Predictors and Outcomes of Erythrocytosis After Sodium-Glucose Cotransporter-2 Inhibitors in Type 2 Diabetes Mellitus

Panita Prasathinphimai, Laddaporn Wongluechai

Division of Nephrology, Department of Internal Medicine, Maharat Nakhon Ratchasima Hospital, Bangkok, Thailand

Abstract

Background: Current evidence suggests that treatment with sodium-glucose cotransporter-2 inhibitors (SGLT2i) may increase hemoglobin levels. An increase in hemoglobin may be beneficial in improving cardiovascular and renal outcomes. This study examined changes in hemoglobin, the prevalence, and predictors of erythrocytosis in patients with type 2 diabetes mellitus (T2DM) who received SGLT2i. The associations between erythrocytosis with cardiovascular events and renal outcomes were also investigated.

Methods: This retrospective study was conducted in patients with T2DM who received SGLT2i for at least 3 consecutive months between January 2020 and December 2022. Hemoglobin and hematocrit were collected at baseline and after 3-12 months of SGLT2i treatment until the end of the study. Erythrocytosis was defined as an increase in hemoglobin level ≥2 gm/dL from baseline during the study period.

Results: Three hundred thirty-six patients were included in the study. The prevalence of erythrocytosis was 125 patients (37.2 %). The hemoglobin levels increased over time with median differences from baseline of 0.7, 1, 1.3, and 1.5 gm/dL at 3, 6, 12, and >24 months, respectively. The predictors of erythrocytosis were age >60 years, chronic kidney disease, using thiazide and beta-blockers, lower hemoglobin, and estimated glomerular filtration rate at baseline. Cardiovascular and renal outcomes were not different between the erythrocytosis and non-erythrocytosis groups.

Conclusion: A gradual increase in hemoglobin levels was observed in patients with T2DM after SGLT2i treatment. Erythrocytosis was common but was not associated with adverse cardiovascular events or renal outcomes.

Keywords: SGLT2 inhibitors; hemoconcentration; DM; cardiovascular disease; AKI; CKD progression

Corresponding author: *Laddaporn Wongluechai*
Email: *eve306@gmail.com*

Received: 24 February 2024; Revised: 17 April 2024; Accepted: 17 April 2024

ปัจจัยทำนายและผลลัพธ์ของภาวะความเข้มข้นเลือดเพิ่มสูงขึ้นหลังได้รับยา Sodium-Glucose Cotransporter-2 Inhibitors ในผู้ป่วยโรคเบาหวานชนิดที่ 2

ปนิตา ปราสาทหินพิมาย, ลัดดาพร วงษ์ลือชัย

หน่วยโรคไต ภาควิชาอายุรศาสตร์ โรงพยาบาลมหาราชนครราชสีมา

บทคัดย่อ

บทนำ: จากการศึกษาพบว่ายากลุ่ม Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) อาจทำให้ความเข้มข้นของเลือดสูงขึ้นได้ ความเข้มข้นเลือดที่สูงขึ้นนี้อาจส่งผลดีต่อผู้ป่วยทั้งทางระบบหัวใจและหลอดเลือดและระบบไต การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาการเปลี่ยนแปลงของความเข้มข้นเลือด ความชุกและปัจจัยทำนายการเกิดภาวะความเข้มขันเลือดเพิ่มสูงขึ้น (erythrocytosis) และเปรียบเทียบการเกิดผลลัพธ์ต่อระบบหัวใจและหลอดเลือดและไต ระหว่างกลุ่มผู้ป่วยที่มีภาวะความเข้มขันเลือดเพิ่มสูงขึ้นกับกลุ่มที่ไม่พบภาวะดังกล่าว ในผู้ป่วยโรคเบาหวานชนิดที่ 2 หลังจากได้รับยา SGLT2i

ระเบียบวิธีวิจัย: การศึกษาแบบย้อนหลังระหว่างเดือนมกราคม 2563 – ธันวาคม 2565 ในผู้ป่วยโรคเบาหวานชนิดที่ 2 ที่ได้รับยาในกลุ่ม SGLT2i ติดต่อกันนานมากกว่า 3 เดือน โดยมีการเก็บข้อมูลระดับฮีโมโกลบิน และ/หรือ ฮีมาโตคริต ก่อนให้การรักษา และ 3-12 เดือนหลังจากได้รับยาไปจนกระทั่งสิ้นสุดการศึกษา ผู้ป่วยที่มีการเพิ่มขึ้นของฮีโมโกลบิน ≥2 มิลลิกรัม/เดซิลิตร จากก่อนการรักษาถือว่ามีภาวะความเข้มขันเลือดเพิ่มสูงขึ้น

ผลการศึกษา: มีผู้ที่ผ่านเกณฑ์การคัดเข้าและออกจำนวนทั้งหมด 336 คน หลังได้รับยา SGLT2i พบว่าความเข้มข้นเลือดมีการเพิ่มขึ้นตามระยะเวลาที่ผ่านไป โดยมีค่ามัธยฐานของการเพิ่มขึ้นของฮีโมโกลบินอยู่ที่ 0.7, 1, 1.3, 1.5 กรัม/เดซิลิตร ที่ระยะเวลา 3, 6, 12, >24 เดือนตามลำดับ มีผู้ป่วยที่เข้าข่ายภาวะความเข้มข้นเลือดเพิ่มสูงขึ้นร้อยละ 37.2 ปัจจัยที่ทำนายภาวะความเข้มข้นเลือดเพิ่มสูงขึ้นได้แก่ อายุมากกว่า 60 ปี, เป็นโรคไตเรื้อรัง, ได้รับยาขับปัสสาวะกลุ่ม thiazide และ ยา beta-blockers, มีค่าฮีโมโกลบินและอัตราการกรองของไตตั้งต้นต่ำ ในขณะที่ไม่พบความสัมพันธ์ระหว่างภาวะความเข้มข้นเลือดเพิ่มสูงขึ้นกับผลลัพธ์ต่อระบบหัวใจและหลอดเลือดและระบบไต

สรุป: ฮีโมโกลบินมีระดับเพิ่มขึ้นเรื่อย ๆ ในผู้ป่วยเบาหวานชนิดที่ 2 หลังได้รับการรักษาด้วย SGLT2i โดยพบความชุกของภาวะความเข้มขันเลือดเพิ่มสูงขึ้นที่ค่อนข้างสูง ในขณะที่ไม่พบความสัมพันธ์ระหว่างภาวะดังกล่าวกับผลลัพธ์ของระบบหัวใจและหลอดเลือดและระบบไต

คำสำคัญ: เลือดข้น; ยาเบาหวาน; หัวใจขาดเลือด; หลอดเลือดแดงอุดตัน; หลอดเลือดหัวใจอุดตัน; ไตวาย; ไตเรื้อรัง

Introduction

Type 2 diabetes mellitus (T2DM) is highly prevalent and associated with microvascular and macrovascular complications, leading to an increased risk of death.[1-3] Sodium-Glucose Cotransporter-2 inhibitors (SGLT2i) were introduced in 2013-2014.[6] In 2015, the landmark clinical trial (EMPA-REG) that investigated cardiovascular and renal outcomes which involved more than 7,000 participants found that empagliflozin significantly reduced the risk of the primary composite endpoint including cardiovascular death, nonfatal heart attack, or nonfatal stroke.[7] The subsequent study of empagliflozin in patients with chronic kidney disease (CKD) revealed a significant reduction in the composite renal outcome of the

ผู้ประพันธ์บรรณกิจ: *ลัดดาพร วงษ์ลือชัย*
อีเมล: *eve306@gmail.com*

รับบทความ: 24 กุมภาพันธ์ 2567; ปรับปรุงแก้ไข: 17 เมษายน 2567; รับตีพิมพ์: 17 เมษายน 2567

progression of kidney disease, death from renal causes, or death from cardiovascular causes.[8] Similarly, the study of dapagliflozin in patients with CKD (DAPA-CKD) that evaluated over 4,000 patients with an estimated glomerular filtration rate (eGFR) between 25-75 ml/minute/1.73 m^2 and the urinary albumin-to-creatinine ratio of 200 - 5,000 mg/gm also found a reduction in the composite renal outcome.[9] Therefore, Kidney Disease: Improving Global Outcomes 2022 and American Diabetes Association 2022 guidelines recommend SGLT2i as the first-line treatment in T2DM with CKD.[10,11]

In the EMPA-REG study, an increase in hemoglobin of 0.8 g/dL and hematocrit of 4.8 % in the empagliflozin group compared with -0.1 g/dL and 0.9% in the placebo group was observed. The beneficial effect on cardiovascular outcome was also suggested.[7] The results from the Dapagliflozin effect on cardiovascular events (DECLARE TIMI 58) also demonstrated a lower rate of cardiovascular death or hospitalization for heart failure in the dapagliflozin group.[12] The results from a systematic review and meta-analysis of 40 randomized controlled trials, which included more than 20,000 patients, demonstrated that SGLT2i caused a significant increase in hematocrit levels [weighted mean difference (95% confidence interval): 2.67 (2.53-2.82), P <0.001).[13]

Anemia is one of the non-traditional risk factors for cardiovascular disease in patients with CKD.[5,14] The results from landmark studies and meta-analysis suggested that the beneficial effects of SGLT2i in correcting anemia in both CKD and non-CKD patients are associated with a reduction in cardiovascular events and CKD progression.[7,13] One of the proposed mechanisms is an increase in erythropoietin production after SGLT2i treatment. Erythropoietin is produced from peritubular fibroblast-like interstitial cells in the renal cortex called renal erythropoietin-producing cells (REPs). SGLT2i induces hypoxia in the renal tubulointerstitium and triggers the upregulation of hypoxia-inducible transcription factors.[15] SGLT2i also decreases proinflammatory molecules produced by stressed renal tubular epithelial cells.[16] These molecules stimulate the conversion of REPs from hypoxia-responsive cells to fibrogenic myofibroblasts that have decreased sensitivity to hypoxic response and produce inflammatory cytokines and fibrotic molecules instead of erythropoietin.[17] The second mechanism involves the inhibition of hepcidin. Hepcidin is an iron regulatory protein that binds to ferroportin in the plasma membrane, thereby inhibiting its ability to transport iron.[18] In T2DM, an increase in proinflammatory cytokines activates STAT3 and increases the gene expression of hepcidin.[19,20] Dapagliflozin reduces circulating concentrations of hepcidin and ferritin and increases the levels of the hepcidin inhibitor, erythroferrone.[18]

Erythrocytosis is defined as a mean increase in red blood cell concentration (hemoglobin or red blood cells per total blood volume) beyond the normal range (hemoglobin >18.5 g/dL in males or >16.5 g/dL in females), or hemoglobin and hematocrit levels surpassing the 99th percentile for the same age and gender group. In addition, erythrocytosis can manifest as an increase in hemoglobin of ≥ 2 g/dL from baseline.[21] Erythrocytosis is caused by both primary and secondary factors. The most common causes of erythrocytosis typically arise from conditions that result in hypoxemia or erythropoietin overproduction. This includes smoking, sleep apnea, living in high altitude areas, carbon monoxide poisoning, cerebellar hemangioblastoma, parathyroid carcinoma, or meningioma. Erythrocytosis is also a common side effect of various drug therapies, including diuretics, testosterone, and recombinant human erythropoietin.[22]

The present study examined the changes in hemoglobin and the predictors of erythrocytosis in patients with T2DM who received SGLT2i treatment. Differences in cardiovascular events and renal outcomes between the erythrocytosis and non-erythrocytosis groups were also investigated.

Materials and Methods

This retrospective cohort study was conducted between January 2020 and December 2022 at Maharat Nakhon Ratchasima Hospital, Thailand. This study was approved by the Research Ethics Committee of Maharat Nakhon Ratchasima Hospital (approval number 65068).

The study included 9,077 patients who were taking SGLT2i (Empagliflozin and Dapagliflozin). The inclusion criteria were as follows: (1) age ≥18 years; (2) diagnosis of T2DM; (3) receiving SGLT2i for more than three consecutive months and (4) having hemoglobin and/or hematocrit levels before and after 3-12 months of the SGLT2i treatment. The exclusion criteria were underlying anemia caused by impaired bone marrow function, active bleeding, history of chronic blood loss, and receiving erythropoietin-stimulating agent injection.

Definitions

In this study, we defined erythrocytosis as the increase in hemoglobin level ≥2 g/dL from baseline before SGLT2i treatment. Cardiovascular events and renal outcomes recorded were acute coronary syndrome, acute stroke, congestive heart failure, acute kidney injury, progression of CKD (sustained decline in eGFR), metabolic acidosis (including diabetic ketoacidosis), and urinary tract infection.

Sample size calculation

The sample size was calculated using the G*Power Version 3.1 program with F tests family, Linear Multiple regression: Fixed Model, R2 deviation from zero. An α level of 0.05, power of 0.8, and 22 factors of interest (including dummy variables) were used, with an effect size of 0.07 (small to medium, based on mean comparison from minimum = 0.01 to 0.1 for maximum sample size). A minimum of 328 patients were required for the study.[23]

Statistical analysis

Data are presented with mean ± standard deviation. Univariate logistic regression analysis was conducted to examine the factors predicting erythrocytosis. Differences between the two groups were compared using the Student T-test or chi-square test. Spearman's correlation was used to analyze the association between two continuous variables. The correlation between the ranges of eGFR and hemoglobin was analyzed by One-way ANOVA. The relationships between erythrocytosis with cardiovascular events and renal outcomes were analyzed using Cox proportional hazards regression models with appropriate adjustments for confounders. All statistical analyses were performed with STATA version SE 17.0 (Stata Corp LLC), using a two-sided significance level of 5%.

Results

Table 1 shows the baseline characteristics and laboratory data of all patients. The average hemoglobin and hematocrit were 12 ± 1.6 g/dL and 36.8 ± 5 %, respectively. The average eGFR was 74.2 mL/min/1.73 m^2. The albuminuria level was <30 mg/g in 100 patients (44.6%), 30-300 mg/g in 88 patients (39.3%), and >300 mg/g in 35 patients (15.6%). Dapagliflozin was administered to 195 patients (58%) and empagliflozin was administered to 141 patients (42%).

Table 1 Baseline characteristics and laboratory data of all patients

Baseline characteristics	N = 336
Female, N (%)	158 (47)
Age >60 years, N (%)	222 (66)
Age (years)	65 ± 10.7
Body mass index (kg/m^2)	27.32 ± 5.3
Co-morbidities, N (%)	
• Hypertension	308 (91.7)
• Dyslipidemia	333 (99.1)
• Coronary arterial disease	87 (25.9)
• Cerebrovascular disease	17 (5.1)
• Chronic kidney disease	124 (36.9)
• Obstructive sleep apnea	26 (7.7)
• Morbid obesity	31 (9.2)
Stages of chronic kidney disease, N (%)	
• Stage 1	122 (36.3)
• Stage 2	95 (28.3)
• Stage 3	110 (32.7)
• Stage 4	8 (2.4)
• Stage 5	1 (0.3)
Hemoglobin (g/dL)	12 ± 1.6
Hematocrit (%)	36.8 ± 5
eGFR (ml/min.1.73m^2)	74.2 ± 25.6
LDL-Cholesterol (mg/dL)	99.1 ± 29.7
Albuminuria (mg/g) (N; %)	(N = 224)
• <30	100 (44.6)
• 30-300	88 (39.3)
• > 300	35 (15.6)
Types of SGLT2i (N; %)	
• Dapagliflozin	195 (58)
• Empagliflozin	141 (42)

eGFR, estimated glomerular filtration rate; LDL, low density lipoprotein; SGLT2i, sodium-glucose cotransporter-2 inhibitors

Changes in hemoglobin and hematocrit levels over time are shown in **Figure 1**. The average hemoglobin and hematocrit levels gradually increased from baseline, with the highest hemoglobin and hematocrit levels observed at >24 months. The differences in the hemoglobin and hematocrit levels from baseline are presented in **Figure 2**. The median differences in hemoglobin from baseline were 0.7, 1, 1.3, and 1.5 g/dL at 3, 6, 12, and >24 months, respectively. The greatest increases in hemoglobin and hematocrit at >24 months were 1.5 g/dL (interquartile range 0.6 - 2.3) and 4.8 % (interquartile range 1.7 - 6.9), respectively. Erythrocytosis was observed in 125 patients (37.2%) at 12-24 months and >24 months. These 125 patients were categorized into the erythrocytosis group, leaving 211 patients in the non-erythrocytosis group.

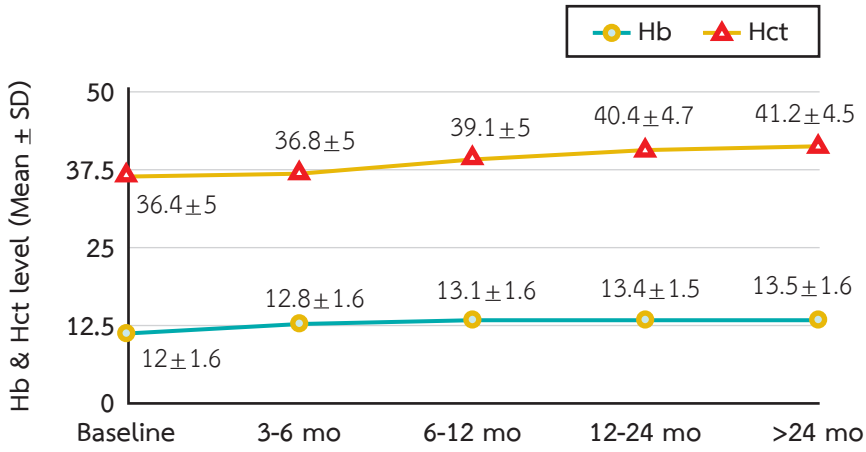

Figure 1 Changes in hemoglobin and hematocrit after sodium-glucose cotransporter-2 inhibitors treatment
Hb, hemoglobin; Hct, hematocrit; mo, months; SD, standard deviation

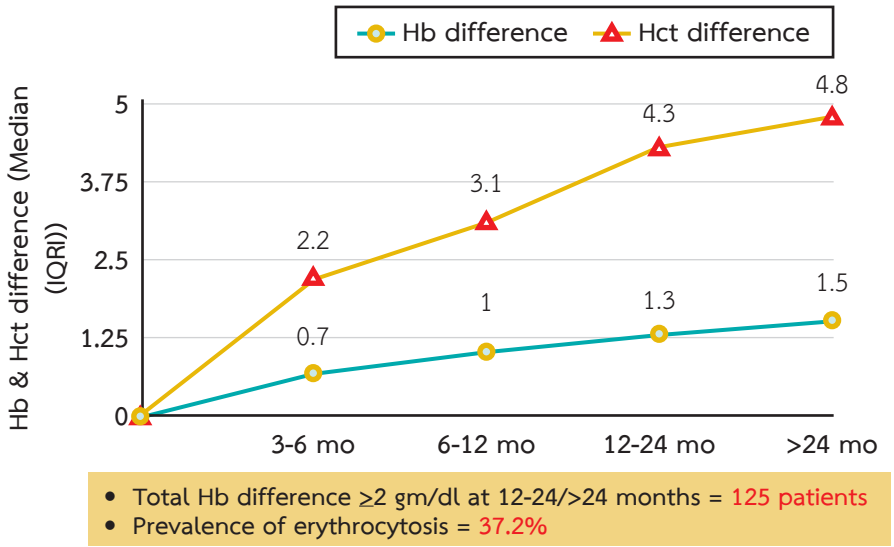

Figure 2 Changes in hemoglobin and hematocrit from baseline after sodium-glucose cotransporter-2 inhibitors treatment
Hb, hemoglobin; Hct, hematocrit; mo, months; IQR, interquartile range

Table 2 shows the results of the predictors of erythrocytosis. Age >60 years, using beta-blockers and thiazides, lower baseline hemoglobin/hematocrit, and kidney function were associated with erythrocytosis. The trends of hemoglobin levels in the group of patients with erythrocytosis and without erythrocytosis are shown in **Figure 3**. In the group with erythrocytosis, the increase in the hemoglobin levels was more evident compared with the group without erythrocytosis.

Table 2 Logistic regression analyses of the predictors of erythrocytosis

Parameters	Non-erythrocytosis (N = 211)	Erythrocytosis (N = 125)	Odds Ratio (95% Confidence Interval)	P
Female (N, %)	97 (64.0)	61 (36)	1.12 (0.72– 1.74)	0.616
Age >60 years (N, %)	128 (57.7)	94 (42.3)	1.97 (1.20 - 3.21)	0.007
Co-morbidities (N, %)				
• Hypertension	190 (61.7)	118 (38.3)	1.86 (0.77 - 4.52)	0.169
• Dyslipidemia	210 (63.1)	123 (36.9)	0.29 (0.03 - 3.26)	0.318
• Cardiovascular disease	48 (55.2)	39 (44.8)	1.54 (0.94 - 2.53)	0.088
• Cerebrovascular disease	12 (70.6)	5 (29.4)	0.69 (0.24 - 2.01)	0.497
• Chronic kidney disease	68 (54.8)	56 (45.2)	1.71 (1.08 - 2.69)	0.021
• Obstructive sleep apnea	20 (76.9)	6 (23.1)	0.48 (0.19 - 1.23)	0.128
• Congestive heart failure	17 (68)	8 (32)	0.78 (0.33 - 1.86)	0.577
• Morbid obesity	21 (67.7)	10 (32.3)	0.79 (0.36 - 1.73)	0.551
Antihypertensive drugs (N, %)				
• ACEI/ARB	133 (63)	79 (63.2)	1.01 (0.64 - 1.59)	0.976
• Beta-blocker	59 (28)	53 (42)	1.9 (1.19 - 3.02)	0.007
• Calcium-channel blocker	96 (45.5)	60 (48)	1.11 (0.71 - 1.72)	0.657
• Thiazide	3 (1.42)	9 (7.2)	5.38 (1.43 - 20.26)	0.013
• Furosemide	31 (14.7)	23 (18.4)	1.31 (0.72 - 2.37)	0.372
Antihyperglycemic drugs				
• Sulfonylurea	84 (39.8)	52 (41.6)	1.08 (0.69-1.69)	0.747
• Metformin	156 (73.9)	86 (68.8)	0.78 (0.48-1.27)	0.311
• Insulin	65 (30.8)	40 (32)	1.06 (0.66-1.7)	0.819
• DPP4 inhibitors	108 (51.2)	71 (56.8)	1.25 (0.8-1.96)	0.319
• GLP1-receptor agonist	16 (7.56)	12 (9.6)	1.29 (0.59-2.83)	0.519
Cardiovascular disease drugs				
• Aspirin	95 (45)	58 (46.4)	1.06 (0.68 - 1.65)	0.807
• Clopidogrel	19 (9)	14 (11.2)	1.27 (0.61 - 2.64)	0.514
• Statins	198 (93.8)	118 (94.4)	1.11 (0.43 - 2.85)	0.834
• Ezetimibe	25 (11.9)	13 (10.4)	0.86 (0.42 - 1.76)	0.686
• Cilostazol	6 (2.8)	4 (3.2)	1.13 (0.31 - 4.08)	0.853
• Ticagrelor	2 (1)	3 (2.4)	2.57 (0.42 - 15.59)	0.305
• DOACs	4 (1.9)	4 (3.2)	1.71 (0.42 - 6.96)	0.454
• Warfarin	1 (0.5)	5 (4)	8.75 (1.01-75.77)	0.049
Laboratory data				
• Hemoglobin (g/dL)	12.4 ± 1.5	11.2 ± 1.5	0.59 (0.5 - 0.7)	<0.001
• Hematocrit (%)	38.1 ± 4.5	34.5 ± 4.9	0.84 (0.79 - 0.89)	<0.001
• Creatinine (mg/dl)	0.89 (0.6 - 1.15)	1.02 (0.79-1.33)	1.71 (1.05 - 2.79)	0.031
• eGFR (ml/min/1.73 m^2); median (IQR)	79 (55 - 99)	69 (49 - 92)	0.98 (0.98 – 0.99)	0.005

Parameters	Non-erythrocytosis (N = 211)	Erythrocytosis (N = 125)	Odds Ratio (95% Confidence Interval)	P
CKD stages (N; %)				
• stage 1	84 (39.8)	38 (30.4)	1	
• stage 2	63 (29.9)	32 (25.6)	1.12 (0.63 - 1.99)	0.692
• stage 3	58 (27.5)	52 (41.6)	1.98 (1.16 - 3.39)	0.012
• stage 4	5 (2.4)	3 (2.4)	1.33 (0.30 - 5.84)	0.709
• stage 5	1 (0.5)	0 (0)	NA	NA
Type of SGLT2i (N; %)				
• Dapagliflozin	126 (59.7)	68 (54.4)	1	
• Empagliflozin	82 (38.8)	57 (45.6)	1.29 (0.82-2.02)	0.269

ACEI/ARB; angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide-1; DOACs; direct oral anticoagulants; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; SGLT2i; sodium-glucose cotransporter-2 inhibitors

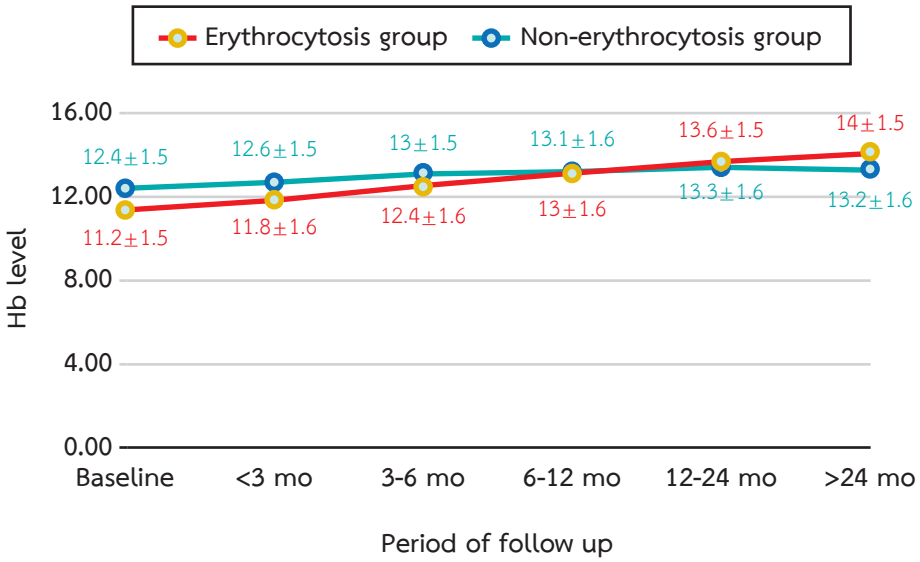

Figure 3 Trends in hemoglobin levels in erythrocytosis and non-erythrocytosis groups
Hb; hemoglobin; mo, months

The eGFR values during the follow-up period of the erythrocytosis and non-erythrocytosis groups are shown in **Figure 4**. The erythrocytosis group had a lower eGFR baseline. An initial drop in eGFR was observed in both groups. Thereafter, a gradual return of eGFR to baseline was observed in both groups, with a tendency towards a heightened preservation of renal function in the erythrocytosis group.

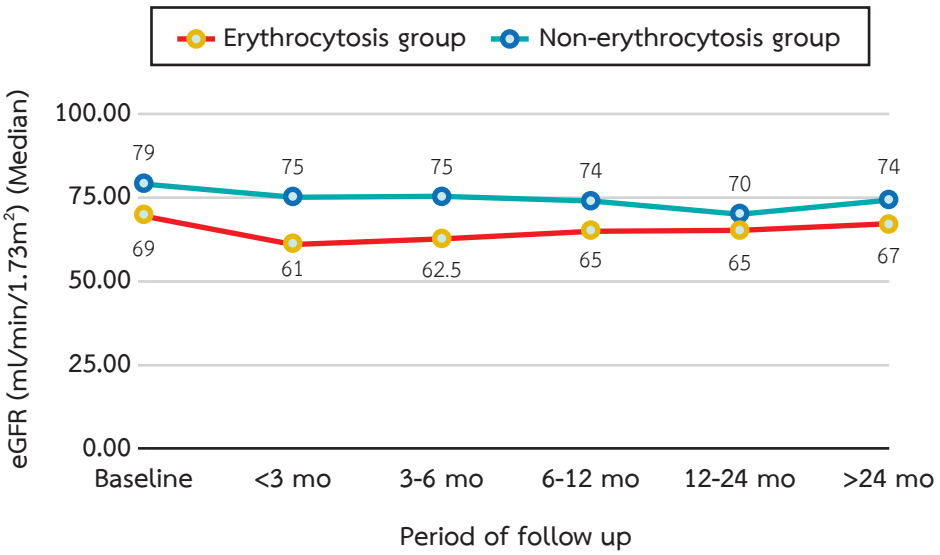

Figure 4 Changes in estimated glomerular filtration rate in the erythrocytosis and non-erythrocytosis group
eGFR, estimated glomerular filtration rate; mo, months

The correlation between hemoglobin levels and eGFR at >24 months is shown in **Figure 5**. There was a weak but significant correlation between hemoglobin levels and eGFR (r = 0.316, P < 0.001). **Figure 6** shows the changes in hemoglobin levels from baseline and the average hemoglobin levels according to the ranges of eGFR (<30, 30-59, ≥60 ml/min/1.73 m^2) at >24 months. The increase in hemoglobin from baseline was lowest in the group with eGFR ≥60 ml/min/1.73 m^2, but between-group differences did not reach statistical significance (P=0.46). The average hemoglobin level at >24 months was highest in the group with eGFR ≥60 ml/min/1.73m² with a significant difference between the 3 groups (P <0.001).

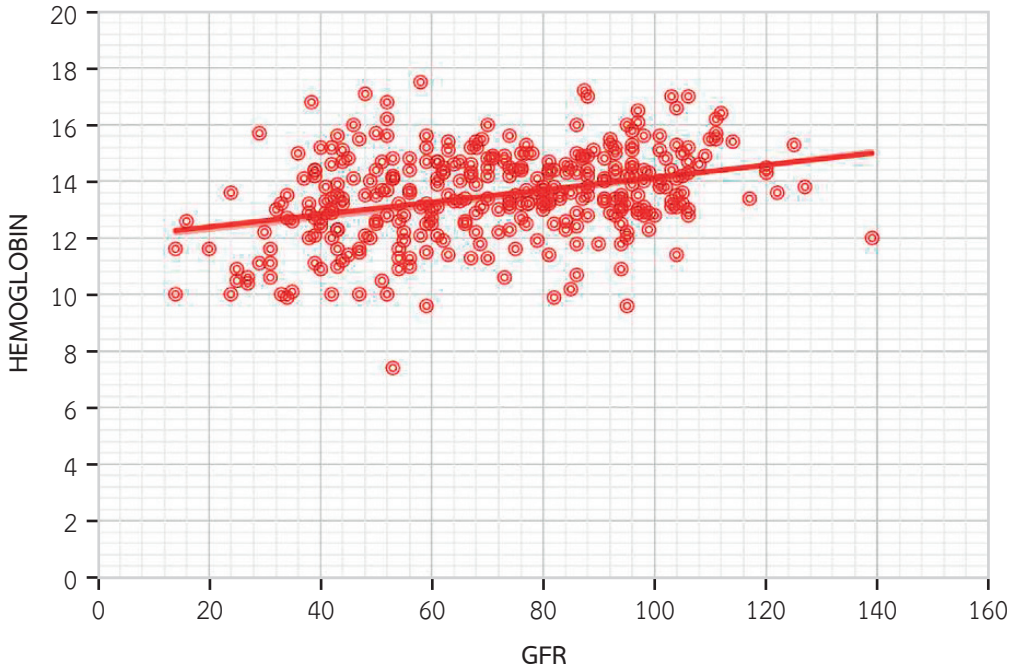

Figure 5 Correlation between hemoglobin levels and estimated glomerular filtration rate at > 24 months
GFR, glomerular filtration rate

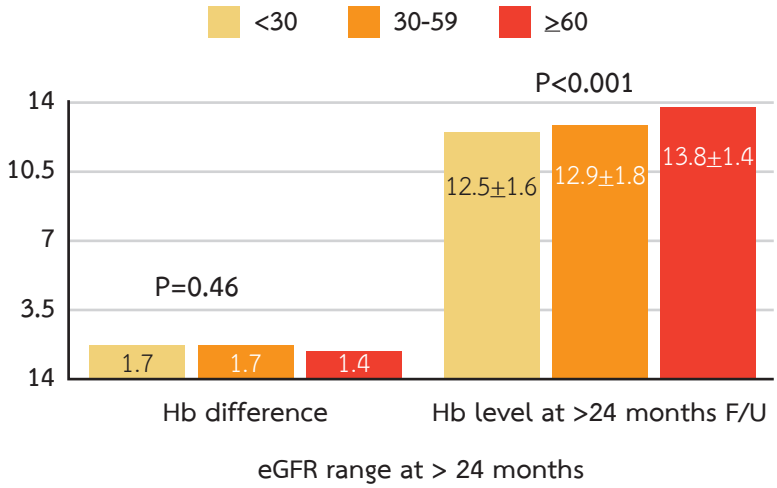

Figure 6 Changes in hemoglobin levels from baseline and the average hemoglobin levels at >24 months according to kidney function
eGFR, estimated glomerular filtration rate; Hb, hemoglobin

Cardiovascular events and renal outcomes

The cardiovascular events and renal outcomes associated with SGLT2i treatment in patients with and without erythrocytosis are presented in **Table 3**. There were no differences in cardiovascular events and renal outcomes between the two groups. A tendency toward an increase in mortality was observed in the non-erythrocytosis group.

Table 3 Cardiovascular events and renal outcomes in the erythrocytosis and non-erythrocytosis groups

Adverse events (N/%)	Non-erythrocytosis (N = 211)	Erythrocytosis (N = 125)	*P*-value
Cardiovascular events	15 (7.1)	10 (8)	0.764
• Acute coronary syndrome	5 (2.4)	4 (3.2)	0.732
• Acute stroke	4 (1.9)	1 (0.8)	0.655
• Congestive heart failure	6 (2.8)	5 (4)	0.546
Deep venous thrombosis	1 (0.5)	0 (0)	1.000
Renal events	21 (10)	15 (12)	0.558
• Acute kidney injury	6 (2.8)	2 (1.6)	0.715
• CKD progression	7 (3.3)	6 (4.8)	0.563
• Metabolic acidosis (including diabetic ketoacidosis)	1 (0.5)	1 (0.8)	1.000
• Urinary tract infection	9 (4.3)	8 (6.4)	0.443
Death from any cause	6 (2.8)	0 (0)	0.057
• Sepsis	2 (1)	0 (0)	0.531
• Thrombotic cardiovascular events	1 (0.5)	0 (0)	1.000
• Heart failure	2 (1)	0 (0)	0.531
• Malignancy	1 (0.5)	0 (0)	1.000

CKD, chronic kidney disease

Discussion

The present study investigated the changes in hemoglobin, prevalence, and predictors of erythrocytosis and cardiovascular events and renal outcomes associated with erythrocytosis after SGLT2i treatment in patients with T2DM. A gradual increase in hemoglobin levels over time was observed after SGLT2i treatment. The prevalence of erythrocytosis was 32.7%. Predictors of erythrocytosis included older age, using thiazide diuretics and beta-blockers, and lower hemoglobin and kidney function at baseline. There was no difference in cardiovascular events and renal outcomes between the erythrocytosis and non-erythrocytosis groups.

An increase in hemoglobin after SGLT2i treatment has been reported previously.[13] Similar to previous studies, the present study demonstrated a significant increase in hemoglobin from baseline after SGLT2i treatment. The prevalence of erythrocytosis in the present study appeared to be higher than that in previous studies that reported a 2-4% increase in hematocrit relative to placebo after 8 weeks of SGLT2i treatment.[24] It is possible that this study had a longer follow-up period, and the continued increase of hemoglobin was observed beyond 8 weeks of treatment. The decline in eGFR at the beginning of treatment with SGLT2i could be explained by the diuretic effect of the drug. However, an increase in hemoglobin was observed beyond the early period indicating that hemoconcentration was not responsible for the increase in hemoglobin and hematocrit. As mentioned earlier, SGLT2i can enhance erythropoiesis through several mechanisms.[15-18]

This study also showed that both erythrocytosis and non-erythrocytosis groups were able to maintain eGFR throughout the study period. There was a trend that suggested better preservation of eGFR in the erythrocytosis group at 24 weeks. The weak correlation between hemoglobin and eGFR was also evident, with the group with lower eGFR at baseline being more likely to develop erythrocytosis. The greater change in hemoglobin after SGLT2i treatment in the group of patients with lower eGFR and hemoglobin at baseline might be partly responsible for the trend toward the preservation of eGFR in the erythrocytosis group. Previous studies have demonstrated an association between the increase in hemoglobin and better renal function after SGLT2i treatment.[7,8,9]

Regarding cardiovascular events and renal outcomes, there was no significant difference in the incidence of cardiovascular events and renal outcomes between the erythrocytosis and non-erythrocytosis groups. However, there was a borderline statistically significant difference in mortality between the two groups, with no deaths in the erythrocytosis group and six deaths in the non-erythrocytosis group. This finding could be partly explained by the lower hemoglobin level in the non-erythrocytosis group.

Limitations

This study was a retrospective observational study; therefore, the study was subjected to selection bias and confounding variables. The effects of SGLT2i on outcomes could not be ascertained because of the lack of a control group. The study was conducted in a single center, thereby limiting the generalizability of the results. The findings from the present study require confirmation from larger randomized trials with longer follow-up periods.

Conclusion

A gradual increase in hemoglobin levels was observed after SGLT2i treatment in patients with T2DM. The prevalence of erythrocytosis was high, and the predictors of erythrocytosis included lower hemoglobin and kidney function at baseline. The presence of erythrocytosis did not significantly affect cardiovascular events and renal outcomes.

References

1. Vejakama P, Ingsathit A, Attia J, Thakkinstian A. Epidemiological Study of Chronic Kidney Disease Progression: A Large-Scale Population-Based Cohort Study. Medicine (Baltimore). 2015;94(4):e475.
2. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes

and Nephropathy. N Engl J Med. 2001;345(12):861–9.
3. Rodby RA, Rohde RD, Clarke WR, Hunsicker LG, Anzalone DA, Atkins RC, et al. The Irbesartan Type II Diabetic Nephropathy Trial: study design and baseline patient characteristics. Nephrol Dial Transplant. 2000;15(4):487–97.
4. Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. QJM. 2015;108(11):879–84.
5. Kendrick J, Chonchol MB. Nontraditional risk factors for cardiovascular disease in patients with chronic kidney disease. Nat Clin Pract Nephrol. 2008;4(12):672–81.
6. Washburn WN, Poucher SM. Differentiating sodium-glucose co-transporter-2 inhibitors in development for the treatment of type 2 diabetes mellitus. Expert Opin Investig Drugs. 2013;22(4):463-86.
7. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117–28.
8. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388(2):117–27.
9. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436–46.
10. Rossing P, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, Khunti K, et al. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S):S1-S127.
11. American Diabetes Association. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. Clin Diabetes. 2022;40(1):10–38.
12. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347–57.
13. Wang X, Fu R, Liu H, Ma Y, Qiu X, Dong Z. The effects of sodium glucose co-transporter (SGLT) 2 inhibitors on hematocrit levels: a systematic review and meta-analysis of randomized controlled trials. Ann Palliat Med. 2021;10(6):6467-81.
14. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999;34(1):125–34.
15. Marathias KP, Lambadiari VA, Markakis KP, Vlahakos VD, Bacharaki D, Raptis AE, et al. Competing Effects of Renin Angiotensin System Blockade and Sodium-Glucose Cotransporter-2 Inhibitors on Erythropoietin Secretion in Diabetes. Am J Nephrol. 2020;51(5):349–56.
16. Souma T, Suzuki N, Yamamoto M. Renal erythropoietin-producing cells in health and disease. Front Physiol. 2015;6:167.
17. Souma T, Nezu M, Nakano D, Yamazaki S, Hirano I, Sekine H, et al. Erythropoietin Synthesis in Renal Myofibroblasts Is Restored by Activation of Hypoxia Signaling. J Am Soc Nephrol. 2016;27(2):428–38.
18. Ghanim H, Abuaysheh S, Hejna J, Green K, Batra M, Makdissi A, et al. Dapagliflozin Suppresses Hepcidin And Increases Erythropoiesis. J Clin Endocrinol Metab. 2020;105(4):dgaa057.
19. Tilg H, Moschen AR. Inflammatory Mechanisms in the Regulation of Insulin Resistance. Mol Med. 2008;14(3–4):222–31.
20. Fleming RE. Iron and inflammation: cross-talk between pathways regulating hepcidin. J Mol Med (Berl). 2008;86(5):491–4.
21. Mithoowani S, Laureano M, Crowther MA, Hillis CM. Investigation and management of erythrocytosis. CMAJ. 2020;192(32):E913–8.
22. Gašperšič J, Kristan A, Kunej T, Zupan IP, Debeljak N. Erythrocytosis: genes and pathways involved in disease development. Blood Transfus. 2021;19(6):518–32.
23. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175–91.
24. Sano M, Goto S. Possible Mechanism of Hematocrit Elevation by Sodium Glucose Cotransporter 2 Inhibitors and Associated Beneficial Renal and Cardiovascular Effects. Circulation. 2019;139(17):1985–7.