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SGLT2 Inhibitor-Associated Erythrocytosis in Patients with Type 2 Diabetes Mellitus: A Three-Patient Case Series and practical approach to evaluation and management.

Mai Elgoukhy[1]; Seifeldin Yahia[2]

[1]Department of Internal Medicine, Sheikh Sultan Bin Zayed Hospital, Sharjah, United Arab Emirates

[2]Consultant Endocrinology and Diabetology, Sheikh Sultan Bin Zayed Hospital, Sharjah, United Arab Emirates

Corresponding Author:

Mai Elgoukhy, MRCPI, MSc Diabetes and obesity, Department of Internal Medicine Sheikh Sultan Bin Zayed Hospital, Sharjah, United Arab Emirates

Email: dr_mai.elgokhy@yahoo.com

Abstract

Background

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have become a cornerstone in the management of type 2 diabetes mellitus (T2DM) because of their established cardiovascular and renal benefits. In addition to improving glycemic control, these agents are associated with increases in hemoglobin and hematocrit levels. While mild hematological changes are commonly observed, clinically significant erythrocytosis remains underrecognized and may prompt investigation for myeloproliferative or secondary causes.(1-2)

Case Presentations

We describe three male patients with T2DM who developed erythrocytosis while receiving dapagliflozin or empagliflozin. All patients were overweight active smokers and demonstrated elevated hemoglobin and hematocrit levels, preserved renal function, normal oxygen saturation, elevated or upper-normal erythropoietin concentrations, and negative JAK2 mutation testing. No patient demonstrated splenomegaly, hyperviscosity symptoms, or thrombotic complications. One patient developed erythrocytosis within six months of dapagliflozin initiation, whereas two patients developed erythrocytosis during long-term SGLT2 inhibitor therapy. Dose reduction in the latter two cases resulted in stabilization or reduction of hemoglobin levels without treatment discontinuation.

Conclusion

SGLT2 inhibitor-associated erythrocytosis is an increasingly recognized clinical entity that may mimic primary or secondary hematologic disorders. Careful evaluation and individualized

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management may allow continuation of therapy while preserving its established cardiometabolic benefits.

Keywords: SGLT2 inhibitors; dapagliflozin; empagliflozin; erythrocytosis; erythropoietin; type 2 diabetes mellitus

Introduction

Sodium-glucose co-transporter-2 (SGLT2) inhibitors have become an essential component of modern diabetes management because of their demonstrated benefits in glycemic control, cardiovascular protection, heart failure outcomes, and chronic kidney disease progression. (3-5)

A consistent observation in clinical trials has been a rise in hemoglobin and hematocrit levels among patients receiving these agents.

Initially attributed to hemoconcentration resulting from osmotic diuresis, increasing evidence suggests that enhanced erythropoiesis plays a major role(6-7). Proposed mechanisms include restoration of renal oxygen sensing, increased erythropoietin production, activation of hypoxia-inducible factor pathways, and improved iron utilization.

Although mild elevations in hemoglobin are common, clinically significant erythrocytosis may raise concern for myeloproliferative disorders or other secondary causes. Awareness of this association is important to avoid unnecessary investigations and inappropriate discontinuation of beneficial therapy(8-9).

We present three patients with T2DM who developed erythrocytosis during treatment with dapagliflozin or empagliflozin and discuss the diagnostic evaluation, potential mechanisms, and management considerations associated with this increasingly recognized phenomenon.

Proposed Mechanisms of SGLT2 Inhibitor-Associated Erythrocytosis

Several mechanisms have been proposed to explain erythrocytosis associated with SGLT2 inhibitor therapy:

Osmotic Diuresis and Hemoconcentration

Early mechanistic studies attributed hematocrit elevation primarily to plasma volume contraction resulting from glucosuria-induced osmotic diuresis, producing a relative erythrocytosis (10).

Enhanced Erythropoietin Production

SGLT2 inhibition reduces proximal tubular glucose reabsorption, decreasing renal oxygen consumption and altering renal oxygen sensing. These changes may stimulate erythropoietin production by peritubular fibroblasts (11).

Hypoxia-Inducible Factor Activation

Experimental data suggest activation of hypoxia-inducible factor-2α (HIF-2α), resulting in upregulation of genes involved in erythropoiesis and iron metabolism (11).

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Improved Iron Availability

SGLT2 inhibitors may enhance iron mobilization through effects on hepcidin regulation and iron recycling, thereby facilitating red blood cell production (11)

Case Presentations

Case 1

A 33-year-old man with T2DM and a body mass index (BMI) of 26 kg/m² was initiated on dapagliflozin 10 mg daily. He was an active smoker with no prior hematologic history. Baseline hemoglobin before treatment was 16.2 g/dL.

Six months after treatment initiation, hemoglobin increased to 17.9 g/dL with hematocrit of 0.57. Red blood cell count increased from 6.0 $\times 10^6/\mu L$ to 6.9 $\times 10^6/\mu L$. Serum erythropoietin concentration was 16.5 mIU/mL. JAK2 mutation testing was negative. Oxygen saturation was 98% on room air, and estimated glomerular filtration rate (eGFR) remained greater than 90 mL/min/1.73 m².

The patient remained asymptomatic without evidence of hyperviscosity symptoms, splenomegaly, or thrombotic complications. Given the strong temporal association with dapagliflozin initiation and the absence of concerning clinical features, therapy was continued with close hematologic surveillance. Hemoglobin remained stable during follow-up.

Case 2

A 45-year-old man with T2DM (BMI 27 kg/m²) had been receiving empagliflozin 10 mg daily for approximately five years. Baseline hemoglobin before treatment initiation was 14.2 g/dL.

During follow-up, hemoglobin increased to 18.6 g/dL with hematocrit of 0.51. Serum erythropoietin concentration was 17.5 mIU/mL, JAK2 mutation testing was negative, oxygen saturation was 97%, and renal function remained preserved.

Because of persistent erythrocytosis, empagliflozin dosage was reduced to 5 mg daily. Follow-up testing demonstrated a reduction in hemoglobin to 17.7 g/dL. No thrombotic complications occurred.

Case 3

A 45-year-old man with T2DM (BMI 28 kg/m²) had been receiving dapagliflozin 10 mg daily for approximately six years. Hemoglobin was 17.5 g/dL with hematocrit of 0.56.

Serum erythropoietin concentration was 17.2 mIU/mL, oxygen saturation was 98%, renal function was preserved, and JAK2 mutation testing was negative. The patient had documented hypogonadism and erectile dysfunction but had never received testosterone replacement therapy or anabolic agents.

Dapagliflozin dosage was reduced to 5 mg daily, resulting in stabilization of hemoglobin levels. No hyperviscosity symptoms, splenomegaly, or thrombotic events were observed.

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Table 1. Clinical Characteristics of the Three Patients

Variable	**Case 1**	**Case 2**	**Case 3**
Age (years)	33	45	45
BMI (kg/m²)	26	27	28
SGLT2 inhibitor	Dapagliflozin	Empagliflozin	Dapagliflozin
Duration of therapy	6 months	5 years	6 years
Baseline Hb (g/dL)	16.2	14.2	Not available
Peak Hb (g/dL)	17.9	18.6	17.5
Hematocrit	0.57	0.51	0.56
Erythropoietin (mIU/mL)	16.5	17.5	17.2
JAK2 mutation	Negative	Negative	Negative
Oxygen saturation (%)	98	97	98
eGFR (mL/min/1.73 m²)	>90	>90	>90
Smoking status	Current smoker	Current smoker	Current smoker
Hyperviscosity symptoms	None	None	None
Splenomegaly	Absent	Absent	Absent
Thrombotic events	None	None	None
Intervention	Observation	Dose reduction	Dose reduction
Outcome	Stable	Hb decreased to 17.7 g/dL	Hb stabilized

Discussion

SGLT2 inhibitor-associated erythrocytosis is increasingly recognized in routine clinical practice. The observed findings in our patients are consistent with previously reported cases demonstrating elevated hemoglobin concentrations, increased erythropoietin levels, and exclusion of primary myeloproliferative disorders through negative JAK2 testing. (7-12)

All patients demonstrated preserved renal function and normal oxygen saturation, reducing the likelihood of chronic hypoxia-related erythrocytosis. The temporal relationship was most evident in Case 1, where hemoglobin increased substantially within six months of dapagliflozin initiation.

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A key clinical challenge is balancing management of erythrocytosis against the well-established cardiovascular and renal benefits of SGLT2 inhibitors. In our series, conservative measures including hydration counseling, smoking cessation advice, laboratory surveillance, and dose reduction when appropriate resulted in favorable outcomes (12). None of the patients required therapeutic phlebotomy or developed thrombotic complications.

Published reports by Chin-Yee et al. and Gangat et al. similarly highlighted erythrocytosis associated with SGLT2 inhibitor therapy and emphasized the importance of distinguishing this entity from polycythemia vera and other hematologic disorders.

Proposed Clinical Management Approach

Based on the available literature and our clinical experience, we propose the following practical management approach:

Observation

Appropriate for asymptomatic patients with mild erythrocytosis and no additional thrombotic risk factors. Serial complete blood count monitoring every 3–6 months is recommended (8).

Dose Reduction

Considered in patients with persistent hemoglobin elevation above 18 g/dL or progressive increases over time (13).

Drug Discontinuation

May be required in patients with persistent erythrocytosis despite dose reduction or when thrombotic risk cannot be adequately controlled (9).

Therapeutic Phlebotomy

Reserved for symptomatic hyperviscosity or markedly elevated hematocrit levels despite conservative management (14).

Limitations

This report represents a small, single-center case series. Formal assessment for obstructive sleep apnea was not performed despite its recognized association with secondary erythrocytosis. Smoking exposure could not be quantified in pack-years, and serial erythropoietin measurements were unavailable. Consequently, a definitive causal relationship cannot be established.

Conclusions

SGLT2 inhibitor-associated erythrocytosis should be recognized as a potential cause of elevated hemoglobin and hematocrit levels in patients with type 2 diabetes mellitus. Appropriate evaluation is necessary to exclude alternative etiologies, particularly myeloproliferative disorders and other causes of secondary erythrocytosis.

In carefully selected asymptomatic patients, conservative management with close monitoring, smoking cessation counseling, adequate hydration, and individualized dose adjustment may permit continuation of SGLT2 inhibitor therapy while preserving its established cardiovascular and renal benefits.

Further prospective studies are needed to better define incidence, mechanisms, long-term outcomes, and optimal management strategies.

Ethics Statement

This case series was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

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No external funding was received.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Both authors contributed to patient management, manuscript preparation, critical revision, and approval of the final manuscript.

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