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Impact of Sodium-Glucose Cotransporter-2 Inhibitors on Hemoglobin and Hematocrit: A Retrospective Analysis (SGLT-2 Inhibitors & Hemoconcentration)

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ABSTRACT

Background: Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors, such as Dapagliflozin and Empagliflozin, are a class of medications used in the management of type 2 diabetes mellitus and, more recently, heart failure and chronic kidney disease. An observed secondary effect of these drugs is an increase in hematocrit (Hct) and hemoglobin (Hb) levels. The mechanisms and clinical significance of these changes are still under investigation. Large cardiovascular outcome trials did not demonstrate a consistent signal for increased thromboembolic events; details on this subject will be mentioned in the discussion section. This study aims to analyze the effect of dapagliflozin and empagliflozin treatment on Hct and Hb in a cohort of 97 patients in our hospital.

Methods: We conducted a retrospective analysis of a dataset containing information on 97 patients treated with either Dapagliflozin (n = 58) or Empagliflozin (n = 39). The dataset included baseline and 3–6-month follow-up measurements of Hct and Hb, along with demographic and clinical data such as age, BMI, smoking status, and diabetes mellitus (DM) status.

Results: Both Dapagliflozin and Empagliflozin were associated with a numerical increase in mean Hct and Hb levels over a 3–6-month period. The increase in hemoglobin/hematocrit was statistically significant for the Empagliflozin group ($p = 0.0107$), but not for the Dapagliflozin group ($p = 0.0642$). There was no statistically significant difference in the magnitude of change in either Hct or Hb between the two drug classes. ANOVA revealed a significant difference in Hct change across different dose groups ($p = 0.0327$), with Dapagliflozin 10mg and Empagliflozin 25mg showing the largest increases. A significant negative correlation was found between baseline hematological parameters and their subsequent change, suggesting a greater effect in patients with lower baseline values.

Conclusion: This analysis supports existing evidence that SGLT2 inhibitors increase hematocrit and hemoglobin. The effect on hematocrit is dose-dependent and slightly more noticeable with Empagliflozin. These findings add to the growing body of knowledge on the pleiotropic effects of SGLT2 inhibitors and highlight the need for further studies to elucidate the mechanisms underlying these hematological changes and their long-term clinical implications.

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Introduction

Sodium-glucose cotransporter 2 inhibitors have become a cornerstone in the management of Type 2 Diabetes (T2D); recently, their indications have been extended to the treatment of HF and CKD regardless of diabetic status [1]. This class of drugs includes Dapagliflozin and Empagliflozin, which primarily exert their effects by inhibiting glucose reabsorption in the proximal renal tubules. This effect leads to glycosuria and subsequently lowers blood glucose levels. In addition to their metabolic effects, SGLT2 inhibitors also exhibit significant cardiovascular and renal protective effects [2].

The modest but consistent increase in hematocrit and hemoglobin levels is an increasingly recognized secondary effect of SGLT2 inhibitor therapy [3].

Understanding hematological effects associated with SGLT2 inhibitors is clinically important. Increased oxygen-carrying capacity may further contribute to the observed cardiovascular benefit, especially in HF patients [4]. On the other hand, concerns about increased blood viscosity and the risk of thromboembolic events have been raised, although this has not been consistently observed in large clinical trials [5].

This study aims to contribute to understanding these effects by analyzing a real-world dataset of 97 patients treated with Dapagliflozin or Empagliflozin. We seek to quantify changes in Hct and Hb over a 3–6-month period and to explore the influence of drug type, dose, and other patient characteristics, including age, BMI, smoking status, and diabetes mellitus.

Methods

Study Design and Data Source

This was a retrospective, observational analysis conducted at our local hospital. The initial cohort was identified through a comprehensive review of the hospital's pharmacy database, which included all adult patients, with or without diabetes, who had been prescribed either Dapagliflozin (10mg, 5mg) or Empagliflozin (10mg, 25mg) as monotherapy or as a combination with Metformin. This initial database extraction yielded 308 patient records.

The study lasted only 6 months, from June 2024 to December 2024. The 3–6-month follow-up interval for assessment of hemoglobin and hematocrit was selected pragmatically, reflecting routine clinical practice at our institution, where patients are typically reviewed approximately every three months following initiation of SGLT2 inhibitor therapy. Furthermore, only patients with normal volume status who initiated treatment with Dapagliflozin or Empagliflozin at our local hospital were included in the final analysis. Exclusion criteria were subsequently applied. Patients were excluded if they were using iron supplements, diuretics, erythropoiesis-stimulating agents, or HIF-prolyl hydroxylase inhibitors, had received a blood transfusion in the previous 30 days, had an eGFR of 30 mL/min or lower, or had stopped SGLT2 inhibitors or ACEI /ARB therapy within the past 30 days.

Data collected included demographic information (age, gender), clinical characteristics (BMI, smoking status, DM status), and hematological parameters (Hb and Hct) measured at baseline and after 3 to 6 months of treatment. Hematocrit and hemoglobin measurements were performed in accordance with standardized laboratory procedures and collected following the institution's routine hospital protocols.
Patients who had started the medications at an external facility or whose initiation records were incomplete were excluded.

After applying these exclusion criteria, the final study cohort comprised 97 patients; these patients represent the population for whom complete treatment initiation and follow-up data are available within our hospital system.

Data Analysis

Descriptive statistics (mean, standard deviation) were calculated for baseline characteristics and for the changes in hematological parameters for each treatment group. The following statistical tests were performed:

- Paired t-tests were used to compare baseline and follow-up Hb and Hct values within each drug class to determine whether the observed changes were statistically significant.
- Independent two-sample t-tests were used to compare the mean ΔHb and ΔHct between the dapagliflozin and empagliflozin groups.
- One-way Analysis of Variance (ANOVA) was conducted to assess whether there were significant differences in ΔHb and ΔHct across the four different dose groups.
- Pearson correlation coefficients were calculated to examine the relationships between ΔHb and ΔHct and continuous variables, including age, BMI, and baseline hematological values.
- Stratified analyses were performed to explore the influence of gender, smoking status, and DM status on the hematological response to SGLT2 inhibitors.

A p-value of < 0.05 was considered statistically significant for all tests.

Results

Patient Characteristics

The analysis included 97 patients, with a mean age of 51.5 ± 10.3 years and a mean BMI of 30.4 ± 5.6 kg/m². The cohort consisted of 64 males (66%) and 33 females (34%). Most patients had a diagnosis of diabetes mellitus (88.7%). Fifty-eight patients (59.8%) were treated with Dapagliflozin and 39 (40.2%) with Empagliflozin.

Changes in Haematocrit and Haemoglobin

Both drug classes were associated with an increase in mean Hct and Hb levels from baseline to the 3–6-month follow-up. For the Empagliflozin group, the mean Hct increased from 43.20% to 44.42%, a statistically significant change (p=0.0107). The Dapagliflozin group showed a similar trend, with mean Hct increasing from 43.29% to 44.09%, but this change did not reach statistical significance (p=0.0642). The changes in Hb were not statistically significant for either group.

When comparing the two drugs directly, there was no significant difference in the mean change in either Hb (p=0.5313) or Hct (p=0.5273) between the Dapagliflozin and Empagliflozin groups. The results are summarized in Table 2 and Figures 1A and 1B.

Table 1: Baseline Characteristics of the Study Cohort

Characteristic	Value
Number of patients, n	97
Age, mean ± SD (years)	51.5 ± 10.3
BMI, mean ± SD (kg/m²)	30.4 ± 5.6
Sex, n (%)	Male: 64 (66.0) Female: 33 (34).
Diabetes mellitus, n (%)	86 (88.7)
SGLT2 inhibitor treatment, n (%)	Dapagliflozin: 58 (59.8). Empagliflozin 39 (40.2).

Table 2: Changes in Hematological Parameters Following SGLT2 Inhibitor Therapy

Outcome	Finding
Change in Hct and Hb (overall)	Both Dapagliflozin and Empagliflozin were associated with a numerical rise in mean hematocrit (Hct) and hemoglobin (Hb) over 3–6 months.
Hct change (within-group comparison)	- Dapagliflozin: Increase not statistically significant (p = 0.0642) - Empagliflozin: Significant increase (p = 0.0107)
Between-group comparison (Dapagliflozin vs empagliflozin)	No significant difference in the magnitude of Hct or Hb change between the two agents.
Dose-response (ANOVA)	Significant difference in Hct change across dose groups (p = 0.0327).
Doses with the largest Hct increase	Dapagliflozin 10 mg and Empagliflozin 25 mg.
Correlation with baseline values	Significant negative correlation between baseline Hct/Hb and subsequent change, indicating greater increases in patients with lower starting levels.

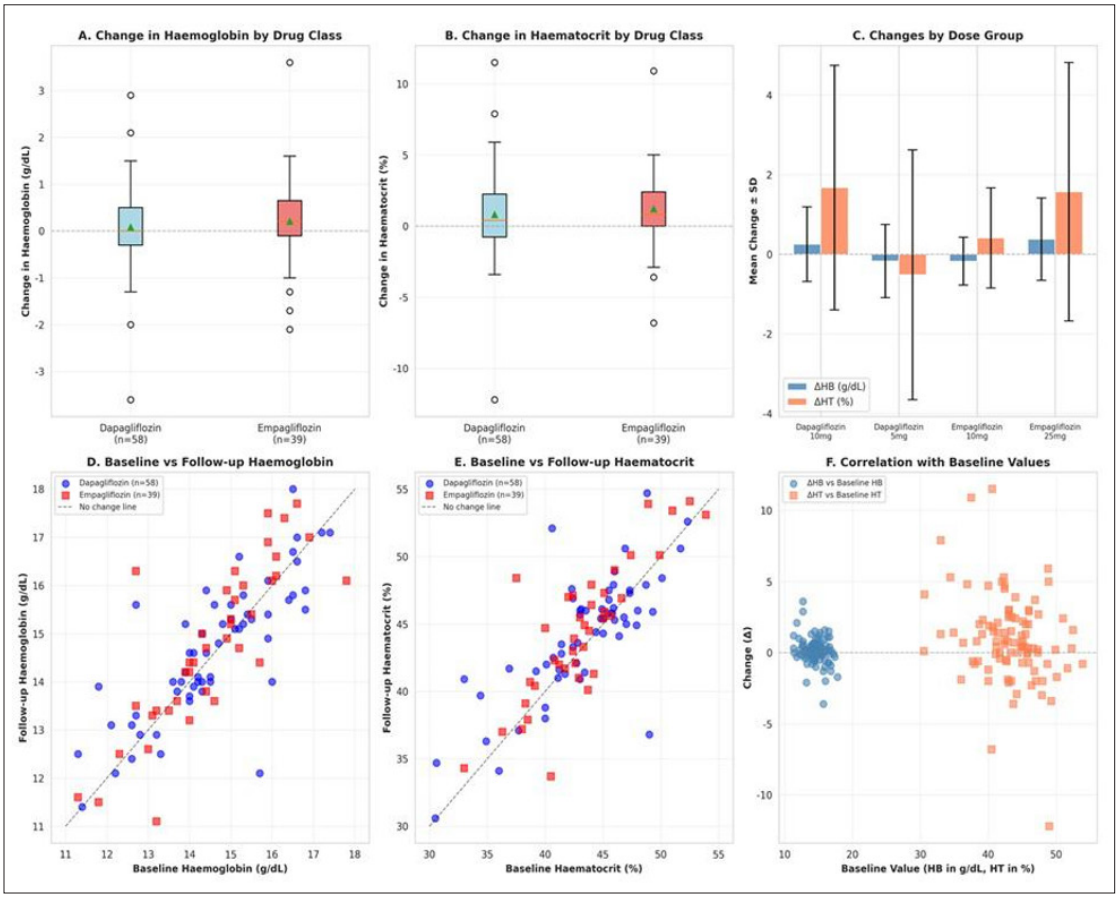

Figure 1: This Figure Presents a Comprehensive Analysis of the Haematological Changes Observed in the Study. (A) Moreover, (B) Shows the Distribution of Changes in Haemoglobin and Haematocrit by Drug Class. (C) Illustrates the Mean Changes Across Different Dose Groups. (D) Moreover, (E) Plot the Follow-Up Values Against Baseline Values for Haemoglobin and Haematocrit, respectively. (F) Explores the Correlation Between Baseline Haematological Values and Their Subsequent Change

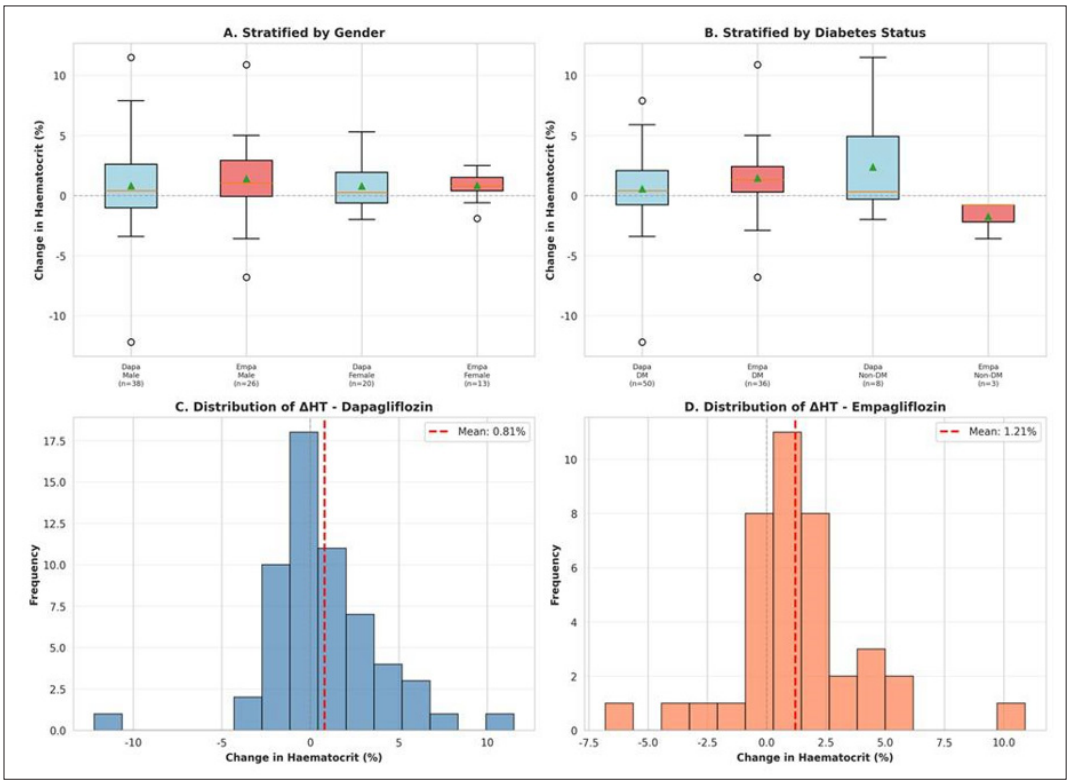

Figure 2: This Figure Details the Stratified Analysis of Haematocrit Changes. (A) Moreover, (B) Shows the Change in Haematocrit Stratified by Gender and Diabetes Status, respectively. (C) Moreover, (D) Shows the Distribution of Haematocrit Changes for the Dapagliflozin and Empagliflozin Groups

Dose Dependent Effects

ANOVA revealed a statistically significant difference in haematocrit change across the four dose groups (F=3.0449, p=0.0327). As shown in Figure 1C, the largest increases in Hct were observed in the Dapagliflozin 10mg (+1.67%) and Empagliflozin 25mg (+1.57%) groups. Conversely, the Dapagliflozin 5mg group showed a slight decrease in mean Hct. No significant dose-dependent effect on haemoglobin was observed.

Correlation with Other Factors

We investigated the influence of several patient characteristics on the observed hematological changes. There was no significant correlation between changes in Hb or Hct and patients' age or BMI.

However, a significant negative correlation was found between the baseline hematological values and their change over the study period. Specifically, patients with lower baseline Hb and Hct levels experienced a greater increase in these parameters (Δ Hb vs Hb 0: r=-0.2564, p=0.0112; Δ Hct vs Hct 0: r=-0.2749, p=0.0064). This relationship is visualized in Figure 1F.

Multivariable Linear Regression Analysis Report

This report presents the results of a multivariable linear regression analysis conducted to evaluate the impact of various predictors on the change in Hemoglobin (ΔHb) and Hematocrit (ΔHct). The analysis adjusted for Age, Sex, BMI, Diabetes Status (DM), Drug type, and Dose. The details of the linear regression analysis report are shown in Tables 3 and 4.

Table 3: The Model for ΔHb Shows that Dose is a Statistically Significant Predictor of the Change in Hemoglobin Levels

Variable	Coefficient (β)	Std. Error	t-statistic	P-value	95% Conf. Interval
Intercept	0.6609	0.910	0.726	0.470	[-1.149, 2.471]
Sex (Male)	0.1285	0.239	0.537	0.593	[-0.348, 0.605]
Diabetes (Yes)	-0.0218	0.335	-0.065	0.948	[-0.688, 0.645]
Drug (Empa)	-0.5340	0.350	-1.528	0.130	[-1.229, 0.161]
Age	-0.0114	0.011	-1.025	0.308	[-0.033, 0.011]
BMI	-0.0163	0.020	-0.804	0.424	[-0.056, 0.024]
Dose	0.0525	0.022	2.366	0.020*	[0.008, 0.097]

Table 4: Like ΔHb, the Model for ΔHct Identifies Dose as the Primary Significant Predictor

Variable	Coefficient (β)	Std. Error	t-statistic	P-value	95% Conf. Interval
Intercept	4.0884	2.936	1.393	0.168	[-1.752, 9.929]
Sex (Male)	0.5286	0.773	0.684	0.496	[-1.008, 2.066]
Diabetes (Yes)	-0.4619	1.081	-0.427	0.670	[-2.613, 1.689]
Drug (Empa)	-1.6218	1.128	-1.438	0.154	[-3.865, 0.622]
Age	-0.0294	0.036	-0.823	0.413	[-0.101, 0.042]
BMI	-0.1024	0.065	-1.569	0.120	[-0.232, 0.027]
Dose	0.1676	0.072	2.342	0.022*	[0.025, 0.310]

The conclusion of the multivariable linear regression analysis indicates that Dose is significantly associated with increases in both Hemoglobin (ΔHb) and Hematocrit (ΔHct) levels, even after adjusting for age, sex, BMI, diabetes status, and drug type. Specifically:

- For every 1 mg increase in dose, ΔHb is expected to increase by approximately 0.0525 units.
- For every 1 mg increase in dose, ΔHct is expected to increase by approximately 0.1676 units.

Other factors, such as Age, Sex, BMI, and Diabetes status, did not show a statistically significant independent effect on the changes in these hematological parameters within this specific cohort.

Analysis Overview

The dataset was preprocessed to calculate the changes in Hemoglobin and Hematocrit from baseline to the 3–6-month follow-up. Categorical variables were encoded, and rows with missing values in the specified predictors or outcomes were excluded to ensure a robust analysis.

Stratified Analysis

Stratified analyses were conducted to assess the impact of gender, smoking, and diabetes status. While there were some numerical differences in the mean changes across subgroups, no clear, consistent patterns emerged.

For instance, in both males and females, Empagliflozin was associated with a slightly larger increase in Hct compared to Dapagliflozin. Small sample sizes limited the analysis in some subgroups, particularly among non-diabetic patients and smokers. The results of the stratified analysis are presented in Figure 2.

Discussion

In the current analysis comprising 97 patients, we confirm that therapy with the SGLT2 inhibitors Dapagliflozin and Empagliflozin is indeed associated with increases in both hematocrit and hemoglobin over 3-6 months. Our findings are consistent with an emerging literature describing this effect across many patient groups [6,7].

The main result of our analysis is a statistically significant rise in hematocrit in the Empagliflozin group and a similar, though nonsignificant, trend in the Dapagliflozin group. The lack of significance for Dapagliflozin might be attributable to a particular dose distribution in our cohort or to residual unmeasured confounding. Interestingly, our ANOVA results suggest a dose-response relationship in hematocrit, the higher the dose of both drugs, the greater the increase in hematocrit. This is consistent with the conclusions of larger clinical trials [8].

While no statistically significant difference was found between the overall effects of Dapagliflozin and Empagliflozin, some real-world studies suggest that Empagliflozin may have a more potent effect on hematocrit elevation [9]. Our data demonstrates a numerical trend in that direction, but confirmation would require a larger sample size.

The negative correlation between baseline hematological values and their subsequent change is a noteworthy finding. Patients with lower baseline Hb and Hct levels, approaching anemia, could benefit most from the erythropoietic effects of SGLT2 inhibitors. This could be an important clinical consideration, especially among patients with CKD or HF, for whom anemia is a highly prevalent and prognostically significant comorbidity [10].

The underlying mechanism of these hematological changes is likely multifactorial. Although hemoconcentration may contribute, particularly in the early stage of therapy, the sustained increase in red cell mass suggests a more direct effect on erythropoiesis [11]. Studies indicate that SGLT2 inhibitors may enhance renal oxygenation and decrease breakdown of hypoxia-inducible factor (HIF), thereby increasing EPO production [12,13]. Additionally, SGLT2 inhibitors have been shown to improve iron homeostasis by reducing hepcidin levels, a key regulator of iron availability [14]. This improved iron utilization may further support increased red blood cell production.

From a pathophysiological standpoint, increased red cell mass raises whole-blood viscosity, which in turn alters shear stress, enhances platelet margination toward the vascular endothelium, and promotes platelet activation and thrombin generation. Experimental and clinical data have consistently shown that higher hematocrit levels increase blood viscosity in a nonlinear fashion, particularly at low shear rates, thereby impairing microvascular flow and favoring a prothrombotic milieu [15,16]. In patients with Polycythemia vera, elevated hematocrit is directly associated with increased risk of both arterial and venous thrombosis, and strict hematocrit control (<45%) significantly reduces cardiovascular death and major thrombotic events, as demonstrated in the CYTO-PV study [17]. These findings provide strong clinical proof-of-concept that even modest increases in hematocrit may translate into clinically meaningful thrombotic risk in susceptible populations.

Although large cardiovascular outcome trials with SGLT2 inhibitors—such as EMPA-REG OUTCOME and DECLARE-TIMI 58—did not demonstrate a consistent signal for increased thromboembolic events, these trials were not specifically designed or powered to evaluate hematocrit-mediated thrombosis, and patients with markedly elevated baseline hematocrit were uncommon in the enrolled populations [2-18]. Therefore, while clinically significant polycythemia or thrombosis appears rare in the context of SGLT2 inhibitor therapy, the well-established

association between elevated hematocrit, hyper-viscosity, and thrombotic risk in other conditions, particularly myeloproliferative disorders, supports consideration of closer hematologic monitoring in high-risk individuals [12-17]. In patients with baseline hematocrit values near the upper reference limit, even modest pharmacologically induced increases may theoretically shift viscosity into a range associated with higher thrombotic risk [17-19]. Therefore, the association of SGLT2 inhibitors with improved outcomes or potential risks is still not clear

Several limitations exist in this study. Being a retrospective analysis of a small dataset, it is prone to possible confounding variables and selection bias. The 3-6month follow-up is relatively short, and long-term changes in hematological parameters are missing. More importantly, EPO levels or iron studies were not available, without which the exact underlying mechanism could not be elucidated.

Conclusion

In summary, this study adds to the growing real-world evidence that treatment with Dapagliflozin and Empagliflozin is associated with a quantifiable increase in both hematocrit and hemoglobin. The increase in hematocrit is dose-dependent and was marginally statistically significant in the Empagliflozin group. The magnitude of the increase was greater among patients with low baseline hematological values. These findings further underscore the complex and pleiotropic effects of SGLT2 inhibitors. To date, although short-term increases in hemoglobin and hematocrit have been consistently observed, the long-term hematological effects of these agents remain incompletely understood. Additional research with extended follow-up is required to elucidate better the clinical implications of these hematologic changes, including their potential therapeutic benefits and possible risks.

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