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Effect of Dapagliflozin on N-Terminal Prohormone of Brain Natriuretic Peptide and Some Biochemical Parameters in Patients with Heart Failure

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Abstract

The cardiovascular system benefits from dapagliflozin, a member of the class of hypoglycemia medications known as SGLT-2 inhibitors. The purpose of the current research is to compare the levels of NT-Pro BNP, creatinine, urea, K, and Na in patients to those in healthy individuals (controls). There were 150 participants in the research: 100 patients with Type 2 Diabetes Mellitus (T2DM) and heart failure (HF), and 50 controls. Based on age, the patients are split into two groups (40-70). Whereas the second group (B) just received Lasix, the first group (A) received both Lasix and dapagliflozin. Compared with the control group, group B's serum concentration of NT-Pro BNP, creatinine, and urea increased significantly ($p \leq 0.050$). Compared to controls, group B had a significant drop in serum Na concentration ($p \leq 0.05$). Serum concentrations of NT-Pro BNP, Creatinine, Urea, and Na in group B are not significantly different from those in group A at the time of admission. When compared to group A, group B exhibits significant differences in serum K concentration. Serum concentrations of NT-ProBNP, Creatinine, Urea, Potassium, and Sodium do not differ significantly between groups B and A at 7 days, according to the data. Additionally, in comparison with the day of baseline, the concentration of serum NT-pro-BNP in patients in groups B and A was significantly lower on the seventh day of baseline. Dapagliflozin works well to lower NT-Pro BNP levels and alleviate the symptoms of HF. It improves cardiac function, quality of life, and reduces fluid retention.

Keywords: Lasix, Dapagliflozin, Kidney Function Tests, NT-Pro BNP, Heart Failure.

Introduction

HF can be defined as a chronic disease where the heart is unable to pump blood to other organs effectively due to anomalies and changes in the hemodynamic, neurological, renal, and hormonal systems (1). Over a million hospital admissions annually in Europe and the US are attributed to the 26 million people globally who have HF. Although the results for ambulatory heart failure patients with a lower ejection fraction (EF) have improved with the development of several evidence-based medications as well as device regimens, hospitalized heart failure (HHF) patients continue to have an unacceptably high post-discharge death rate (2). Risk factors for cardiovascular disease (CVD) include high blood pressure, hyperglycemia, high cholesterol, and a high body mass index (BMI). Although the risk for CHD increases with age for both sexes, it was demonstrated that women's risk increases more than men's (3,4). CVD includes ischemic heart disease, peripheral arterial disease, HF, strokes, and several other cardiac and

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vascular illnesses (5,6). Major factors that raise mortality and morbidity rates worldwide include coronary artery disease (CAD) and type 2 diabetes.

Without the use of insulin, blood sugar levels are lowered by SGLT2 inhibitors, which are drugs with a unique mode of action (7). These medications are rapidly taking their position in the management of diabetes, particularly in light of recent research on their benefits and effectiveness. For patients with type 2 diabetes requiring additional glucose-lowering therapy and who have acceptable profiles for risk factors, SGLT2 inhibitors might be a viable alternative, especially in cases where they are unable or unwilling to start taking insulin (8,9). Inhibitors regarding the sodium-glucose cotransporter 2 (SGLT2), which increase urine excretion and lower levels of blood glucose through blocking the reabsorption of filtered glucose, were initially developed as therapy for type 2 diabetes. Dapagliflozin, an inhibitor of SGLT-2, was demonstrated to have positive effects on cardiovascular events like hypotension and cardiovascular death in patients with HF and T2DM, and a decreased risk of CVD. Dapagliflozin acts only on the kidneys, inhibiting glucose binding by attaching to the plasma membrane regarding proximal tubular cells that surround the glomeruli and binding to the external surface of functional SGLT-2 (10-13). In HF patients, diuretics are the main therapy for hypervolemia. Choosing the appropriate diuretic is essential for effective treatment, and this is primarily based on the clinical situation of the patient and the presence of additional co-morbidities (14). Among the several HF management strategies, diuretic medicine (Lasix) is commonly acknowledged as the main treatment for HF symptoms (15, 16). Lasix (furosemide), a strong diuretic, can be defined as a common prescription drug utilized for treating hypertension and edema (17). Lasix improves pulmonary congestion, relieves fluid overload symptoms, and lessens dyspnea. In conclusion, loop diuretics provide 2 main functions. They are responsible for maintaining normal body volume in patients with chronic HF and lessening pulmonary congestion in critically decompensated heart patients (18, 19). In hospitalized patients with HF, the study's objective has been to investigate the potential impact of dapagliflozin on serum NT-Pro BNP, creatinine, urea, and serum electrolytes (sodium and potassium).

Materials and Methods

Design of study

At the AL-Nasiriyah Heart Center and Biochemistry Lab in the College of Science/University of Thi-Qar, the presented study was carried out between September 2024 and March 2025 on 150 subjects, involving 50 controls, and 100 patients, as indicated in Table 1. The research was carried out on the total number of ostensibly healthy people and patients who were separated into:

Control group: included fifty (50) supposed healthy subjects [25 males and 25 females] with ages (30-70)

Group(A): included fifty (50) patients with type 2 diabetes and HF [22males and 28 females] with an age range of 40-70 years were received dapagliflozin and Lasix.

Group(B): included fifty (50) patients with type 2 diabetes and HF [24 males and 26 females] with an age range of 40-70 years, were received Lasix.

Inclusion

The study comprised patients who had HF and type 2 diabetes who were between the ages of 40 and 70. The control group was compared to them following seven days of Lasix and dapagliflozin treatment.

Exclusion

Patients with Gout, type 1 diabetes, breastfeeding, GFR≤30, Renal failure, arthritis diseases, and pregnant women have been excluded from this study.

Collection of a blood sample

The serum sample is separated as well as stored at a temperature of -20°C for future measurement regarding biochemical parameters, unless utilized immediately. Approximately 5 ml blood samples from HF/DM patients and controls have been taken, left to clot at room temperature in empty disposable tubes, followed by centrifugation in order to separate them at 3000 xg for 10min.

Statistical Analysis

The results of the statistical analyses have been represented in the form of (mean ±SD) with LSD with the use of SPSS version 15.0. The one-way ANOVA test has been utilized for examining the differences between the various research groups. A P-value has been deemed statistically significant if it is P≤0.050. The Student's t-test was utilized for comparing the means between groups.

Results and Discussion

The concentrations of NT-pro-BNP in patient groups have been much higher than in controls (p≤0.05). The serum NT-pro-BNP concentrations in patients in groups B and A at baseline didn't differ significantly, according to Table 3. On the seventh day of baseline, however, a significant difference in the serum NT-pro-BNP concentrations between groups B and A was discovered. Additionally, it was discovered that, on the seventh day of baseline, the concentrations of serum NT-pro-BNP in patients in groups B and A were significantly lower than on the first day of baseline. NT-pro BNP is employed for prognostic and diagnostic evaluations in HF (20). NT-pro BNP was elevated in HF patients (21). Through dapagliflozin therapy, the peptide level was significantly lower, which may have been caused by an increase in AMPK activation due to hypoglycemic drug exposure. According to some research, dapagliflozin could help with type 2 diabetes problems associated with CVD (22,23). Natriuretic peptides, which are the most frequently used biomarkers in mode run HF care, constitute one of the major risk factors for heart failure. Treatment with dapagliflozin was well tolerated and yielded superior outcomes in spite of the range of the concentrations of NT-proBNP (24). Dapagliflozin's effect on cardiac remodeling could account for the reduction in NT-proBNP, as SGLT2 inhibitors have the potential to reduce left ventricular mass (25). In comparison to control patients, dapagliflozin was found to reduce NT-proBNP levels. Dapagliflozin also alleviated symptoms and reduced the incidence of cardiovascular mortality as well as worsening HF events across the range of the baseline NT-proBNP levels (26). Poorer outcomes in HFrEF are highly correlated with higher NT-proBNP levels. Alongside the decrease in body weight and NT-proBNP brought on by pharmaceutical therapy, fluid loss had to have occurred. The presented research has demonstrated that dapagliflozin has a positive impact on NT-proBNP levels as well as weight in patients with HF (27).

When comparing the concentrations of urea in the patient groups to those of the controls, there is no significant difference (p≤0.05) between the two groups. Serum urea concentrations have been substantially higher in group A compared to group B at baseline and on the seventh day of hospitalization, according to Table 3. Additionally, compared to the day of admission, the urea concentrations in groups B and A showed a significant increase on the seventh day of admission. Because SGLT2i loop diuretics double block Henle's loop as well as the proximal tubules, they could have a complementary effect on diuresis when taken together. Since loop diuretics are used for treating most HF patients, SGLT2i might be helpful for DM patients who have HF. Generally speaking, compensatory mechanisms to preserve salt as well as fluid balance are triggered by the distal tubule's increased sodium input and the proximal tubule's suppression of sodium reabsorption (28). In the case when diuresis is increased and body fluid levels are decreased,

another process that is triggered to improve water retention is increased synthesis of copeptin, a surrogate vasopressin marker. Higher vasopressin production and/or higher glucosuria caused by volume contraction may be the cause of the reduction in free water clearance (28). In the case when medullary blood flow is decreased, diuretic effects that lower plasma volume are expected to cause the descending limb of Henle, which is sodium-impermeable, to extract more water. To maintain fluid balance, this boosts the sodium concentration and increases its passive reabsorption further along the ascending loop of Henle (29). Dapagliflozin reduces plasma volume as demonstrated by increases in osmotic as well as natriuretic diuresis, a reduction in the weight of the body and systolic blood pressure, and activation of the compensatory mechanisms previously discussed. Plasma volume shrinkage may be the cause of increases in blood urea concentrations (30, 31).

The concentration of creatinine in the patient groups has been significantly higher than the concentration in controls ($p \leq 0.05$) in Table 2. Serum creatinine concentration at baseline has not been significantly different between groups (B and A) of patients, according to Table 3. When comparing the seventh day of admission to the day of admission, the creatinine concentrations in the two groups (B and A) showed a significant increase. Lasix (furosemide) will raise the creatinine level. It must be noted that long-term diuretic treatment could overstress renal function, increase salt reabsorption, and raise creatinine levels (32). Dapagliflozin significantly decreased the risk of developing end-stage kidney disease, dying due to cardiovascular or renal causes, or experiencing a protracted decline in estimated GFR of at least 50% (33). Regardless of eGFR, it reliably reduces blood pressure, body weight, and the ratio of urine albumin to creatinine (34), showing a link between type 2 diabetes and measures of renal function. T2D patients have elevated levels of urea and creatinine (35).

Additionally, Table 2 demonstrates a significant drop in Na concentration in patient groups when compared with the controls ($p \leq 0.05$). The baseline serum Na concentrations in patients in groups B and A did not differ significantly, according to Table 3. On the seventh day of baseline, however, a significant difference in serum Na concentrations between groups B and A was discovered. Additionally, it was discovered that group A patients' serum Na concentration had significantly decreased on the seventh day of admission in comparison with the first day. According to the same data, patients in group B had a significantly higher serum Na level on the seventh day of baseline than on the first day. Through blocking the proximal convoluted tubule's ability to reabsorb glucose and salt, SGLT2i functions in the kidneys. The first glucosuria increases flow into the distal parts of the nephron and is associated with osmotic diuresis as well as natriuresis (36). To promote fluid excretion in ADHF cases, SGLT2i might be added to loop diuretics. Renal blood flow is improved, and effective intravascular volume is restored by its unique capacity for mobilizing fluid and salt from the interstitium into the vascular space. This might lead to improved renal perfusion and a decrease in renin secretion (37). Thus, the intravascular volume replenishment and interstitium action of SGLT2i could help treat hyponatraemia. Additionally, SGLT2i increases the amount of salt that reaches the macula densa, which lowers renin. Increased chloride transport to the macula densa affects volume homeostasis, lowers the plasma volume set point, and could influence the pathophysiology of hyponatremia in ADHF (38). Particularly in patients who had hyponatremia at randomization, dapagliflozin added to normal ADHF therapy increases blood sodium levels as well as shortens the duration of hyponatremia. This suggests that dapagliflozin might be a new way to treat ADHF

(38, 39). An electrolyte imbalance and a drop in intravascular volume might be associated with an osmotic diuresis caused by the increased excretion of glucose in the urine associated with SGLT2 inhibition. Thus, in the case when using SGLT2 inhibitor medication, patients with type 2 DM should be concerned about the likelihood of osmotic diuresis and its impact on the fluid or electrolyte balance (40).

The concentration of K in patient groups was much lower than the concentrations in the controls ($p \leq 0.05$) in Table 2. The serum K concentrations in patients in groups B and A at baseline did not differ significantly, according to Table 3. On the seventh day of baseline, however, a significant difference in serum K concentrations between groups B and A was discovered. Additionally, it was discovered that patients in groups A and B had significantly lower serum K concentrations on the seventh day of baseline than on the first day. According to the same data, on the seventh day of baseline, patients in group A had a significantly lower serum K level than patients in group B. Diuresis characteristics improved in the case when furosemide was combined with dapagliflozin. In contrast with diuretics alone, dapagliflozin usage was not linked to hypokalemia or WRF. Acute dapagliflozin was thought to reduce the dosage of necessary furosemide, thus reducing the drug's adverse effects, such as hypokalemia and renal problems, in line with what we found (41,42). Using loop diuretics alone results in low potassium levels in AHF, which can lead to arrhythmias and other issues. Additionally, excessive loop diuretic use increases the risk of adverse effects by impairing kidney function (43).

Table 1: Data of researched groups

Group	NO.	Sex (M/F)	Age (mean±SD)	BMI (Kg/m^2)	Diseases	The Drugs
A	50 Patients	(22/28)	40-70	28.83±7.38	HF/DM	Dapaglifozin and Lasix
B	50 patients	(24/26)	40-70	28.94±7.88	HF/DM	Lasix
C	50 Controls	(25/25)	40-70	25.5±4.78	……..	…… ……

-No: Number of subjects.
Data are presented as mean ±SD with the use of SPSS version 15.0
The one-way ANOVA test has been utilized for examining the variables between the various research groups
-A: HF with type 2 diabetic patients' group is receiving Dapagliflozin and Lasix
-B: HF with type 2 diabetic patients' group received Lasix.
-C: Controls group

Table 2: Concentrations of serum NT-Pro BNP, Urea, Creatinine, Na, and K in patients and control groups

Groups	No.	NT-ProBNP (pg/ml)	Urea (mg/dL)	Creatinine (mg/dL)	Na(mmol/L)	K (mmol/L)
Controls	50	176.59±21.02^{c}	22.42±3.91^{b}	0.76±16^{b}	142.19±15.22^{b}	4.94±0.59^{a}
A	50	5129.41±950.00^{a}	44.08±9.88^{a}	0.89±0.09^{a}	134.29±2.43^{a}	4.51±0.13^{b}
B	50	5158.00±886.00^{a}	41.48±5.93^{a}	0.99±0.01^{a}	137.67±5.43^{a}	4.36±0.22^{b}
LSD		14.22	3.24	0.12	4.23	0.14

-No: Number of subjects.
-LSD: Least Significant Difference.
-A: HF with type 2 diabetic patients' group is receiving Dapagliflozin and Lasix
-B: HF with type 2 diabetic patients' group received Lasix.
-C: Controls group

Table 3: Comparison of variation in serum NT-pro BNP, Urea, Creatinine, Na, and K levels in the study groups over the period of time.

Group	At admission	At 7th day	P-value
Serum NT-pro BNP (pg/ml)(Mean±SD)			
A	5082.41±950.00	3158.00±924.00	0.000
B	5138.00±886.00	2579.00±781.00	0.000
p-value	0.062	0.000	
Serum Urea (mg/dL) (Mean ±SD)			
A	44.08±9.88	55.70±8.30	0.007
B	41.48±5.93	49.54±6.21	0.001
P-value	0.345	0.032	
Serum Creatinine (mg/dL)(Mean±SD)			
A	0.89±0.09	1.01±0.18	0.008
B	0.99±0.01	1.27±0.22	0.010
P-value	0.421	0.042	
Serum Sodium (mmol/L) (Mean±SD)			
A	134.29±2.43	131.45±3.86	0.022
B	137.67±5.43	143.37±4.57	0.001
P-value	0.145	0.006	
Serum Potassium (mmol/L)(Mean±SD)			
A	4.51±0.13	3.86±0.21	0.008
B	4.36±0.22	4.04±0.39	0.028
P-value	0.062	0.003	

-p-value was considered significant if it was ≤0.05
-A: HF with type 2 diabetic patients' group is receiving Dapagliflozin and Lasix
-B: HF with type 2 diabetic patients' group received Lasix.

Conclusion

For treating HF, dapagliflozin is a great therapy. Despite being an anti-diabetic drug, Dapagliflozin and Lasix both decreased NT-Pro BNP levels compared to the controls, which decreased the risk of mortality and deteriorating HD and enhanced symptoms. When taken as supplemental therapy for HF, dapagliflozin does not worsen renal function or induce a decline in serum potassium as well as sodium levels. Therefore, after treatment, sodium and potassium levels decreased, but creatinine and urea levels increased in comparison to the controls. Larger dosages of the loop diuretic (Lasix) may be the cause of this observation.

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