistically significant at the 0.05 level; * — significant compared at admission to group at 4th day; *^{a} — significant compared A to B admission to hospital; Data denoted as Mean±Standard Deviation; NT-proBNP — N-terminal fragment of brain natriuretic propeptide; pg/ml — picograms per milliliter.

Results

The description of investigated group was shown in (Table 1) 100 patients with ADHF were enrolled in the study 50 patients were treated with iv Furosemide (group A) 24 (48%) of them were males and the remaining 26 (52%) were females while, other 50 patients treated with iv Furosemide plus dapagliflozin (group B) 26 (52%) males while, other 24 (48%) females. Age distribution among participants showed that 26% of the patients in the both groups (A and B) and age groups more than 70 years, whereas patients younger than 30 years represent 10%, 6% in groups (A & B) respectively listed in (Table 1).

Table 2 showed significant reduction in body weight and BMI of patients during 4th day of hospital admission compared with days of admission in both groups (A and B) (group A: 79.56±12.07 vs 81.40±12.13; group B: 78.58±4.17 vs 81.56±9.56).

Table 4

Some clinical features of participants at hospital admission and during 4th day of admission

Parameter		Group A (Mean±SD)	Group B (Mean±SD)	p-value
SpO_2	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)	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*	0.001*	
SBP	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	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	At admission	36.56±4.45	32.27±3.56	0.004

Note: The p-value is statistically significant at the 0.05 level; * — significant compared at admission to group at 4th day, *a — significant compared A to B admission to hospital; Data denoted as Mean±Standard Deviation; SpO_2 — Oxygen Saturation, SBP — Systolic Blood Pressure, DBP — Diastolic Blood Pressure, EF — Ejection Fraction.

Table 5

Assessment of serum urea concentration of participants

		Group A	Group B	p-value
Urea (mg/dL) (Mean±SD)	At admission	48.08±14.88	41.48±5.93	0.006*a
	At 4th day	56.20±8.10	50.62±7.21	0.023*a
	p-value	0.000*	0.018*	

Note: The p-value is statistically significant at the 0.05 level; * — significant compared at admission to group at 4th day, *a — significant compared A to B admission to hospital; Data denoted as Mean±Standard Deviation; mg/dL — milligram per deciliter.

Table 6

Assessment of serum creatinine concentration of participants

		Group A	Group B	p-value
Creatinine (mg/dL) (Mean±SD)	At admission	0.87±0.12	0.96±0.14	0.021*a
	At 4th day	0.98±0.21	1.21±0.23	0.038*a
	P-value	0.013*	0.022*	

Note: The p-value is statistically significant at the 0.05 level; * — significant compared at admission to group at 4th day, *a — significant compared A to B admission to hospital; Data denoted as Mean±Standard Deviation; mg/dL — milligram per deciliter.

Table 3 showed no significant difference in serum NT-proBNP concentration at day of admission between groups (A and B) while both groups (A and B) showed significant reduction in serum NT-proBNP concentration during 4th day of admission.

Results in Figure 1 showed that patients display a positive correlation body weight with serum concentration of NT-proBNP in both groups (A and B) (r=0.38, p=0.048; r=0.46, p=0.003) respectively.

Some Clinical Features of Participants at Hospital Admission and During 4th day of admission: Table 4 showed (SpO_2, HR, blood pressure and EF) of all participants in both groups (A and B). There was no significant difference between the mean SpO_2 at admission, while there was significant elevation (p=0.007) between the mean of SpO_2 during 4th day in groups (A) and group (B). At the same time 40% of patients in group B had SpO_2 >95 during 4th day (p=0.007) compared to patient in group A (14%).

There was significant reduction in HR of patients at 4th day of admission in both groups (A and B) as compared to their mean at hospital admission.

Regarding blood pressure, there was significant (p=0.041) reduction in systolic BP and diastolic BP of group B during 4th day compared to their values at hospital admission. In the same manner patients in group A showed significant reduction in systolic BP and diastolic BP during 4th day of admission compared with their values at admission. While, there was significant difference in EF between groups A and B.

Table 5 showed that serum urea concentrations in groups (A) were significantly higher on the day of hospital admission and on the fourth day of hospitalization than in groups (B). Additionally, the

blood urea concentrations of both groups (A and B) demonstrated a significant rise on the fourth day of admission as comparison to the day of admission (group B: 50.62±7.21 vs 41.48±5.93, p=0.018; group A: 56.20±8.10 vs 48.08±14.88, p<0.0001).

Table 6 showed that serum creatinine concentrations in groups (B) were significantly higher on the day of hospital admission and on the fourth day of hospitalization than in groups (A). At the same time both groups (A and B) showed significant elevation in serum urea concentration at 4th day of admission as compared to the day of admission (group A: 0.98±0.21 vs 0.87±0.12, p=0.013; group B: 1.21±0.23 vs 0.96±0.14, p=0.022).

Discussion

HF is a major health problem that affects both genders and it represents a leading cause of morbidity and mortality despite optimal medical and device treatment; deaths from HF account for 35% of the total cardiovascular disease mortality in women. Women represent approximately a quarter of people with HF with reduced ejection fraction (HFrEF), while they account for over half of those with HF with preserved EF (HFpEF) [16]. Women with HF showed typical demographic and clinical characteristics they were older, and had higher BMI, and systolic blood pressure. This pattern has consistently been reported in many studies as characteristic for women with HF. Women more frequently suffered from diabetes and had worse health-related quality of life. Among men, ischemic heart disease and myocardial infarctions were the main etiological factors for heart failure, which correspond to higher frequencies of pre-existing heart failure and more previous hospitalizations in men than in women [17]. For patients <55 years, the risk of either of these outcomes decreased with increasing age up to age 55. After 55 years of age, the risk for death or all-cause hospitalization, and death or HF hospitalization, increased with increasing age. The higher risk of hospitalization for any cause and non-cardiovascular hospitalization 30 days after discharge in older patients identified in this analysis is likely a reflection of the increased comorbidities within this age group [18].

There were no significant differences in body weight and BMI between groups (A and B) of patients at admission. However, body weight and BMI of group B patients during 4th day of admission where significantly lower compared to patient during 4th day of admission in group A.

It was found that dapagliflozin, compared with control, reduced NT-proBNP levels in patients with HFrEF. Dapagliflozin also reduced the risk of worsening HF events and cardiovascular death, and improved symptoms, across the spectrum of baseline NT-proBNP levels. Also, it was confirmed the strong association between higher NT-proBNP levels and

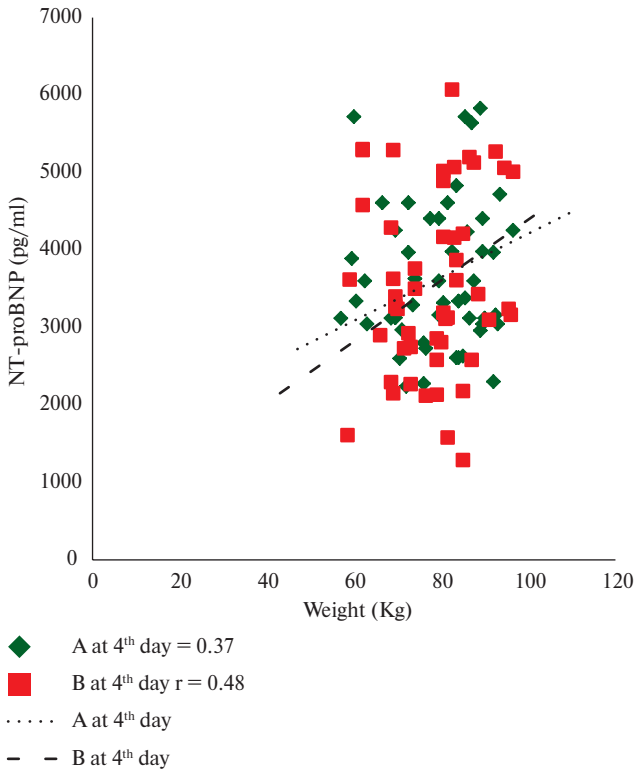

Figure 1 The correlation of weight with serum NT-proBNP.
Note: The p-value is statistically significant at the 0.05 level; r — correlation coefficient, A — iv Furosemide, B — iv Furosemide plus dapagliflozin, pg/ml — picograms per milliliter, Kg — kilogram.

worse outcomes in HFrEF. Because body weight and NT-proBNP were decreased at 4th day of drug treatment, fluid loss must have been induced at the same time. Importantly, fluid loss itself generally leads to neurohumoral activation. Consistently, plasma renin activity and plasma aldosterone concentration were increased in dapagliflozin group [19].

Limitations of the study. A larger cohort of patients is required to confirm the results of the current study. Guidelines recommend that patients should be euvolaemic at discharge, and the rationale for oral diuretic on discharge is to prevent recurrence of congestion. However, many patients leave the hospital with residual signs of congestion, and those who do are at greater risk of adverse outcomes. Achieving decongestion during admission and being "alive and well" at a specific time point after discharge are important outcomes for patients and clinicians. This may be achievable in a large pragmatic trial of adjuncts to diuretic therapy using a combination of established diuresis and decongestion endpoints at the point of discharge and a combination of hospitalization and mortality endpoints and quality of life (QoL).

Conclusion

The present study has reported a positive effect of dapagliflozin to reduce level of NT-proBNP and weight

in patient with ADHF. Dapagliflozin also reduced the risk of worsening HF events and cardiovascular death, and improved symptoms, across the spectrum of baseline NT-proBNP levels. Also, it was confirmed the strong association between higher NT-proBNP levels and worse outcomes in HFrEF. Because body weight and NT-proBNP were decreased at 4th day of drug treatment, fluid loss must have been induced at the same time. The present study has reported a positive effect of dapagliflozin to reduce level of pro-BNP and weight in patient with ADHF.

Relationships and Activities: none.

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