Effect of Dapagliflozin on hemoglobin level in heart failure patients with chronic kidney disease and/or diabetes

DOI: https://doi.org/10.32007/jfacmedbagdad.6441973

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Abstract:
Background: Heart failure is a complex clinical syndrome caused by any functional or structural cardiac disease that reduces the ventricle's ability to fill or pump blood. Anemia is frequent in patient with heart failure and is associated with deterioration through the activation of neuro-hormonal pathways. Dapagliflozin is a selective and reversible inhibitor of Sodium-glucose co-transporter-2 (SGLT2). Dapagliflozin increases hemoglobin level through different mechanisms such increasing plasma concentration by diuresis or increasing Erythropoietin synthesis.

Objective: To evaluate the effect of additional dapagliflozin into conventional therapy on hemoglobin in heart failure patients with chronic kidney disease (CKD) with or without diabetes mellitus DM.

Patients and Methods: This was prospective clinical study conducted at medical wards at Nasiriyah Heart Center during the period from the 1st November / 2021 to the end of July / 2022. The research was conducted on 120 participants with heart failure and renal impairment. The patients were divided into two groups. The first group included 60 patients who were administered dapagliflozin in addition to conventional medication and the other group consisted of 60 patients who received only conventional therapy. Both groups were matched regarding socio-demographic characteristics. Hemoglobin concentration, was recorded on day 1 as a baseline visit then followed up after four months.

Results: Before treatment there were no significant differences in sociodemographic and clinical parameters between the two groups. In the dapagliflozin group, hemoglobin level was significantly higher than pre-therapeutic level (12.53 g/L vs 11.85 g/L, P= 0.016). Patients in the control group had significantly lower mean level of hemoglobin after treatment compared to baseline level (11.88 g/L vs 12.56 g/L, P= 0.001).

Conclusion: The study shows that dapagliflozin increases the concentration of hemoglobin and corrects anemia in patients with heart failure with CKD compared to the control group.

Keywords: Heart failure, Dapagliflozin, Hemoglobin, CKD

Introduction:
According to the American Heart Association, heart failure (HF) is "a complex clinical syndrome that can emerge from any structural or functional cardiac disease that decreases the capacity of the ventricle to fill or pump blood [1] The European Society of Cardiology describes HF as referred to a clinical syndrome with well-known symptoms and signs, including fluid retention, pulmonary crackles, and dyspnea. Other signs include ankle edema, fatigue, and dyspnea. It is caused by dysfunction in the structure and/or function of the heart.

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as a result of which stroke volume is reduced and/or intracardiac pressures are elevated at rest or during activity [2]. The incidence of HF increases by 1% each year in persons over 65 years of age. Even with appropriate treatment, HF 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 HF hospitalizations. The rate of survival is increasing due to improvement in medical care [3]. Although it is difficult to determine the underlying etiology of HF in a patient with several potential causes, the most common causes of HF are Coronary artery diseases, atrial fibrillation, hypertension, and diabetes [4] HF and CKD share in a multitude of risk factors, such as age, high blood pressure, diabetes, and coronary heart diseases. Furthermore, more than half of all patients with HF may have moderate to severe renal insufficiency. Chronic renal disease is associated with...
higher mortality and morbidity in HF patients [5]. Anemia is common in HF patients, especially the elderly. Among the factors that contribute to the emergence of anemia in HF are iron deficiency, poor erythropoietin synthesis or resistance, stimulation of the renin-angiotensin-aldosterone system, the existence of underlying renal insufficiency, and activation of pro-inflammatory cytokines. [6] Patients with anemia have worse symptoms, more functional impairment, more rehospitalization, and higher mortality than those who do not have anemia. Darbepoetin, an erythropoiesis-stimulating hormone, does not lower the risk of mortality or hospitalization due to HF, but it did enhance the quality of life. According to several studies, intravenous iron improves symptoms, quality of life, and functional abilities. [7] Dapagliflozin is a selective and reversible inhibitor of Sodium-glucose co-transporter-2 (SGLT2) proteins, which are expressed in the proximal convoluted tubule of the kidney, and are mainly responsible for reabsorbing glucose and salt from the tubular lumen. SGLT2 inhibitors will decrease glucose reabsorption in the kidney resulting in glycosuria [8] The majority of the benefits of SGLT2 inhibitors in HF 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, resulting in a decrease in left ventricular preload and afterload [9]. Renin-angiotensin-aldosterone system and sympathetic nervous system are also less activated when more sodium is delivered to the macula densa. Additionally, higher ketone body production and usage by the heart improves cardiac metabolism and prevents 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 [10] Although the exact mechanisms by which SGLT2 inhibitors increase hemoglobin levels are not fully understood, the reduction in plasma volume carried on by diuresis and natriuresis may be the cause of the increase in hematocrit. Other mechanisms for increasing hemoglobin are enhanced erythropoiesis after SGLT2 inhibitor therapy, the reduction of hypoxia and oxidative stress in the tubular interstitial region of the renal cortex, as well as the restoration of interstitial fibroblast-like cells’ ability to produce Erythropoietin. SGLT2 inhibitors suppress hepcidin, which may lead to improved iron absorption and utilization as well as improved red blood cell formation. [11] This study aims to investigate the impact of dapagliflozin on hemoglobin among HF patients with renal impairment with or without diabetes mellitus.

**Patients and methods:**
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 study groups included a total of 120 adult Iraqi patients diagnosed with congestive HF 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 of HF.

**Exclusion 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.

**Methods:**

One hundred and twenty adult Iraqi patients with congestive HF and have an estimated glomerular filtration rate ≥25 and ≤75 mL/min/1.73m2 were enrolled in this study. Only 100 patients completed follow-up. The patients were divided into two groups, the first group consisted of 60 patients who received dapagliflozin 10 mg once daily in addition to the conventional therapy. The dosage of dapagliflozin was 10 mg /day

**Statistical analysis:**

The data were analyzed using the 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. The independent t-test and Analysis of Variance (ANOVA) (two tailed) were used to compare the continuous variables. A P – value of less than 0.05 was considered significant.

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

**Table 1: Sociodemographic and clinical characteristics of the study groups**

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Study Groups</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dapagliflozin (%)</td>
<td>Controls (%)</td>
</tr>
<tr>
<td></td>
<td>n=50</td>
<td>n=50</td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 – 49</td>
<td>7 (14.0)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>50 – 59</td>
<td>11 (22.0)</td>
<td>17 (34.0)</td>
</tr>
<tr>
<td>60 – 69</td>
<td>12 (24.0)</td>
<td>13 (26.0)</td>
</tr>
<tr>
<td>≥ 70</td>
<td>20 (40.0)</td>
<td>16 (32.0)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (78.0)</td>
<td>38 (76.0)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (22.0)</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8 (16.0)</td>
<td>16 (32.0)</td>
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<tr>
<td>Overweight</td>
<td>28 (56.0)</td>
<td>18 (36.0)</td>
</tr>
<tr>
<td>Obese</td>
<td>14 (28.0)</td>
<td>16 (32.0)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>24 (48.0)</td>
<td>30 (60.0)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>26 (52.0)</td>
<td>20 (40.0)</td>
</tr>
<tr>
<td><strong>Risk Factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>39 (78.0)</td>
<td>42 (84.0)</td>
</tr>
<tr>
<td>CMP</td>
<td>16 (32.0)</td>
<td>13 (26.0)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>38 (76.0)</td>
<td>40 (80.0)</td>
</tr>
<tr>
<td>DM</td>
<td>38 (76.0)</td>
<td>31 (62.0)</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>1 (2.0)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (4.0)</td>
<td>1 (2.0)</td>
</tr>
</tbody>
</table>

Before treatment, the mean levels of Hemoglobin showed no statistically significant differences (P ≥ 0.05) between the dapagliflozin group and the control group. After treatment, a statistically significant difference in the mean hemoglobin, the dapagliflozin group higher than the control group (12.5 g/L vs 11.9 g/L, P= 0.038) and (58.0 vs 54.1, P= 0.023), respectively (Table 2) In the dapagliflozin group, the mean hemoglobin level was significantly higher after treatment than the pre-therapeutic level (12.5 g/L vs 11.9 g/L, P= 0.016), whereas After treatment, patients in the control group had a significantly lower mean of hemoglobin level compared to baseline level (11.9 g/L vs 12.6 g/L, P= 0.001). (Table 2).

**Table 2: Comparison of the mean hemoglobin levels between the two study groups before and after treatment**

<table>
<thead>
<tr>
<th>Hemoglobin (g/L)</th>
<th>Study Groups</th>
<th>Controls</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Treatment</td>
<td>11.9 ± 2.17</td>
<td>12.6 ± 1.80</td>
<td>0.178</td>
</tr>
<tr>
<td>After treatment</td>
<td>12.5 ± 1.31</td>
<td>11.9 ± 1.71</td>
<td>0.038</td>
</tr>
<tr>
<td>T-test within the group</td>
<td>0.016</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

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

**Discussion:**
Baseline Socio-Demographic of the study population. The mean of patient’s age for both groups of 62 – 63 years was a little higher than the mean age (58 years) of the patients in the Iraqi study conducted at the Baghdad Teaching Hospital and the Iraqi Centre of Heart Diseases 2019 [12]. The male preponderance in both study groups agrees with the Egyptian study conducted at cardiology centers in 2020 representing diverse geographic regions of Egypt [13] About half of the participants in our study were smokers which is higher than in a European study 2020) [14] where 13% of participants were smokers. According to a John Hopkins Bloomberg School of Public Health study in 2022 smokers have a twofold increased risk of developing (HF) compared to nonsmokers [15]. Our study showed that most participants were either overweight or obese in both groups. Obesity has a deleterious impact on hemodynamics, LV structure, and function, and is connected to structural and functional cardiac problems. As a result, obesity is linked to an increase in the incidence and prevalence of HF [16] Risk factors and co-morbidities of study population at baseline. It can be hard to detect a particular cause of HF in patients. The majority of comorbid illnesses do not happen independently of HF, but rather share a number of risk factors and have a role in the pathogenesis of HF. In this study, it was found that the prevalence of ischemic heart disease or coronary artery disease was high in HF patients in both groups which agrees with the DAPA_HF study done by P. Jhund et al., 2021 [17] which ischemic heart disease was the
main cause of HF. In the current study, hypertension and DM were the most common comorbidities in both groups. About third of patients had atrial fibrillation in both groups. The proportion of patients with hypertension and atrial fibrillation in both groups in our study was similar to the study done by Conrad et al., 2018 [18] who found hypertension increased the incident cases of HF ,atrial fibrillation was present in (40%) of patients with HF . DM cases in our study was much higher than that in other studies such as including that of Groenewegen et al., 2020 [19] found DM in about 40% of patients with HF rEF. The high prevalence of DM in our study may be due to the Iraqi lifestyle and to the prevalent obesity or overweight. In our study, a high prevalence of hypertension was anticipated since hypertension exerts more strain on the heart and causes structural and functional abnormalities in the myocardium, including left ventricular enlargement, which can lead to HF [20]. Effect of dapagliflozin on hemoglobin concentration. In our study, in dapagliflozin group, there was a significant increase in the concentration of hemoglobin, which agrees with the results 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. Several potential mechanisms lie behind the increased hemoglobin concentration following dapagliflozin treatment. Apotential 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 is by Hepcidin suppression and modification of other iron-regulating proteins [21]. Study limitations. Our study had several limitations, including small sample size and a short study period. There was also no information on iron, reticulocyte, ferritin, transferrin, or hepcidin levels.

Conclusion:
Dapagliflozin leads to a significant increases in hemoglobin concentration, which can positively affect the management and prevention of anemia in patients with with CKD.

Authors’ contributions:
Ahmed Adel: collecting patients, following them up, and following up the analyses with doctors.

Dr. Tahseen AL Kinany: providing and supervising patients and following up the progress of their health condition.

Dr. Huda Al Kadi: supervising and following up the research.

References:
تأثير عقار داباجيغلوزين على مستوى هيموجلوبين في الدم

المقدمة: حدد عدل عبد طالب ماجستير فارماكولوجي كلية الطب / جامعة بغداد الدكتوراه؛ هي أرائه في فرع الفارماكولوجي كلية الطب / جامعة بغداد الدكتور تحسين علي الكناني / كلية الطب / جامعة بغداد

المختصر: قصور القلب هو مرض كلي بركاني مميت تنتج عن اضطراب قلب وظيفي أو هيكلي يجعل من ضعف القلب على تعويض الدم أو ضخه. فقر الدمشائع لدى مرضى قصور القلب ويرتبط بالتدفق من خلال تشويه المسار الجلوكوزية العصبية. عقار داباجيغلوزين هو مثبط انتقائي قابل للانعكاس للثاني عشرة المضاعفات المكملة للداتم (SGLT2). يزيد داباجيغلوزين من مستوى الهيموجلوبين في مرضى قصور القلب المصابين بمرض الكلى المزمن. 

الهدف: تقييم تأثير الداباجيغلوزين الإضافي على الهيموجلوبين في مرضى قصور القلب المصابين بمرض الكلى المزمن (CKD) أو بدون داء السكري DM وأو بدون نقص في الكلى.

المصطلحات المفتاحية: قصور القلب، داباجيغلوزين، داء السكري، مرض الكلى.

المراجعات:


