# Short Term Renal Safety of Dapagliflozin in Heart Failure Patients with Chronic Kidney Disease and/Or Diabetes

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**Abstract**
Background: Heart failure is complex clinical syndrome that can result from any anatomical or functional cardiac disease that decreases the ability of the ventricle to fill or eject blood. More than half of heart failure patients may have moderate to severe renal insufficiency. The presence of chronic kidney disease in a patient with heart failure is associated with increased morbidity and mortality in these patients. Dapagliflozin is a selective and reversible inhibitor of Sodium-glucose co-transporter-2 (SGLT2) The majority of the advantages of SGLT2 inhibitors in heart failure are linked to reduced salt reabsorption in the renal tubule, increased natriuresis and osmotic diuresis, lower plasma volume and blood pressure, improved cardiac energy metabolism, inflammation reduction, sympathetic nervous system inhibition, and prevention of adverse cardiac remodeling, Objective: To evaluate the safety and efficacy of additional dapagliflozin into conventional therapy on Renal function in heart failure patients. Patients and Methods: This was prospective clinical study conducted at medical wards at Nasiriya Heart Center during the period from the 1st of November / 2021 to the end of July / 2022. The study included 120 patients with heart failure with renal insufficiency. The patients were divided into two groups, first group consisted of 60 patients who received dapagliflozin in addition to conventional therapy and the other group consisted of 60 patients who received only conventional therapy. Both groups were matched Socio demographic data. Renal function test, hemoglobin concentration, blood pressure, ejection fraction, body mass index were recorded on day 1 as a baseline visit then followed up after four months. Results: Before treatment there was no significant difference in sociodermographic and clinical parameters between two groups After treatment, Patients in the dapagliflozin group had significantly lower mean levels of BMI, serum creatinine, systolic and diastolic blood pressure compared with control group (BMI; 25.98 kg/m2 vs 27.53 kg/m2, P= 0.035), (serum creatinine; 1.32 mg/dl vs 1.79 mg/dl, P= 0.043), (systolic blood pressure; 109.4 mmHg vs 121.6 mmHg, P= 0.005), and (diastolic blood pressure; 67.16 mmHg vs 75.62 mmHg, P= 0.002). Further, hemoglobin and GFR levels were significantly increased in the dapagliflozin group than in the control group (12.53 g/L vs 11.88 g/L, P= 0.038) and (58.02 vs 54.12, P= 0.023), respectively. No significant difference was detected in blood urea and ejection fraction levels between the two groups. Conclusion: The study shows clinical and biochemical benefit from the addition of dapagliflozin tconventional therapy where dapagliflozin resulted in significant lower rate of decline decline eGFR anreduce the progression of kidney disease compared to the control group.
Keywords: Heart failure, Dapagliflozin, chronic kidney disease, creatinine, Urea, Hemoglobin

## 1. Introduction

HF is described as "a complex clinical syndrome that can result from any anatomical or functional cardiac disease that decrease the ability of the ventricle to fill or eject blood" according to the American Heart Association (AHA) [1].

The European Society of Cardiology describes heart failure as a clinical syndrome with well-known symptoms and signs, including fluid retention, pulmonary crackles, and dyspnea. Other signs include ankle edema, fatigue, and dyspnea. Caused by an anatomical and/or functional heart abnormality, resulting in decreased cardiac output and/or elevated intracardiac pressures at rest or during exercise [2].

The incidence of heart failure increases by 1% each year in persons over 65 years of age. Even with appropriate treatment, heart failure is a fatal condition that worsens with time. In developed nations, the five-year survival rate is around 50%. In recent decades, there has been a consistent rise in the incidence and number of heart failure hospitalizations. The rate of survival is increasing due to improvement in medical care [3].

Coronary artery disease, either alone or in association with hypertension, is the most common cause of heart failure in Western developed countries, although it is very hard to determine what is the major etiology of heart failure in a patient with numerous potential causes (for example, coronary artery disease, hypertension, diabetes mellitus, atrial fibrillation) [4].

Heart failure and chronic kidney disease share in a multitude of risk factors, such as age, high blood pressure, diabetes, and coronary heart disease. And

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over 50% of heart failure patients may have moderate to severe renal insufficiency. The presence of chronic kidney disease in a patient with heart failure is associated with increased morbidity and mortality in these patients [5].

Heart failure is more likely to develop in 17–21% of patients with diagnosed CKD. An estimated 44% of patients on hemodialysis have heart failure [6]. Long-term of reduction in renal perfusion is thought to be one of the major mechanisms of deteriorated kidney function in patients with heart failure However, the estimated GFR was similar in Reduced ejection or preserved ejection heart failure. Reduced renal blood flow in heart failure may be explained by enhancement to enhancement in vasoconstrictive mediators (epinephrine, angiotensin II, Endothelin) and side effect of pharmacotherapy used in management of heart failure such as hypovolemic associated with diuresis, RAAS inhibitors, or drug-induced hypotension [7].

The aim of therapy for chronic heart failure is to relieve signs and symptoms, improve quality of life, decrease the need for hospitalizations, reduce mortality and prolong survival [8].

The main goals of heart failure therapy with or without renal insufficiency are to reduce preload and afterload, treat myocardial ischemia minimize left ventricular hypertrophy, and suppress neruohormonal hyperactivity, particularly the sympathetic nervous system as well as the renin-angiotensin-aldosterone [9]. Beta-blocker therapy is associated with a decreased risk of mortality or readmission in heart failure with chronic kidney disease [10].

Inhibition of the renin-angiotensin system is recommended for patients with HFrEF to minimize morbidity and mortality. ACEi ,ARNi or ARB are indicated as first-line therapy [11].

Aldosterone antagonists (spironolactone and eplerenone) block the adverse effects of aldosterone activation, which include increased sodium and water reabsorption, and increase myocardial remodeling and fibrosis Aldosterone antagonists are recommended for all heart failure patients with reduced ejection fraction in order to lower the mortality rate and hospitalization in addition to an ACE-I and a beta-blocker [11].

Dapagliflozin is a selective and reversible inhibitor of Sodium-glucose co-transporter-2 (SGLT2). SGLT2 proteins, which are expressed in the proximal convoluted tubule of the kidney, are mainly responsible for reabsorbing glucose and salt from the tubular lumen. SGLT2 inhibitors will decrease glucose reabsorption in the kidney resulting in glycosuria [12].

The majority of the benefits of SGLT2 inhibitors in heart failure are due to a decrease in sodium reabsorption in the renal tubule, Increased natriuresis and osmotic diuresis, as well as decreased plasma volume and blood pressure, result in a decrease in left ventricular preload and afterload [13].

The sympathetic nervous system and the renin-angiotensin-aldosterone system are also less activated when more sodium is delivered to the macula densa Additionally, higher ketone body production and usage by the heart improve cardiac metabolism and prevent myocardial remodeling. Another advantage of SGLT2i is that it has a nephroprotective effect due to afferent arteriolar constriction, which lowers glomerular hyperfiltration and urinary albumin excretion [14].

This study aimed to assess the safety and efficacy of dapagliflozin on renal function by measurement of glomerular filteration rate and creatinine level, among heart failure patients with chronic kidney disease with or without diabetes mellitus

### Ethical considerations

Ethical and scientific approvals were obtained from the scientific committee of the department of pharmacology/ College of medicine University of Baghdad and scientific Committee of Thi-Qar Health Department. The patients were informed that their personal information will not be used for any other reason other than the study purpose.

### Study population

The studied group included a total of 120 Iraqi adult patients diagnosed with left ventricular systolic dysfunction with impairment of renal function according to the American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines for the diagnosis and management Heart failure

## 2. Inclusion Criteria

1. patients with left ventricular dysfunction and estimated glomerular filtration rate (eGFR) ≥25 and ≤75 mL/min/1.73m2 (CKD-EPI Formula) at visit 1 regardless of the presence or absence of diabetes.
2. patients over 18 years old

### Exclusion criteria

Patients with type 1 diabetes mellitus, renal failure on dialysis, polycystic kidney disease or lupus nephritis. patients requiring or with a recent history of immunosuppressive therapy for kidney disease. Pregnant and lactating women. Patients who were lost to follow-up and stimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73m$^2$.

### Drug used

The patients used (dapagliflozin tablet, Farxiga, AstraZeneca) in aditional to conventional therapy. The dosage of dapagliflozine was 10 mg /day

## 3. Methods

120 Iraqi patients with left ventricular systolic Dysfunction with estimated glomerular filtration rate (eGFR) ≥25 and ≤75 mL/min/1.73m$^2$ were enrolled in this study. only 100 patients were completed follow_up the patients divided into two groups , first

group consist of 60 patients who received dapagliflozin 10 mg once daily in addition to conventional therapy and the other group consists of 60 patients received only conventional therapy were offered as needed including diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, mineralocorticoid receptor blockers and other drugs needed for management of underlying diseases or comorbidities.

All the selected patients were evaluated on day 1 as a baseline such information regarding sociodemographic, risk factors for cardiovascular disease and possible causes of left ventricular systolic dysfunction, a complication of heart failure, evaluation of renal function tests, evaluation of ejection fraction by echo study. clinical followed_up was done 4 months later by assessing the change in renal function test, ejection fraction, hemoglobin concentration, development of side effects and titrating of doses of study drug and other drugs needed by the patients for the study, a particular patients information sheet was created to record the information about each subject page.

parameter level measured by using Roche Cobas C311 Germany to Measurement of urea and Creatitine concentration, auto analyzer sysmex to Measurement of Hemoglobin, Echocardiography mindray.

## 4. Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data were presented as mean, standard deviation and ranges. Categorical data were presented by frequencies and percentages. Independent t-test and Analysis of Variance (ANOVA) (two tailed) was used to compare the continuous variables accordingly. Independent t-test (two tailed) was used to compare the continuous variables among study groups accordingly. A level of P – value less than 0.05 was considered significant.

## 5. Results

In the dapagliflozin group, patients' age ranged from 40 to 85 years with a mean of 63.46 and standard deviation (SD) of ± 11.20 years, and 20 patients (40%) aged ≥ 70 years. In the control group, the age ranged from 42 to 82 years with a mean of 62.42 ± 10.25 years, and 17 patients (34%) were found in the age group of (50 – 59) years.

Table 3.1: Sociodemographic and clinical characteristics of the study groups

| Patients' characteristics | Study Groups | | P- Value |
|---|---|---|---|
| | Dapagliflozin Group (%) n= 50 | Control Group (%) n= 50 | |
| Age (Years) | | | |
| 40 - 49 | 7 (14.0) | 4 (8.0) | 0.460 |
| 50 - 59 | 11 (22.0) | 17 (34.0) | |
| 60 - 69 | 12 (24.0) | 13 (26.0) | |
| ≥ 70 | 20 (40.0) | 16 (32.0) | |
| Gender | | | |
| Male | 39 (78.0) | 38 (76.0) | 0.812 |
| Female | 11 (22.0) | 12 (24.0) | |
| BMI | | | |
| Normal | 8 (16.0) | 16 (32.0) | 0.083 |
| Overweight | 28 (56.0) | 18 (36.0) | |
| Obese | 14 (28.0) | 16 (32.0) | |
| Smoking | | | |
| Smoker | 24 (48.0) | 30 (60.0) | 0.229 |
| Non-smoker | 26 (52.0) | 20 (40.0) | |
| Risk Factor | | | |
| Ischemic CMP | 39 (78.0) | 42 (84.0) | 0.128 |
| Atrial Fibrillation | 16 (32.0) | 13 (26.0) | 0.509 |
| HT | 38 (76.0) | 40 (80.0) | 0.629 |
| DM | 38 (76.0) | 31 (62.0) | 0.098 |
| Liver Disease | 1 (2.0) | 2 (4.0) | 0.558 |
| COPD | 2 (4.0) | 1 (2.0) | 0.558 |

Before treatment, the comparison in the mean levels of clinical parameters showed no statistically significant differences (P ≥ 0.05) between the dapagliflozin group and the control group in terms of all clinical parameters (Table 2).

Table 2: Comparison between study groups by certain clinical parameters, before treatment

| Clinical Parameters | Study Groups | | P - Value |
|---|---|---|---|
| | Dapagliflozin Group Mean ± SD | Control Group Mean ± SD | |
| Hemoglobin (g/L) | 11.85 ± 2.17 | 12.56 ± 1.80 | 0.178 |
| Urea (mg/dl) | 54.25 ± 26.22 | 47.71 ± 22.82 | 0.186 |
| Serum Creatinine (mg/dl) | 1.26 ± 0.28 | 1.37 ± 0.42 | 0.488 |
| GFR | 58.14 ± 14.42 | 56.10 ± 15.42 | 0.187 |
| EF% | 31.76 ± 7.54 | 32.28 ± 7.88 | 0.737 |
| SBP (mmHg) | 122.7 ± 23.01 | 125.9 ± 29.58 | 0.545 |
| DBP (mmHg) | 77.34 ± 12.09 | 78.74 ± 14.86 | 0.607 |

After treatment, we found that there was a statistically significant difference in the mean

levels of BMI, hemoglobin, serum creatinine, GFR, and blood pressure. Patients in the dapagliflozin group had significantly lower mean levels of BMI, serum creatinine, systolic and diastolic blood pressure compared with control group (BMI; 25.98 kg/m$^2$ vs 27.53 kg/m$^2$, P= 0.035), (serum creatinine; 1.32 mg/dl vs 1.79 mg/dl, P= 0.043), (systolic blood pressure; 109.4 mmHg vs 121.6 mmHg, P= 0.005), and (diastolic blood pressure; 67.16 mmHg vs 75.62 mmHg, P= 0.002). Further, hemoglobin and GFR levels were significantly increased in the dapagliflozin group than in the control group (12.53 g/L vs 11.88 g/L, P= 0.038) and (58.02 vs 54.12, P= 0.023), respectively. No significant difference was detected between the two groups in regard to blood urea and ejection fraction levels (Table 3).

Table 3: Comparison between study groups by certain clinical parameters, after treatment

| Clinical Parameters | Study Groups | | P - Value |
|---|---|---|---|
| | Dapagliflozin Group Mean ± SD | Control Group Mean ± SD | |
| BMI (kg/m$^2$) | 25.98 ± 2.92 | 27.53 ± 4.22 | 0.035 |
| Hemoglobin (g/L) | 12.53 ± 1.31 | 11.88 ± 1.71 | 0.038 |
| Urea (mg/dl) | 50.63 ± 20.49 | 51.14 ± 31.76 | 0.226 |
| Serum Creatinine (mg/dl) | 1.32 ± 0.36 | 1.79 ± 0.58 | 0.043 |
| GFR | 58.02 ± 18.70 | 54.12 ± 23.67 | 0.023 |
| EF% | 32.62 ± 9.56 | 30.22 ± 8.10 | 0.179 |
| SBP (mmHg) | 109.4 ± 18.52 | 121.6 ± 24.28 | 0.005 |
| DBP (mmHg) | 67.16 ± 11.37 | 75.62 ± 14.90 | 0.002 |

## Dapagliflozin group

In the dapagliflozin group, the comparison of clinical parameters before and after treatment revealed that BMI, systolic and diastolic blood pressure levels were significantly decreased after treatment compared to that before treatment (25.98 kg/m2 vs 28.08 kg/m2, P= 0.010), (109.4 mmHg vs 122.7 mmHg, P= 0.001), and (67.16 mmHg vs 77.34 mmHg, P= 0.001), respectively. On the other hand, hemoglobin level was significantly increased than pre-therapeutic level (12.53 g/L vs 11.85 g/L, P= 0.016). Other clinical parameters of this group including the ejection fraction, urea revealed no significant difference (P ≥ 0.05) before and after receiving the treatment (Table 4).

Table 4: Comparison of clinical parameters in the dapagliflozin group

| Clinical Parameters | Dapagliflozin Group Mean ± Std. Dev | P-Value |
|---|---|---|
| BMI (kg/m2) | | |
| Before Therapy | 28.08 ± 3.39 | 0.010 |
| After Therapy | 25.98 ± 2.92 | |
| Hemoglobin (g/L) | | |
| Before Therapy | 11.85 ± 2.17 | 0.016 |
| After Therapy | 12.53 ± 1.31 | |
| Urea (mg/dl) | | |
| Before Therapy | 54.25 ± 26.22 | 0.097 |
| After Therapy | 50.63 ± 20.49 | |
| Serum Creatinine (mg/dl) | | |
| Before Therapy | 1.26 ± 0.28 | 0.126 |
| After Therapy | 1.32 ± 0.36 | |
| GFR | | |
| Before Therapy | 58.14 ± 14.42 | 0.419 |
| After Therapy | 58.02 ± 18.70 | |
| EF% | | |
| Before Therapy | 31.76 ± 7.54 | 0.223 |
| After Therapy | 32.62 ± 9.56 | |
| SBP (mmHg) | | |
| Before Therapy | 122.7 ± 23.01 | 0.001 |
| After Therapy | 109.4 ± 18.52 | |
| DBP (mmHg) | | |
| Before Therapy | 77.34 ± 12.09 | 0.001 |
| After Therapy | 67.16 ± 11.37 | |

## Control group

After treatment, patients in the control group had significantly lower mean level of hemoglobin compared to baseline level (11.88 g/L vs 12.56 g/L, P= 0.001). No significant difference (P ≥ 0.05) was found in the mean levels of the other clinical parameters (Table 5).

| Table 5: Comparison of clinical parameters in the control group | | |
|---|---|---|
| Clinical Parameters | Control Group Mean ± Std. Dev | P-Value |
| BMI (kg/m2) | | |
| Before Therapy | 27.50 ± 4.21 | 0.912 |
| After Therapy | 27.53 ± 4.22 | |
| Hemoglobin (g/L) | | |
| Before Therapy | 12.56 ± 1.80 | 0.001 |
| After Therapy | 11.88 ± 1.71 | |
| Urea (mg/dl) | | |
| Before Therapy | 47.71 ± 22.82 | 0.097 |
| After Therapy | 51.14 ± 31.76 | |
| Serum Creatinine (mg/dl) | | |
| Before Therapy | 1.37 ± 0.42 | 0.088 |
| After Therapy | 1.79 ± 0.58 | |
| GFR | | |
| Before Therapy | 56.10 ± 15.42 | 0.558 |
| After Therapy | 54.12 ± 23.67 | |
| EF% | | |
| Before Therapy | 32.28 ± 7.88 | 0.086 |
| After Therapy | 31.22 ± 8.10 | |
| SBP (mmHg) | | |
| Before Therapy | 125.9 ± 29.58 | 0.317 |
| After Therapy | 121.6 ± 24.28 | |
| DBP (mmHg) | | |
| Before Therapy | 78.74 ± 14.86 | 0.206 |
| After Therapy | 75.62 ± 14.90 | |

## Side effects

Side effects among the patients in the dapagliflozin group were genital tract infection in 2 patients (4%), urinary tract infection in 4 patients (8%), volume depletion in 4 patients (8%) while hypoglycemia was recorded in one patient (Figure 1).

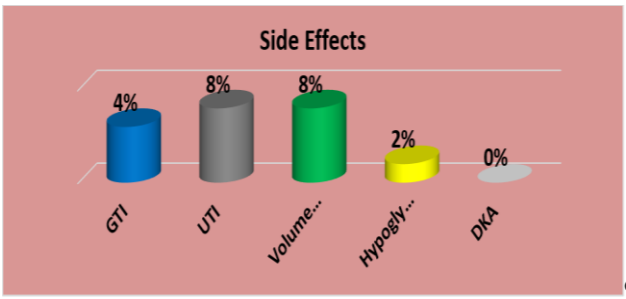


*Figure 1: Side effects among the patients in the dapagliflozin*

## 6. Discussion

Effect on renal function test from baseline to the end of treatment in our study, dapagliflozin compared with the control group showed slowed eGFR decline from 58.14 ± 14.42 to 58.02 ± 18.70 in the dapagliflozin group versus from 56.10 ± 15.42 to 54.12 ± 23.67 in the control group we found significant statistical differences between groups after the follow-up (p=0.023). The beneficial effects of SGLT2 inhibitors on renal function are thought to be caused by a number of mechanisms.

Firstly, SGLT2i slowing the progression of nephropathy by reductions in the renal absorption of glucose and sodium in the proximal tubules are thought to reduce hyperfiltration by increasing sodium delivery to the macula densa, which activates tubuloglomerular feedback, leading to afferent arteriolar vasoconstriction and a reduction in intraglomerular hyperfiltration. Osmotic diuresis induced by SGLT2i is particularly relevant in the reduction of interstitial volume overload [15]. SGLT2i also reduces kidney damage by inhibiting multiple pathways associated with tubular hypoxia and fibrosis, including as oxidative stress and inflammasome activity, regardless of diabetes.

Other contributory mechanisms of renoprotective of SGLT2 inhibitors may include decrease sympathetic activity, a reduction in blood pressure, sustained control of glycemia, reduction in body fat and body weight and a decrease in stress on the vascular wall due to natriuresis [16].

Among participants There was no statistical difference between dapagliflozin and control groups in effect on ejection fraction after therapy, (31.76 ± 7.54 vs 32.28 ± 7.88 p =0.737). Within the dapagliflozin group the mean of ejection fraction increased from 31.76 ± 7.54 to 32.62 ± 9.56 p= 0.223 but was not statistically significant while in the control group the mean of ejection fraction decreased from32.28 ± 7.88 to 31.22 ± 8.10 p =0.086 but not a significant statistic which is comparable to a study by Singh et al [17] which showed no significant effect of dapagliflozin on left ejection fraction. Mechanism of dapagliflozin in the improvement of ejection fraction by improving ventricular loading conditions and reducing preload via diuretic and natriuresis. SGLT-2 inhibitors can also reduce plasma volume by selectively reducing interstitial fluid, followed by reduced preload, decreased arterial stiffness, and blood pressure, which, in turn, would reduce afterload, leading to an improved coronary circulation Some researchers hypothesized that SGLT-2 inhibitors could block the

Na+/H+ exchanger (NHE) 1 isoform. By blocking NHE, SGLT-2 inhibitors may raise mitochondrial calcium levels while decreasing cytoplasmic sodium and calcium levels [18]

## Effect dapagliflozin on hemoglobin concentration

In our study, there was a significant Statistically significant difference between the two groups after treatment (11.88 ± 1.71 g/dL) in the control group and (12.53 ± 1.31 g/dL) in the dapagliflozin group p= 0.038. In dapagliflozin group, there was significant increase in concentration of dapagliflozin from 11.85 ± 2.17 g/dL to 12.53 ± 1.31 g/dL (p=0.016)

The result in our study agrees with an American study by Ghanim et al [19] which showed a significant increase in hemoglobin in the dapagliflozin group, from 13.4 ± 0.3 g/dL to 13.9 ± 0.4 g/dL (P = 0.02)

Several potential mechanisms lie behind the increased Hb concentration following dapagliflozin treatment, a potential mechanism that could explain the increase in hematocrit may be the result of decreased plasma volume brought on by SGLT2 inhibitor-related natriuresis and diuresis. Prior studies have demonstrated that SGLT2 inhibitor therapy temporarily raises EPO levels. Consequently, more erythropoiesis could be the cause of elevated hematocrit, Relative hypoxemia in the renal medulla may cause EPO to be produced after using SGLT2 inhibition. The distal tubule might be overworked as a result of sodium escaping proximal reabsorption, which would lead to a temporary rise in oxygen consumption and a fall in oxygen tension. Another mechanism by which dapagliflozin increases hematocrit by Hepcidin suppression and modification of other iron-regulating proteins [20].

Effect dapagliflozin on body mass index In the present study , after treatment ,there was a Statistically significant difference between dapagliflozin and control groups (25.98 ± 2.92 kg/m2) vs (27.53 ± 4.22 kg/$m^2$ ) p=0.035 .we found a decrease in body mass index in dapagliflozin groups ( 28.08 ± 3.39 kg/$m^2$ to 25.98 ± 2.92 kg/$m^2$ p= 0.010 ) but in the control group there was no statistical difference ( 27.50 ± 4.21 kg/m2 to 27.53 ± 4.22 kg/m2 p=0.912 ) after treatment which is aligned with Huang et al [21].that in which BMI significantly decreased from 26.13±2.35 kg/m2to 24.08±2.33 kg/m2 in dapagliflozin group but they did not find any significant statistical difference in the control group (25.94±2.51 kg/m2 to 25.3±2.21 kg/m2)

It is unclear how exactly SGLT2 inhibitors work to lower body weight Recent clinical trials showed that urinary glucose excretion and mild osmotic diuresis were two mechanisms by whichSGLT2 inhibitors induce weight loss and contributed to enhanced energy loss. [22].

Effect on blood pressure In the current study, Dapagliflozin group compared with the control group showed a significant clinically meaningful drop n both SBP from (122.7 ± 23.01 mmHg) to (109.4 ± 18.52 mmHg), p=0.001 and in DBP from (77.34 ± 12.0 mmHg) to (67.16 ± 11.37mmHg) p= 0.001.

The decrease in the dapagliflozin group in our study was more than in other studies such as the study by Papadopoulou et al [23]. who found the decrease in the dapagliflozin group was from(117.41 ± 10.52 mmHg )to(113.30 ± 8.75 mmHg) in SBP and from (78.88 ± 7.25 mmHg) to ( 77.25 ± 6.54 mmHg)

The mechanism by which SGL2 reduces blood pressure is not well understood. There are numerous hypotheses that attempt to explain this mechanism. SGLT2i may cause plasma volume contraction, resulting in a sharp decrease in blood pressure A additional study demonstrates that reducing SNS activity after 16 weeks contributes to long-term BP lowering. SNS activity may have been reduced due to improvements in hyperglycemia, insulin resistance, and hyperinsulinemia [24].

## Study limitations

Our study had several limitations, including a small number of patients and a short study time. Some parameters require a long period of time for results to be confirmed. The relatively short follow-up limits the longer-term changes in eGFR. We were unable to investigate the connection with other measures of renal function, such as urinary albumin: creatinine ratio because urinary albumin was not collected. our studies do not provide any additional information on how SGLT2 inhibitors preserve kidney function We did not collect any objective or quantitative data on food or exercise therapy. There was also no information on serum erythropoiesis markers such as iron, ferritin, transferrin, hepcidin, and reticulocytes.

# 7. Conclusion

1. Dapagliflozin significantly slowed the rate of decline eGFR
2. Dapagliflozin significant reduced body weight
3. Treatment with dapagliflozin resulted in clinically increases in hemoglobin concentration Which or and resulted in correction and prevention of anemia
4. Dapagliflozin resulted in a statistically significant reduction of systolic and diastolic blood pressues.

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