# Article

# Anemia in ESKD

*Jolanta Malyszko, MD, PhD, FASN*
*Department of Nephrology, Dialysis and Internal Medicine, Warsaw Medical University, Warsaw, Poland*

## Learning Objectives

1. To define the prevalence and associated outcomes of anemia for patients with CKD and ESRD
2. To describe the pathophysiology underlying CKD-associated anemia
3. To identify optimal therapies for individual patients, recognizing the indications and pitfalls of newer therapies

## Introduction

CKD-associated anemia is common. The prevalence of anemia increases as the GFR declines, and anemia is virtually universal among patients receiving dialysis. Among patients with CKD, anemia is associated with increased risk of ESKD, cardiovascular events, mortality, and decreased quality of life. This chapter reviews recent studies in iron deficiency and anemia in patients with CKD (1).

## Epidemiology

A number of recent studies have assessed the prevalence of iron deficiency and anemia in patients with CKD. A study examined the prevalence of anemia among 51,163 patients with nondialysis CKD identified in the National Health and Nutrition Examination Survey (NHANES) data from 1999–2000 to 2017–2018. Approximately 25% of patients with CKD had anemia (defined as hemoglobin <12 g/dL in women and <13 g/dL in men). Among them, 1.9% had severe anemia eligible for erythropoiesis stimulating agent (ESA) treatment (defined as hemoglobin <10 g/dL). The prevalence of anemia and severe anemia increased with the progression of CKD and, in patients with stage 5 CKD, was present in 66.1% and 12.7%, respectively (2). Female sex, age >75 years, Black race, and diabetes were associated with increased risk of anemia.

In another study that included data from over 5 million routine outpatient visits in the United States from 2016 to 2019, severe anemia (hemoglobin <10 g/dL) was present in 3.1%, 7.5%, 17.4%, and 29.7% of men with CKD stages 3A, 3B, 4, and 5, respectively. Prevalence was higher in women: 3.9, 8.6, 19.4, and 37.6 for CKD stages 3A, 3B, 4, and 5, respectively. As was observed in the previously cited study, older age and Black race were associated with risk of anemia (3). Among anemic individuals, iron indices were only tested in 15.6% of men and 19.6% of women. Among those who were tested, approximately 40% and 50% of men and women with stage 5 CKD had tests suggesting iron deficiency.

Anemia, but not iron deficiency, was associated with increased risk ESKD, cardiovascular disease, stroke, heart failure, and death after multiple adjustments including for CKD, age, and race among other variables. The authors plausibly hypothesize that the reason that anemia, but not iron deficiency, was associated with worse outcomes is likely explained by the fact that anemia is a marker for chronic disease and more severe CKD, and iron deficiency provides an alternative cause for anemia than these causal comorbidities. It is notable that this study also showed that anemic patients with stage 4 and 5 CKD were undertreated; fewer than 4% of patients who were eligible were treated with ESAs. It is not clear how many iron-deficient individuals were treated with iron.

A retrospective observational study from Italy reported adults diagnosed between January 2014 and December 2016 with non–dialysis-dependent CKD (4). Among 101,143 individuals, approximately 40% were anemic. Anemia prevalence increased with CKD severity and was present in almost 80% of individuals with stage 5 CKD. The percentage of eligible patients treated with ESAs was 12.8% among those with hemoglobin <11 g/L and 15.5% among those with hemoglobin <10 g/L. Among those with the higher hemoglobin threshold, ESA use was increased for patients with stage 5 CKD (39.8% versus 6.7% in stage 3A).

Among patients with stage 5 CKD, intravenous iron was given to 16.4% of those with anemia. Intravenous iron use was higher for patients with ESA-treated disease (31%–33%). The use of oral iron was not reported in this study.

As has been shown in other studies, anemia was associated with a higher risk of ESKD and with higher mortality (4). The percentage of patients who were treated by nephrologists in this study is not known.

CKD-associated anemia appears to be undertreated even by nephrologists. This was suggested by a study by Lopes *et al.* (5) who presented longitudinal data from 2818 patients with stage 3–5 CKD from Brazil, Germany, and the United States who were followed by nephrologists and were not receiving iron or ESAs at the time of enrollment in CKDopps. At 12 months, among patients with hemoglobin <10 g/dL, only 40% were prescribed either iron or ESA. Among those with iron deficiency (*i.e.*, transferrin saturation [TSAT] <20%), only 26% and 6% were prescribed oral and intravenous iron, respectively. CKD stage 4/5 was diagnosed in 1885 patients. For CKD stage 5, the proportion of patients who were prescribed oral iron was much lower (16%) than intravenous iron (29%) and ESA (41%).

Compared with patients with nondialysis CKD, a greater percentage of patients receiving dialysis receive treatment with iron or ESAs. A retrospective, longitudinal, observational study demonstrated that among 1632 patients receiving dialysis in France, 1286 (roughly 79%) were anemic (6). Among patients with anemia, 83% received ESAs with or without iron, and 77% received iron. Most of those who were treated were treated with both ESAs and iron.

 

Effective iron repletion has been shown to decrease the ESA dose in patients with CKD not receiving dialysis and patients with CKD receiving dialysis. Among maintenance patients receiving hemodialysis, more aggressive iron repletion reduces risk of cardiovascular events and death. This was demonstrated in the PIVOTAL multicenter trial that compared proactive high-dose intravenous iron (targeting TSAT >40%) to reactive, lower-dose intravenous iron (targeting TSAT >20%, ferritin <200) among 2141 patients receiving hemodialysis. There was a reduction in the composite endpoint of myocardial infarction, stroke, heart failure, or death among patients receiving treatment with high-dose proactive iron versus a lower dose (7).

- The risk and severity of anemia increases as GFR declines.
- CKD-associated anemia is undertreated in nondialysis CKD but more likely to be treated in patients receiving dialysis.
- CKD-associated anemia is associated with adverse outcomes.
- Treatment of iron deficiency reduces cardiovascular outcomes and improves survival in patients receiving hemodialysis.

## Etiology and Pathophysiology

CKD-associated anemia is largely due to decreased erythropoietin and absolute or functional iron deficiency (8,9). Absolute iron deficiency is a deficiency of total body iron (*i.e.*, both stored and circulating), whereas functional or relative iron deficiency is a decrease in circulating iron with normal or increased iron stores (10–12).

There have been major advances over the past decade in our understanding of the regulation of erythropoietin (EPO) expression and iron homeostasis. The pathogenesis of CKD-associated anemia and iron deficiency was reviewed in recent KDIGO controversies conference review (10). Updates are briefly described below, although a detailed description of pathophysiology is beyond the scope of this topic.

Hepcidin is a hormone synthesized in the liver that provides negative regulation of iron uptake from gut and iron release from stores, both via the degradation of the iron channel, ferroportin, which is expressed in enterocytes, hepatocytes, and macrophages. Hepcidin is increased in settings of increased iron uptake, inflammation, infection and in CKD. Hepcidin is decreased in the settings of decreased iron uptake, erythropoiesis, and hypoxia (11).

Hypoxia inducible factors (HIFs) are transcription factors that regulate EPO expression in response to oxygenation/hypoxia. HIFs are negatively regulated by prolyl hydroxylase domain–containing proteins. Under conditions of adequate oxygenation, domain-containing proteins hydroxylate HIFs, which targets them for ubiquitination and degradation. Under conditions of hypoxia, HIFs accumulate and activate transcription of numerous genes including EPO, EPO receptors, transferrin receptors, and genes that increase iron absorption from the gut. HIFs indirectly decrease hepcidin by stimulating erythropoiesis. Erythroblasts generate erythroferrone (ERFE), which decreases hepcidin. Serum ERFE concentrations have been shown to directly correlate with EPO levels and dose, and some studies, though not all, have shown inverse correlations with hepcidin and ferritin levels (13–15). A recent cohort study demonstrated an association between serum ERFE concentrations and a composite outcome of mortality and nonfatal cardiovascular events among 1123 patients receiving hemodialysis and 745 patients with CKD (15). The association persisted after adjustment for traditional cardiovascular risk factors and was amplified by ESA treatment.

HIF inhibitors are pharmacologic agents that block prolyl hydroxylation, which increases erythropoiesis (11). HIF inhibitors are discussed below in the section about treatment.

### *FGF23*

Changes in iron homeostasis and erythropoiesis affect FGF23 levels which contributes to CKD-mineral and bone disorder. Iron deficiency, ESAs, and inflammation have been shown to increase FGF23 concentrations in patients with CKD (10,16). Conversely, increased FGF23 may worsen anemia and iron deficiency (17,18). Specific intravenous iron preparations (particularly ferric carboxymaltose) have been shown to increase FGF23 levels by decreasing cleavage. Increased FSF23 is associated with hypophosphatemia, hyperphosphaturia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism (19).

### *Lead and Iron and Anemia in Patients Receiving Dialysis*

Lead causes anemia by decreasing gastrointestinal iron absorption and heme synthesis, and by increasing RBC destruction (20–22). Patients with CKD and ESKD are vulnerable to toxic effects of even low-level lead contamination because of enhanced absorption of lead across the GI tract (due to hypocalcemia, iron deficiency, and malnutrition) (23,24), and because of decreased excretion (25). A recent study demonstrated lower hemoglobin concentrations and higher ESA use in patients with advanced CKD who live in cities with relatively higher lead levels in community water sources (26). This was a large analysis that used the USRDS to identify patients initiating dialysis between 2005 and 2017. Lead concentrations were obtained from the Environmental Protection Agency Safe Water Information System. A dataset was generated that included 597,968 patients with incident ESKD who lived in 9566 cities with 21,113 water supplies. Among all identified patients, 86% lived in cities with detectable 90th percentile lead levels, and 2% lived in areas with lead levels above the Environmental Protection Agency actionable lead level. Before hemodialysis initiation, corrected for ESA use, higher lead concentrations were associated with lower hemoglobin, with 0.02 g/dL decrease in hemoglobin for each 0.01 mg/L increase in water lead for the specific community water source. For each 0.01 mg/L higher lead concentration, there was a 0.4% increase in the prevalence of ESA use. Among 209, 912 patients who initiated dialysis, higher lead levels also associated with lower hemoglobin and ESA use. Notably, lead levels were highest in water sources serving Black patients compared with White patients. An additional study demonstrated that among 143,754 patients receiving hemodialysis, patients from communities with low-level lead contamination had a higher adjusted risk of iron deficiency manifested by transferrin saturation

<20% and/or ferritin <200 ng/mL (27). As observed in an accompanying editorial, these data illustrate the clinical relevance of low-level lead exposure for adults, particularly those with CKD. These data also illuminate the striking racial inequality in lead exposure that exists today and contributes to disparities in kidney disease (28).

- Patients with ESKD who are exposed to higher water lead concentrations have lower hemoglobin and evidence of iron deficiency and are more likely to require an ESA before dialysis.
- Lead levels are higher in water sources serving Black patients compared with White patients.

## *Treatment/Management*

Current options for treatment of anemia include oral and intravenous iron and ESAs. Novel therapies, including oral and dialysate/intravenous iron preparations and HIF stabilizers, are discussed here.

## *Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitors*

Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs), also called HIF stabilizers, are pharmacologic agents that block prolyl hydroxylation, obiquitination, and degradation of HIF (11). HIF accumulation and signaling increase expression of HIF target genes, including EPO and iron metabolism genes (29,30). Available HIF-PHIs or those being studied include roxadustat, daprodustat, vadadustat, molidustat, desidustat, and enarodustat.

The role for HIF-PHIs in treatment of anemia in CKD and ESKD is not clear. Multiple clinical trials have demonstrated improvements in anemia compared with placebo for patients with CKD (31,32) and ESKD (33–36).

Because of cardiovascular safety concerns with ESAs, the cardiovascular safety of HIF-PHIs has been carefully scrutinized by regulators in the European Union and United States. Additional analyses were thus performed in the CKD and dialysis populations to determine whether HIF-PHIs were noninferior to ESAs for cardiovascular safety (37,38).

These data were recently reviewed by a KDIGO controversies conference. The consensus among conference participants is that large trials of patients with nondialysis CKD to date have not conclusively demonstrated that HIF-PHIs are noninferior to placebo or ESAs for cardiovascular safety (39). However, there was consensus that, with the exception of roxadustat, HIF-PHIs met the criteria for noninferiority in trials of patients receiving dialysis. Discordant results in analysis of patients receiving incident dialysis and patients receiving prevalent dialysis in roxadustat trials has generated persistent concerns about the cardiovascular safety of roxadustat.

Other issues noted by KDIGO were as follows (39):

- HIF-PHIs have been associated with higher risk of thrombotic events.
- HIF-PHI have not yet been shown to have a benefit on blood pressure or kidney disease progression.
- HIF-PHI do not reduce the need for iron.
- HIF-PHI should not be used in polycystic kidney disease because of HIF-pathway mediated cyst growth observed in preclinical trials.

Because of concerns of cardiovascular safety, roxadustat has not been approved in the United States, although daprodustat has (GSK press release: Jesduvroq [daprodustat] approved by US FDA for anemia of chronic kidney disease in adults on dialysis. Available at: https://us.gsk.com/en-us/media/press-releases/jesduvroq-daprodustat-approved-by-us-fda-for-anemia-of-chronic-kidney-disease-in-adults-on-dialysis/ Accessed June 1, 2023).

## *Iron*

***Ferric citrate.*** Ferric citrate is a phosphate binder that was approved by the US Food and Drug Administration in 2014 and shown to provide effective iron repletion (40,41). A phase intravenous multicenter study including 202 patients showed acceptable safety profile, good control of serum phosphorus, and improvement of iron parameters with ferric citrate in patients with low baseline ferritin and TSAT (40,41). The effect of ferric citrate on ESA dose was subsequently studied in a randomized trial (ASTRIO) (42). In ASTRIO, 93 patients receiving hemodialysis were randomly assigned to receive 24 weeks of ferric citrate or continue non-iron-based phosphate binders. Compared with non-iron-based phosphate binders, ferric citrate reduced the ESA dose but did not change the hemoglobin concentration.

A meta-analysis including 16 randomized trial and 1754 patients assessed effectiveness safety and possible cost savings of ferric citrate (43). Compared with other phosphate binders, ferric citrate had a comparable effect on serum phosphate but improved hemoglobin concentration. In eight studies, ferric citrate was cost effective, and adverse effects were mild.

## *Ferric Pyrophosphate Citrate*

Ferric pyrophosphate citrate is a water-soluble form of iron that may be added to dialysate and provide iron directly to transferrin, thus avoiding iron sequestration within macrophages (44). In a randomized trial (PRIME) including 103 patients receiving hemodialysis, compared with placebo, the addition of ferric pyrophosphate citrate to dialysate resulted in a 35% reduction in ESA dose and a 51% decrease in intravenous iron use at 9 months (44). A more recent study demonstrated that ferric pyrophosphate could also be given intravenously rather than added to dialysate (45). In this study, ferric pyrophosphate was given intravenously to 27 patients during dialysis via the pre- or post-dialyzer lines. This method was well tolerated and delivered a comparable amount of drug as was observed with dialysis delivery. The intravenous delivery allows the use of ferric pyrophosphate citrate during hemodiafiltration as well as hemodialysis. Safety and adequate pharmacokinetics of intravenous delivery were also demonstrated in 14 healthy individuals and 12 patients receiving hemodialysis (46). In a comparison of 26 Asian and 65 non-Asian populations who received ferric pyrophosphate, there were no pharmacokinetic differences observed (47). In a prospective quality improvement project including 93 patients receiving hemodialysis at a single center, the use of ferric pyrophosphate was associated with higher hemoglobin levels, and lower ferritin and ESA doses, suggesting more efficient erythropoiesis (48). The use of ferric pyrophosphate is cost effective due to decreased use of ESAs and intravenous iron. In one study of 100 patients receiving

hemodialysis, the use of ferric pyrophosphate resulted in cost savings of $296,751 (49).

***Liposomal (sucrosomial) iron.*** Liposomal (sucrosomial) iron is a preparation of ferric pyrophosphate enclosed within a phospholipid membrane that has been shown to be absorbed well from the gastrointestinal tract (50). Liposomal iron causes fewer gastrointestinal side effects because the iron does not come into contact with the intestinal mucosa. Liposomal iron has improved bioavailability because it bypasses intestinal hepcidin-ferroportin (51). In a trial including 99 patients with CKD, liposomal iron increased hemoglobin to a comparable level as intravenous iron, though iron levels were more stable after intravenous iron therapy (52). Use of this oral preparation could provide significant cost and time saving (53). A second trial including 24 patients receiving hemodialysis demonstrated safety of sucrosomial iron but showed that, although hemoglobin was stable on oral iron, iron indices (TSAT and ferritin) were decreased compared with intravenous iron (54).

### *Other Treatments*

***PRS-080.*** PRS-080 is an engineered ligand-binding protein that has been shown in a phase 1 trial to neutralize hepcidin (55). An intravenous infusion of PRS-080 was administered to 48 healthy volunteers and 24 patients with ESKD. Compared with placebo, PRS-080 suppressed hepcidin in a dose-dependent fashion for approximately 48 hours. TSAT and iron were both increased, with no observed changes in ferritin reticulocytes, or hemoglobin suggesting mobilization of iron.

***Anti–Interleukin-6 ligand antibody.*** Interleukin (IL)–6 is an inflammatory cytokine that induces hepcidin (56,57).

Ziltivekimab, an anti-IL-6 ligand antibody, was administered to patients receiving hemodialysis selected for a single-nucleotide polymorphism that confers increased susceptibility to IL-6–mediated inflammation (58). Patients who received ziltivekimab every 2 weeks for 12 weeks had reduced levels of C-reactive protein, serum amyloid A, and fibrinogen and were observed to determine whether a decreased ESA dose was required. Compared with placebo, patients receiving ziltivekimab had decreased ESA resistance, and increased iron, TIBC, transferrin saturation, and albumin.

***Sodium-glucose cotransporter 2 inhibitors.*** Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown in randomized trials to increase hemoglobin (59). Other effects observed with SGLT2s include increased EPO concentration, increased reticulocyte counts, and decreases in hepcidin and ferritin, suggesting that the SGLT2 effect is unrelated to hemoconcentration (39). Some have suggested that the heart failure benefit and erythropoiesis may share a common mechanism. There are multiple hypotheses as to the mechanism underlying SGLT2-stimulated erythropoiesis (60–71), but no one mechanisms has proved.

- HIF-PHIs effectively increase hemoglobin in patients with CKD and ESKD.
- HIF-PHIs are not better than, and may be inferior to ESAs, for cardiovascular outcomes.

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