Erythrocytosis and CKD: A Review

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Erythrocytosis or polycythemia is defined as an increase in red blood cell concentration above the age- and sex-specific normal levels. Unlike anemia, which is very common in patients with chronic kidney disease (CKD), erythrocytosis is less frequent but requires specific understanding by health care professionals in order to provide the best care. Erythrocytosis, especially when undiagnosed and untreated, can lead to serious thrombotic events and higher mortality. Classic causes of erythrocytosis associated with CKD include cystic kidney diseases, kidney or other erythropoietin-secreting neoplasms, high-altitude renal syndrome, overdosage of erythropoietin-stimulating agents, androgen therapy, heavy smoking, chronic lung disease, obstructive sleep apnea, IgA nephropathy, post–kidney transplant erythrocytosis, renal artery stenosis, and congenital etiologies. After ruling out the common acquired causes of erythrocytosis and/or in the presence of suggestive parameters, primary erythrocytosis or polycythemia vera (PV) should be considered, and patients should be screened for *JAK2V617F* somatic mutation. The newest entity inducing erythrocytosis is linked to the use of sodium/glucose cotransporter 2 (SGLT2) inhibitors that hypothetically activate hypoxia-inducible factor 2α (HIF-2α) and in some cases unmask PV. This Review focuses on the pathogenesis, renal manifestations and management of PV, the pathophysiology of erythrocytosis induced by SGLT2 inhibitors and the relevance of timely *JAK2* mutation screening in these patients.

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Introduction

Erythrocytosis is defined as an increase in the concentration of red blood cells or red cell mass above the age- and sex-specific normal ranges.[1] Erythropoiesis is regulated by erythropoietin (Epo) with normal Epo levels ranging between 5 and 25 U/L.[2,3] Erythrocytosis is either primary or secondary. Primary erythrocytosis includes polycythemia vera (PV), where Epo-independent red cell production relates to a somatic *JAK2* mutation in a hematopoietic stem cell. Secondary erythrocytosis results from hypoxia-driven Epo secretion or pathological Epo overproduction.[1,2] Cutoffs of hemoglobin and hematocrit used to diagnose erythrocytosis, extrapolated from the PV diagnostic criteria, are above 16.5 g/dL and 49% for men and 16 g/dL and 48% for women, respectively.[4]

Erythrocytosis or polycythemia can cause hypertension and cardiac events.[5] However, the primary concern accompanying erythrocytosis is the risk of thrombotic events due to increased blood viscosity.[6-8] Thrombosis incidence is 4.5 cases per 100 person-years in PV and 6.24 in chronic lung disease.[6] Nguyen et al[7] found a prevalence of thrombotic events of 29% in patients with PV and 26% in patients with secondary erythrocytosis. These rates decreased to 14% in PV patients and 0 in secondary erythrocytosis after erythrocytosis diagnosis.[7] Therefore, diagnosing and properly managing erythrocytosis improves outcomes.

In patients with chronic kidney disease (CKD), anemia is common due to impaired Epo production. Thus, erythrocytosis is rare in CKD; but if it is present, it requires further investigation and management. This review starts out from the established causes of erythrocytosis associated with CKD and focuses on emerging risk factors such as IgA nephropathy (IgAN) and the use of sodium/glucose cotransporter 2 (SGLT2) inhibitors.

Erythropoiesis

Epo is secreted by peritubular interstitial cells of the kidney in adults and minimally by the liver.[8] Epo gene expression is controlled by hypoxia-inducible transcription factors (HIFs) that are oxygen-labile transcriptional activators. During hypoxia sensing, Epo binds to the membrane receptor of a myeloid progenitor cell in the bone marrow. Epo receptor's activation induces the phosphorylation of *JAK2* tyrosine kinase. This activates *JAK2* downstream pathways leading to the maturation and proliferation of erythroid progenitor cells and their ultimate differentiation into erythrocytes. Epo further promotes the survival of erythroid progenitor cells by rescuing them from apoptosis.[8,9]

Established Causes of Erythrocytosis

Volume depletion may be the most common cause of erythrocytosis. Primary erythrocytosis includes PV whereas secondary erythrocytosis is divided into congenital, acquired, and drug-related and is associated with either high or normal Epo levels (Table 1; Box 1).[1,2,10] High Epo levels (>15.1 mU/mL) are specific (98%) but not sensitive (47%) for secondary erythrocytosis.[11]

Kidney Hypoxia and Excessive Erythropoietin Production

Cystic Kidney Disease and Dialysis

Unlike other forms of CKD, CKD due to autosomal dominant polycystic kidney disease (ADPKD) commonly presents with normal hemoglobin levels even in dialysis,

Table 1. Etiologies of Erythrocytosis Associated With Chronic Kidney Disease

	Pathophysiology	Epo Level	Associated Kidney Lesion	Management Tips
Primary Erythrocytosis				
Chronic myeloproliferative neoplasms including PV	*JAK2* mutation	Low or normal	Glomerular sclerosis and IgA deposits	• Refer to hematology: hydroxyurea needs dose adjustment in advanced CKD/ruxolitinib/Peg-interferon/ pipobroman (less used) • Low-dose aspirin • Avoid ESA treatment if anemia occurs • Avoid iron treatment
Secondary Erythrocytosis (Congenital)				
HIF-2α and *PHD2* mutations, autosomal recessive *VHL* mutation, Epo receptor gene mutation, *HFE* mutations (H63D and C282Y)	Germinal mutation in the oxygen sensing pathway (HIF-2α, PHD2, VHL) and increased bioavailability of iron with *HFE* mutation.	High or normal (subnormal if EpoR mutation)	No specific kidney disease	Few options: phlebotomy if symptomatic; low-dose aspirin/ruxolitinib needs further study
Secondary Erythrocytosis (Acquired)				
High-altitude polycythemia	Central hypoxia	High or normal	Glomerulosclerosis	RAS inhibitors
Chronic lung disease, obstructive sleep apnea, smoking	Central hypoxia	High or normal	Found in patients with ESKD	Smoking cessation, oxygen therapy, low-dose aspirin
Renal artery stenosis and ESKD (including dialysis patients)	Decreased renal blood flow, local renal hypoxia, IGF-1	High or normal	Kidney ischemia	RAS inhibitors, low-dose aspirin
Cystic kidney diseases (mainly ADPKD)	Overproduction of Epo	High or normal	Cysts	Nephrectomy might be considered; RAS inhibitors
Kidney cancer or another Epo-secreting tumor	Overproduction of Epo/local renal hypoxia	High or normal	Kidney mass	Tumor resection
After kidney transplant	Overproduction of Epo, enhanced IGF-1	High or normal	All kidney diseases	RAS inhibitors
IgA nephropathy	High ratio of polymeric IgA1/monomeric IgA1, high Gd-pIgA1 make the TfR1 of erythroid progenitor cells more sensitive to Epo	Normal	IgA deposition	RAS inhibitors
Secondary Erythrocytosis (Drug-associated)				
Overdosage of ESAs	Epo exogenous administration	High	All kidney diseases	Dose adjustment
HIF-PHIs Androgen therapy	Activation of HIF-1α and HIF-2α Enhances responsiveness of progenitor cells to Epo	High High or normal	All kidney diseases No specific kidney lesion, prescribed in diabetes and hypogonadism	Dose adjustment Avoid androgen therapy
SGLT2 inhibitors	Local renal hypoxia, activation of HIF-2α	High or normal	Diabetic nephropathy mainly	Screen for PV, screen for HH

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; Epo, erythropoietin; EpoR, erythropoietin receptor; ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; Gd-pIgA1, galactose-deficient polymeric IgA1; HFE, homeostatic iron regulator; HIF, hypoxia inducible factor; HIF-PHIs, hypoxia-inducible factor prolyl hydroxylase inhibitors; HH, hereditary hemochromatosis; IgAN, Immunoglobulin A nephropathy; IGF-1, insulin-like growth factor 1; JAK2, JAK2, Janus kinase 2; Peg, pegylated; PHD, prolyl hydroxylase; PV, polycythemia vera; RAS, renin-angiotensin system; SGLT2, sodium/glucose cotransporter 2; TfR1, transferrin receptor 1; VHL, von-Hippel Lindau.

Box 1. Examples of Combined Etiologies of Erythrocytosis in Patients With CKD

1. Post-kidney transplant erythrocytosis and autosomal dominant polycystic kidney disease
2. PV and SGLT2 inhibitors
3. PV and IgA nephropathy
4. PV and renal artery stenosis
5. Hemochromatosis, testosterone, and SGLT2 inhibitors

Abbreviations: CKD, chronic kidney disease; PV, polycythemia vera; SGLT2, sodium/glucose cotransporter 2.

and patients may develop erythrocytosis after kidney transplantation.[12] Erythrocytosis occurs also in patients with acquired cystic kidney disease[13] and can be reversible after nephrectomy.[14] The pathophysiology of erythrocytosis in cystic kidney diseases combines high Epo production and kidney hypoxia although not all cysts overproduce Epo.[15] An approach to erythrocytosis in dialysis patients is summarized in Box 2.

Kidney Cancer

Clear cell renal cell carcinoma constitutes 75% of kidney cancers and is a recognized cause of secondary erythrocytosis.[16] Loss of von Hippel-Lindau (VHL) gene function activates HIFs that promote Epo production. Erythrocytosis is usually reversible after tumor resection. DNA damage during acute kidney injury (AKI) or CKD triggers the transformation of injured kidney cells into malignant cell clones in an adenoma-carcinoma sequence.[17] Along this process, altered oxygen sensing stimulates Epo production and ultimately erythrocytosis.[17]

Post–Kidney Transplant Erythrocytosis

Post–kidney transplant erythrocytosis (PTE) is defined as a hemoglobin level of >17 g/dL.[18] Its prevalence ranges between 8% and 22%.[18-22] Its multifactorial pathogenesis includes increased Epo secretion by native kidneys and other erythrocytosis-contributing growth factors.[18] ADPKD, male gender, history of smoking, deceased-donor status, and prior dialysis are risk factors for PTE.[23] Angiotensin II also activates the Epo-dependent red cell proliferation in these patients[24] and renin-angiotensin system (RAS) inhibitors reduce the development of PTE.[21,25] RAS inhibitors and mycophenolic acid lowered PTE prevalence from 18.7% (1993-1996) to 8.1% (1997-2005).[20] PTE occurs in the first 2 years after transplant and is reversible in most of cases.[25]

Central Hypoxia Concomitant of Kidney Disease

In patients receiving dialysis, smoking, chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea have all been reported as causing erythrocytosis.[26,27] A recent study from the People's Republic of China that included 47,209 patients with COPD showed more deaths associated with hemoglobin levels above 14 g/dL in patients with advanced CKD compared with those without CKD.[27]

Box 2. Key Messages in Case of Erythrocytosis in a Patient Treated With Dialysis

1. Rule out excessive ultrafiltration.
2. Stop ESA and iron therapy.
2. Rule out cystic kidney disease, hydronephrosis, and kidney cancer.
3. Make sure the patient is not receiving androgen therapy.
4. High serum Epo level helps diagnosing secondary erythrocytosis.
5. Screen for *JAK2* mutation. The presence of iron deficiency anemia can mask PV. Other suggestive parameters for PV are leukocytosis, thrombocytosis, splenomegaly, or pruritus.
6. If PV is diagnosed, adapt the dose of hydroxyurea and avoid ESA and iron therapy.
7. Consider adding a RAS inhibitor and aspirin in case erythrocytosis persists.

Abbreviations: Epo, erythropoietin; ESA, erythropoiesis-stimulating agent; JAK2, JAK2, Janus kinase 2; PV, polycythemia vera; RAS, renin-angiotensin system.

Although this observational study does not demonstrate the role of a high hemoglobin level in causing higher mortality, it emphasizes that high hemoglobin levels in COPD patients with CKD warrant careful follow-up observation.[27]

Central Hypoxia-Induced Kidney Disease: High-Altitude Renal Syndrome

Individuals living at >2,500 meters above sea level have a higher prevalence of Epo-dependent erythrocytosis, hyperuricemia, hypertension, decreased renal blood flow with preserved glomerular filtration rate (GFR), glomerulomegaly, and proteinuria.[28-33] This has been called high-altitude renal syndrome.[29] Kidney biopsies of 416 Tibetan individuals were analyzed: 39 had polycythemia, 17 of 39 had high-altitude polycythemia-related kidney disease, and 22 had other glomerular diseases.[30] Most were men (88%), with a mean age of 44 years and mean proteinuria of 2.5 g/day. The kidney biopsies showed lesions of focal and segmental glomerulosclerosis, podocyte foot process effacement, glomerular hypertrophy and sclerosis, and glomerular basement membrane thickening. Importantly, this study revealed, by immunohistochemistry, HIF-2α in kidney tissues, specifically in the nuclei of podocytes.[30]

The most effective treatment of polycythemia and proteinuria in these patients is RAS inhibitors,[34] with anecdotal reports on acetazolamide efficacy in patients resistant to enalapril and spironolactone.[35]

Myeloproliferative Neoplasms Including Polycythemia Vera

Pathogenesis

Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) include PV, essential thrombocythemia, and primary myelofibrosis. MPN are caused by a unique mutation in Janus kinase 2 (*JAK2*), a tyrosine kinase bound to the Epo receptor of hematopoietic stem cells and

normally activated by the binding of growth factors or cytokines to hematopoietic stem cell receptors, namely Epo binding to the Epo receptor in red blood cells. This mutation comprises valine to phenylalanine substitution at position 617 (V617F) in the pseudokinase *JAK2* domain.[36] *JAK2 V617F* mutation is found in 95% of PV and 60% of other MPN. Elevated activity of *JAK2 V617F* mutated protein deregulates signaling from cytokine receptors and maintains constant activation of different downstream pathways.[37] Screening for *JAK2* mutation is essential when diagnosing PV.

Epidemiology and Diagnosis

The annual incidence of PV in Europe, North America, Asia, and Australasia is 0.84 per 100,000.[38] The prevalence is more difficult to determine. In South Korea, the prevalence is estimated at 2.8-5.4 per 100,000 for PV, but it is higher in Denmark when using sensitive assays for *JAK2* detection.[38]

The most recent PV diagnostic criteria are summarized in Box 3.[39] Symptoms and parameters highly suggestive of PV in the presence of erythrocytosis are pruritus, leukocytosis, thrombocytosis, iron deficiency, splenomegaly, and a history of thrombotic event.

Renal Manifestations

Kidney disease is found in one-fourth to one-third of patients with MPN, but due to their high bleeding risk and antiplatelet/anticoagulant therapy, kidney biopsies are rarely performed.[40] However, it is crucial to assess kidney function, especially in patients with PV, because CKD is associated with worse prognosis and shorter time to thrombosis.[40] Kidney biopsies of patients with PV mostly show ischemic glomerular lesions, glomerular sclerosis, glomerular hypercellularity, crescents, and IgA deposits.[41]

Management

Thrombotic events in patients with PV occur with higher hematocrit levels hence a hematocrit of <45% is set as a treatment target.[42] Furthermore, the Current European LeukemiaNet recommends a complete hematologic response in patients with PV including white blood cells ≤10 × 10^9/L, hematocrit < 45%, and platelet count < 400×10^9/L.[43] Interventions to lower hematocrit and prevent thrombotic events in PV patients rely on cytoreductive therapy (hydroxyurea, anagrelide, interferon-α), low-dose aspirin, and phlebotomy.[43]

Medications that are currently used to control erythropoiesis in patients with PV are hydroxyurea and pegylated interferon.[44] As hydroxyurea is eliminated via the kidney, its accumulation causes cytopenia, so dosage adjustment is necessary in advanced CKD when the hemoglobin falls below the desired target. If anemia occurs because of bleeding or hydroxyurea accumulation, erythropoiesis-stimulating agents should be avoided because they can induce a rebound erythrocytosis. Ruxolitinib is an orally administered *JAK1* and *JAK2* inhibitor used in patients with splenomegaly, who are intolerant to hydroxyurea, or with symptoms reminiscent of transformation to myelofibrosis; it might be more effective in reducing PV-related pruritus.[44]

New Recognized Cause of Erythrocytosis: IgA Nephropathy

IgAN is the most common primary glomerular disease. Its pathogenesis relies on a 4-hit phenomenon. The first hit is the overproduction of aberrantly glycosylated, galactose-deficient IgA1 (Gd-IgA1) by plasmocytes localized in mucosae.[45] Polymeric IgA1 (pIgA1) with or without Gd-IgA1 is recognized as self-antigen by IgG or IgM autoantibodies, which constitutes the second hit or the formation of the immune complex IgG-pIgA1 or IgM-pIgA1. The subsequent circulation of these immune complexes represents the third hit. The fourth hit is the deposition of these immune complexes in glomeruli, inducing mesangial proliferation and other well-known lesions of IgAN.

In the large NephroTest study, 3.5% of patients with IgAN had erythrocytosis.[46] Moreover, after kidney transplantation, patients with IgAN recovered faster to normal hemoglobin levels compared with other kidney diseases.[46] Following these observations, Cohen et al[45] recently demonstrated, in a study combining clinical and in vitro

Box 3. International Consensus Classification (ICC) Criteria for Polycythemia Vera Diagnosis (2022)

Diagnosis of polycythemia vera requires meeting either all 3 major criteria or the first 2 major criteria plus the minor criterion.

Major Criteria

1. Elevated hemoglobin concentration (hemoglobin > 16.5 g/dL in men; hemoglobin > 16.0 g/dL in women) or elevated hematocrit (hematocrit > 49% in men; hematocrit > 48% in women) or increased red blood cell mass (>25% above mean normal predicted value).
2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation.[a]
3. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size).[b]

Minor Criterion

1. Subnormal serum erythropoietin level.

[a]It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level <1%); in negative cases, consider searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15.
[b]A bone marrow biopsy may not be required in cases with sustained absolute erythrocytosis (hemoglobin levels > 18.5 g/dL in men or > 16.5 g/dL in women and hematocrit values > 55.5% in men or > 49.5% in women) and the presence of a *JAK2* V617F or *JAK2* exon 12 mutation.

analyses and comparing IgAN patients with controls, that high polymeric Gd-IgA1 increases the sensitivity of erythroid precursors to Epo by interacting with their transferrin receptor 1 (TfR1).

IgAN has also been described in patients with PV.[47] Clinical trials assessing SGLT2 inhibitors in CKD did not analyze hemoglobin levels in patients with IgAN, despite the fact that EMPA-KIDNEY included 853 patients with glomerular diseases and DAPA-CKD included 270 patients with IgAN.[48,49] Further research is needed to elucidate the impact of SGLT2 inhibitors and RAS inhibitors on hemoglobin in patients with IgAN.

Emerging Data on New Onset Erythrocytosis Upon Therapy With SGLT2 Inhibitors

Pathogenesis

Figure 1 illustrates 2 mechanisms behind SGLT2 inhibitor–mediated erythrocytosis. This erythrocytosis can be purely Epo-dependent secondary to kidney hypoxia, or it can unmask Epo-independent PV-related erythrocytosis. A third less well-documented cause is the presence of underlying hemochromatosis in patients receiving combined SGLT2 inhibitors and testosterone therapy.

SGLT2 Inhibitors Causing Epo-dependent Erythrocytosis Without PV

Several hypotheses have been proposed to account for SGLT2 inhibitor–mediated erythrocytosis.[50-52] SGLT2 inhibitors or gliflozins, used to treat type 2 diabetes and/or CKD and/or heart failure, block the SGLT2 at the level of the proximal tubule. These drugs have a modest diuretic effect, and the increase in hemoglobin was first attributed to hemoconcentration.[52-55] However, increased reticulocyte count and hepcidin suppression pointed to a different pathophysiology. It is well-known that diabetic kidneys are prone to tubulointerstitial hypoxia. This suggested that SGLT2 inhibitors might improve hypoxia by reducing workload on the proximal tubule, leading to normal Epo secretion and hemoglobin increase.[52]

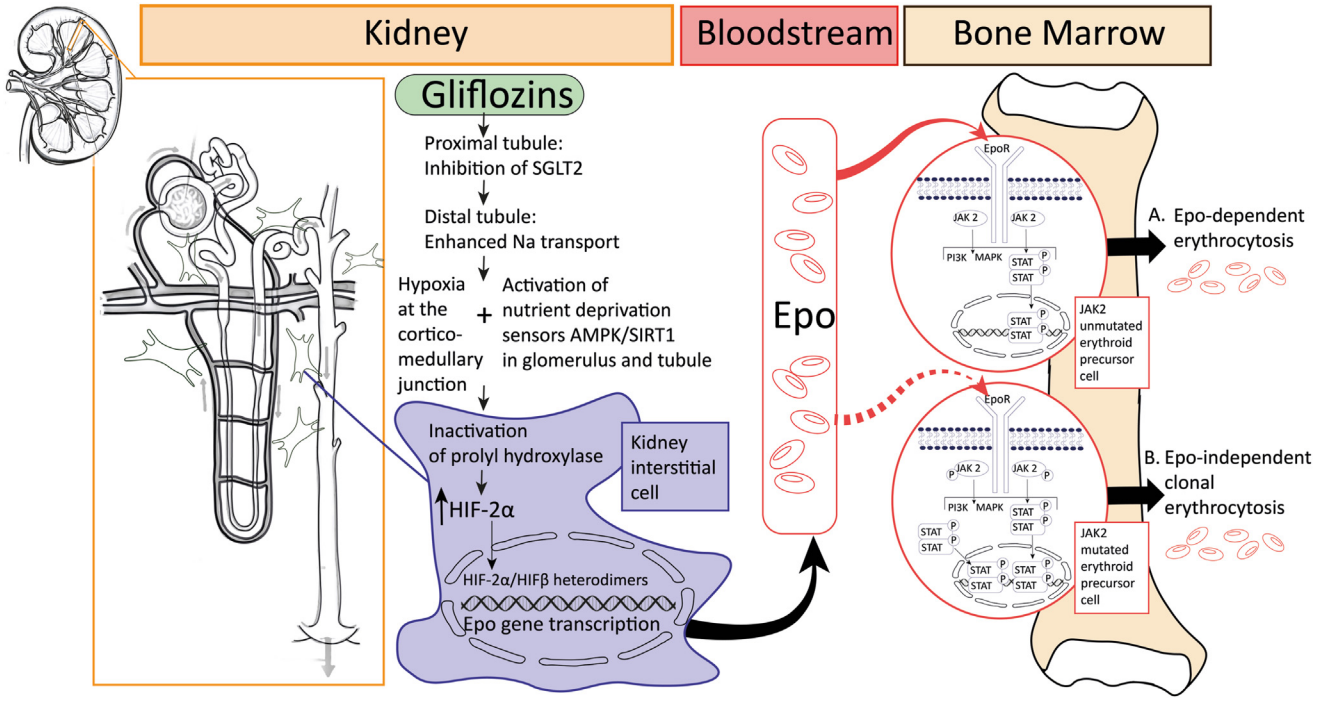


Figure 1. SGLT2 inhibitors-mediated erythrocytosis: Epo-dependent and Epo-independent pathways. (A) Gliflozins block the SGLT2 at the level of the proximal tubule in the kidney. This enhances sodium delivery to distal nephron segments in the outer medulla and cortical medulla and may cause intensified hypoxia at the corticomedullary junction. Hypoxia inhibits the PHD in the peritubular interstitial cells. PHD prevents the degradation of HIF units and leads to an increase in HIF-2α subunits. Gliflozins may also enhance nutrient-deprivating sensors specifically SIRT1 and AMPK at the tubular and glomerular level which also activate HIF-2α subunits. HIF-2α will subsequently bind to HIF-β subunits. These translocated heterodimers HIF-2α/HIF-β at the nuclear level will induce gene transcriptions, specifically Epo. Epo will be released in the blood circulation. In the bone marrow, Epo will bind to the Epo receptor at the membrane of the myeloid progenitor cell which activates JAK2/STAT pathway and induces a proliferation of erythrocytes. (B) If *JAK2* mutation is present in the erythroid progenitor cell in the bone marrow, *JAK2* downstream pathways STAT, MAPK, and PI3K will be constantly activated independently of Epo and will lead to clonal erythrocytosis. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; Epo, erythropoietin; HIF, hypoxia-inducible factor; JAK2, Janus kinase 2; MAPK, mitogen-activated protein kinase; PHD, prolyl hydroxylase; PI3K, phosphatidylinositol 3-kinase; SGLT2, sodium/glucose cotransporter 2; SIRT1, sirtuin1; STAT, signal transducer and activator of transcription.

Very recently, Gullasken et al[56] used blood oxygenation level–dependent magnetic resonance imaging (BOLD-MRI) to show reduced medullary oxygenation in patients treated with empagliflozin. They concluded that medullary kidney hypoxia might act on HIFs and enhance erythropoiesis, which advanced the hypothesis that SGLT2 inhibitors enhance sodium delivery to distal nephron segments in the outer and cortical medulla and cause intensified hypoxia at the corticomedullary junction.[51] Hypoxia inhibits prolyl hydroxylase (PHD) in peritubular interstitial cells. PHD prevents the degradation of HIF units and increases HIF-2α subunits.[51] Gliflozins also enhance nutrient-deprivating sensors specifically sirtuin1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) at tubular and glomerular levels, activating HIF-2α subunits. HIF-2α subsequently binds to HIF-β subunits. These heterodimers HIF-2α/HIF-β induce gene transcriptions, producing Epo. Epo binds to the Epo receptor of the myeloid progenitor cell, activating the JAK2/signal transducer and activator of transcription (STAT) pathway and erythrocytes' proliferation.

Although Gullasken et al[56] demonstrated a reduced kidney medullary oxygenation in patients treated with empagliflozin, several studies have shown an AKI reduction in patients taking SGLT2 inhibitors.[57] The mechanism behind the lower AKI risk remains unclear, but SGLT2 inhibitors would improve cortical oxygenation. So far, none of the proposed concepts can fully explain the reduced risk of AKI and concomitantly the enhanced kidney hypoxia-sensing. A recent post hoc analysis of the EMPA-REG OUTCOME trial showed that hematocrit is the strongest mediator of SGLT2 inhibitors' kidney benefits.[58] Further research is needed to better understand the exact pathomechanism behind the Epo-dependent SGLT2 inhibitor–mediated erythrocytosis.

SGLT2 Inhibitors Unmasking Epo-independent, PV-related Erythrocytosis

In 2016, the World Health Organization lowered hemoglobin thresholds for diagnosing PV in men and women to prevent missing the diagnosis. Nevertheless, PV can still coexist with lower hemoglobin levels and be unmasked during conditions of secondary erythrocytosis.[59-61] If a causative *JAK2* mutation is present, *JAK2* downstream pathways, STAT, mitogen-activated protein kinase, and phosphatidylinositol 3-kinase are constantly activated, independent of Epo, leading to clonal erythrocytosis.[37]

SGLT2 Inhibitors and Testosterone Therapy Unmasking Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive iron overload disorder particularly prevalent in populations of Celtic origin. Erythrocytosis secondary to hereditary hemochromatosis can lead to inappropriate screening for PV.[62] It is mostly caused by a mutation in the *HFE* gene that regulates iron metabolism via hepcidin but can also result from the *HJV* or *TRF2* gene mutations that also control hepcidin.[62] The 2 most common *HFE* mutations include *C282Y* pathogenetic variant and *H63D*.[62] Recently, erythrocytosis was reported in 5 patients with diabetes and hypogonadism who were prescribed SGLT2 inhibitors and testosterone. This erythrocytosis revealed an underlying heterozygosity in the *H63D* variant of the *HFE* gene, which is usually clinically silent.[63] The authors outlined the synergistic mechanisms of testosterone and SGLT2 inhibitors that suppress hepcidin and increase Epo. Patients with *H63D* heterozygosity have slightly increased indices of iron overload that can be unmasked and increased with SGLT2 inhibitors.[63] It is noteworthy that erythrocytosis was previously reported in 2 patients with type 2 diabetes treated for 4 months with empagliflozin and dapagliflozin in combination with testosterone therapy, but genetic screening for hereditary hemochromatosis was not performed.[64]

Clinical Studies

Clinical trials have outlined substantial renal and cardiovascular beneficial effects of SGLT2 inhibitors in patients with diabetes, CKD, and/or heart failure.[65] In parallel, since 2010 interventional and observational studies have reported an increase in hemoglobin ranging between 0.5 and 1 g/dL after treatment with SGLT2 inhibitors. In EMPAREG OUTCOME, the mean increase of hematocrit and hemoglobin from baseline was 4.8% and 0.8 g/dL in patients under 10 mg of empagliflozin, 5.0% and 0.8 g/dL under 25 mg versus 0.9% and −0.1 g/dL with placebo.[66] A post hoc analysis of CREDENCE that studied canagliflozin demonstrated a mean change in hemoglobin of 0.7 g/dL from baseline over 2.6 years of follow-up observation.[67]

Importantly, the CANVAS program, which included 10,142 participants with type 2 diabetes and high cardiovascular risk, showed a hazard ratio of 1.97 with canagliflozin versus placebo for amputations, with a similar risk in women and men, without clear explanation of the mechanism behind these ischemic events.[68] A pooled post hoc analysis of dapagliflozin trials showed a significant increase in hemoglobin in patients with and without baseline anemia or CKD.[69] It reported erythrocytosis in 182 patients (7%) treated with dapagliflozin at week 24 versus 31 patients (1%) treated with placebo.[69] Hemoglobin values at week 24 in patients with polycythemia ranged between 16.1 and 18.8 g/dL,[69] and erythrocytosis was not associated with a higher risk of thrombotic events.

In fact, higher hemoglobin with SGLT2 inhibitors has been linked to more favorable cardiovascular outcomes. A recent meta-analysis included 78 studies and 36,669 participants with a mean age of 58.9 years and a mean estimated GFR (eGFR) of 78.6 mL/min/1.73 m^2.[70] Seven SGLT2 inhibitors were assessed over 4 to 208 weeks: empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, luseogliflozin, ertugliflozin, and bexagliflozin. All gliflozins significantly increased hematocrit and hemoglobin with a weighted mean difference of 2.27% and 0.62 g/dL,

respectively.[70] Only dapagliflozin showed a dose-dependent relationship, although a similar relationship was found with empagliflozin dosage in a case series.[59] In this meta-analysis, the hemoglobin increase was associated with cardiovascular protection.[70] Tofogliflozin was also studied in patients with type 2 diabetes and a mean eGFR of 31 mL/min/1.73 m^2 and led to discontinuation of erythropoiesis-stimulating agents in 48% of cases at 1 year.[71]

Furthermore, SGLT2 inhibitors impact iron parameters. A substudy of the EMPA-HEART (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes) CardioLink-6 randomized clinical trial measured Epo levels, red blood cell morphology, and iron indices in 90 patients.[72] Empagliflozin was associated at 6 months with Epo increase, accompanied by an increase in hemoglobin/hematocrit and reduced ferritin. Another randomized, placebo-controlled trial, which including 52 patients with type 2 diabetes and obesity, showed a significant increase in hemoglobin in the dapagliflozin arm, with a significant reduction in circulating hepcidin and ferritin; a transient increase in Epo and erythroferrone (the hepcidin inhibitor); increased plasma transferrin levels and expression of TfR1, TfR2 in mononuclear cells; a decrease in HIF-1α expression in mononuclear cells; and increase in PHD-2.[73] The recent post hoc analysis of the DELIGHT trial included 360 patients with type 2 diabetes and CKD.[74] Dapagliflozin compared with placebo caused a significant increase in hemoglobin by 0.57 g/dL, reduced ferritin by 18.6%, and reduced inflammation markers.[74]

Finally, SGLT2 inhibitors could unmask severe cases of erythrocytosis caused by genetic mutations (Table 2). The increase in hemoglobin and hematocrit after SGLT2 inhibitor initiation triggered the mounting referral of patients to hematology clinics.[75] Simultaneously, the increased availability of molecular testing for gene mutations unveiled the genetic causes of erythrocytosis.[61] In addition to hemochromatosis cases reported in 2022,[63] *JAK2* mutation was lately discovered in several cases of erythrocytosis secondary to SGLT2 inhibitors. In 2018, Das et al[76] documented the first case of PV and *JAK2* mutation, unmasked by initiating 100 mg of canagliflozin daily in a 51-year-old patient with diabetes and obesity. After 6 months of therapy, the patient's hemoglobin had increased to 16.9 g/dL, which was reversible upon canagliflozin withdrawal.[76] In 2022, a retrospective study from Ontario, Canada, analyzed 891 patients tested for *JAK2* mutation between 2015 and 2021.[61] A total of 106 patients were positive for *JAK2* mutation, including 2 cases of erythrocytosis mediated by SGLT2 inhibitors and 1 case on testosterone therapy.[61] The group of *JAK2*-unmutated erythrocytosis included 95 patients (12.1%) with erythrocytosis induced by gliflozins,[61] pointing to the substantial proportion of secondary erythrocytosis caused by SGLT2 inhibitors. The leading causes of secondary erythrocytosis in this study were smoking and obstructive sleep apnea.

In 2023, Gangat and Tefferi reported on 9 patients treated with empagliflozin (n = 5), dapagliflozin (n = 3), and canagliflozin (n = 1) who developed erythrocytosis, which unmasked an underlying MPN, including 5 cases of PV. Their hemoglobin increased by 2.7 g/dL to reach a mean of 17.5 g/dL at the time of diagnosis.[59]

SGLT2 Inhibitor-Mediated Erythrocytosis and Thrombotic Events

Two reports from the same research group assessed thrombotic events in patients with SGLT2 inhibitors-mediated erythrocytosis.[75,77] The most comprehensive[77] included 100 patients with type 2 diabetes treated with empagliflozin, dapagliflozin, and canagliflozin. All were negative for *JAK2* mutation. Their hemoglobin increased by a median of 2.5 g/dL to reach 18 g/dL after a median of 9 months. Other causes of secondary erythrocytosis were identified in 61% of this cohort. The Epo levels were inappropriately normal or increased in all patients. After a 24-month follow-up period on SGLT2 inhibitors, 10 thrombotic events were documented (7 arterial and 3 venous) that were not correlated with hemoglobin levels and occurred despite aspirin and phlebotomy.[77]

Proposed Management of SGLT2 Inhibitor–Mediated Erythrocytosis

Hemoglobin levels need to be closely monitored in patients treated with SGLT2 inhibitors, especially in patients who had a normal or high normal hemoglobin level before initiating treatment. Once erythrocytosis is diagnosed, it is appropriate to rule out common secondary causes and, if absent, to screen for *JAK2* mutation (Box 4). In most cases with secondary erythrocytosis, RAS inhibitors can be introduced to lower hemoglobin and hematocrit and control blood pressure. A dose reduction of SGLT2 inhibitors may also help decrease the hemoglobin level.

Patients with erythrocytosis may experience headache, dizziness, blurred vision, fatigue, tinnitus, paresthesia, shortening of breath, palpitations, and confusion.[2] Patients who present with symptoms attributable to high hematocrit can be offered phlebotomy.[2] Patients who manifest thrombotic events will need antiplatelet or anticoagulant therapy and preventive phlebotomy. The decision to withhold SGLT2 inhibitors will depend on their indication and benefits, on thrombotic events, and on the capacity of achieving hematocrit control with phlebotomy.[2,60]

Conclusions

This Review underscored established and recently recognized causes of erythrocytosis that can be encountered in patients with CKD. Erythrocytosis is an important effect of SGLT2 inhibitors not well-reported in the respective CKD clinical trials, which mostly included patients with subnormal hemoglobin levels. The distinction between Epo-dependent and Epo-independent erythrocytosis is of

Table 2. Clinical Studies Reporting Erythrocytosis Mediated by SGLT2 Inhibitors and Unmasking Genetic Mutations

Authors (Year)	Study Design	Drug Used	Diabetes/ CKD	No. of Participants + Age	Thrombotic Events	Change in Hb/ Ht After SGLT2 Inhibitor Started	Change in Hb/ Ht After SGLT2 Inhibitor Stopped	Genetic Mutation
Das et al (2018)[76]	Case report	Canagliflozin 100	Diabetes	N = 1 Mean age = 51 y	No	At 6 mo, Hb/Ht increased to 16.9/55%	At 1 mo later, Hb/Ht decreased to 14.1/46.4%	*JAK2* mutation
Chin-Yee et al (2022)[61]	Retrospective study	Several gliflozins (not specified)	Not reported	N = 97 on gliflozins (out of 891 tested for *JAK2*) Mean age = 59 y	Not reported	Hb = 17 g/dL	Hb decreased by a mean of 1.47 g/dL in 15 patients who stopped SGLT2 inhibitors	*JAK2* mutation in 2 out of 97
Schumacher and Gosmanov (2022)[63]	Case series	• Empagliflozin • Dapagliflozin	• Diabetes • eGFR 52-86	N = 5 Age = 56-71 y	No	Ht increased from a range of 43.4%-49.1% to 55%-59%	Ht decreased back to 48-50% when stopping testosterone	HH; H63D *HFE* mutation
Gangat and Tefferi (2023)[60]	Case series	• Empagliflozin (n = 5) • Dapagliflozin (n = 3) • Canagliflozin (n = 1)	• Diabetes • CKD not reported	N = 9 Median age = 65 y	Yes	At a median follow-up of 32 mo, increase of Hb/Ht by 2.3 g/dL/7.4% to reach 17.5 g/dL/53.1%	Four out of 9 patients needed SGLT2 inhibitor withdrawal to normalize Hb/Ht levels	*JAK2* mutation

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; Hb, hemoglobin; HFE, homeostatic iron regulator; HH, hereditary hemochromatosis; Ht, hematocrit; JAK2, Janus kinase 2; SGLT2, sodium/glucose cotransporter 2.

Box 4. Key Messages in Case of Erythrocytosis Associated With SGLT2 Inhibitors

1. Follow hemoglobin closely after the initiation of SGLT2 inhibitors.
2. Rule out dehydration and well-known secondary causes of erythrocytosis.
3. Screen for *JAK2* mutation based on the ICC criteria. The presence of iron deficiency anemia can mask PV. Other suggestive parameters for PV are leukocytosis, thrombocytosis, splenomegaly, or pruritus.
4. Remember the high rate of thrombosis when erythrocytosis is left untreated.
5. Adapt the dose of hydroxyurea in patients with advanced CKD and PV. Avoid ESA and iron therapy in patients with end-stage kidney disease and PV if anemia is induced by overdosage of hydroxyurea.
6. IgA nephropathy is a newly established cause of erythrocytosis, and treatment with SGLT2 inhibitors may induce higher rates of erythrocytosis.
7. Treatment with testosterone aggravates erythrocytosis mediated by SGLT2 inhibitors.
8. Patients on combined SGLT2 inhibitors and testosterone need close monitoring and might require genetic screening for hereditary hemochromatosis in case of erythrocytosis development.
9. Consider reducing the dose of SGLT2 inhibitor in an attempt to reach normal hemoglobin.
10. Future research needs to assess the association between thrombotic events and erythrocytosis in patients on SGLT2 inhibitors.

Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; ICC, International Consensus Classification; JAK2, JAK2, Janus kinase 2; PV, polycythemia vera; SGLT2, sodium/glucose cotransporter 2.

utmost importance. The latter requires screening for *JAK2* mutation if secondary causes are ruled out and if other suggestive parameters like leukocytosis, thrombocytosis, and pruritus are present. Even in Epo-dependent cases, thrombotic events can occur, and patients treated with SGLT2 inhibitors, including those with CKD, need to be followed thoroughly with monitoring of hemoglobin levels.

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References

1. McMullin MF. The classification and diagnosis of erythrocytosis. *Int J Lab Hematol*. 2008;30(6):447-459. doi:10.1111/j.1751-553X.2008.01102.x
2. Gangat N, Szuber N, Tefferi A. JAK2 unmutated erythrocytosis: 2023 update on diagnosis and management. *Am J Hematol*. 2023;98(6):965-981. doi:10.1002/ajh.26920
3. Hodges VM, Rainey S, Lappin TR, Maxwell AP. Pathophysiology of anemia and erythrocytosis. *Crit Rev Oncol Hematol*. 2007;64(2):139-158. doi:10.1016/j.critrevonc.2007.06.006
4. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405. doi:10.1182/blood-2016-03-643544
5. Krishnamoorthy P, Gopalakrishnan A, Mittal V, et al. Gaisböck syndrome (polycythemia and hypertension) revisited: results from the national inpatient sample database. *J Hypertens*. 2018;36(12):2420-2424. doi:10.1097/HJH.0000000000001805
6. Olivas-Martinez A, Corona-Rodarte E, Nuñez-Zuno A, et al. Causes of erythrocytosis and its impact as a risk factor for thrombosis according to etiology: experience in a referral center in Mexico City. *Blood Res*. 2021;56(3):166-174. doi:10.5045/br.2021.2021111
7. Nguyen E, Harnois M, Busque L, et al. Phenotypical differences and thrombosis rates in secondary erythrocytosis versus polycythemia vera. *Blood Cancer J*. 2021;11(4):75. doi:10.1038/s41408-021-00463-x
8. Fisher JW. Erythropoietin: physiology and pharmacology update. *Exp Biol Med (Maywood)*. 2003;228(1):1-14. doi:10.1177/153537020322800101
9. Jelkmann W. Regulation of erythropoietin production. *J Physiol*. 2011;589(Pt 6):1251-1258. doi:10.1113/jphysiol.2010.195057
10. Semenza GL. Regulation of erythropoiesis by the hypoxia-inducible factor pathway: effects of genetic and pharmacological perturbations. *Annu Rev Med*. 2023;74:307-319. doi:10.1146/annurev-med-042921-102602
11. Messinezy M, Westwood NB, El-Hemaidi I, Marsden JT, Sherwood RS, Pearson TC. Serum erythropoietin values in erythrocytoses and in primary thrombocythaemia. *Br J Haematol*. 2002;117(1):47-53. doi:10.1046/j.1365-2141.2002.03386.x
12. Gonçalves S, Guerra J, Santana A, Abreu F, Mil-Homens C, Gomes da Costa A. Autosomal-dominant polycystic kidney disease and kidney transplantation: experience of a single

center. *Transplant Proc*. 2009;41(3):887-890. doi:10.1016/j.transproceed.2009.01.069
13. Adeniyi M, Sun Y, Servilla KS, Hartshorne MF, Tzamaloukas AH. Spontaneous erythrocytosis in a patient on chronic hemodialysis. *Hemodial Int*. 2009;13(suppl 1):S30-S33. doi:10.1111/j.1542-4758.2009.00417.x
14. Blake-James B, Attar KH, Rabbani S, Yeghen T, Owen R, Peters J. Secondary polycythaemia associated with unilateral renal cystic disease. *Int Urol Nephrol*. 2007;39(3):955-958. doi:10.1007/s11255-006-9014-8
15. Fasolino J, Oklu R, Palmer J, Hommos MS. Polycythemia secondary to renal cysts. *J Nephrol*. 2022;35(6):1743-1746. doi:10.1007/s40620-021-01215-7
16. Hsieh JJ, Purdue MP, Signoretti S, et al. Renal cell carcinoma. *Nat Rev Dis Primers*. 2017;3:17009. doi:10.1038/nrdp.2017.9
17. Peired AJ, Lazzeri E, Guzzi F, Anders HJ, Romagnani P. From kidney injury to kidney cancer. *Kidney Int*. 2021;100(1):55-66. doi:10.1016/j.kint.2021.03.011
18. Vlahakos DV, Marathias KP, Agroyannis B, Madias NE. Post-transplant erythrocytosis. *Kidney Int*. 2003;63(4):1187-1194. doi:10.1046/j.1523-1755.2003.00850.x
19. Frei D, Guttmann RD, Gorman P. A matched-pair control study of postrenal transplant polycythemia. *Am J Kidney Dis*. 1982;2(1):36-42. doi:10.1016/s0272-6386(82)80041-3
20. Kiberd BA. Post-transplant erythrocytosis: a disappearing phenomenon? *Clin Transplant*. 2009;23(6):800-806. doi:10.1111/j.1399-0012.2008.00947.x
21. Nouri-Majalan N, Ghafari A, Moghaddasi S. Effect of angiotensin II type-1 receptor blockers on stable allograft kidneys: prospective randomized study. *Transplant Proc*. 2009;41(7):2832-2834. doi:10.1016/j.transproceed.2009.07.021
22. Hofstetter L, Rozen-Zvi B, Schechter A, et al. Post-transplantation erythrocytosis in kidney transplant recipients—a retrospective cohort study. *Eur J Haematol*. 2021;107(6):595-601. doi:10.1111/ejh.13696
23. Mekraksakit P, Boonpheng B, Leelaviwat N, et al. Risk factors and outcomes of post-transplant erythrocytosis among adult kidney transplant recipients: a systematic review and meta-analysis. *Transpl Int*. 2021;34(11):2071-2086. doi:10.1111/tri.14016
24. Mulas O, Mola B, Costa A, et al. Renin-angiotensin inhibitors reduce thrombotic complications in essential thrombocythemia and polycythemia vera patients with arterial hypertension. *Ann Hematol*. 2023;102(10):2717-2723. doi:10.1007/s00277-023-05417-w
25. Einollahi B, Lessan-Pezeshki M, Nafar M, et al. Erythrocytosis after renal transplantation: review of 101 cases. *Transplant Proc*. 2005;37(7):3101-3102. doi:10.1016/j.transproceed.2005.08.023
26. Nistico A, Iliescu EA, Fitzpatrick M, White CA. Polycythemia due to obstructive sleep apnea in a patient on hemodialysis. *Hemodial Int*. 2010;14(3):333-336. doi:10.1111/j.1542-4758.2010.00461.x
27. Xu L, Chen Y, Xie Z, et al; China collaborative study on AKI (CCS-AKI). High hemoglobin is associated with increased in-hospital death in patients with chronic obstructive pulmonary disease and chronic kidney disease: a retrospective multicenter population-based study. *BMC Pulm Med*. 2019;19(1):174. doi:10.1186/s12890-019-0933-4
28. Aoun M, Chelala D. Where do you live and what do you do? Two questions that might impact your kidney health. *Front Nephrol*. 2022;2:1011964. doi:10.3389/fneph.2022.1011964
29. Arestegui AH, Fuquay R, Sirota J, et al. High altitude renal syndrome (HARS). *J Am Soc Nephrol*. 2011;22(11):1963-1968. doi:10.1681/ASN.2010121316
30. Wang H, Tang C, Dang Z, et al. Clinicopathological characteristics of high-altitude polycythemia-related kidney disease in Tibetan inhabitants. *Kidney Int*. 2022;102(1):196-206. doi:10.1016/j.kint.2022.03.027
31. Hurtado-Arestegui A, Plata-Cornejo R, Cornejo A, et al. Higher prevalence of unrecognized kidney disease at high altitude. *J Nephrol*. 2018;31(2):263-269. doi:10.1007/s40620-017-0456-0
32. Steele AR, Tymko MM, Meah VL, et al. Global REACH 2018: volume regulation in high-altitude Andeans with and without chronic mountain sickness. *Am J Physiol Regul Integr Comp Physiol*. 2021;321(3):R504-R512. doi:10.1152/ajpregu.00102.2021
33. Jefferson JA, Escudero E, Hurtado ME, et al. Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. *Am J Kidney Dis*. 2002;39(6):1135-1142. doi:10.1053/ajkd.2002.33380
34. Plata R, Cornejo A, Arratia C, et al; Commission on Global Advancement of Nephrology (COMGAN), Research Subcommittee of the International Society of Nephrology. Angiotensin-converting-enzyme inhibition therapy in altitude polycythaemia: a prospective randomised trial. *Lancet*. 2002;359(9307):663-666. doi:10.1016/s0140-6736(02)07812-1
35. Vizcarra-Vizcarra CA, Chávez-Velázquez E, Asato-Higa C, Hurtado-Aréstegui A. Treatment of focal and segmental glomerulosclerosis secondary to high altitude polycythemia with acetazolamide. *High Alt Med Biol*. 2022;23(3):286-290. doi:10.1089/ham.2021.0158
36. Vainchenker W, Constantinescu SN. A unique activating mutation in JAK2 (V617F) is at the origin of polycythemia vera and allows a new classification of myeloproliferative diseases. *Hematology Am Soc Hematol Educ Program*. 2005:195-200. doi:10.1182/asheducation-2005.1.195
37. Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. *Nat Rev Cancer*. 2007;7(9):673-683. doi:10.1038/nrc2210
38. McMullin MF, Anderson LA. Aetiology of myeloproliferative neoplasms. *Cancers (Basel)*. 2020;12(7):1810. doi:10.3390/cancers12071810
39. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228. doi:10.1182/blood.2022015850
40. Lucijanic M, Krecak I, Kusec R. Renal disease associated with chronic myeloproliferative neoplasms. *Expert Rev Hematol*. 2022;15(2):93-96. doi:10.1080/17474086.2022.2039117
41. Yang J, Yu X, Hu N, Su T. Clinical and pathological features of renal presentations in polycythemia vera. *Am J Med Sci*. 2022;363(1):33-41. doi:10.1016/j.amjms.2021.10.009
42. Marchioli R, Finazzi G, Specchia G, et al. CYTO-PV Collaborative Group. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368(1):22-33. doi:10.1056/NEJMoa1208500
43. Waggoner M. Polycythemia vera: thinking beyond the hematocrit. *J Adv Pract Oncol*. 2023;14(5):405-413. doi:10.6004/jadpro.2023.14.5.5
44. Mithoowani S, Laureano M, Crowther MA, Hillis CM. Investigation and management of erythrocytosis. *CMAJ*. 2020;192(32):E913-E918. doi:10.1503/cmaj.191587

45. Cohen C, Coulon S, Bhukhai K, et al. Erythrocytosis associated with IgA nephropathy. *EBioMedicine*. 2022;75:103785. doi:10.1016/j.ebiom.2021.103785
46. Moranne O, Froissart M, Rossert J, et al; NephroTest Study Group. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol*. 2009;20(1):164-171. doi:10.1681/ASN.2008020159
47. Wang X, Yang N, Lu C, Xu F, Wang J. Clinical characterization of polycythemia vera associated with IgA nephropathy in a single Chinese center: a case series. *Medicine (Baltimore)*. 2023;102(14):e33493. doi:10.1097/MD.0000000000033493
48. Herrington WG, Staplin N, Wanner C, et al; EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233
49. Wheeler DC, Stefansson BV, Batiushin M, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. *Nephrol Dial Transplant*. 2020;35(10):1700-1711. doi:10.1093/ndt/gfaa234
50. Packer M. Mechanisms leading to differential hypoxia-inducible factor signaling in the diabetic kidney: modulation by SGLT2 inhibitors and hypoxia mimetics. *Am J Kidney Dis*. 2021;77(2):280-286. doi:10.1053/j.ajkd.2020.04.016
51. Heyman SN, Armaly Z, Hamo-Giladi DB, Abassi Z. Novel perspectives regarding the physiologic mechanisms by which gliflozins induce reticulocytosis and erythrocytosis. *Am J Physiol Endocrinol Metab*. 2023;325(5):E621-E623. doi:10.1152/ajpendo.00277.2023
52. Sano M, Takei M, Shiraishi Y, Suzuki Y. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. *J Clin Med Res*. 2016;8(12):844-847. doi:10.14740/jocmr2760w
53. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375(9733):2223-2233. doi:10.1016/S0140-6736(10)60407-2
54. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab*. 2013;15(9):853-862. doi:10.1111/dom.12127
55. Dekkers CCJ, Sjöström CD, Greasley PJ, Cain V, Boulton DW, Heerspink HJL. Effects of the sodium-glucose co-transporter-2 inhibitor dapagliflozin on estimated plasma volume in patients with type 2 diabetes. *Diabetes Obes Metab*. 2019;21(12):2667-2673. doi:10.1111/dom.13855
56. Gullaksen S, Vernstrøm L, Sørensen SS, et al. Separate and combined effects of semaglutide and empagliflozin on kidney oxygenation and perfusion in people with type 2 diabetes: a randomised trial. *Diabetologia*. 2023;66(5):813-825. doi:10.1007/s00125-023-05876-w
57. Zhuo M, Paik JM, Wexler DJ, Bonventre JV, Kim SC, Patorno E. SGLT2 inhibitors and the risk of acute kidney injury in older adults with type 2 diabetes. *Am J Kidney Dis*. 2022;79(6):858-867.e1. doi:10.1053/j.ajkd.2021.09.015
58. Wanner C, Nangaku M, Kraus BJ, et al. How do SGLT2 inhibitors protect the kidney? A mediation analysis of the EMPA-REG OUTCOME trial. *Nephrol Dial Transplant*. Published online February 6, 2024;. doi:10.1093/ndt/gfae032
59. Gangat N, Alkhateeb H, Reichard K, Tefferi A. Sodium-glucose co-transporter-2 inhibitor therapy and unmasking of JAK2-mutated myeloproliferative neoplasm: a Mayo Clinic series of nine consecutive cases. *Am J Hematol*. 2023;98(10):E276-E280. doi:10.1002/ajh.27034
60. Gangat N, Tefferi A. Sodium-glucose co-transporter-2 inhibitor use and erythrocytosis: assessment of risk and need for referral to haematology. *Nephrol Dial Transplant*. 2023;38(12):2670-2672. doi:10.1093/ndt/gfad171
61. Chin-Yee B, Matyashin M, Cheong I, et al. Secondary causes of elevated hemoglobin in patients undergoing molecular testing for suspected polycythemia vera in southwestern Ontario: a chart review. *CMAJ Open*. 2022;10(4):E988-E992. doi:10.9778/cmajo.20210322
62. Langabeer SE. Hemochromatosis, erythrocytosis and the *JAK2* p.V617F mutation. *EJIFCC*. 2017;28(1):92-93.
63. Schumacher KA, Gosmanov AR. Hemochromatosis gene mutation in persons developing erythrocytosis on combined testosterone and SGLT-2 inhibitor therapy. *J Investig Med High Impact Case Rep*. 2022;10:23247096221111774. doi:10.1177/23247096221111774
64. Motta G, Zavattaro M, Romeo F, Lanfranco F, Broglio F. Risk of erythrocytosis during concomitant testosterone and SGLT2-inhibitor treatment: a warning from two clinical cases. *J Clin Endocrinol Metab*. 2019;104(3):819-822. doi:10.1210/jc.2018-01702
65. Mark PB, Sarafidis P, Ekart R, et al. SGLT2i for evidence-based cardiorenal protection in diabetic and non-diabetic chronic kidney disease: a comprehensive review by EURECA-m and ERBP working groups of ERA. *Nephrol Dial Transplant*. 2023;38(11):2444-2455. doi:10.1093/ndt/gfad112
66. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720
67. Oshima M, Neuen BL, Jardine MJ, et al. Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial. *Lancet Diabetes Endocrinol*. 2020;8(11):903-914. doi:10.1016/S2213-8587(20)30300-4
68. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS program collaborative group. canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925
69. Stefánsson BV, Heerspink HJL, Wheeler DC, et al. Correction of anemia by dapagliflozin in patients with type 2 diabetes. *J Diabetes Complications*. 2020;34(12):107729. doi:10.1016/j.jdiacomp.2020.107729
70. Tian Q, Guo K, Deng J, Zhong Y, Yang L. Effects of SGLT2 inhibitors on haematocrit and haemoglobin levels and the associated cardiorenal benefits in T2DM patients: A meta-analysis. *J Cell Mol Med*. 2022;26(2):540-547. doi:10.1111/jcmm.17115
71. Sato K, Babazono T. Successful withdrawal of erythropoiesis-stimulating agent after administration of an SGLT2 inhibitor, tofogliflozin, in people with diabetes. *Diabet Med*. 2022;39(1):e14632. doi:10.1111/dme.14632
72. Mazer CD, Hare GMT, Connelly PW, et al. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. *Circulation*. 2020;141(8):704-707. doi:10.1161/circulationaha.119.044235
73. Ghanim H, Abuaysheh S, Hejna J, et al. Dapagliflozin suppresses hepcidin and increases erythropoiesis. *J Clin Endocrinol Metab*. 2020;105(4):dgaa057. doi:10.1210/clinem/dgaa057
74. Koshino A, Neuen BL, Jongs N, et al. Effects of dapagliflozin and dapagliflozin-saxagliptin on erythropoiesis, iron and inflammation markers in patients with type 2 diabetes and

chronic kidney disease: data from the DELIGHT trial. *Cardiovasc Diabetol*. 2023;22(1):330. doi:10.1186/s12933-023-02027-8

75. Gangat N, Szuber N, Alkhateeb H, Al-Kali A, Pardanani A, Tefferi A. JAK2 wild-type erythrocytosis associated with sodium-glucose cotransporter 2 inhibitor therapy. *Blood*. 2021;138(26):2886-2889. doi:10.1182/blood.2021013996
76. Das L, Bhansali A, Walia R. Unmasking and aggravation of polycythemia vera by canagliflozin. *Diabet Med*. 2018;35(11):1613-1616. doi:10.1111/dme.13706
77. Gangat N, Abdallah M, Szuber N, et al. Sodium-glucose cotransporter-2 inhibitor use and JAK2 unmutated erythrocytosis in 100 consecutive cases. *Am J Hematol*. 2023;98(7):E165-E167. doi:10.1002/ajh.26933