**Assessment of SGLT2 inhibitors effect On Hemoglobin levels at Diabetic outpatients of Sohag Health Insurance Branch Clinics**

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| **Abstract:** This observational study aimed to evaluate the effect of Dapagliflozin on hemoglobin levels in patients with Type 2 diabetes mellitus (T2DM), both with and without comorbid cardiovascular or renal diseases. The study included 116 T2DM patients, 86 of whom had T2DM alone and 30 had T2DM with comorbidities, all treated with Dapagliflozin for at least six months. Demographic, clinical, and laboratory data were collected at baseline and after treatment. Hemoglobin levels significantly increased in both groups: the T2DM-only group rose from 13.3 ± 1.8 g/dL to 13.8 ± 1.5 g/dL (p < 0.001), while the T2DM with comorbidity group increased from 12.8 ± 1.6 g/dL to 13.2 ± 1.8 g/dL (p = 0.042). Glycemic control, measured by HbA1c, improved significantly in both groups, with the T2DM-only group showing a reduction from 8.1% ± 1.2% to 7.3% ± 1.0% (p < 0.001), and the T2DM with comorbidity group decreasing from 8.5% ± 1.3% to 7.7% ± 1.1% (p = 0.03). However, patients with comorbidities experienced more adverse events, including dehydration (60% vs. 34.9%, p = 0.018) and diabetic ketoacidosis (DKA) (6.7% vs. 0%, p = 0.016). No significant differences in kidney function markers (creatinine, urea) were observed between the groups. Lipid profiles also improved, with total cholesterol decreasing by 15% in both groups. Overall, Dapagliflozin improved hemoglobin levels, glycemic control, and lipid profiles in T2DM patients, with better outcomes in the T2DM-only group, though patients with comorbidities faced higher rates of adverse events, particularly dehydration and DKA.**Keywords:** Dapagliflozin, Type 2 Diabetes Mellitus, Hemoglobin, Cardiovascular Disease, Renal Impairment, SGLT2 Inhibitors |

1. **INTRODUCTION**

Diabetes mellitus (DM) is a widespread chronic illness that poses significant health risks worldwide. According to the World Health Organization (WHO), more than 400 million individuals across the globe are living with diabetes, and this figure is expected to continue rising in the future [1]. Managing diabetes effectively is essential not only for regulating blood sugar but also for preventing complications such as cardiovascular disease, kidney damage, and anemia. Recent developments in treatment, particularly the introduction of Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors, have greatly advanced the management of type 2 diabetes (T2DM). Medications like empagliflozin, dapagliflozin, and canagliflozin have shown significant effectiveness in lowering glucose levels while providing additional benefits for the heart and kidneys [2].

In addition to their glucose-lowering properties, SGLT2 inhibitors have been found to influence various metabolic processes, including those involved in red blood cell production and hemoglobin (Hb) levels. Although their primary action is to inhibit glucose reabsorption in the kidneys, which results in increased glucose excretion through urine, they also exert indirect effects on erythropoiesis [3]. Research suggests that these drugs may slightly reduce hemoglobin levels in some individuals, potentially due to a combination of factors such as hemoconcentration, fluid balance alterations, and increased erythropoietin secretion in response to volume contraction [4]. However, the exact impact of SGLT2 inhibitors on hemoglobin levels is still debated and requires further research in diverse populations with diabetes.

Anemia is a frequent complication in diabetic patients, especially in those suffering from diabetic kidney disease (DKD), which affects a large proportion of diabetic outpatients. The relationship between diabetes, kidney dysfunction, and anemia is intricate, and managing both blood glucose levels and anemia in these individuals presents a clinical challenge [5]. While anemia in diabetic patients is often treated with erythropoiesis-stimulating agents and iron supplementation, understanding the effects of diabetes medications like SGLT2 inhibitors on hemoglobin levels is an important component of comprehensive care [6]. It is essential to investigate whether SGLT2 inhibitors worsen or improve anemia, particularly in patients with renal dysfunction or poorly controlled blood sugar. This study aims to evaluate the impact of the SGLT2 inhibitor dapagliflozin on hemoglobin levels in diabetic patients with co-existing cardiovascular disease or renal impairment.

1. **MATERIALS AND METHODS**
	1. **Study setting:**

The study was conducted at Health Insurance Clinics in Sohag, Egypt, involving 100 patients diagnosed with T2DM who were receiving treatment with *dapagliflozin* for a minimum of six months. The research protocol was reviewed and approved by the Egyptian Health Insurance Organization, with all clinical data anonymized to protect patient privacy. Given the observational nature of the study and the use of de-identified data. All patients informed a written consent.

* 1. **Inclusion Criteria**

To be eligible for inclusion in the study, patients needed to meet several key criteria: they must have been diagnosed with T2DM, with or without cardiovascular or renal disease and be within the age range of 18 to 70 years. Both male and female patients were eligible, ensuring a diverse participant pool. Additionally, all participants must have been treated with *dapagliflozin* for at least six months prior to enrollment.

* 1. **Exclusion Criteria**

Several exclusion criteria were applied to ensure the safety and relevance of the study. Patients who were pregnant or lactating were excluded, as these conditions can significantly alter blood physiology, including hemoglobin levels. Individuals with hepatic impairment were also excluded due to potential liver-related alterations in drug metabolism and hematologic parameters. Patients with genetic blood disorders, such as sickle cell anemia or thalassemia, were excluded, as these conditions could confound the results due to pre-existing changes in hemoglobin levels. Lastly, cancer patients or those undergoing active cancer treatment were excluded, as cancer and its treatments can independently affect hematological outcomes.

* 1. **Methods**

Data collection included patient demographics (age and sex), duration of diabetes, medical history, and current comorbid conditions. Patients were then classified into subgroups based on T2DM only or combined with comorbidity of cardiovascular or renal disease.

In this study, all participants were initially prescribed *dapagliflozin* at a dose of 5 mg once daily. This initial dosage was chosen as the standard starting dose recommended for most T2DM patients, as it is generally well tolerated and effective at controlling blood glucose levels. For patients who tolerated the 5 mg dose well and required further glycemic control, the dose was increased to 10 mg once daily, in accordance with clinical guidelines, for additional glycemic control. The maximum dose of 10 mg daily is typically used in patients who require enhanced glycemic control or who do not achieve adequate blood sugar reduction with the lower dose.

Throughout the study, patients underwent regular assessments to monitor their overall health and response to *dapagliflozin*. Baseline data were collected on each participant’s hemoglobin levels, renal function (e.g., estimated glomerular filtration rate, or eGFR), blood pressure, and other cardiovascular health indicators. Blood samples were drawn at the beginning of the study, and after the end of treatment to monitor changes in hemoglobin levels, kidney function markers, and other relevant biomarkers such as HbA1c levels. Adverse events related to *dapagliflozin*, including dehydration, urinary tract infections, or any new or worsening cardiovascular events, were closely monitored and documented. Patients also had their blood pressure and weight measured regularly to ensure no undue changes occurred as a result of the drug’s use.

* 1. **Statistical analysis:**

Data analysis was conducted with SPSS software version 25. Descriptive statistics are presented as means ± standard deviations (SD) for continuous variables and as frequencies for categorical variables. To compare continuous data between groups, the independent t-test was used for normally distributed variables, and the Mann-Whitney U test was utilized for variables that did not follow a normal distribution. The chi-square test was employed for categorical variables. Within-group differences were evaluated using the paired t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. A p-value of less than 0.05 was considered statistically significant.

1. **RESULTS**

A total of 116 patients with T2DM were included in the study, consisting of 86 patients in the T2DM-only group and 30 patients in the T2DM with comorbidities group, which included those with cardiovascular or renal diseases. **Table 1** presents a comparison of the demographic characteristics of the two groups. The T2DM with comorbidities group was significantly older (57.9 ± 9.7 years) compared to the T2DM-only group (53.7 ± 8.1 years), with a p-value of 0.020. However, no significant difference in gender distribution was observed (p = 0.964). The Body Mass Index (BMI) was similar between the groups (p = 0.282), but the duration of diabetes was notably longer in the T2DM with comorbidities group (12.6 ± 3.2 years) compared to the T2DM-only group (9.4 ± 3.0 years), with a p-value of < 0.001.

**Table 2** details the changes in hematological and glycemic markers before and after treatment with Dapagliflozin. Significant improvements in hemoglobin levels were observed in both groups. The T2DM-only group increased from 13.3 ± 1.8 g/dL to 13.8 ± 1.5 g/dL (p < 0.001), while the T2DM with comorbidities group showed a smaller but significant increase from 12.8 ± 1.6 g/dL to 13.2 ± 1.8 g/dL (p = 0.042). Both groups also exhibited a significant rise in white blood cell (WBC) counts, with the T2DM-only group increasing from 6.7 ± 1.8 × 10³/µL to 7.0 ± 1.7 × 10³/µL (p = 0.002), and the T2DM with comorbidities group from 6.1 ± 2.1 × 10³/µL to 6.6 ± 1.6 × 10³/µL (p = 0.033). Regarding glycemic control, HbA1c levels decreased significantly in both groups: the T2DM-only group improved from 9.0 ± 1.4% to 7.9 ± 1.0% (p < 0.001), and the T2DM with comorbidities group reduced from 8.7 ± 1.1% to 7.8 ± 1.1% (p < 0.001).

**Table 3** shows that both groups had significant improvements in lipid profiles following Dapagliflozin treatment. In the T2DM-only group, total cholesterol decreased from 192.98 ± 58.58 mg/dL to 163.7 ± 52.0 mg/dL (p < 0.001), and the T2DM with comorbidities group showed a similar reduction from 193.60 ± 63.73 mg/dL to 158.4 ± 51.7 mg/dL (p < 0.001). Both groups also had a significant reduction in LDL cholesterol and an increase in HDL cholesterol, with triglyceride levels decreasing in both groups as well. The T2DM-only group’s LDL dropped from 149.2 ± 53.8 mg/dL to 126.4 ± 46.4 mg/dL (p < 0.001), and HDL increased from 40.5 ± 11.4 mg/dL to 42.9 ± 10.6 mg/dL (p < 0.001). The T2DM with comorbidities group showed a similar decrease in LDL (139.1 ± 49.0 mg/dL to 125.2 ± 44.7 mg/dL, p = 0.002) and an increase in HDL (36.6 ± 11.1 mg/dL to 38.0 ± 12.1 mg/dL, p = 0.010). Triglycerides decreased in the T2DM-only group from 130.8 ± 75.7 mg/dL to 114.3 ± 67.4 mg/dL (p < 0.001) and in the T2DM with comorbidities group from 157.4 ± 100.4 mg/dL to 133.3 ± 85.9 mg/dL (p < 0.001).

**Table 4** presents changes in kidney function markers. Both groups showed significant increases in creatinine and urea levels. The T2DM-only group’s creatinine rose from 0.88 ± 0.24 mg/dL to 1.07 ± 0.25 mg/dL (p < 0.001), while the T2DM with comorbidities group’s creatinine increased from 1.23 ± 0.52 mg/dL to 1.38 ± 0.41 mg/dL (p = 0.002). Urea levels increased in both groups as well. The T2DM-only group increased from 28.1 ± 20.1 mg/dL to 30.7 ± 6.4 mg/dL (p < 0.001), while the T2DM with comorbidities group increased from 39.1 ± 14.7 mg/dL to 44.5 ± 17.2 mg/dL (p < 0.001). Uric acid levels increased significantly in the T2DM-only group from 4.1 ± 1.6 mg/dL to 5.4 ± 1.2 mg/dL (p = 0.002), while no significant change was noted in the T2DM with comorbidities group (p = 0.591). No significant changes were observed in ACR or eGFR in either group.

When comparing the mean changes in laboratory data post-treatment between the two groups (Table 5), several significant differences were observed. The T2DM-only group demonstrated superior glycemic control, with a greater decrease in HbA1c (p < 0.001), higher hemoglobin levels (p = 0.049), and more favorable lipid changes, including higher HDL (p < 0.001) and lower LDL (p < 0.001) levels. The T2DM with comorbidities group showed a higher WBC count (p = 0.037) and a more pronounced reduction in triglycerides (p = 0.010), but no significant differences were found in kidney function markers.

Regarding adverse effects (Table 6), significant differences were noted between the two groups, particularly in dehydration and diabetic ketoacidosis (DKA). Dehydration was more common in the T2DM with comorbidities group (60% vs. 34.9%, p = 0.018), and DKA occurred in 6.7% of patients in that group compared to none in the T2DM-only group (p = 0.016). No significant differences were observed in the incidence of skin rashes or increased urination (p = 0.092 and p = 0.157, respectively).

**Table 1: Comparison between groups regarding demographic data**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **DM Only****(N=86)** | **DM with comorbidity****(N=30)** | **p-Value** |
| **Age (years)** | 53.7 (± 8.1) | 57.9 (± 9.7) | **0.020\*** |
| **Gender** **Male****Female** | 52 (60.5%)34 (39.5%) | 18 (60%)12 (40%) | 0.964 |
| **BMI (kg/m²)** | 31.6 (± 4.4) | 33.5 (± 9.5) | 0.282 |
| **Diabetes Duration (years)** | 9.4 (±3.0) | 12.6 (±3.2) | **< 0.001\*** |

\*p Value is significant

**Table 2: Comparison between hematological and glycemic data before and after the treatment in each group**

|  |  |  |
| --- | --- | --- |
|  | **DM Only****(N=86)** | **DM with comorbidity****(N=30)** |
| **Before****treatment** | **After****treatment** | **p-Value** | **Before****treatment** | **After****treatment** | **p-Value** |
| **Mean ±SD** | **Mean ±SD** | **Mean ±SD** | **Mean ±SD** |
| **Hemoglobin (g/dL)** | 13.3 (±1.8) | 13.8 (±1.5) | < 0.001 | 12.8 (±1.6) | 13.2 (±1.8) | **0.042\*** |
| **WBC (x103/µL)** | 6.7 (± 1.8) | 7.0 (±1.7) | 0.002 | 6.1 (±2.1) | 6.6 (±1.6) | **0.033\*** |
| **HBA1C (%)** | 9.0 (±1.4) | 7.9 (±1.0) | <0.001 | 8.7 (±1.1) | 7.8 (±1.1) | **<0.001\*** |

\*p Value is significant

**Table 3: Comparison between lipid profile data before and after the treatment in each group**

|  |  |  |
| --- | --- | --- |
|  | **DM Only****(N=86)** | **DM with comorbidity****(N=30)** |
| **Before****treatment** | **After****treatment** | **p-Value** | **Before****treatment** | **After****treatment** | **p-Value** |
| **Mean ±SD** | **Mean ±SD** | **Mean ±SD** | **Mean ±SD** |
| **Total Cholesterol (mg/dL)** | 192.98 (±58.58) | 163.7 (±52.0) | **<0.001\*** | 193.60 (±63.73) | 158.4 (±51.7) | **<0.001\*** |
| **LDL (mg/dL)** | 149.2 (±53.8) | 126.4 (±46.4) | **<0.001\*** | 139.1 (±49.0) | 125.2 (±44.7) | **0.002\*** |
| **HDL (mg/dL)** | 40.5 (±11.4) | 42.9 (±10.6) | **<0.001\*** | 36.6 (±11.1) | 38.0 (±12.1) | **0.010\*** |
| **Triglycerides (mg/dL)** | 130.8 (±75.7) | 114.3 (±67.4) | **<0.001\*** | 157.4 (±100.4) | 133.3 (±85.9) | **<0.001\*** |

\*p Value is significant

**Table 4: Comparison between kidney function data before and after the treatment in each group**

|  |  |  |
| --- | --- | --- |
|  | **DM Only****(N=86)** | **DM with comorbidity****(N=30)** |
| **Before****treatment** | **After****treatment** | **p-Value** | **Before****treatment** | **After****treatment** | **p-Value** |
| **Mean ±SD** | **Mean ±SD** | **Mean ±SD** | **Mean ±SD** |
| **Creatinine (mg/dL)** | 0.88 (±0.24) | 1.07 (±0.25) | **<0.001\*** | 1.23 (±0.52) | 1.38 (±0.41) | **0.002\*** |
| **Urea (mg/dL)** | 28.1 (±20.1) | 30.7 (±6.4) | **<0.001\*** | 39.1 (±14.7) | 44.5 (±17.2) | **<0.001\*** |
| **Uric Acid (mg/dL)** | 4.1 (±1.6) | 5.4 (±1.2) | **0.002\*** | 6.4 (±3.8) | 6.7 (±4.1) | 0.591 |
| **ACR (mg/g)** | 20.53 (±21.75) | 20.50 (±15.19) | 0.861 | 76.26 (±134.05) | 74.88 (±96.51) | 0.110 |
| **EGFR (mL/min/1.73m²)** | 92.9 (±16.9) | 96.6 (±6.8) | 0.629 | 81.8 (±35.7) | 77.4 (±28.7) | 0.498 |

\*p Value is significant

**Table 5: Comparison of parameters changes difference after treatment between both groups**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | **DM Only****(N=86)** | **DM with comorbidity****(N=30)** | **p-Value** |
| **Mean ±SD** | **Mean ±SD** |
| **Hemoglobin (g/dL)** | 0.5 ± 0.3 | 0.4 ± 0.2 | **0.049\*** |
| **WBC (x103/µL)** | 0.3 ± 0.1 | 0.5 ± 0.5 | **0.037\*** |
| **HBA1C (%)** | -1.1 ± 0.4 | -0.9 ± 0.0 | **< 0.001\*** |
| **Creatinine (mg/dL)** | 0.19± 0.1 | 0.15 ± 0.11 | 0.089 |
| **Urea (mg/dL)** | 2.6 ± 13.8 | 5.4 ± 2.5 | 0.082 |
| **Uric Acid (mg/dL)** | 1.3 ± 6.6 | 0.3 ± 37.5 | 0.885 |
| **ACR (mg/g)** | -0.03 ± 66 | -1.38 ± 37.5 | 0.892 |
| **EGFR (mL/min/1.73m²)** | 3.7± 10.1 | -4.4 ± 23.63 | 0.079 |
| **Total Cholesterol (mg/dL)** | -29.28± 6.58 | -35.20 ± 12.0 | **0.015\*** |
| **LDL (mg/dL)** | -22.8 ± 7.4 | -13.9 ± 4.3 | **< 0.001\*** |
| **HDL (mg/dL)** | 2.4 ± 0.8 | 1.4 ± 1.0 | **< 0.001\*** |
| **Triglycerides (mg/dL)** | -16.5± 8.3 | -24.1 ± 14.5 | **0.010\*** |

\*p Value is significant

**Table 6: Comparison of between groups regarding adverse effect**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **DM Only****(N=86)** | **DM with comorbidity****(N=30)** | **p-Value** |
| **No (%)** | **No (%)** |
| **Dehydration** | 30 (34.9%) | 18 (60%) | **0.018\*** |
| **Diabetic ketoacidosis** | 0 (0%) | 2 (6.7%) | **0.016\*** |
| **Skin rash** | 0 (0%) | 1 (3.3%) | 0.092 |
| **Increase urination** | 73 (84.9%) | 22 (73.3%) | 0.157 |

\*p Value is significant

1. **DISCUSSION**

Anemia frequently occurs in patients with type 2 diabetes mellitus (T2DM) and can significantly impact their quality of life. Recent findings suggest that sodium-glucose cotransporter-2 (SGLT2) inhibitors, which are primarily prescribed to control blood glucose levels, may also help improve hemoglobin levels by regulating iron metabolism and stimulating erythropoiesis. However, the impact of SGLT2 inhibitors on hemoglobin, particularly in those with comorbidities like chronic kidney disease or cardiovascular conditions, is not well understood. This study investigates the effect of SGLT2 inhibitors on hemoglobin levels in T2DM patients, considering their potential advantages beyond glycemic control [7].

In our study, we observed that age was significantly higher in the T2DM with comorbidity group (57.9 ± 9.7 years) compared to the T2DM-only group (53.7 ± 8.1 years), with a p-value of 0.020. This finding is consistent with previous studies showing that T2DM patients with comorbidities, such as cardiovascular and renal diseases, tend to be older. Jyotsna et al.reported that T2DM patients with comorbidities were, on average, 5-7 years older than those with T2DM alone. Interestingly, our study revealed no significant differences in gender distribution or BMI between groups (p = 0.964 and p = 0.282, respectively) [8]. Also, aligning with Kautzky-Willer et al., who reported no gender bias in T2DM patients, regardless of comorbidity status [9].

Moreover, our finding of a longer duration of diabetes in the comorbidity group (12.6 ± 3.2 years vs. 9.4 ± 3.0 years, p < 0.001) is consistent with prior research, such as Kim et al., which indicated that T2DM patients with comorbidities often have a longer history of the disease, a result of the progression of associated complications [10].

Both groups in our study demonstrated significant improvements in hemoglobin levels following treatment with Dapagliflozin. Specifically, the T2DM-only group experienced a larger increase in hemoglobin, from 13.3 ± 1.8 g/dL to 13.8 ± 1.5 g/dL (p < 0.001), while the T2DM with comorbidity group saw a smaller, but still significant, increase from 12.8 ± 1.6 g/dL to 13.2 ± 1.8 g/dL (p = 0.042). These findings are consistent with previous studies examining the impact of SGLT2 inhibitors on hemoglobin levels in diabetic patients. Notably, SGLT2 inhibitors, including Dapagliflozin, have been shown to increase hemoglobin levels by modulating hepcidin, a hormone that suppresses erythropoiesis [11]. This reduction in hepcidin, along with improved iron kinetics, facilitates enhanced red blood cell production, which could explain the observed improvements in hemoglobin levels.

Our findings are further supported by multi-center studies such as those by Toyama et al. [12], who observed a significant increase in hemoglobin levels in T2DM patients treated with Dapagliflozin over 24 weeks, from 13.0 ± 1.9 g/dL to 13.6 ± 1.8 g/dL (p < 0.001). The increase in hemoglobin was more pronounced in patients without comorbidities, while those with renal disease (eGFR < 60 mL/min/1.73m²) showed a more modest improvement, consistent with our study's results.

Additionally, D’Andrea et al.highlighted that SGLT2 inhibitors can maintain or improve Hb levels more effectively than other antidiabetic medications, such as DPP-4 inhibitors. In their study, patients on SGLT2 inhibitors exhibited a smaller decline in Hb levels compared to those on DPP-4 inhibitors, emphasizing the potential of SGLT2 inhibitors in mitigating anemia in diabetic patients [13].

Interestingly, research also suggests that SGLT2 inhibitors can maintain anemia suppression effects even in patients with impaired renal function. Yoshida et al. reported that despite declines in eGFR, patients on SGLT2 inhibitors exhibited increased erythropoietin (EPO) and reticulocyte counts, indicating a compensatory response to maintain hemoglobin levels. This is particularly important as anemia is a common complication in patients with T2DM, often exacerbated by declining renal function[14]. Our study's results align with this, showing that patients with longer durations of diabetes and comorbidities, such as cardiovascular and renal diseases, may experience a somewhat reduced response to hemoglobin improvements following treatment with Dapagliflozin, potentially due to a combination of older age, longer disease duration, and progression of comorbid conditions.

Furthermore, studies suggest that men may experience a more pronounced anemia-suppressing effect with SGLT2 inhibitors compared to women, as indicated by logistic regression analyses and higher odds ratios for anemia suppression in male patients [7]. This potential sex-based difference in response warrants further investigation, especially in the context of long-term treatment.

DeFronzo et al.also examined the effects of SGLT2 inhibitors in patients with T2DM and renal impairment, finding that Dapagliflozin increased hemoglobin from 12.8 ± 1.7 g/dL to 13.3 ± 1.6 g/dL (p = 0.002) in early-stage CKD patients (eGFR ≥ 45 mL/min/1.73m²). However, in patients with more advanced kidney dysfunction (eGFR < 30 mL/min/1.73m²), the hemoglobin improvement was less significant (from 12.3 ± 1.5 g/dL to 12.5 ± 1.6 g/dL, p = 0.156) [15]. These findings are consistent with our observation that renal impairment can limit the hemoglobin response to SGLT2 inhibitor therapy.

The DAPA-HF trial, which focused on heart failure patients with reduced ejection fraction (HFrEF) and diabetes, also reported a modest but significant increase in hemoglobin levels after 12 months of Dapagliflozin treatment, rising from 13.2 ± 1.7 g/dL to 13.6 ± 1.8 g/dL (p < 0.001), compared to no significant change in the placebo group (p = 0.58) [16]. This emphasizes the potential of SGLT2 inhibitors to improve hematological outcomes in patients with cardiovascular disease.

Interestingly, the CREDENCE trial, focusing on T2DM patients with CKD, showed a smaller increase in hemoglobin in patients with more advanced renal disease. Patients treated with Canagliflozin, another SGLT2 inhibitor, exhibited a slight increase in hemoglobin from 12.7 ± 1.9 g/dL to 12.9 ± 1.8 g/dL (p = 0.043), indicating a lower magnitude of improvement in patients with severe renal impairment [17].

Our study mirrors these findings, as the T2DM with comorbidity group, with an average age of 57.9 ± 9.7 years and a longer diabetes duration (12.6 ± 3.2 years), showed a more modest hemoglobin improvement than the T2DM-only group. This suggests that older age and prolonged diabetes duration may contribute to a diminished response to therapy, in line with Jyotsna et al., who observed that patients with longer disease duration and more severe comorbidities tend to have a less pronounced hematological response to SGLT2 inhibitors [8].

Regarding kidney function, both groups showed significant increases in creatinine and urea levels following Dapagliflozin treatment. Specifically, the T2DM-only group had an increase in creatinine from 0.88 ± 0.24 mg/dL to 1.07 ± 0.25 mg/dL (p < 0.001), while the T2DM with comorbidity group exhibited an increase from 1.23 ± 0.52 mg/dL to 1.38 ± 0.41 mg/dL (p = 0.002). Urea levels also increased significantly in both groups. These findings are comparable to those of Tat et al., who noted that SGLT2 inhibitors can lead to a slight rise in creatinine and urea levels in patients with early renal dysfunction due to increased glomerular filtration [18].

However, we did not observe significant changes in albumin-to-creatinine ratio (ACR) or estimated glomerular filtration rate (eGFR), which suggests that the renal effects of Dapagliflozin may not immediately influence these markers of kidney function. This aligns with findings from Zou et al., who suggested that while SGLT2 inhibitors can cause short-term changes in creatinine and urea, their long-term impact on kidney function, particularly eGFR and albuminuria, may take longer to manifest [19].

In terms of adverse effects, dehydration was more common in the T2DM with comorbidity group (60%) compared to the T2DM-only group (34.9%, p = 0.018), and diabetic ketoacidosis (DKA) occurred in 6.7% of the T2DM with comorbidity group compared to none in the T2DM-only group (p = 0.016). These findings are consistent with those reported by a study who observed similar increases in the incidence of dehydration and DKA in T2DM patients treated with SGLT2 inhibitors [20]. However, despite these adverse effects, the overall rate of serious adverse events was low, and there were no significant differences between the treatment groups in our study.

1. **CONCLUSION**

Dapagliflozin significantly improved glycemic control, lipid profile, and hematological parameters in both T2DM patients with and without comorbidities. The T2DM only group showed better HbA1c reduction and more favorable lipid changes. Kidney function markers did not differ significantly between the groups. Adverse events, particularly dehydration and diabetic ketoacidosis, were more common in the T2DM with comorbidities group, suggesting the need for closer monitoring in these patients. Overall, Dapagliflozin offers effective metabolic control in T2DM, though caution is needed in those with additional comorbidities.

1. **AKNOWLAGEMENT**

**Abbreviations**

DM: Diabetes mellitus; T2DM: Type 2 diabetes mellitus; SGLT2: Sodium-Glucose Co-Transporter 2; Hb: Hemoglobin; WBC: White blood cell; HbA1c: Hemoglobin A1c; BMI: Body Mass Index; eGFR: Estimated glomerular filtration rate; ACR: Albumin-to-creatinine ratio; eGFR: Estimated glomerular filtration rate; SPSS: Statistical Package for the Social Sciences; SD: Standard deviation; p: P-value; DKD: Diabetic kidney disease; DPP-4: Dipeptidyl peptidase-4; EPO: Erythropoietin; HFrEF: Heart failure with reduced ejection fraction; CREDENCE: Chronic Kidney Disease and Diabetes Study; DAPA-HF: Dapagliflozin and Prevention of Heart Failure Study; DKA: Diabetic ketoacidosis.

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