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Effects of SGLT2 Inhibitors on Hematologic Parameters in Patients with Type 2 Diabetes Mellitus: A Retrospective Study

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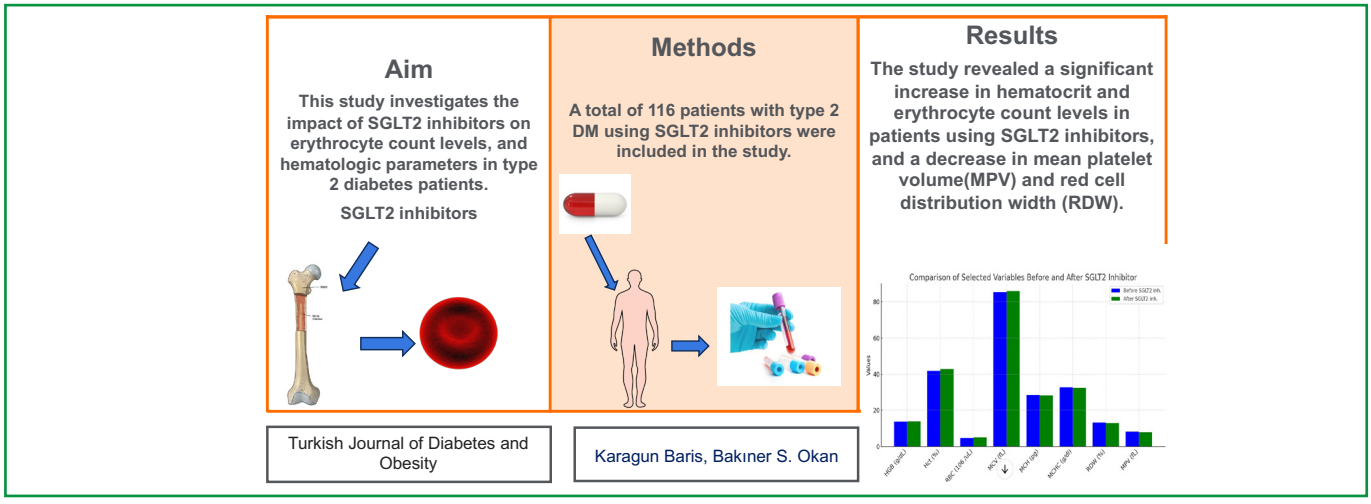
GRAPHICAL ABSTRACT



ABSTRACT

Aim: SGLT2 (Sodium-Glucose Cotransporter 2) inhibitors have demonstrated significant benefits in reducing cardiovascular events and improving renal outcomes in patients with type 2 diabetes mellitus (DM). However, their effects on hematopoiesis are not fully understood. This study aimed to investigate the impact of SGLT2 inhibitors on hematocrit, erythrocyte count levels, and various hematologic parameters in patients with type 2 DM.

Material and Methods: A total of 116 patients with type 2 DM using SGLT2 inhibitors were included in the study. Demographic and clinical characteristics, as well as laboratory parameters, were collected at baseline and during control examinations. The patients were stratified based on the specific SGLT2 inhibitor received (dapagliflozin or empagliflozin), and comparisons were made between baseline and control values.

Results: The study found a significant increase in hematocrit and erythrocyte count levels among patients using SGLT2 inhibitors compared to baseline values (p=0.002; p<0.001). This increase was more pronounced in patients treated with empagliflozin compared to dapagliflozin. Additionally, mean platelet volume (MPV) and red cell distribution width (RDW) values decreased following SGLT2 inhibitor use, potentially indicating favorable cardiovascular effects (p=0.038; p=0.005).

Conclusion: SGLT2 inhibitors exert significant effects on hematopoiesis, leading to increased hematocrit and erythrocyte count levels in patients with DM. These findings contribute to our understanding of the hematologic effects of SGLT2 inhibitors and highlight their potential benefits beyond glycemic control in patients with type 2 DM. Further research is warranted to elucidate the underlying mechanisms and clinical implications of these findings.

Keywords: *Dapagliflozin, Erythrocytosis, Empagliflozin, Hematologic parameters*

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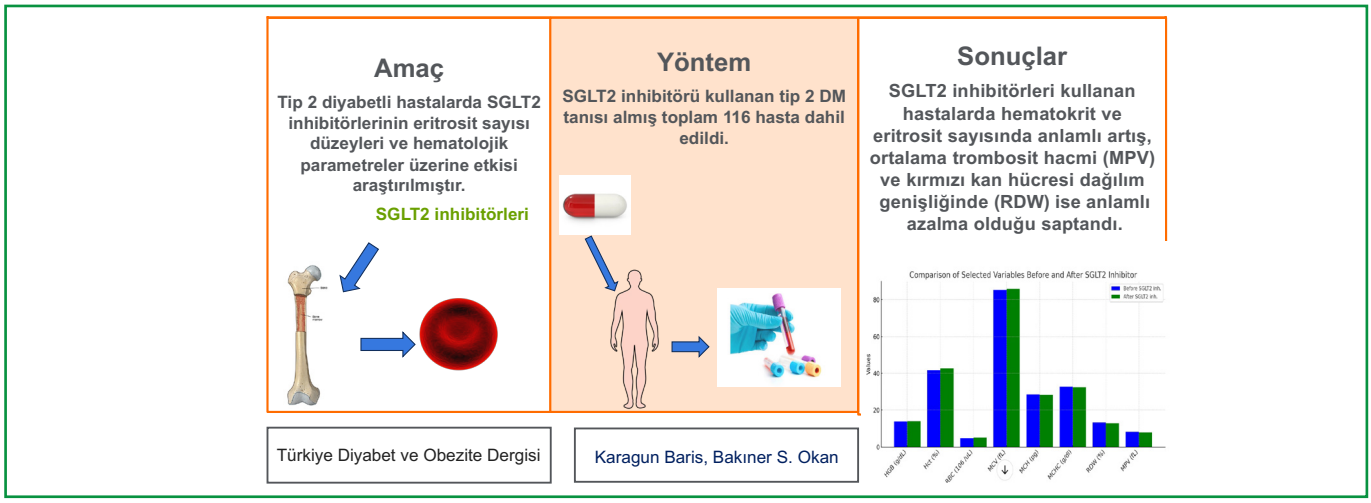
Tip 2 Diyabetli Hastalarda SGLT2 İnhibitörlerinin Hematolojik Parametreler Üzerindeki Etkileri: Retrospektif Bir Çalışma

GRAFİKSEL ÖZET



ÖZ

Amaç: SGLT2 (Sodyum-Glukoz Kotransporter 2) inhibitörleri, tip 2 diyabetes mellitus (DM) hastalarında kardiyovasküler olayları azaltmada ve böbrek sonuçlarını iyileştirmede önemli faydalar göstermiştir. Ancak, bu ilaçların hematopoez üzerindeki etkileri tam olarak anlaşılmamıştır. Bu çalışma, SGLT2 inhibitörlerinin tip 2 DM hastalarındaki hematokrit, eritrosit sayısı düzeyleri ve çeşitli hematolojik parametreler üzerindeki etkilerini araştırmayı amaçladı.

Gereç ve Yöntemler: Çalışmaya SGLT2 inhibitörleri kullanan toplam 116 tip 2 DM hastası dahil edilmiştir. Demografik ve klinik özellikler ile laboratuvar parametreleri, başlangıçta ve kontrol muayenelerinde toplanmıştır. Hastalar, aldıkları spesifik SGLT2 inhibitörüne (dapagliflozin veya empagliflozin) göre gruplandırılmış ve başlangıç ile kontrol değerleri arasında karşılaştırmalar yapılmıştır.

Bulgular: Çalışma, SGLT2 inhibitörleri kullanan hastalar arasında hematokrit ve eritrosit sayısı düzeylerinde başlangıç değerlerine kıyasla anlamlı bir artış olduğunu buldu (p=0.002; p<0.001). Bu artış, dapagliflozin ile tedavi edilen hastalara kıyasla empagliflozin ile tedavi edilen hastalarda daha belirgindi. Ayrıca, ortalama trombosit hacmi (MPV) ve kırmızı hücre dağılım genişliği (RDW) değerleri SGLT2 inhibitörü kullanımından sonra azaldı ve bu durum potansiyel olarak olumlu kardiyovasküler etkileri gösterebilir (p=0.038; p=0.005).

Sonuç: SGLT2 inhibitörleri, hematopoez üzerinde önemli etkiler göstererek DM hastalarında hematokrit ve eritrosit sayısı düzeylerinde artışa yol açar. Bu bulgular, SGLT2 inhibitörlerinin hematolojik etkilerini anlamamıza katkıda bulunur ve tip 2 DM hastalarında glisemik kontrolün ötesindeki potansiyel faydalarını vurgular. Bu bulguların altında yatan mekanizmaları ve klinik sonuçları açıklığa kavuşturmak için daha fazla araştırma gereklidir.

Anahtar Sözcükler: *Dapagliflozin, Eritrositoz, Empagliflozin, Hematolojik parametreler*

INTRODUCTION

Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors are a group of oral antidiabetic medicine which consist of canagliflozin, empagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin. The primary site of expression for SGLT2 is the proximal renal tubule, where it plays a crucial role in facilitating glucose reabsorption (1). SGLT2 inhibitors facilitate the renal clearance of glucose, leading to reduction in elevated blood glucose levels in individuals diagnosed with diabetes (2). This class of drugs decreases the reabsorption of sodium in the proximal renal tubule, resulting in elevated excretion of sodium in the urine, and finally, this natriuretic impact causes a reduction in both intravascular and interstitial volume (3,4). SGLT inhibitors not only enhance glycemic control in persons diagnosed with Type 2 diabetes mellitus (DM) but also mitigate the risk of cardiovascular mortality, reduce hospitalizations resulting from heart failure, and slow the advancement of end-stage kidney disease (5). Vulvovaginal candidal infections are the major adverse effects associated with SGLT2 medications. Additional infrequent adverse effects encompass urinary tract infections, perineal necrotizing fasciitis, euglycemic diabetic ketoacidosis (DKA), heightened susceptibility to lower extremity

amputation, and bone fractures (6). The association between SGLT2 inhibitors and erythrocytosis is becoming more well acknowledged (7). The initial identification of this syndrome is ascribed to hemoconcentration caused by natriuresis and the constriction of plasma volume. However, the impact of SGLT2 inhibitors on the reduction of urine plasma volume is transient (8). The rise in hematocrit and red blood count associated with SGLT2 treatment is attributed to enhanced erythropoiesis rather than hemoconcentration. This increase is thought to be a result of improved oxygenation and more effective erythropoietin production prompted by SGLT2i treatment (9,10). Hypoxic conditions in renal tubular cells reduce erythropoietin (EPO) production by transforming EPO-producing fibroblasts into myofibroblasts. SGLT-2 inhibitors relieve metabolic stress on tubules, hence enhancing their microenvironment. This reverses myofibroblasts into fibroblasts, partially restoring EPO production and correcting anemia (11–13). The mechanism behind erythrocytosis induced by SGLT2 inhibitors may involve several factors. Stimulation of EPO production can occur via the hypoxia-inducible factor 2 alpha (HIF2a) pathway. Additionally, SGLT2 inhibitors may influence iron metabolism by affecting hepcidin levels, which could further impact erythropoiesis (14–16). In addition to erythrocytosis, SGLT-2 inhibitors have been shown to affect other hemorheological parameters. It was observed that while blood viscosity and erythrocyte aggregation appeared to increase with SGLT2 inhibitor use, erythrocyte deformability showed a notable improvement. This could potentially have beneficial effects on the cardiovascular system (17).

Understanding the complex interactions between hematological parameters and SGLT-2 inhibitor use is crucial, as they significantly impact the cardiovascular safety and overall efficacy of SGLT-2 inhibitors in pratical application. The literature has provided limited discussion on the erythropoiesis associated with SGLT2 inhibitors. The goal of this research is to examine the impact of SGLT-2 inhibitors on erythrocytosis and other hematological parameters, shedding light on the mechanisms behind these changes and their potential protective effects on the cardiovascular system.

METHODS

This retrospective research was realized out at the University Hospital in Adana, Türkiye. The study included patients aged 18 and above, diagnosed with type 2 diabetes, and prescribed either dapagliflozin or empagliflozin, both of which are classified as SGLT2 inhibitors, between January 2019 and January 2024. The individuals enrolled in the study had been on a regimen of SGLT-2 inhibitors for a minimum duration of 3 months. The demographic profiles of the patients, along with their initial assessments and subsequent follow-up laboratory findings, were recorded from the hospital's database. The time to obtain follow-up results varied among patients, with the average being 6 (4-12) months. The exclusion criteria included diseases that result in secondary polycythemia, such as obstructive sleep apnea, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease (COPD), as well as testosterone replacement therapy and erythropoietin-secreting tumors (e.g., hepatocellular carcinoma, renal cell carcinoma, adrenal adenoma). A power analysis was performed out using G*Power software 3.1.9.6. Considering the reference study (16), the analysis was set at an alpha error of 0.05, a desired power of 95%, and an effect size of 0.755. This analysis determined a required minimum total sample size of 25 patients. In order to an enhance the study's power, the sample size was expanded to include 116 patients. The study took approval from the institutional Ethics Committee of Baskent University and was accomplished in accordance with the moral guidelines specified in the Helsinki Declaration (KA24/160).

Statistical Analysis

The data were examined using the SPSS (Statistical Package for Social Sciences) 18.0 software. The descriptive analyses yielded frequency data represented by the number (n) and percentage (%). Numerical data were reported as the arithmetic mean ± standard deviation (SD) and the median (1st-3rd quartile (IQR)). The suitability of numerical data for a normal distribution was evaluated using the Kolmogorov-Smirnov test. The Paired Samples T test was used to evaluate numerical variables in the two dependent groups with a normal distribution. The Wilcoxon Signed Rank test was used to examine the distribution of numerical variables in the two dependent groups with a non-normal distribution. The Mann Whitney U test was used to assess the distribution of numerical variables in two independent groups with non-normal distribution, and the Independent Samples T test was used to assess numerical variables in two independent groups with normal distribution. Two-way analysis of variance was used to assess the distribution of numerical data based on two independent variables. The Spearman Correlation study was done to look at the link between non-normally distributed numerical data. Correlation relationships can be categorized as follows: a correlation is considered low if the value of rho (ρ) falls between 0.05 and 0.30, low-moderate if it falls between 0.30 and 0.40, moderate if it falls between 0.40 and 0.60, good if it falls between 0.60 and 0.70, very good if it falls between 0.70 and 0.75, and excellent if it falls between 0.75 and 1.00. A statistical significance criterion of $p < 0.05$ was used for the tests.

RESULTS

The study encompassed 116 type 2 DM patients who were prescribed SGLT2 inhibitors. Among them, 52 (44.8%) were female, and 64 (55.2%) were male, with an average age of 59.77 ± 9.47 years. Of the patients, 45.7% received dapagliflozin, while 54.3% received empagliflozin. Table 1 displays the demographic and clinical attributes of all patients. The distribution of other oral antidiabetic medications used by the patients was as follows: 87 patients (75%) were using Metformin, 26 patients (22.4%) were using Pioglitazone, 24 patients (20.7%) were using Gliclazide, and 44 patients (37.9%) were using Insulin

Table 1: Demographic and clinical characteristics in patients.

Variables	Values (n=116)
Gender (female/male) , n (%)	52(44.8)/64(55.2)
Age (years ±SD)	59.77 ± 9.47
FPG (mg/dl), median(min.-max.)	148(121.25-188.25)
HbA1c (%), median(min.-max.)	7.50 (6.70-8.70)
Creatinine (mg/dl), median(min.-max.)	0.80 (0.63-0.90)
ALT (mg/dl) , median(min.-max.)	24 (18-34)
Duration of DM (years±SD)	15.42 ± 7.44
Smoking, n (%)	23 (19.8)
Time on SGLT2 inhibitors (months), median(min.-max.)	6.0 (4.0-12.0)
Dapagliflozin, n (%)	53 (45.7)
Empagliflozin, n (%)	63 (54.3)

n (%); Mean ± Standard Deviation; Median (IQR). **FPG:** Fasting plasma glucose; **ALT:** Alanine aminotransferase

Table 2 displays the distribution of laboratory values for all participants diagnosed with DM who were included in the study, both before and after receiving treatment with SGLT2 inhibitors. Hematocrit and RBC count significantly increased compared to the baseline after SGLT2 inhibitors administration (p=0.002; p<0.001). It was determined that MCHC, RDW, and MPV values declined significantly (p=0.019; p=0.038; p=0.005, respectively).

Individuals who received dapagliflozin revealed a statistically significant increase in RBC count compared to their initial levels (p<0.001). Additionally, RDW and MPV values exhibited a significant decrease (p=0.001, and p=0.019) (Table 3).

The group that received empagliflozin revealed a significant rise in both hematocrit and RBC count compared to the first measurement. In addition, there was a substantial decrease in the MCHC values (p values; p<0.001; p<0.001; p=0.020, respectively) as shown in Table 4.

The study's results indicated that the distribution of laboratory parameters after the administration of either empagliflozin or dapagliflozin in the groups was statistically similar. (p > 0.05) (Table 5). However, it was shown that the delta RDW level was considerably elevated in individuals receiving empagliflozin compared to those receiving dapagliflozin (p = 0.002). The study found no statistically significant impact of smoking, metformin usage, or other therapies on the difference in delta RDW.

A statistically significant negative correlation was discovered between the length of diabetes and hemoglobin levels (rho = -0.238, p = 0.010). Similarly, a significant negative correlation was identified between the length of diabetes and the hematocrit levels measured after SGLT2 inhibitor

Table 2: Before and after SGLT2 inhibitor laboratory test results (n=116).

Variables	Before SGLT2 inh.	After SGLT2 inh.	p
HGB (g/dL±SD)	13.75 ± 1.76	13.85 ± 1.93	0.369*
Hct (%±SD)	41.66 ± 5	42.77 ± 5.07	0.002*
RBC (10^6/uL) , median(min.-max.)	4.75 (4.46-5.20)	5.10 (4.72-5.45)	<0.001**
MCV (fL) , median(min.-max.)	85.25 (82.02-89.95)	85.86 (81.96-89.95)	0.389**
MCH (pg) , median(min.-max.)	28.50 (26.56-29.87)	28.32 (26.25-29.55)	0.236**
MCHC (g/dl±SD)	32.72 ± 1.49	32.35 ± 1.82	0.019*
RDW (%), median(min.-max.)	13.27 (12.31-14.07)	12.90 (12.05-13,85)	0.038**
WBC (10^3/µL) , median(min.-max.)	7.97 (6.84-9.09)	7.84 (6.57-9.35)	0.982**
MPV (fL) , median(min.-max.)	8.11 (7.49-9.10)	7.79 (7.08-8.83)	0.005**
PLT (10^3/µL) , median(min.-max.)	237.80 (200.40-307.47)	247.70 (198.10-302.82)	0.866**

*: Paired Samples T Testi, **: Wilcoxon Testi. **HGB:** Hemoglobin, **MCH:** Mean corpuscular hemoglobin, **RDW:** Red blood distribution width, **MCHC:** Mean corpus-cular hemoglobin concentration, **MCV:** Mean cell volume, **Htc:** Hematocrit, **RBC:** Red blood cell, **WBC:** White blood cell, **PLT:** Platelet count.

Table 3: Before and after Dapagliflozin laboratory test results (n=53).

Variables	Before SGLT2 inh.	After SGLT2 inh.	p value
HGB (g/dL)	14.03 ± 1.97	14± 2.09	0.870*
Hct (%)	42.13 ± 5.31	42.74 ± 5.34	0.295*
RBC (10^6/uL)	4.82 (4.51-5.37)	5.1 (4.88-5.51)	<0.001**
MCV (fL)	84.90 (82.74-90.25)	85.88 (83.2-89.21)	0.580**
MCH (pg)	28.60 (27.34-30.15)	28.42 (26.93-29.96)	0.989**
MCHC (g/dl)	33.12 (32.33-33.90)	32.90 (31.78-33.6)	0.195**
RDW (%)	13.60 (12.60-14.97)	12.68 (11.72-13.98)	0.001**
WBC (10^3/µL)	7.84 ± 1.83	7.83 ± 2.07	0.983*
MPV (fL)	8.10 (7.55-9.1)	7.74 (7.08-8.93)	0.019**
PLT (10^3/µL)	236 (200-299.4)	234.1 (194.1-295.95)	0.620**

*: Paired Samples T Testi, **: Wilcoxon Testi. **HGB:** Hemoglobin, **MCH:** Mean corpuscular hemoglobin, **RDW:** Red blood distribution width, **MCHC:** Mean corpus-cular hemoglobin concentration, **MCV:** Mean cell volume, **Htc:** Hematocrit, **RBC:** Red blood cell, **WBC:** White blood cell, **PLT:** Platelet count.

Table 4: Before and after Empagliflozin laboratory test results (n=63).

Variables	Before SGLT2 inh.	After SGLT2 inh.	p value
HGB (g/dL)	13.51 ± 1.54	13.73 ± 1.8	0.104*
Hct (%)	41.26 ± 4.73	42.79 ± 4.87	<0.001*
RBC (10^6/uL)	4.73 ± 0.64	5.05 ± 0.58	<0.001*
MCV (fL)	85.12 ± 7.31	85.23 ± 7.76	0.832*
MCH (pg)	28.24 (26.26-29.73)	28.15 (25.97-29.42)	0.153**
MCHC (g/dl)	32.59 ± 1.38	32.05 ± 1.85	0.020*
RDW (%)	13.08 (12.25-13.79)	13.04 (12.23-13.72)	0.771**
WBC (10^3/µL)	8.19 (6.98-9,3)	8 (6.57-10.02)	0.804**
MPV (fL)	8.25 ± 1.35	7.936± 1.38	0.054*
PLT (10^3/µL)	243.2 (200.2-324)	256.1 (199.8-304)	0.739**

*: Paired Samples T Testi, **: Wilcoxon Testi. **HGB:** Hemoglobin, **MCH:** Mean corpuscular hemoglobin, **RDW:** Red blood distribution width, **MCHC:** Mean corpus-cular hemoglobin concentration, **MCV:** Mean cell volume, **Htc:** Hematocrit, **RBC:** Red blood cell, **WBC:** White blood cell, **PLT:** Platelet count.

administration (rho = -0.278, p = 0.003). It was found that the MCHC level measured after SGLT2 inhibitor administration exhibited a statistically significant negative correlation with age, while showing a positive correlation with the duration of SGLT2 inhibitor use, as well as ALT levels (rho and p values, respectively; rho = -0.226; p = 0.015; r = 0.269; p = 0.004; rho = 0.221; p = 0.017). Additionally, a statistically significant inverse relationship was discovered between the duration of SGLT2 inhibitor use and RDW levels measured after SGLT2 inhibitor administration (rho = -0.210, p = 0.024) (Table 6).

There appears to be a statistically significant positive link between the change (delta) in hematocrit levels and HbA1c (rho = 0.206; p = 0.026). Similarly, a statistically significant negative correlation was found between the change in MCHC levels and fasting blood glucose levels (rho = -0.227; p = 0.014). A statistically significant inverse relationship was found between the change in RDW levels and the duration of SGLT2 inhibitor treatment and ALT. (rho and p values, respectively; rho=-0.299; p = 0.001; rho =-0.197; p = 0.034). A negative correlation was observed between the change in MPV levels and the duration of SGLT2 inhibitor treatment (rho = -0.249; p = 0.007) (Table 6).

DISCUSSION

This study intended to explore the impact of SGLT2 inhibitors on hematocrit, RBC count levels, and various other hematologic parameters. The key findings of the study suggest that individuals using SGLT2 inhibitors experienced increases in both RBC count and hematocrit levels. This finding constitutes a valuable addition to our understanding of how SGLT2 inhibitors influence erythrocytosis. The ob-

Table 5: Distribution of Control and Delta Laboratory Parameters by SGLT2i Type(n=116)

	Variables	Dapagliflozin (n=53)	Empagliflozin (n=63)	p value
Control	HGB (g/dL)	14 ± 2.09	13.3 ± 1.80	0.469*
	Hct (%)	42.74 ± 5.34	42.79 ± 4.87	0.956*
	RBC (10^6/uL)	5.1 (4.88-5.51)	5.10 (4.62-5.42)	0.107**
	MCV (fL)	85.88 (83.2-89.21)	85.79 (80.90-90.53)	0.971**
	MCH (pg)	28.42 (26.93-29.96)	28.15 (25.97-29.42)	0.446**
	MCHC (g/dl)	32.71 ± 1.72	32.05 ± 1.85	0.052*
	RDW (%)	12.68 (11.72-13.98)	13.13 (12.23-13.72)	0.241**
	WBC (10^3/µL)	7.83 ± 2.07	8.42 ± 2.4	0.165*
	MPV (fL)	7.74 (7.08-8.93)	7.95 (6.9-8.67)	0.788**
	PLT (10^3/µL)	251.91 ± 91.31	255.83 ± 79.44	0.806*
Delta	HGB (g/dL)	-0.03 ± 1.43	0.21 ± 1.05	0.293*
	Hct (%)	0.61 ± 4.21	1.53 ± 3.22	0.184*
	RBC (10^6/uL)	0.25 (-0.01-0.64)	0.24 (0.03-0.51)	0.6**
	MCV (fL)	0.11 ± 3.72	0.1 ± 4.08	0.998*
	MCH (pg)	0.2 (-0.85-0.81)	-0.17 (-1.10-0.43)	0.217**
	MCHC (g/dl)	-0.62 (-1.75-0.47)	-0.29 (-0.96-0.56)	0.162**
	RDW (%)	-0.78 (-1.53-0.09)	0.00 (-0.77-0.99)	0.002**
	WBC (10^3/µL)	-0.14 (-1.03-1.22)	-0.24 (-1.02-1.05)	0.851**
	MPV (fL)	-0.42 ± 1.21	-0.28 ± 1.15	0.526*
	PLT (10^3/µL)	1(-17.65-33)	1.60 (-29.7-25)	0.551**

*: Independent Samples T Testi, **: Mann Whitney U Testi. **HGB:** Hemoglobin, **MCH:** Mean corpuscular hemoglobin, **RDW:** Red blood distribution width, **MCHC:** Mean corpus-cular hemoglobin concentration, **MCV:** Mean cell volume, **Htc:** Hematocrit, **RBC:** Red blood cel, **WBC:** White blood cell, **PLT:** Platelet count.

served increase in hematocrit and RBC count levels during the control examination emphasizes the potential impact of SGLT2 inhibitors on the hematopoietic system.

SGLT2 inhibitors have demonstrated substantial advantages in decreasing the likelihood of cardiovascular events and enhancing renal consequences in people with type 2 diabetes mellitus. Clinical trials have consistently shown that SGLT2 inhibitors offer significant benefits for patients with type 2 DM. These benefits include a reduction in major adverse cardiovascular events (MACE), comprising cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, when compared to placebo (18,19). Additionally, SGLT2 inhibitors have demonstrated renal protective effects, such as slowing the progression of chronic kidney disease (CKD) and decreasing the risk of end-stage renal disease (ESRD) or the necessity for renal replacement therapy (20,21). SGLT2 inhibitors have revealed beneficial effects in vulnerable patient populations, including the geriatric population and those with chronic kidney disease undergoing peritoneal dialysis (22,23). Similar to these findings, SGLT2 inhibitors have been demonstrated to exert numerous pleiotropic effects (24).

SGLT2 inhibitors have been shown to influence hematopoiesis and they can regulate hematopoiesis and promote erythropoiesis by affecting various cellular pathways. Nevertheless, the specific intermediary pathways have not been completely clarified, although it is probable that cellular mechanisms are implicated (25). These cellular mechanisms involve increased production of erythropoietin (EPO) through hypoxia-induced activation of HIF2a, modulation of iron metabolism via hepcidin, and/or hemoconcentration (7,26). In our study, we noted a noteworthy increment in hematocrit and RBC count levels among patients using SGLT2 inhibitors compared to their baseline values. The elevation in hematocrit and erythrocyte count levels aligns with findings reported in the literature (14–16,27). The patients in the study were stratified based on the SGLT2 inhibitor they received (empagliflozin or dapagliflozin) and then compared according to their baseline values. We noted statistically a significant increase in hematocrit and RBC count levels among patients treated with empagliflozin compared to their baseline values. Similarly, we observed a statistically significant increase in RBC counts and a notable, though not statistically significant, rise in hematocrit

Table 6: The correlation between demographic, clinical, and laboratory parameters post-administration of SGLT2 inhibitor and delta findings.

		HGB (g/dL)	Hct %	RBC (10^6/uL)	MCV (fL)	MCH (pg)	MCHC (g/dl)	RDW (%)	WBC (10^3/uL)	MPV fL	PLT (10^3/uL)
Age (years)	rho	-0.175	-0.100	-0.213	0.068	-0.044	-0.226	0.148	-0.042	0.003	-0.082
	p	0.060	0.287	0.022	0.466	0.642	0.015	0.112	0.653	0.977	0.384
FPG (mg/dL)	rho	0.038	0.060	0.009	0.036	0.010	-0.023	0.005	0.019	-0,011	0.069
	p	0.688	0.521	0.920	0.701	0.918	0.806	0.956	0.838	0.910	0.465
HbA1c	rho	0.065	0.071	0.118	0.024	0.019	0.006	-0.105	0.027	0.150	-0.090
	p	0.485	0.448	0.207	0.799	0.838	0.946	0.261	0.777	0.108	0.336
Creatinine (mg/dL)	rho	0.188	0.204	-0.001	0.163	0.156	0.001	-0.121	0.088	0.045	-0.210
	p	0.043	0.028	0.996	0.080	0.094	0.996	0.196	0.348	0.635	0.024
ALT (IU/L)	rho	0.131	0.082	0.151	-0.019	0.101	0.221	-0.037	-0.057	0.031	-0.123
	p	0.162	0.384	0.105	0.841	0.278	0.017	0.691	0.691	0.738	0.190
Duration of DM (years)	rho	-0.238	-0.278	-0.169	-0.053	-0.050	0.026	0.012	-0.097	-0.152	0.026
	p	0.010	0.003	0.069	0.572	0.593	0.780	0.895	0.298	0.103	0.784
Time on SGLT2 inhibitors (months)	rho	0.048	-0.019	-0.015	-0.077	-0.008	0.269	-0.210	0.029	-0.085	0.022
	p	0.610	0.839	0.877	0.408	0.928	0.004	0.024	0.759	0.364	0.813
						DELTA					
		HGB (g/dL)	**Hct %**	**RBC (10^6/uL)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dl)**	**RDW (%)**	**WBC (10^3/uL)**	**MPV fL**	**PLT (10^3/uL)**
Age (years)	rho	0.010	0.089	0.108	-0.061	-0.135	-0.086	0.117	0.144	0.013	-0.025
	p	0.917	0.341	0.250	0.513	0.149	0.357	0.211	0.122	0.892	0.787
FPG (mg/dL)	rho	0.013	0.112	0.108	0.012	-0.127	-0.227	0.114	0.055	-0.007	0.024
	p	0.891	0.232	0.247	0.900	0.174	0.014	0.223	0.560	0.941	0.796
HbA1c	rho	0.156	0.206	0.175	0.177	0.034	-0.105	0.062	-0.017	0.149	-0.060
	p	0.094	0.026	0.060	0.057	0.720	0.262	0.511	0.857	0.110	0.521
Creatinine (mg/dL)	rho	-0.034	0.053	0.015	-0.042	-0.128	-0.115	0.183	0.249	0.102	-0.048
	p	0.713	0.572	0.873	0.656	0.169	0.219	0.050	0.007	0.277	0.612
ALT (IU/L)	rho	-0.073	-0.152	-0.007	-0.072	-0.009	0.071	-0.197	-0.029	-0.148	0.176
	p	0.433	0.104	0.944	0.443	0.924	0.449	0.034	0.754	0.112	0.059
Duration of DM (years)	rho	0.046	0.002	0.155	0.008	0.020	0.018	-0.127	0.047	-0.160	-0.037
	p	0.627	0.984	0.097	0.935	0.828	0.847	0.174	0.619	0.085	0.696
Time on SGLT2 inhibitors (months)	rho	0.030	-0.046	-0.112	-0.099	0.027	0.088	-0.299	0.131	-0.249	-0.083
	p	0.749	0.626	0.229	0.292	0.773	0.350	0.001	0.162	0.007	0.376

rho= Spearman korelasyon katsayısı. **FPG:** Fasting plasma glucose, **ALT:** alanine aminotransferase, **HGB:** hemoglobin, **MCH:** mean corpuscular hemoglo-bin, **RDW:** red blood distribution width, **MCHC:** mean corpuscular hemoglobin concentration, **MCV:** mean cell vol-ume, **Htc:** hematocrit, **HGB:** Hemoglobin, **RBC:** red blood cel, **WBC:** white blood cell, **PLT:** platelet count.

levels compared to baseline values in patients treated with dapagliflozin.

A thorough meta-analysis of randomized controlled trials' findings showed that SGLT2 inhibitors exhibited a class effect by elevation hematocrit levels and among them, empagliflozin demonstrated the most pronounced effect on hematocrit levels, followed by canagliflozin, ertugliflozin, dapagliflozin, and ipragliflozin (28). In our study, it was noteworthy the analysis of delta data indicated a greater increase in hematocrit favoring empagliflozin, consistent with the findings of this meta-analysis. The exact reason why empagliflozin exhibits a greater potency in increasing hematocrit levels compared to dapagliflozin has not received enough clarification in the literature.

In the study, we observed a reduction in MPV and RDW values following the use of SGLT2 inhibitors compared to baseline values. Elevated MPV has been associated with various inflammatory and chronic conditions, as well as numerous cardiovascular diseases, making it a significant indicator of cardiovascular risk (29,30). Similarly, RDW, which serves as an indicator of increased anisocytosis, has also been linked to elevated cardiovascular risk (31). The

decrease in MPV and RDW observed in our study could potentially indicate the favorable cardiovascular effects of SGLT inhibitors.

Individuals with type 2 diabetes mellitus exhibit a low serum erythropoietin level, which further falls as the level of glycosylated hemoglobin increases (32). The excessive uptake of glucose by tubular epithelial cells can lead to metabolic stress in the proximal tubules, creating a hypoxic setting. This, in turn, can drive the transformation of erythropoietin-producing fibroblasts into myofibroblasts. This phenomenon can potentially account for the reduced serum erythropoietin levels observed in people with type 2 diabetes mellitus (13). During the control examination, a study found a negative link between the length of diabetes and the levels of hematocrit and hemoglobin. In our study, we hypothesize that the observed correlation may be attributed to the diminishing levels of erythropoietin and subsequent reduction in hematocrit. This decline is likely a consequence of prolonged exposure to a hypoxic microenvironment, which becomes more pronounced with the duration of diabetes. Similarly, our analysis revealed a positive statistically significant correlation between changes in hematocrit (hematocrit delta) and HbA1c levels. This suggests that higher HbA1c levels, reflecting lower erythropoietin levels, may correspond to greater potential benefits from SGLT2 inhibitors. SGLT2 inhibitors reduce ATP consumption and metabolic stress in cells of the proximal tubular epithelium, thereby decreasing hypoxia. This reduction enables the transformation of myofibroblasts into erythropoietin-producing fibroblasts, which in turn enhances hematopoiesis and increases hematocrit levels (13).

This study has a number of intrinsic limitations. The study's sample size might not have been sufficiently large to fully capture the effects of SGLT2 inhibitors on people with diabetes mellitus. A larger sample size would offer increased statistical power and enhance the reliability and generalizability of the study findings to the wider population of individuals using these inhibitors for diabetes management. Additionally, its retrospective nature, relying on past data and medical records, could introduce limitations during data collection and analysis. Expanding to multiple centers and employing prospective designs could improve the study's external validity and mitigate potential biases.

In conclusion, the findings indicate a significant correlation between the use of SGLT2 inhibitors and increased levels of hematocrit and RBC count, suggesting a potential impact on erythropoiesis. A reduction in (MPV and RDW following SGLT2 inhibitor use observed in the study may indicate potential cardiovascular benefits. Further investigation is required to elucidate the fundamental mechanisms of the effects of SGLT2 inhibitors on hematopoiesis and to explore their potential implications for clinical practice.

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Author Contributions
Baris Karagun and **Okan Sefa Bakıner** performed the literature searches and selected the studies. **Baris Karagun** drafted the manuscript. **Baris Karagun** designed the study and revised the manuscript. All authors have read and approved the final manuscript. Data availability statement: The data that support the findings of this study are available from the corresponding author, **Baris Karagun**, upon reasonable request.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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