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Effect of Dapagliflozin on Oxidative Stress in Patients with Heart Failure

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***Abstract*— Dapagliflozin has emerged as a promising therapeutic agent for reducing cardiovascular risk in patients with type 2 diabetes mellitus and concomitant heart failure (HF).The present study aims to investigate the impacts of dapagliflozin on some oxidative stress markers, including nitric oxide (NO) , fasting blood glucose (FBG), superoxide dismutase (SOD), and catalase (CAT), in patients with HF in comparison with healthy controls.**

The study included 150 participants : 100 patients who had type 2 diabetes mellitus (T2DM) and HF, and 50 normal subjects (controls). Based on age, the patients were divided into two groups (40-70 years). Group A received both Lasix and Dapagliflozin , whereas Group B received Lasix only. According to the data, serum FBG and GAL-3 concentrations in groups A and B were significantly higher than those in the control ($p \leq 0.05$). In comparison to the controls, groups A and B showed a significant decrease in serum CAT, SOD, and NO concentrations($p \leq 0.05$). There was no been any significant difference in serum concentration of Gal3, FBG, CAT, SOD, and NO between groups A and B upon admission, according to the results. Significant differences were observed in the concentrations of serum Gal3, FBG, CAT, SOD, and NO between groups A and B at 7 days. Additionally, patients in groups A and B had significantly lower serum Gal3 and FBG concentrations than on the day of baseline, and patients in groups Aand B had significantly higher serum CAT, SOD, and NO concentrations than on the day of baseline. Dapagliflozin administration in patients with heart failure and type 2 diabetes for seven days led to decreased FBG and GAL-3 levels, and increased SOD, CAT, and NO levels. These findings suggest its role in reducing oxidative stress and improving cardiac and vascular function in a short time.

***Keywords*— Dapagliflozin, Heart Failure, Galectin-3, Oxidative Stress.**

I. INTRODUCTION

Heart failure is a clinical condition characterized by symptoms and indicators brought on by a structural or functional heart defect. Elevated natriuretic peptide levels and objective proof of systemic or pulmonary congestion support this diagnosis [1]. Approximately 25 years ago, HF syndrome was initially identified as a growing epidemic. The overall number of patients with HF is rising continually nowadays as a result of an aging and expanding population [2]. HF is one of the major causes of disease, death, and poor quality of life [3].

Oral antidiabetic sodium-glucose cotransporter inhibitors (SGLT2i) diminish cardiovascular morbidity and death in type 2 diabetes mellitus (DM2), and The CV benefits of the Dapagliflozin derive from the reduction of blood glucose, weight, and blood pressure , the increase in natriuresis, the preservation of renal function, and possible direct CV effects [4]. In a range of HF patients, dapagliflozin reduces The risks of HF hospitalizations, cardiovascular death, and all-cause mortality [5]. Dapagliflozin might reduce cardiotoxicity through PI3K/AKT/Nrf2 signaling by reducing fibrosis, inflammation, oxidative stress, hypertrophy, and mitochondrial dysfunction [6]. Through restoring NO bioavailability, ROS production, and eNOS activity through SIRT1 activation in endothelial cells induced by oxidative stress, Dapagliflozin enhances endothelial dysfunction [7].

Lasix (Furosemide) is a common loop diuretic used to treat edema, or fluid retention, from a variety of causes, including high blood pressure, renal illness, and heart failure. It is regarded as the first-line treatment for patients with congestive heart failure-related edema [8].It increased

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the activity regarding oxidative stress indicators and antioxidant enzymes (SOD and CAT), Which is why, furosemide exhibited anti-inflammatory qualities [9].

Advances in cardiovascular research have identified oxidative stress as one of the major pathophysiological pathways in HF development and progression. Oxidative stress can be defined as the imbalance between the body's natural antioxidant defense system and ROS production. In healthy conditions, small ROS levels are produced intracellularly; the antioxidant defense system readily reduces these ROS, which are involved in cell signaling [10]. The study's goal is to investigate the potential effects of dapagliflozin on hospitalized HF patients' serum levels of fasting blood glucose (FBG), superoxide dismutase (SOD), Catalase (CAT), Galectin-3 (GAL3), Nitric Oxide (NO), and Nitric Oxide (NO).

II.MATERIALS AND METHODS

A. Design of the study

This research was carried out between September 2024 and March 2025 at the AL-Nasiriyah Heart Center and Biochemistry Laboratory in the College of Science/University of Thi-Qar. Out of the 150 individuals In the study, 22 were male and 28 were female with HF with T2DM, 25 were male and 25 were female controls, and 24 were male and 26 were female with HF with T2DM who received Lasix

B. Collection of Blood samples

Five milliliters of blood from HF/DM patients and controls are drawn, left to clot at room temperature in disposable, empty tubes, and then centrifuged to separate the serum at 3000 xg for ten minutes. The serum is then stored at -20 ^{0}C for future biochemical parameter measurements using a spectrophotometer.

For Biochemical analysis including, the determination of fasting serum glucose (FBG), and blood samples were collected [11]. Serum GAL-3,SOD and CAT were measured with the use of ELISA(Enzyme Linked Immunosorbent Assay) technology by Fine Test,China through a spectrophotometer, and using Griess reagent to quantify serum Nitric Oxide [12]. The study excluded patients with gout, breastfeeding, type 1 diabetes, renal failure, GFR≤30, arthritis, and pregnancy**.**

III.RESULTS AND DISCUSSION

The present study includes 150 subjects, with differences in clinical characteristics between patients with heart failure and type 2 diabetes and the control groups. Characteristic date for all studied groups shown in Table 1. .

Table 1: Characteristics of studied groups.

Group	NO.	Sex (M/F)	Age(year) (mean ±LSD)	Diseases	The drugs
A	50 Patients	(22/28)	40-70	HF/DM	Dapagliflozin and Lasix
B	50 patients	(24/26)	40-70	HF/DM	Lasix
C	50 Controls	(25/25)	40-70	.....	.....

Data are presented as mean ±LSD 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.

p-value was considered significant if it is ≤0.05

A. Serum Fasting Blood Glucose Concentrations (FBG):

Asignificant increase in fasting blood glucose (FBG) concentrations was observed in the patient groups compared to the control group ($p \leq 0.05$), as presented in Table 2.

Between both groups A and B of patients at baseline, Table (3) revealed no significant differences in serum RBS concentration. On the seventh day of baseline, however, a significant difference in serum FBG concentration levels between groups A and B was discovered. Additionally, in comparison with the day of baseline, the concentration of serum FBG in patients in groups A and Bwas significantly lower on the seventh day. HF is known to be more likely in those with T2DM. T2DM and HF are becoming more prevalent worldwide[13]. In T2DM, dapagliflozin, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor, is recommended for enhancing glycaemic control [14]. By blocking the proximal tubule of the kidney's ability to reabsorb glucose and salt, SGLT2 inhibitors lower blood pressure without increasing heart rate, lower body weight, and prevent atherosclerotic cardiovascular disease (CVD) [15] .

B. Serum Galectin -3Concentrations (GAL3):

Compared to the controls, patients had a considerable increase in GAL3 concentration ($p \leq 0.050$), as shown in table2.

Table 3 shows that there is no been any significant difference in baseline serum GAL3 concentration between groups A and B. On the seventh day of the baseline period , however, a significant difference in serum GAL3 concentration between groups B and A was discovered. Additionally, it was found that patients' serum GAL3 concentrations in groups B and A were significantly lower on the seventh day of baseline than on the first day.

Lately, it was demonstrated that the presence of HF is positively correlated with the concentration of Galectin-3 (Gal3), the only chimera-type member of the lectin family that is widely expressed in human tissues and functions as a galactosidas ebinding protein. Increased cardiovascular and all-cause mortality risk, along with comorbidities, are linked to higher Gal-3 concentrations [16]. Gal-3 promotes monocyte migration to the artery wall, which exacerbates inflammation as well as atheroma in atherosclerosis. However, in hypertension and other cardiomyopathies, its absence has the opposite effect, enhancing function and remodeling [17].

C. Serum Nitric Oxide Concentrations (NO) were significantly lower than those in the control groups ($p \leq 0.05$):

In both groups A and B of patients at baseline, there was no been any significant difference in serum NO concentration. On the seventh day of baseline, however, a significant difference in serum NO concentration between group A and group B was discovered. Additionally, it was discovered that patients in group A and group B had much higher serum NO concentrations on the seventh day of baseline than on the first day.

Nitric oxide (NO) is a gaseous molecule that promotes the relaxation of smooth muscle cells within the vascular system. Due to its strong affinity for oxyhaemoglobin, NO is swiftly absorbed by oxyhaemoglobin in red blood cells, restricting the vasodilatory effects of inhaled NO to vented areas of the lung. NO therefore has the unique ability to induce pulmonary vasodilatation specifically in the portions of the lung with adequate ventilation. Inhaled nitric oxide is utilized to address a range of cardiopulmonary disorders, including pulmonary hypertension in both pediatric and adult populations [18]. Senescence of endothelial cells contributes to the early decline of vascular functions in diabetic patients [19]. In senescent endothelial cells, dapagliflozin reversed decreases in NO production and eNOS phosphorylation [20]. Through enhancing vascular endothelial function, raising NO synthesis by boosting the activity of NO-producing enzyme (eNOS), and decreasing inflammation as well as oxidative stress, which sustain NO levels [21].

D. Serum Superoxide Dismutase Concentrations (SOD):

Compared with the control group, patients had a significant decrease in SOD concentration ($p \leq 0.05$).

Between both groups B and A of patients at baseline, Table (3) revealed no significant differences in serum SOD concentration. On the seventh day of baseline, however, a significant difference in serum SOD concentrations between groups A and B was discovered. Additionally, it was discovered that, on the seventh day of baseline, the serum SOD concentrations in patients in group B and group A have been much higher than on the first day of baseline.

In the physiopathology and development of HF, oxidative stress and oxidative function are thought to be significant. The development of reactive oxygen species (ROS) and the availability of endogenous antioxidant enzymes and other defenses are both out of balance during oxidative stress [22] . The Superoxide dismutase (SOD), is a class of enzymes that limits the body's biological oxidant cluster enzyme system, which can efficiently respond to oxidation, inflammation, lipid metabolism, and cellular OS, . They may also help to avoid the harmful effects of free radicals and maintain a dynamic equilibrium between the body's generation and scavenging of biological oxidants [23]. Through blocking NADPH oxidases and/or regulating antioxidant enzymes like the

glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), Dapagliflozin lessens diabetic cardiomyopathy [24]. Dapagliflozin raises T-SH, SOD, and TAC levels, which may be beneficial in cardiomyopathy induced on by oxidative stress [25]. By reducing ROS levels and increasing the anti-oxidant enzymes like glutathione peroxidase as well as SOD, dapagliflozin not only lowers hyperglycemia, but also inhibits the development of DM-associated glomerulosclerosis and oxidative stress [26]. Antioxidant enzymes like SOD may work better and maybe increase their levels as a protective response if inflammation is reduced, since it may also reduce the signaling pathways that encourage ROS production [27]. Through the increased of the expression of Sirtuin 1 (Sir2-like proteins), dapagliflozin may benefit cardiomyocytes. Through boosting the expression of anti-oxidants like catalase and manganese superoxide dismutase (MnSOD), nuclear Sirtuin 1 (Sir2-like proteins) in cardiomyocytes prevents myocyte damage from oxidative stress. Age-dependent increases in cardiac hypertrophy can be mitigated by overexpressing Sirtuin1 (Sir-2-like proteins) in the heart, according to studies [28].

E. Serum Catalase Concentrations (CAT):

Table (2) shows a significant decrease in concentration of CAT in the patient group compared with the control group ($p \leq 0.05$). Between both groups A and B of patients at baseline, Table (3) revealed no significant differences in serum CAT concentration. On the seventh day of baseline, however, a significant difference in

serum CAT concentration between groups A and B was discovered. Additionally, it was discovered that patients in groups A and B had much higher serum CAT concentrations on the seventh day of baseline than on the first day. In terms of cardioprotection, SGLT2i was the most significant. In addition to improving the anti-inflammatory, antioxidant, and anti-fibrotic effects in DCM, SGLT2i increased serum insulin, as well as myocardial antioxidants GSH and CAT, and decreased the rise in serum blood glucose, CK-MB, and LDH, a marker of diabetic myocardial histological alterations. Enhances CAT activity by lowering oxidative stress linked to HF, which enhances cell function, decreases tissue damage, and lowers reactive ROS levels, which lessens the strain on the endogenous antioxidant system, including CAT, and enhances mitochondrial function, which may result in increased production of antioxidant enzymes [29-30]. It also enhances the heart's autophagic function [31]. Furosemide increased the activity of antioxidant enzymes (CAT and SOD) and oxidative stress indicator levels. Consequently, furosemide showed anti-inflammatory properties [32].

Table 2: Concentration of serum NO, GAL3, SOD, and CAT in patients and control groups

Groups	No.	FBG mg/dL	GAL 3 ng/mL	NO (µmol/L) (Mean±SD)	SOD (pg/ml) (Mean±SD)	CAT (pg/mL)(Mean±SD)
Control	50	91.30±7.29[b]	0.86±0.21[b]	17.22±2.01[a]	6.23[a]	65.32±5.13[a]
A	50	265.30±17.59[a]	2.87±0.48[a]	10.22±1.34[b]	2.88±0.93[b]	36.52±4.98[b]
B	50	259.10±22.72[a]	3.02±0.71[a]	10.84±2.03[b]	3.01±0.86[b]	35.20±7.21[b]
LSD		2.87	0.43	1.87	0.52	3.21

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

Tabele 3: Comparison of variation in serum CAT, SOD, and NO levels in the study group over the period .

Group	At admission	At 7th day	P-value
Serum FBG (mg/dL) (Mean ±SD)			
A	265.30±17.59	136.40±7.24	0.005
B	259.10±22.72	128.24±9.13	0.003
P-value	0.473	0.022	
Serum GAL3 (ng/mL) (Mean± SD)			
A	2.87±0.48	2.67±0.67	0.000
B	3.02±0.71	2.47±0.66	0.000
P-value	0.137	0.045	
Serum NO (µmol/L)(Mean±SD)			
A	10.22±1.34	12.34±2.00	0.023
B	10.84±2.03	15.22±3.12	0.007
P-value	0.120	0.008	
Serum SOD (pg/ml)(Mean±SD)			
A	2.88±0.93	2.96±0.78	0.043
B	3.01±0.86	3.44±1.08	0.005
p-value	0.089	0.006	
Serum CAT (pg/ml) (Mean ±SD)			
A	36.52±4.98	37.05±3.78	0.048
B	35.20±7.21	39.18±6.33	0.007
P-value	0.079	0.043	

IV.CONCLUSIONS

Although dapagliflozin is primarily an antidiabetic medication, it has proven to be an effective therapy for heart failure. In this study, both dapagliflozin and Lasix treatments reduced GAL-3 levels compared to the controls group..Since GAL-3 is associated with inflammation, fibrosis, remodeling, and malfunction,leading to reduced risks of worsening HF and eventually death, and improved symptoms while and increasing NO levels compared to the control,leading to an antioxidant and vasodilator which enhances blood flow and reduces damage from free radicals and inflammation and increases SOD and CAT levels compared to the controls. led to reduces oxidative stress by decreasing the production of ROS.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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