**Evaluation of Dapagliflozin in Experimentally Induced Heart Failure with and without Type2 Diabetes Mellitus in Rats**

**Abstract:**

**Background:** Heart failure is a functional or structural heart disorder impairing ventricular filling or ejection of blood to the systemic circulation. T2DM is a metabolic disease characterized by chronic hyperglycemia, considered an important cause of heart failure. Dapagliflozin, a member of the SGLT2 inhibitor class, improve glycemic control in adults with T2DM and reduce the risk of hospitalization for heart failure. The American College of Cardiology (ACC) recently released calls for use of dapagliflozin in HFrEf with or without diabetes mellitus. **Aim of the study:** The present study was designed to evaluate the effect of dapagliflozin in-vivo in the experimentally induced HF with and without T2DM on body weight, FBG, ECG, NT-pro BNP, LVW/WHW and histopathological changes. And also, in-vitro on isolated mammalian heart and isolated strips of rabbit aorta. **Materials and methods:** Rats for in-vivo study, were classified into: Group I: control normal group. Group II: non treated diabetic group of HF(diseased group). Group III: It was treated with dapagliflozin for 4 weeks. Group IV:non treated non diabetic group of HF(diseased group). Group V: It was treated with dapagliflozin for 4 weeks. Rabbits for in-vitro experiments on isolated heart and strips of aorta. **Results**: Regarding in-vivo study, treated groups showed significant improvement in all parameters and improvement of the histopathological changes. Regarding in-vitro study, dapagliflozin produced neither effect on isolated mammalian heart nor on isolated strips of rabbit aorta. **Conclusion**: Dapagliflozin showed improvement of parameters of HF with or without diabetes mellitus. Dapagliflozin has protective cardiac effects.

**Key words:** Heart failure; diabetes mellitus; dapagliflozin.

# INTRODUCTION

Heart failure remains a highly prevalent disorder worldwide (1). It is characterized by orthopnea, , palpitations and fatigue due to low cardiac output and pulmonary congestion(2). Coronary artery disease and diabetes mellitus have become the predominant predisposing factors for heart failure (3).

The pathogenesis of heart failure involves excessive neuroendocrine activation leads to release of neuro-hormones and pro-inflammatory cytokines following an initial cardiac insult. Pathogenic mechanisms of diabetic cardiovascular complications include activation of four pathways (polyol, advanced glycation end-products , protein kinase C , and hexosamine) (4).

The current management of HF includes the primary combination therapy that includes diuretics, a renin-angiotensin system inhibitor, a beta-blocker, Ivabradine only alleviates symptoms (5). Significant attention has been paid to the benefit of SGLT2 inhibitors on cardiovascular outcomes in T2DM patients with or without pre-existing cardiovascular disease(6).

Dapagliflozin increases the amount of glucose excreted in the urine and improves plasma glucose levels in patients with T2DM by inhibiting SGLT-2 in the renal proximal tubule(7).

# Materials and methods

# An experimental study

## Animals

### In Vivo study:

Rats: Fifty adult male rats (brought from the Experimental Animal Breeding Farm Helwan - Cairo) with a weight ranging between 150-200 gm at the beginning of the study from February 2022 to May 2023 were used for in vivo experiments. They have been acclimated for a week and will be placed in cages in a well-ventilated room (at room temperature) in the Department of Pharmacy, Faculty of Medicine, Benha. Mice were fed standard food with water. This study was approved by the ethical committee of Benha Faculty of Medicine {M.S.35.10.2021}

### In Vitro study:

Rabbits: of local strain ranging 1-1.5 kg of both sexes were used for experiments on isolated heart and aortic strips.

## Drugs and chemicals

Dapagliflozin hemihydrates (powder) (Janssen, USA), Streptozotocin (STZ) Sigma (St. Louis, MO, USA), Heparin, ampoule (Novo Industry, Demark), Isoprenaline HCL (Sigma CO., USA), Norepinephrine bitartarate(powder ) [Sigma,USA], Adrenaline hydrochloride tartarate(powder) [B.D.H, England], Histamine (powder) [sigma,USA], Formalin [El-Gomhoria Pharmaceutical Chemical Co.], High fat diet(HFD) (Faculty of Veterinarian Medicine, Zagazig University) , Normal saline (FIPCO), Urethane (prolabo, Paris) Glucose commercial diagnostic kits (biodiagnostic, Egypt),Glucose kits (Roche Diagnostic, Germany), Rat N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) (Elabscience, United States), ELISA Kit Sodium Assay Kit Quantitative (Colorimetric) (Abcam, UK), Potassium Assay Kit : Quantitative (Colorimetric) (Elabscience, United States).

## Design of the work:

### In-Vivo study

In this experimental study, rats were classified into 5 equal groups (10 rats in each group). **Group (I)** : normal control group (standard diet + tap water), injected normal saline. **Group (II)** : T2DM & HF (given high fat diet for 8 weeks and in the 7th week given Streptozotocin STZ 25 mg/kg i.p single dose) and continue to week 11th (8). **Group (III)** : the same as G2 but dapagliflozin is administered orally on week7th up to the Week11th(9). **Group ( VI)** : non diabetic group of HF given Isoproterenol i.p 5 mg/kg for 7 days(10). **Group (V)** : as that of G4 but given dapagliflozin 1mg/kg orally on day 7 up to 4 weeks(11).

The total body weight was serially measured every day from the start till the end of the experiment. One day before the end of experiment, all animals were fasted overnight for 12 hours for measuring FBG. At 8 am of the last day of the experiment, all animals were anesthetized by urethane (1.5 g/kg body weight)(11) then lead II ECG (R-R interval , amplitude of R & T waves)was performed, Four millilters blood sample was obtained from retro-bulbar venous plexus using a sterile hematocrit tube(12). All blood samples were incubated at 37°C for 2 hours until clotting, then centrifuged at 3000 rpm for 15 Min, then serum was collected and kept at -20°C till used for determination of NT-proBNP, serum Na +and K+ levels.

### Biochemical assays

1. Measurement of fasting blood glucose:

By GOD-PAP enzymatic colorimetric method(13)

1. Measurement of NT-proBNP:

By quantitative sandwich enzyme immunoassay technique(14)

1. Measurement of Na+:

By enzymatic colorimetric method(15)

1. Measurement of K+:

By turbidimetric method(16)

### Histopathological study:

All animals were dissected 10 minutes after having received heparin (500 U, i.p.) and their hearts, livers and lungs were quickly excised. The whole heart and left ventricle were weighed. Their hearts, livers and lungs kept in formaldehyde to be stained with hematoxylin and eosin for histopathological examination.

* Heart histopathological changes

Heart was cut into transverse sections from the ventricle and interventricular septum, each section was fixed, stained with H&E and examined under light microscope for either areas of congestion, inflammatory foci or necrosis of cardiomyocytes(17).

* Liver histopathological changes

Three pieces of liver tissue were removed and immersion fixed in 10% buffered formalin, embedded in paraffin blocks and 4 micron thick sections were cut. Then processed for staining with H&E for areas of congestion and vacuolar degenerations(18).

* Lung histopathological changes

Three pieces of lung tissue were removed and immersion fixed in 10% buffered formalin ,embedded in paraffin blocks and 4 micron thick sections were cut. Then processed for staining with hematoxylin and eosin for areas of congestion and inflammation(19)**.**

### In-Vitro study:

**1-Experiments on isolated rabbit’s heart preparation (a modification Of Langendorff’s method):-**

The rabbit weighing 1.0-1.5Kg was sacrified. The chest was opened, the heart quickly excised, and transported to a dish containing oxygenated Ringer-Locke solution and fixed through the aorta to the cannula of the langendorff’s apparatus. The temperature was kept constant at 37t throughout the experiment. A hook was attached to the apex of the heart and was attached by a thread to a side way lever which recorded the contractions of the ventricle on slowly moving drum. Dapagliflozin was added in gradually increasing doses 10ug up to 100ug in cannula(20).

**2-Experiments on isolated rabbit aortic strip preparation:-**

The rabbit was sacrificed. The abdominal cavity was opened, the theoracic aorta was exposed and was cut as near as possible to the heart, transferred to a dish of Kreb's solution. Then, it was cut spirally to prepare a continuous strip about 2 mm wide and 2-3 cm long. One end of the strip was tied to a hook in an organ bath containing oxygenated kreb's solution and the other end to a magii-Ying lever of transducer. The preparation was allowed to settle for 90 minutes. Dapagliflozin was added in gradually increasing doses 10ug up to 100ug (21).

# Statistical analysis:

These data were summarized in terms of mean ± Standard Deviation (SD), tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 20 (Chicago IL USA, 2000), using ANOVA test (P value) to compare mean of more than two groups of quantitative data. A *P* value <0.05 was considered statistically significant.

# Results

Induction of HF either by HFD-STZ (diabetic group) or isoproterenol (non-diabetic group) resulted in significant elevation in body weight in diabetic group, but significant decrease in non-diabetic group. Also, elevation of FBG, serum sodium and potassium levels. Structural and functional features of heart are similar to diabetic cardiomyopathy namely cardiac hypertrophy as evidenced by increase left ventricular weight to whole heart weight ratio, contractile disorders in the form of significant increase in height of R wave and T wave (inverted with isoproterenol in contrast) in lead II of ECG(figure 1). Regarding serum level of NT pro-BNP, there was significant increase compared to control normal group as shown in table (1,2). Histopathological changes of heart showed structural changes in the form of distortion of myocardial cells, increase intercellular gaps and extracellular matrix as compared to normal group (figure 2). Histopathological changes of liver showed steatosis, presence of hydropic changes, necro-inflammatory foci and congestion (figure 3). Histopathological changes of lung showed edema, inflammatory cell infiltration and congestion (figure 4).

Administration of dapagliflozin 1mg/kg orally for 4 weeks, resulted in significant improvement of body weight, FBG, serum sodium and potassium levels. Also, significant reduction in left ventricular weight to whole heart weight ratio, height of R wave and T wave and restore the near normal pattern in lead II of ECG (figure 1)as well as significant decrease in NT pro-BNPserum levels compared to their higher values nontreated HF groups. On the other hand, this reduction in their levels was insignificant as when compared to control group(table 1,2) and also histopathological examination of heart showed lesser degree of hypertrophy and distortion in the myocardial cells which were better arranged with lesser degree of intracellular gaps and extracellular matrix (figure 2). Histopathological examination of liver and lung tissues showed improvement, mild degree of inflammation and congestion (figure 3,4).

**Table 1 :** BW, FGB, Serum Na, Serum K, Nt pro BNP, HR, R-R interval, Amplitude of R wave, Amplitude of T wave in G1, G2, G3.

|  |  |  |  |
| --- | --- | --- | --- |
| Groups  Parameters | Normal control group. | Diseased diabetic HF group | Dapagliflozin treated diabetic HF group |
| **BW (gm)** | 286.67±7.23\*= | 385.17±10.68**&=** | 299.0±6.81**&\*** |
| **FBG**  **(mg/dl)** | 86.83±2.79**\*=** | 233.14±48.87**&=** | 127.0±9.88&\* |
| **Serum Na (mmol/L)** | 86.78±4.87**\*=** | 142.09±5.82**&=** | 101.04±5.50**&\*** |
| **Serum K (mmol/L)** | 0.082±0.007**\*** | 0.25±0.077**&=** | 0.133±0.004\* |
| **Nt pro BNP (PG/ML)** | 118.18±2.33**\*=** | 316.73±14.62**&=** | 140.82± |
| **R-R interval** | 0.201±0.012**\*=** | 0.157±0.006**&=** | 0.189±0.002&\* |
| **Amplitude of R wave (mv)** | 0.491±0.061**\*=** | 0.648±0.029**&=** | 0.544±0.031&\* |
| **Amplitude of T wave (mv)** | 0.232±0.033**\*=** | 0.375±0.019**&=** | 0.305±0.024&\* |
| **LVW/WHW (mg/g)** | 38.52±0.354**\*=** | 44.32±0.747**&=** | 39.69±1.31&\* |
| **HR (bpm)** | 340.83±28.0 | 431.67±23.17 | 355.0±35.07 |

Data was represented as means±SD. (n=10)

**&**: Significant versus control(G1)at (P< 0.001)

**\***: Significant versus diseased diabetic HF group(G2) at (P< 0.001)

**=**:Significant versus dapagliflozin treatde diabetic HFgroup(G3) at (P< 0.001)

**Table 2 :** BW, FGB , Serum Na, Serum K, Nt pro BNP, HR, R-R interval, Amplitude of R wave, Amplitude of T wave in G1,G4,G5.

|  |  |  |  |
| --- | --- | --- | --- |
| Groups  Parameters | Normal control group. | Diseased nondiabetic HF group | Dapagliflozin treated nondiabetic HF group |
| **BW (gm)** | 246.78±11.57\*= | 237.20±10.68**&=** | 248.0±14.91**&\*** |
| **FBG**  **(mg/dl)** | 86.83±2.79**\*=** | 110.89±4.83**&=** | 85.83±3.65&\* |
| **Serum Na (mmol/L)** | 87.09±5.38**\*=** | 145.67±6.80**&=** | 103.04±2.96**&\*** |
| **Serum K (mmol/L)** | 0.081±0.006**\*** | 0.422±0.231**&=** | 0.133±0.004\* |
| **Nt pro BNP (PG/ML)** | 117.86±2.20**\*=** | 341.42±15.83**&=** | 137.63±4.68&\* |
| **R-R interval** | 0.205±0.016**\*=** | 0.145±0.008**&=** | 0.175±0.005&\* |
| **Amplitude of R wave (mv)** | 0.467±0.019**\*=** | 0.743±0.029**&=** | 0.618±0.015&\* |
| **Amplitude of T wave (mv)** | 0.243±0.038**\*=** | -0.448±0.012**&=** | 0.312±0.019&\* |
| **LVW/WHW (mg/g)** | 39.6±0.632**\*=** | 60.95±1.09**&=** | 41.05±0.653&\* |
| **HR (bpm)** | 340.83±28.0 | 431.67±23.17 | 355.0±35.07 |

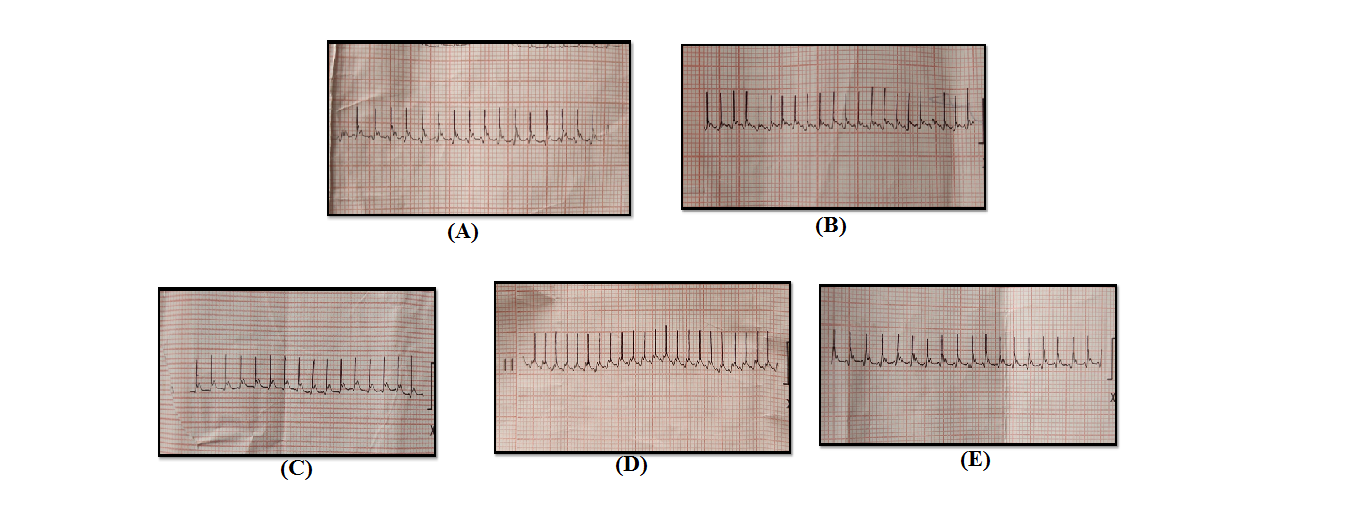
Data was represented as means±SD. (n=10)

**&**: Significant versus control(G1)at (P< 0.001)

**\***: Significant versus diseased nondiabetic HF group(G4) at (P< 0.001)

**=**:Significant versus dapagliflozin treated nondiabetic HFgroup(G5) at (P< 0.001)

### ECG changes:

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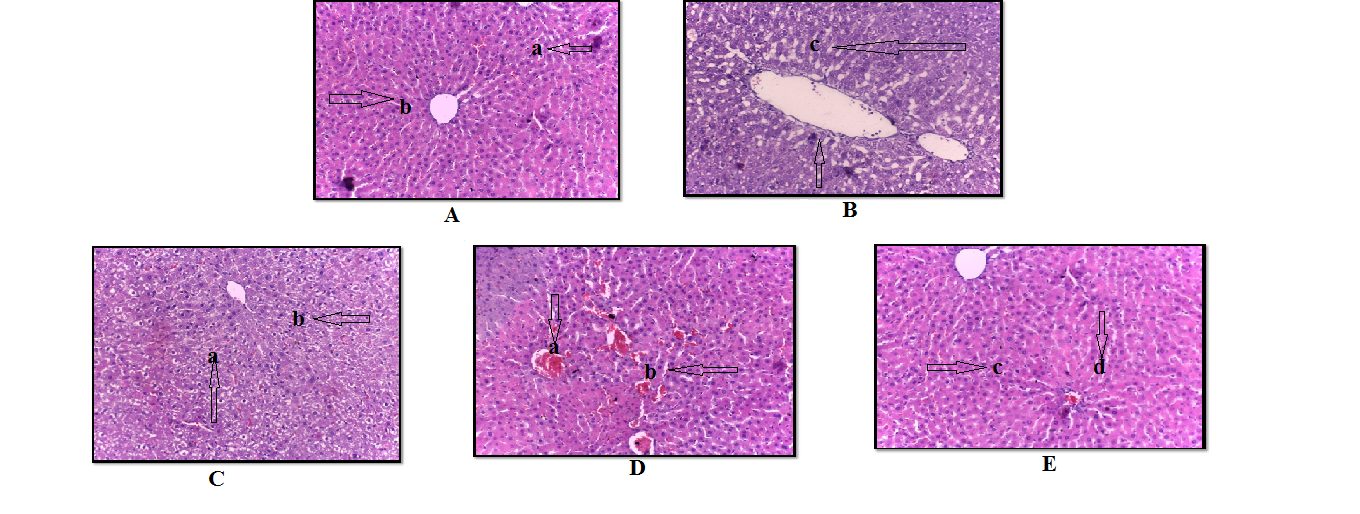
**Figure (1): A.** ECG Tracing (lead II) of control normal rats. **B.** ECG Tracing (lead II) of non – treated diabetes heart failure rats (group II). **C.** ECG Tracing (lead II) of dapagliflozin-treated diabetic heart failure rats (Group III) **D.** ECG Tracing (lead II) of non-treated non-diabetic heart failure rats (Group IV). **E.** ECG Tracing (lead II) of dapagliflozin treated non diabetic heart failure rats (group V).

### Histopathological study:

### Heart

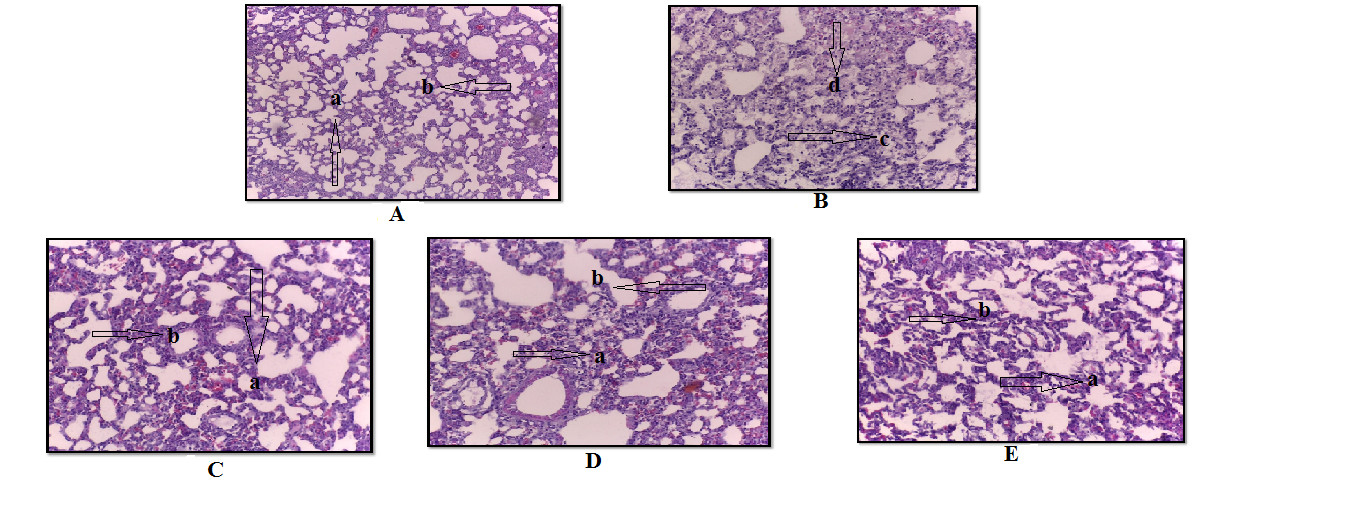
**Figure (2): A.** Aphotomicrograph of a cut section in the heart of normal control group( G1) showing intact cardiomyocytes(a) (H&E,×400) **B.** A photomicrograph of cut section in the heart of non treated diabetic HF group(G2) showing areas of congestion(a), hemorrhage, vacuolar degeneration(c) & necroinflammatory foci of cardiomyocytes (b) (H&E,×400)**C.** Aphotomicrograph of cut section in the heart of dapagliflozin treated diabetic HF group(G3)showing small area of degeneration and intermascular spacing (a)with congestion (H&E,×400) **D**. A photomicrograph of a cut section in the heart of non treated non diabetic HF group(G4) showing areas of vacuolar degeneration(b) and necrosis of cardiomyocytes (arrows) with edema (a) ( H&E,×400) **E.** Aphotomicrograph of of a cut section in the heart of dapagliflozin treated non diabetic HF group(G5) showing mild degeneration (a)and necrosis of cardiomyocytes with mild congestion (b)and inflammation (H&E,×400).

### liver

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**Figure (3): A.** A photomicrograph of a cut section of liver of normal control group (G1) showing intact polyhedral shaped hepatocytes(a) radiating from central vein(b) (CV) and separated by blood sinusoids(H&E,×400) **B.** A photomicrograph of a cut section of liver of nontreated diabetic HF group(G2) showing congested and dilated central vein(b) (CV), swelling and severe vacuolar degeneration of hepatocytes (c) besides congested blood sinusoids ( H&E,×400) **C.** A photomicrograph of a cut section of liver of dapagliflozin treated diabetic HF group(G3) showing mild hydropic degenerative changes (a)and pyknosis of hepatocytes which radiating from central vein(b) (CV) and normal sized blood sinusoids (H&E,×400) **D.** A photomicrograph of a cut section of liver of nontreated non diabetic HF group(G4) showing congested central vein (CV)(a) and Centro lobular vacuolar degeneration of hepatocytes with pyknotic nuclei(b) ( H&E,×400) **E.** A photomicrograph of a cut section of liver of dapagliflozin treated non diabetic HF group (G5) showing intact central vein (CV), small area of degeneration and necrosis of hepatocytes with nuclear pyknosis(c) (arrow head) and mild dilated blood sinusoids(d) (H&E,×400).

### Lung



**Figure (4): A.** A photomicrograph of a cut section of lung of normal control group (G1) showing intact normal lung architecture( H&E×200) **B.** A photomicrograph of a cut section of lung of non treated diabetic HF group (G2) showing emphysema(d), congestion, severe inflammation and edema(c) (H &E×200) **C.** A photomicrograph of a cut section of lung of dapagliflozin treated diabetic HF group(G 3) showing mild inflammation(b) and congestion(a)( H&E×200) **D.** A photomicrograph of a cut section of lung of non treated non diabetic HF group (G4) showing lung with inflammation, congestion(a), minimal fibrosis & emphysema(b)( H&E×200) **E.** A photomicrograph of a cut section of lung of dapagliflozin treated non diabetic HF group(G 5) showing lung with mild inflammation (b)and improved architecture (H&E×200).

### In vitro study

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**Figure (5):** **A.** No effect elicited for dapagliflozin on isolated rabbit’s heart. **B.** No effect elicited for dapagliflozin on isolated rabbit’s aortic strip.

# Discussion

The present work was designed to investigate how ‘antidiabetic drugs’ became valuable tools in treating heart failure, regardless of whether type 2 DM is present or not. SGLT2 inhibitors were originally designed to treat hyperglycemia in patients with type 2 diabetes. Nowadays, dapagliflozin and empagliflozin are the first SGLT2 inhibitors to be approved by the U.S. Food and Drug Administration (FDA) for both type 2 diabetes and heart failure risk reduction(22).

In our present work we investigated the potential beneficial effects of dapagliflozin in experimentally induced diabetic (High-fat diet along with low-dose STZ) and nondiabetic (Isoproterenol) groups of heart failure on the following parameters; body weight, FBG, serum sodium and potassium levels, NT pro-BNP, ECG ( R-R interval - heart rate – amplitude of R and T waves ), LVW/WHW ratio and histopathology of heart, liver and lung.

In addition, it was designed to find the mode and site of action of dapagliflozin on isolated mammalian heart and isolated strips of rabbit aorta.

The data of the present work revealed that induction of HF on top of STZ DM typeII resulted in a significant elevation in body weight, FBG, serum sodium and potassium levels and structural and functional features similar to diabetic cardiomyopathy namely cardiac hypertrophy as evidenced by increase LVW/WHW ratio, contractile disorders in the form of significant increase in height of R wave and T wave in lead II of ECG as well as significant increase in NT pro-BNP serum levels and also structural changes in the form of distortion of myocardial cells, increase intercellular gaps and extracellular matrix as compared to normal group. Histopathological examination of liver and lung showed marked degree of inflammation and congestion. .

The mechanism involved in the development of HF by HFD and STZ were assessed by many investigatorsthat is related to multiple factors including metabolic inflexibility in which heart shifts from glucose to fatty acid oxidation to provide energy(23), interfere with excitation–contraction coupling and mitochondrial Ca2+ uptake and finally, these changes produce oxidative stress and mitochondrial dysfunction, glucotoxicity, lipotoxicity, increased oxidative/nitrosative stress, activated renin- angiotensin and adrenergic system, endothelial dysfunction, abnormal calcium handling and eventually induction of cardiac dysfunction and cardiac hypertrophy(24)**.**

High-fat diet along with low-dose STZ model is generally used for T2DM and heart failure rat induction**(25)**.High-fat diet (HFD)-mediated obesity in the mice before STZ injection mimic human situation of prediabetes results in higher body fat percentage , hyperglycemia and hyperinsulinemia(26).

These results are in aggrement with a previous study (27) that concluded that model of HFD and low dose STZ showed that level of FBG and body weight were significantly elevated in rats fed on HFD. HFD results in increased tolerance to hepatic insulin, inflammation and impaired expression of lipogenic genes in the liver, saturated fat facilitate weight gain in adipose tissue by increasing the white adipose tissue (WAT) and increased de novo lipogenesis*.*

These data also are in aggrement withseveral studies (28)**,** (25)who concluded serum NT-proBNP and TUG1 as novel biomarkers for elderly hypertensive patients with HFrEF, increased heart rate and NT pro-BNP serum levels during HFand concluded that increase R and T-wave voltage and increase LVW/WHW indicate left ventricular hypertrophy in ECG alterations precedes cardiac hypertrophy in rats.

Experimental induction of HF in normal rats by Isoproterenol 5 mg/kg for 7 daysslightly reduce BW. However, FBG undergoing some increase in nontreated nondiabetic group of HF compared to their levels in normal control group. Also, showed significant increase in serum sodium and serum potassium in non treated non diabetic group of HF compared to their levels in normal control group. Their cardiac parameters showed marked elevation in serum levels of NT-proBNP and LVW/WHW ratio showed significant increase. ECG showed significant increase in HR with significant decrease in RR interval marked elevation in amplitude of R wave and inverted T wave amplitude**.**

Histopathological examination of heart showed hypertrophy and distortion in the myocardial cells. Histopathological examination of liver and lung showed marked degree of inflammation and congestion.

Persistent β-adrenergic stimulation with ISO results in cardiomyocyte injury, the generation of reactive oxygen species (ROS), arrhythmias, ventricular hypertrophy and increased fibrosis, and inflammation and collagen deposition(29)**.**

The plasma concentration of aldosterone hormone is increased in patients with HF as a consequence of neurohormonal changes, which has a negative effect on overall health conditions(30).

These results are in aggrement with a previous study(31) who recommended thatbody weight was slightly reduced and FBG undergoing some increase in the model of isoproterenol-induced heart failure in the rat that, is associated with nitric oxide-dependent functional alterations of cardiac function. It increases serum glucose levels by promoting glycogenolysis, which occurs in a cyclic-GMP mediated fashion.

Our results are in aggrement with several studies (32)that discussed Effect of injection of different doses of isoproterenol on the hearts of mice and the ability of the ECG to detect pathological changes rat heart. Longer QT interval, negative Q and S waves, higher R amplitude and inverted T wave were typical characteristics for isoprenaline 5mg/kg dosage in rats.Voltage criteria showed that Sokolow-Lyon index is a good predictor of left ventricular hypertrophy in isoproterenol-induced cardiac remodeling without systemic hypertension.

In the present study, it was observed that daily administration of dapagliflozin 1mg/kg/day orally in experimentally induced HF in diabetic and nondiabetic rats for 4 weeks produced significant improvement in body weight and FBG and significant improvement of Na+ and K+ levels in the form of decreased Na+ and K+ levels. In addition, significant reduction in LVW/WHW ratio, height of R wave and T wave and restore the near normal pattern in lead II of ECG as well as significant decrease in NT pro-BNPserum levels compared to their higher values nontreated diabetic HF group and insignificant compared to control group. Histopathological examination of heart showed lesser degree of hypertrophy and distortion in the myocardial cells. Histopathological examination of liver and lung showed lesser degree of inflammation and congestion.

The mechanism of desirable cardiovascular effects seen with SGLT2 inhibitor treatment may be multifactorial. Some of the conventional theories are regarding its diuretic and antihypertensive effects, dapagliflozin causes osmotic diuresis and reduce renin-angiotensin-aldosterone system (RAAS) activation(33). Intravascular volume is reduced due to glucosuria and natriuresis, reducing heart muscle wall tension and oxygen demand, improved endothelial function, reduced arterial stiffness and changes in sympathetic nervous activity(reduces the heart rate and blood pressure) (34). It was proposed that SGLT2 inhibitors could favor oxygenation of the failing ischemic heart by enhancing the synthesis of erythropoietin, reduce cardiac remodeling by a direct inhibition of the myocardial sodium–hydrogen exchanger. SGLT2 inhibition reduces serum leptin and increases adiponectin concentrations, potentially offering some cardioprotection. In addition, it may induce autophagy by increasing catabolism due to constant glucosuria and increase circulating ketones, especially in the fasting state(35).

The present study demonstrated that dapagliflozin significantly lowered serum levels of Na and K. This is probably due to a reduction in the activity of the RAAS system, further reduces the secretion of aldosterone as the consequent natriuresis effect of dapagliflozin reduces the fluid overload(30)***.***

These results are in consistent with that obtained by several studies(36) who discussed the desirable cardiovascular effects seen with SGLT2 inhibitor treatment that caused improvement of cardiac parameters and a significant reduction in decreaseNT pro-BNPserum levels.

In aggrement with our results a previous study (29) reported that dapagliflozin significantly reduced the workload on the ventricular wall to a higher degree and decrease serum levels of NT-proBNP. The protective effects of DAPA observed in this study may be due to its potent antioxidant properties, which protect cardiac tissue from oxidative damage and help to maintain myocardial cell membrane integrity and function.

Our results on isolated rabbit’s heart revealed that dapagliflozin in gradual increasing doses produced no effect. These obtained data are in line with Sha Chen who studied direct cardiac effects of SGLT 2 inhibitors and reported that dapagliflozin did not affect healthy cardiac properties, but can improve cardiac function during ischaemic and reperfused conditions(36).

Our results on isolated rabbit’s aortic strip revealed that dapagliflozin in gradual increasing doses produced no effect. Moreover, dapagliflozin didn’t affect the precontracted rabbit aortic strip by norepinephrine.

These results are in contradiction with that obtained by previous study (37). who studied effect of SGLT 2 inhibitors on vascular cell function and arterial remodelling and reported that dapagliflozin dilates precontracted rabbit aortic rings in a concentration-dependent manner. Finally, the results of the present study need furthermore experimental and clinical investigations.

# Conclusion

Dapagliflozin showed improvement of parameters of HF with or without diabetes mellitus.. It is found that dapagliflozin has protective cardiac effects.

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