Original Article

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The Impact of SGLT2 Inhibitors on Hemoglobin Levels in Type 2 Diabetes: Potential Benefits Beyond Glycemic and Renal Outcomes

Emre Hoca, Nilsu Kalayci

University of Health Sciences Türkiye, Istanbul Haseki Training and Research Hospital, Clinic of Internal Medicine, Istanbul, Türkiye

Abstract

Aim: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are antidiabetic agents with proven cardiovascular and renal benefits. Recent evidence suggests they may also increase hemoglobin (Hb) levels through mechanisms beyond hemoconcentration. This study aimed to evaluate the effect of SGLT2 inhibitors on Hb levels in type 2 diabetes mellitus (T2DM) patients without anemia or advanced kidney disease.

Methods: The data of 12,511 patients who attended the diabetes outpatient clinic between November 2023 and March 2025 were scanned retrospectively. Among them, 216 T2DM patients were analyzed; 130 were using SGLT2 inhibitors (dapagliflozin or empagliflozin). Laboratory and demographic data were compared between users and non-users. Correlation and multivariate linear regression analyses were performed.

Results: Hemoglobin levels were significantly higher in SGLT2 inhibitor users than non-users (14.44±1.23 vs. 13.76±1.12 g/dL, $p<0.001$). This effect was consistent across SGLT2 agents and independent of glycemic control, renal function, or liver enzymes. Male gender and serum creatinine were also positive predictors of Hb levels. Hemoconcentration alone could not explain the increase in Hb and may reflect improved erythropoiesis via renal mechanisms.

Conclusion: Sodium-glucose cotransporter 2 inhibitor use is associated with elevated Hb levels in T2DM patients, supporting their potential role in anemia prevention in the course of chronic diseases.

Keywords: Anemia, diabetes mellitus, erythropoiesis, hemoglobins, sodium-glucose transporter 2 inhibitors

Introduction

Diabetes mellitus (DM) is one of the most common causes of mortality and morbidity worldwide, affecting people of all ages, genders, and communities, with an increasing prevalence (1,2). Many comorbidities may develop during diabetes, and these may lead to a decrease in the quality of life and an increase in mortality (3-5). For this reason, the aim of recently developed and still being developed antidiabetic drugs is to benefit from their sugar-lowering effects and prevent possible comorbidities.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the drug group recommended for first-line treatment in almost all current guidelines in the course of type 2 diabetes (T2D) due to their favorable effects in all these conditions (6,7). Sodium-glucose cotransporter 2 inhibitors are oral antidiabetic agents that increase urinary glucose excretion by inhibiting SGLT2 cotransporters responsible for glucose reabsorption in the proximal tubules of the kidneys and provide glycemic control through an insulin-independent mechanism. The concomitant increased sodium excretion reverses tubuloglomerular feedback, and thus, intraglomerular pressure is reduced. This is the basic pathophysiology of the positive renoprotective effects of this group of drugs (8,9). In addition, osmotic diuresis is due to increased sodium excretion, and consequently, cardiovascular protective effects occur by

Corresponding Author: Emre Hoca, MD, University of Health Sciences Türkiye, Istanbul Haseki Training and Research Hospital, Department of Internal Medicine, Istanbul, Türkiye

E-mail: emrehoca89@gmail.com **ORCID:** orcid.org/0000-0003-4232-7362

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reducing cardiac stress due to volume reduction (10). In numerous clinical and observational studies conducted in recent years, significant increases in hemoglobin (Hb) and hematocrit (Hct) levels have been observed in patients using SGLT2 inhibitors (11,12). These increases cannot be explained solely by hemoconcentration resulting from intravascular volume reduction caused by their diuretic effects. Increasing evidence suggests that more complex physiopathological mechanisms, such as increased erythropoietin (EPO) production from peritubular capillary cells as a result of reduced renal hypoxia, suppression of renal inflammation, reduction of oxidative stress and improvement of tubulointerstitial microcirculation, are involved in this effect.

We hypothesized that the use of SGLT2 inhibitors in patients with T2DM would be associated with higher Hb levels compared to non-users, independent of glycemic control or renal function. Investigating the effect of SGLT2 inhibitors on Hb levels may help clarify whether these agents contribute to anemia management and their established role in glycemic control and cardiorenal protection. Besides demonstrating our clinical experience, we aimed to evaluate the change in Hb levels in individuals with T2D using SGLT2 inhibitors and provide data on the hematological effects of these agents. In addition to other positive effects of SGLT2 inhibitors, it was also aimed to evaluate the possibility of their use in the correction of anemia, which can be seen in the course of some chronic diseases.

Materials and Methods

Compliance with Ethical Standards

This retrospective, cross-sectional study was approved by the University of Health Sciences Türkiye, Istanbul Haseki Training and Research Hospital Scientific Research Ethics Committee (approval no.: 58-2024, date: 01.08.2024). The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

Participants

The data of 12,511 patients who attended the diabetes outpatient clinic between November 2023 and March 2025 were analyzed retrospectively. Patient and laboratory data were collected and analyzed using the hospital information operating system. All data of patients were anonymized. Being older than 18 years old, having a Hb level above 12 g/dL for women and 13 g/dL for men [by the World Health Organization's (WHO) diagnostic criteria for anemia], having T2D, and having accessible history and treatment records were defined as inclusion criteria. Hemoglobin levels below the WHO -defined anemia thresholds, iron or vitamin B12 deficiency, ongoing iron replacement or EPO therapy, hepatic failure, hematologic malignancy, and advanced renal dysfunction-specifically chronic kidney disease (CKD) stages 4-5 or acute kidney injury-as defined by the Kidney disease: Improving Global Outcomes classification were determined as exclusion criteria. Two hundred sixteen patients met the inclusion criteria and were enrolled in the study, as shown in the flow diagram (Figure 1). Due to national drug availability and regulatory approval, only dapagliflozin and empagliflozin are in routine clinical use in Türkiye. Consequently, the SGLT2 inhibitor group in this study consisted exclusively of patients receiving either of these two agents. Since only 3 patients in our cohort were using SGLT2 inhibitors as monotherapy, we included patients who used SGLT2 inhibitors in combination with other antidiabetic medications [metformin, sulfonylureas, dipeptidyl peptidase–4 (DPP-4) inhibitors, pioglitazone, and insulins]. To evaluate the independent effect of SGLT2 inhibitors on Hb levels and minimize the confounding influence of other antidiabetic drugs, we performed multiple regression analyses adjusting for concomitant medication use. Few patients were using glucagon-like peptide-1 receptor agonists; they were not included in the statistical analysis. Since SGLT2 inhibitors have been available in our country and our clinic only since 2018, it was possible to obtain data regarding the duration of their

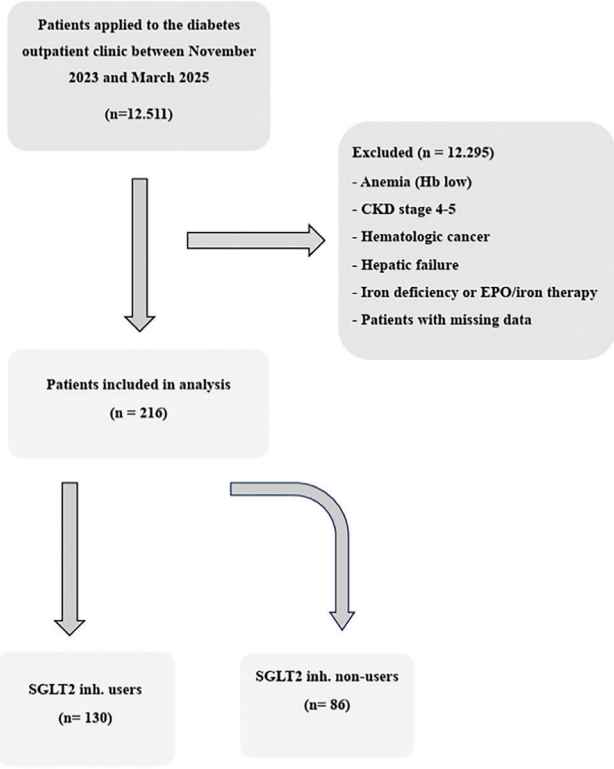

Figure 1. Flow diagram of the study
SGLT2: Sodium-glucose cotransporter 2, CKD: Chronic kidney disease, EPO: Erythropoietin, Hb: Hemoglobin

use. However, due to limitations in the hospital information system and the absence of comprehensive national drug records for earlier periods, it was not feasible to access reliable data on the duration of use for other antidiabetic medications that have been on the market for a longer time.

Data Collection

Information on patients' age, gender, and antidiabetic treatment regimens was extracted from their medical records. Laboratory results-including fasting blood samples collected after a minimum of 8 hours without food-were used to assess parameters such as complete blood count, liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], lipid profile [total cholesterol, low-density lipoprotein, high-density lipoprotein (HDL), triglycerides], HbA1c, fasting glucose, urea, creatinine, and spot urine protein-to-creatinine ratio. Where necessary, additional data were retrieved from the hospital's electronic medical record system to ensure completeness. Complete blood count parameters, including Hb concentration, were measured using the Mindray BC-6800 Plus Auto Hematology Analyzer (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). Hemoglobin concentration was determined photometrically after conversion to methemoglobin using the M-6LH LYSE reagent as part of Mindray's proprietary diluent and lysing system.

Statistical Analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences version 25.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive data were summarized as mean ± standard deviation, and when appropriate, median, maximum, and minimum values were also reported to reflect variable distributions better. Categorical variables were compared using the chi-square test. The Kolmogorov-Smirnov test was used to determine the normality of continuous variables. Comparisons between the two groups were conducted using the t-test or the Mann-Whitney U test based on the data distribution. Correlative analyses between Hb and clinical or biochemical variables (e.g., age, lipid profile, renal markers) were performed using Spearman's or Pearson's correlation coefficients, selected based on the underlying distribution characteristics of each parameter. Patients were categorized as "+" for users and "-" for non-users according to medication use for subgroup analyses. In multivariate analysis, we included SGLT2 inhibitor use and relevant demographic/clinical data to explore their independent associations with Hb levels. A p-value of <0.05 was considered statistically significant.

Results

Two hundred sixteen patients with T2DM were included in the study, of whom 130 (60.2%) were using SGLT2 inhibitors and 86 (39.8%) were not. The mean age of the participants was 57.09±8.9 years, and 49.5% were female. The baseline demographic and laboratory characteristics of the patients are presented in Table 1. There were no statistically significant differences in age, gender distribution, glycemic parameters (HbA1c, glucose), or lipid profiles between the two groups (Table 2).

The mean Hb level was significantly higher in the SGLT2 inhibitor group compared to non-users (14.44±1.23 vs. 13.76±1.12 g/dL, $p<0.001$) (Table 2, Graphic 1). Subgroup analysis revealed that this increase was consistent among both dapagliflozin (14.45±1.17 g/dL) and empagliflozin (14.40±1.27 g/dL) users, (Table 3, Figure 2). In gender-stratified analysis, Hb levels were significantly higher in males than females (14.84±1.08 vs. 13.49±0.98 g/dL, $p<0.001$) (Table 3). High-density lipoprotein, cholesterol levels were significantly higher in female patients than in males (47.1±11.6 vs. 40.4±9.4 mg/dL, $p<0.001$).

More detailed subgroup analyses showed no difference in Hb levels between patients with and without other antidiabetic drugs (metformin, DPP-4 inhibitors, sulfonylureas, pioglitazone, and insulin). The distribution of concomitant antidiabetic medications differed between the SGLT2 inhibitor user group (n=130) and the non-user group (n=86). Metformin was more frequently used among SGLT2 inhibitor users than non-users (83.8% vs. 67.4%) (Table 4).

Correlation analyses demonstrated that Hb levels were negatively associated with age ($r=-0.217$, $p=0.001$), diabetes duration ($r=-0.187$, $p=0.006$) and HDL-cholesterol ($r=-0.241$, $p<0.001$), while positively correlated with creatinine ($r=0.248$, $p<0.001$), white blood cell (WBC) count ($r=0.163$, $p=0.017$), and AST ($r=0.164$, $p=0.016$) (Table 5).

In the multivariate linear regression analysis (Table 6), male gender ($B=1.160$, $p<0.001$), serum creatinine levels ($B=0.884$, $p=0.010$), and use of SGLT2 inhibitors ($B=0.643$, $p<0.001$) were found to be independent positive predictors of Hb levels. Age was identified as a significant negative predictor ($B=-0.020$, $p=0.008$).

Table 1. Baseline clinical and demographic characteristics of all participants		
Variable	**Mean ± SD**	**Median (min.-max.)**
Age (years)	57.09±8.9	58 (23-80)
Gender (F/M)	107/109	
HbA1c (%)	7.93±1.64	7.8 (5.1-15.5)
Glucose (mg/dL)	156.41±560.2	139 (58-430)
Total cholesterol (mg/dL)	177.58±41.2	176 (97-326)
HDL-cholesterol (mg/dL)	43.7±11.1	42 (23-73)
LDL-cholesterol (mg/dL)	101.04±35.17	96 (30-251)
Triglyceride (mg/dL)	169.92±104.81	141 (41-685)
Hb (g/dL)	14.17±1.23	14 (12-17.3)
WBC (10^3/μL)	8.27±2.05	7.98 (4.73-17.17)
PLT (10^3/μL)	260.77±66.15	252 (90-607)
Urea (mg/dL)	34.68±10.52	34 (12-76.1)
Creatinine (mg/dL)	0.88±0.21	0.84 (0.5-1.81)
AST (U/L)	16.18±8.99	14 (6-64)
ALT (U/L)	25.98±17.14	22 (5-146)
Spot urine P/C ratio (mg/day)	205.95±311.68	132 (8-3028)

SD: Standard deviation, F: Female, M: Male, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, P/C: Protein to creatinine ratio

Table 2. Comparison of laboratory and demographic parameters between SGLT2 inhibitor users and non-users			
Variable	**SGLT2 inh. (+) (n=130)**	**SGLT2 inh. (-) (n=86)**	**p**
Age (years)	56.72±8.78	57.66±9.27	0.449
Gender (F/M)	62/68	45/41	0.505
Diabetes duration (years)	9.83±5.11	10.12±4.83	0.675
HbA1c (%)	7.94±1.64	8.02±2.08	0.755
Glucose (mg/dL)	153.97±59.54	160.09±61.49	0.466
Total cholesterol (mg/dL)	175.05±40.00	181.41±42.87	0.268
HDL-cholesterol (mg/dL)	44.25±11.20	42.88±10.88	0.372
LDL-cholesterol (mg/dL)	97.99±34.00	105.65±36.60	0.118
Triglyceride (mg/dL)	168.17±102.60	172.57±108.61	0.763
Hb (g/dL)	14.44±1.23	13.76±1.12	**<0.001**
WBC (10^3/μL)	8.47±2.17	8.03±1.83	0.125
PLT (10^3/μL)	265.10±72.04	254.23±55.85	0.238
Creatinine (mg/dL)	0.85±0.19	0.92±0.23	**0.025**
Urea (mg/dL)	35.09±9.46	34.08±11.99	0.492
ALT (U/L)	25.00±15.30	27.45±19.60	0.386
AST (U/L)	15.59±8.05	17.07±10.23	0.238
Spot urine P/C ratio (mg/day)	197.02±318.45	218.96±303.43	0.210

Statistical significant p values were expressed in bold ($p \leq 0.05$)
SGLT2 inh.: Sodium-glucose transporter 2 inhibitors, F: Female, M: Male, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, P/C: Protein to creatinine ratio

Table 3. Subgroup comparison of hemoglobin levels by SGLT2 agent type and gender			
SGLT2 inh.	**Hb (Mean ± SD)**	**Hb [Min.-max. (median)]**	**p**
Empagliflozin (n=92)	14.40±1.27	12.2-17.1 [14.3]	0.831
Dapagliflozin (n=38)	14.45±1.17	12.1-17.3 [14.3]	
Gender			**p**
Female (n=107)	13.49±0.98	12-17 (13.3)	**<0.001**
Male (n=109)	14.84±1.08	13-17.3 (14.8)	
Statistical significant p values were expressed in bold (p≤0.05) SGLT2 inh.: Sodium-glucose transporter 2 inhibitors, Hb: Hemoglobin			

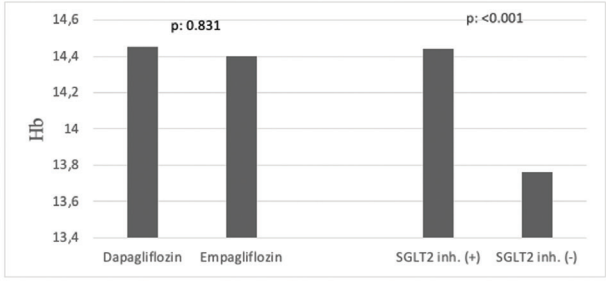

Figure 2. Comparison of mean hemoglobin levels between SGLT2 İnhibitor users and non-users
SGLT2: Sodium-glucose transporter 2, Hb: Hemoglobin

Table 4. Distribution of concomitant antidiabetic medications in SGLT2 inhibitor users and non-users			
Antidiabetic Medication	**SGLT2 inh. users (n=132)**	**Non-users (n=84)**	**p-value**
Metformin	84.1% (111)	66.7% (56)	**0.003**
DPP-4 inhibitors	53.8% (71)	47.6% (40)	0.377
Pioglitazone	26.5% (35)	34.5% (29)	0.209
Sulfonylureas	12.1% (16)	17.9% (15)	0.241
Insulin	53.8% (71)	66.7% (56)	0.061
Statistical significant p values were expressed in bold (p≤0.05) SGLT2 inh.: Sodium-glucose transporter 2 inhibitors, DPP-4: Dipeptidyl peptidase-4			

Table 5. Correlations between hemoglobin levels and clinical parameters		
	R	**p**
Age*	-0.217	**0.001**
Diabetes duration*	-0.187	**0.006**
SGLT2 inh. duration*	0.014	0.871
HbA1c*	-0.077	0.261
LDL-cholesterol*	-0.035	0.610
HDL-cholesterol*	-0.241	**<0.001**
Triglyceride*	0.103	0.132
Creatinine*	0.248	**<0.001**
Urea*	-0.047	0.489
WBC*	0.163	**0.017**
PLT*	-0.051	0.456
ALT**	0.079	0.248
AST*	0.164	**0.016**
Spot urine P/C **	-0.151	0.051
*Pearson correlation, **Spearman (non-parametric) correlation ***Statistical significant p values were expressed in bold (p ≤0.05) SGLT2 inh.: Sodium-glucose transporter 2 inhibitors, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, P/C: Protein to creatinine ratio		

Table 6. Multivariate linear regression analysis for predictors of hemoglobin levels				
	B	**S.E.**	**%95 CI for B (lower-upper)**	**p**
(Constant)	13.818	0.609	12.617-15.018	**<0.001**
Age	-0.023	0.008	-0.038- -0.007	**0.004**
Male gender	1.109	0.143	0.826-1.391	**<0.001**
Creatinine	0.843	0.357	0.139-1.547	**0.019**
HDL-cholesterol	-0.005	0.007	-0.018-0.008	0.471
AST	0.008	0.008	-0.007-0.024	0.268
SGLT2 inh.	0.685	0.136	0.418-0.953	**<0.001**
Statistical significant p values were expressed in bold (p≤0.05) SGLT2 inh.: Sodium-glucose transporter 2 inhibitors, HDL: High-density lipoprotein, AST: Aspartate aminotransferase, CI: Confidence İnterval, SE: Standard error				

Discussion

In this retrospective observational study, we evaluated the association between SGLT2 inhibitor use and Hb levels in patients with T2DM who did not have clinical anemia or advanced kidney disease. Our findings revealed that individuals using SGLT2 inhibitors had significantly higher Hb levels than non-users, even after adjusting for confounding variables such as age, sex, creatinine levels, and liver function tests. This suggests that SGLT2 inhibitors exert hematopoietic effects independent of their glucose-lowering and volume-reducing properties.

The observed mean Hb value among SGLT2 inhibitor users (14.44±1.23 g/dL) was significantly higher than that of non-users (13.76±1.12 g/dL, $p<0.001$), aligning with the results of multiple prior studies. A meta-analysis by Kanbay et al. (11) reported that SGLT2 inhibitors significantly increase Hb and Hct levels and highlighted that this effect was not solely attributable to hemoconcentration. A decrease in WBC and platelet (PLT) levels is also expected in hemoconcentration due to volume depletion (13,14). Although Hb levels were significantly higher in patients using SGLT2, the absence of a significant increase in WBC and PLT levels suggests that the Hb-raising effect of SGLT2 inhibitors cannot be explained only by hemoconcentration. While intravascular volume contraction through osmotic diuresis plays a role, recent evidence points to the involvement of renal and systemic mechanisms, including upregulation of EPO synthesis, improved renal oxygenation, and decreased renal inflammation and oxidative stress.

Type 2 diabetes mellitus is associated with an increased risk of anemia due to chronic low-grade inflammation, functional iron deficiency, elevated hepcidin levels, and reduced EPO production, even in patients without advanced kidney disease. Although diabetes duration was inversely correlated with Hb levels, it did not differ significantly between groups. Therefore, it is unlikely that diabetes duration explains the higher Hb levels observed in SGLT2 inhibitor users. Also in our analysis, no significant correlation was observed between the duration of SGLT2 inhibitor use and Hb levels. This suggests that the hematological effect of these agents may occur independently of treatment duration, reducing concerns about potential bias related to differences in drug exposure time between patients.

Mechanistically, SGLT2 inhibition reduces sodium and glucose reabsorption in the proximal renal tubules, decreasing tubular workload and oxygen consumption. This leads to a reduction in renal cortical hypoxia, a key stimulus for peritubular fibroblast-derived EPO production. Furthermore, several studies have shown that SGLT2 inhibitors can enhance hypoxia-inducible factor (HIF) pathways, further promoting erythropoiesis (15,16). Thus, the Hb rise observed in our patients likely reflects a pharmacologically induced improvement in renal oxygen sensing and erythropoietic signaling. Anemia is a common and often underrecognized comorbidity in patients with diabetes, particularly those with CKD or heart failure. Most of the studies in the literature, some of which we have emphasized above, have observed an increase in Hb values caused by SGLT2 inhibitors in CKD patients. It is important that similar effects were observed in our study group, which included patients who had not yet developed advanced CKD. Emerging evidence also suggests that SGLT2 inhibitors play a protective role against the development of anemia in patients with heart failure. Beyond their glycemic and cardiorenal benefits, these agents have been shown to stimulate erythropoiesis through enhanced EPO production, suppression of hepcidin, activation of HIF-2 , and improved iron mobilization (17). Therefore, their use in diabetic patients with or at risk of anemia due to chronic disease states may provide added hematological benefit, potentially preventing the onset of anemia even before it becomes clinically evident. The observed increase in Hb levels suggests that SGLT2 inhibitors may have a role in either early anemia prevention or correction.

Our study also demonstrated that Hb levels were independently associated with male gender and creatinine levels and inversely associated with age. These associations are well-established in the literature and reflect physiological sex-based differences in EPO response, renal reserve, and hematopoietic capacity. Interestingly, serum creatinine-within a non-pathological range-was positively correlated with Hb levels, potentially indicating that mild reductions in renal clearance may stimulate EPO production as a compensatory mechanism (18).

Although an inverse correlation was initially observed between HDL cholesterol and Hb levels in the bivariate analysis, further investigation suggests that this relationship is mainly attributable to sex-based differences. Specifically, in our sample, women had significantly higher HDL levels and significantly lower Hb levels than men-a pattern consistent with known physiological differences (19). This was confirmed by subgroup analysis showing that female sex was associated with an approximately 6.7 mg/dL higher HDL level ($p<0.001$) and also emerged as the strongest positive predictor of Hb in multivariate regression. Importantly, HDL was not independently associated with Hb after adjusting for gender and other confounding variables, indicating that the observed inverse correlation was likely spurious. These findings emphasize the value of accounting for demographic confounders, particularly gender, when interpreting associations between laboratory parameters in metabolic studies.

The lack of significant association between Hb levels and glycemic indices (HbA1c, fasting glucose) in

our analysis supports the notion that the hematologic benefits of SGLT2 inhibitors occur independently of or before glucose control. This reinforces the emerging view that SGLT2 inhibitors have pleiotropic effects extending beyond glycemic management, including cardiovascular, renal, and hematologic health improvements.

In our study, serum creatinine levels were significantly lower in patients using SGLT2 inhibitors despite the absence of significant differences in HbA1c or liver enzyme levels between groups. Although SGLT2 inhibitors are known to cause a transient rise in creatinine during the first days to weeks of therapy due to hemodynamic changes, several studies have demonstrated that renal function tends to stabilize or improve after this early phase, particularly in patients without advanced kidney disease (20,21). This suggests that our patients may have been captured during an intermediate phase of treatment-long enough for favorable changes in renal hemodynamics to emerge but not sufficient for measurable changes in glycemic or hepatic parameters to occur. Furthermore, our study's observation of lower creatinine levels in SGLT2 inhibitor users suggests that these agents may confer renal protection even in real-world patients who are not highly selected for clinical trials. This is clinically relevant because our cohort reflects everyday clinical practice, including patients with varying degrees of metabolic control and diverse comorbidities. Importantly, our findings indicate that improvements in renal parameters may occur independently of HbA1c reductions, underscoring the multifactorial benefits of SGLT2 inhibitors in routine care. Additionally, the cross-sectional design of our study precludes assessment of baseline trends.

Although the differences in AST and ALT levels between groups in our study were not statistically significant, we observed numerically lower transaminase levels among patients using SGLT2 inhibitors. This trend may be clinically relevant, particularly in the context of recent findings by Jang et al. (22), who demonstrated that SGLT2 inhibitors were associated with higher rates of non-alcoholic fatty liver disease (NAFLD) regression and reduced liver-related adverse outcomes compared to other oral antidiabetic agents in a large cohort of patients with TD2 and concomitant NAFLD. Possible mechanisms underlying this hepatoprotective effect of SGLT2 inhibitors include reduced hepatic steatosis through promotion of weight loss and redistribution of visceral fat, decreased hepatic inflammation and oxidative stress, modulation of insulin resistance, and attenuation of lipotoxicity *via* increased ketone body production and improved adipokine profiles such as increased adiponectin levels. These multifactorial effects may explain the lower liver enzyme levels observed in our SGLT2 inhibitor group, even without significant differences in glycemic control. Our findings, therefore, align with emerging evidence suggesting that SGLT2 inhibitors could offer hepatic benefits beyond their glycemic and renal effects, potentially positioning them as a favorable therapeutic option in patients with diabetes who are at risk for NAFLD or metabolic-associated liver injury.

Unexpectedly, the spot urine protein-to-creatinine ratio was higher among patients using SGLT2 inhibitors despite the well-established antiproteinuric effects of this drug class. This unexpected result may be attributed to the cross-sectional nature of the study and indication bias, as patients with higher baseline proteinuria are often preferentially treated with SGLT2 inhibitors due to their recognized renal protective effects in previous studies (23). Consequently, the SGLT2 user group in our cohort may have included a larger proportion of individuals with more advanced or active proteinuric kidney involvement at the time of drug initiation. Since baseline proteinuria levels were unavailable and longitudinal follow-up was not performed, it is impossible to determine whether SGLT2 inhibitor use led to reductions in proteinuria over time. Prospective studies are needed to assess the temporal changes in protein excretion following initiation of therapy.

Interestingly, metformin use, which is known to be associated with vitamin B12 deficiency and potentially lower Hb levels in long-term use, was significantly more common in the SGLT2 inhibitor group. Despite this, Hb levels were higher in SGLT2 inhibitor users, suggesting that the observed Hb increase is unlikely to be confounded by metformin use. Pioglitazone has been reported to cause reductions in Hb levels, primarily through hemodilution resulting from fluid retention, a known effect of peroxisome proliferator-activated receptor gamma agonists (24). This fluid retention leads to an expansion of plasma volume, thereby diluting red blood cells and lowering measured Hb and Hct values. Although rare, bone marrow suppression and decreased EPO production due to increased plasma volume have also been suggested as potential mechanisms contributing to pioglitazone-associated anemia. However, in our study, the proportion of patients using pioglitazone did not differ significantly between the SGLT2 inhibitor users and non-users. Therefore, the potential Hb-lowering effect of pioglitazone is unlikely to have significantly influenced our findings regarding Hb levels between the groups, and we believe that discussing this effect in depth is not directly relevant for interpreting the results of our analysis.

Study Limitations

Nonetheless, our study has limitations. As a retrospective, single-center study, our work has certain limitations, including the possibility of selection and information bias. We did not have access to data such as

iron stores, EPO levels, reticulocyte counts, or inflammatory markers, which would have helped clarify the mechanisms underlying the observed changes in Hb. Likewise, we were unable to assess treatment duration or adherence adequately. Despite these limitations, the significant increase in Hb levels among patients using SGLT2 inhibitors supports previous findings on the hematologic effects of these agents. More studies are needed, especially in patients with subclinical anemia or chronic conditions with impaired erythropoietic activity.

Conclusion

Our results indicate that SGLT2 inhibitor use is associated with higher Hb levels in T2D patients who do not have anemia, independent of kidney function or blood sugar control. This suggests that these drugs positively affect red blood cell production. Their potential role in preventing or improving anemia, especially in patients with chronic conditions, should be explored further in prospective studies.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Istanbul Haseki Training and Research Hospital Scientific Research Ethics Committee (approval no.: 58-2024, date: 01.08.2024).

Informed Consent: As the study was retrospective, informed consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.H., N.K., Concept: E.H., Design: E.H., Data Collection or Processing: E.H., N.K., Analysis or Interpretation: E.H., Literature Search: E.H., N.K., Writing: E.H.

Conflict of Interest: No conflicts of interest were declared by the authors.

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