Iron Deficiency in Chronic Kidney Disease: Updates on Pathophysiology, Diagnosis, and Treatment

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ABSTRACT
Anemia is a complication that affects a majority of individuals with advanced CKD. Although relative deficiency of erythropoietin production is the major driver of anemia in CKD, iron deficiency stands out among the mechanisms contributing to the impaired erythropoiesis in the setting of reduced kidney function. Iron deficiency plays a significant role in anemia in CKD. This may be due to a true paucity of iron stores (absolute iron deficiency) or a relative (functional) deficiency which prevents the use of available iron stores. Several risk factors contribute to absolute and functional iron deficiency in CKD, including blood losses, impaired iron absorption, and chronic inflammation. The traditional biomarkers used for the diagnosis of iron deficiency anemia (IDA) in patients with CKD have limitations, leading to persistent challenges in the detection and monitoring of IDA in these patients. Here, we review the pathophysiology and available diagnostic tests for IDA in CKD, we discuss the literature that has informed the current practice guidelines for the treatment of IDA in CKD, and we summarize the available oral and intravenous (IV) iron formulations for the treatment of IDA in CKD. Two important issues are addressed, including the potential risks of a more liberal approach to iron supplementation as well as the potential risks and benefits of IV versus oral iron supplementation in patients with CKD.


PATHOPHYSIOLOGY OF IDA
Iron metabolism is tightly regulated at multiple stages of the red blood cell (RBC) life cycle (Figure 2). Although

Anemia, defined as a hemoglobin (Hgb) concentration of <13 g/dl in men and <12 g/dl in women, is an important complication of CKD.1 The prevalence of anemia increases across the advancing stages of CKD, with estimates anywhere from 7% to >50% in the more advanced stages of the disease.2 Multiple mechanisms contribute to the development of anemia in CKD, the most important being relative deficiency of erythropoietin (EPO). As such, erythropoiesis-stimulating agents (ESAs) have been considered a staple for the management of anemia in patients with CKD (Figure 1). Several well conducted studies in patients with CKD indicate that use of ESAs to normalize Hgb in patients with CKD may worsen cardiovascular (CV) outcomes.3–6 Thus, the current guidelines advise a target Hgb below the definition of normal in patients with CKD.1

Many patients with anemia and CKD suffer from iron-deficiency anemia (IDA).1,7 This is due to both true paucity of iron stores (absolute IDA) and relative (functional) iron deficiency; the latter being due to underlying inflammation which impairs the body’s ability to appropriately utilize the iron sequestered in the tissues.8 Repletion of iron stores is often necessary in patients with CKD for the treatment of IDA and to maximize the efficacy of ESAs. The traditional biomarkers used to detect iron deficiency in CKD are often unreliable, rendering the diagnostic and monitoring processes difficult. To best manage IDA in CKD, a thorough understanding of its pathophysiology and treatments is necessary. In this text, we review the mechanisms of IDA, the potential aids and pitfalls in the diagnosis of IDA, and the available treatment formulations for IDA in patients with CKD. We furthermore provide an in-depth discussion of the current literature as it pertains to target levels of Hgb and iron indices.
the development of erythroid lineage from a multipotential myeloid stem cell is regulated by EPO, the differentiation from erythroblasts into reticulocytes is an iron-dependent process. Hence, iron deficiency will limit responsiveness to EPO. Iron is absorbed in the gastrointestinal tract and bound to serum transferrin. Subsequently, iron is either transported to the liver and spleen, where it is bound to ferritin for storage, or to the bone marrow where it is used for erythropoiesis. Although dietary intake is typically sufficient to replace most of the daily losses of iron, the majority of iron stores are replenished by macrophage phagocytosis of the destroyed RBCs and iron recycling, a process influenced by EPO. Iron metabolism is further regulated by hepcidin. A peptide hormone synthesized predominately in the liver, hepcidin regulates the uptake of iron from the gut and the release of iron from the iron stores. Hepcidin production is stimulated by increased iron uptake, inflammation, and infection; it is suppressed in the setting of iron deficiency and hypoxia. CKD is associated with increased hepcidin levels.

Hypoxia-inducible factor (HIF) is an important transcription factor in the regulation of erythropoiesis, iron metabolism, and multiple other processes involved in the maintenance of homeostasis. HIF, a key mediator of cellular adaptation to oxygen deprivation, comprises an oxygen-sensitive α-subunit (HIF-1α, HIF-2α, or HIF-3α) and a stable β-subunit. HIF heterodimers activate the transcription of genes whose promoters contain hypoxia response elements, whereas recruitment of coactivators such as p300/CREB-binding protein is required in HIF-mediated transcription. HIF-α proteins are regulated by prolyl-4-hydroxylase domain–containing proteins 1–3 (PHD1–3), ferrous- and 2-oxoglutarate-dependent oxygenases, whose activity is dependent on oxygen. Under normoxic conditions, PHDs hydroxylate HIF-α at proline residues, allowing targeting for ubiquitination by the von Hippel-Lindau (pVHL)-E3 ubiquitin ligase complex and subsequent proteasomal degradation. Under hypoxic conditions, HIF-α is stabilized and, after nuclear translocation, it dimerizes with the HIF-β subunit, forming heterodimers that activate 100–200 genes, including EPO and other genes involved in iron metabolism. Furthermore, HIF reduces serum levels of hepcidin indirectly through stimulation of EPO-induced erythropoiesis. Compounds that pharmacologically inhibit PHDs activate HIF signaling under normoxic conditions and may represent effective treatments of anemia in CKD. These concepts are summarized in Figure 3.
**Figure 3.** Hypoxia signaling controls erythropoiesis by coordinating EPO synthesis with the expression of genes involved in iron metabolism. Under well oxygenated conditions, the three oxygen-labile HIF-α subunits (HIF-1α, HIF-2α, and HIF-3α) are hydroxylated at specific proline (Pro) residues by PHD enzymes. Prolyl hydroxylation targets HIF-α proteins for ubiquitination by the von Hippel-Lindau (pVHL)-E3-ubiquitin ligase complex with subsequent proteasomal degradation. Under conditions of reduced PHD activity (for example hypoxia or pharmacologic inhibition), HIF-α escapes hydroxylation and translocates to the nucleus, where it forms a heterodimer with the constitutively expressed HIF-β subunit. The effective HIF-α/HIF-β complex activates the transcription genes whose promoters contain hypoxia response elements. The HIF-mediated activation of transcription requires the recruitment of coactivators such as p300/CREB-binding protein. An additional layer of regulation is due to factor-inhibiting HIF (FIH), which hydroxylates a specific asparagine (Asn) residue abrogating transcriptional cofactor recruitment. HIF-α stabilization results in the activation of genes in diverse biologic processes. For instance, HIF-2α induces EPO production from renal peritubular fibroblasts and hepatocytes, promoting erythroid progenitors’ cell viability, proliferation, and differentiation through EPO receptor (EPOR) signaling. Genes expressed in duodenum, duodenal cytochrome b reductase (DCYTB) and divalent metal transporter-1 (DMT1) along with ferroportin (FPN) are activated by HIF-2, increasing iron uptake while HIF signaling also controls the expression of iron transport genes transferrin (Tf) and transferrin receptor (TfR). O₂, oxygen; OH, hydroxide.

**ABSOLUTE VERSUS FUNCTIONAL IRON DEFICIENCY**

It is important to differentiate between absolute (or storage) iron deficiency and functional (or relative) iron deficiency. In absolute iron deficiency, the total body iron stores are depleted, limiting the production of RBCs. Contributing factors to absolute iron deficiency include decreased gastrointestinal absorption in patients with CKD and increased blood loss (for example in the setting of uremia-induced platelet dysfunction and the iatrogenic loss from serial blood draws or access-site and circuit issues during the dialysis procedure).8

By contrast, functional iron deficiency occurs due to inefficient utilization of iron stores, stemming from one or both of two main phenomena. The first of these, anemia of chronic inflammation, is known as reticuloendothelial cell iron blockade. This may occur in the absence of EPO supplementation and can occur in inflammatory diseases other than CKD. Specifically, reticuloendothelial cell iron blockade can be triggered by active infection or inflammation, hypoxia, or genetic deficiencies.11 The second process relates to the use of exogenous EPO. Because RBC production increases in response to ESAs, the available iron may be used faster than the existing iron stores are able to release it, leading to a supply/demand mismatch and a “relative” iron deficiency.10

**DIAGNOSIS**

Biomarkers traditionally used in the diagnosis of IDA include Hgb and hematocrit, reticulocyte count, mean corpuscular Hgb, and mean corpuscular volume, most of which are decreased in IDA.23 In the setting of absolute iron deficiency, iron studies typically show a decreased iron level, decreased ferritin, elevated transferrin and total iron binding capacity (calculated as transferrin ×1.389), and decreased transferrin saturation (TSAT; calculated as serum iron/total iron binding capacity×100). However, there is evidence to indicate that the traditional cutoffs of TSAT at ≤20% and serum ferritin at ≤100 ng/ml are not sensitive to detect iron deficiency. In a study of 100 patients with CKD (stages 3–5), these indices identified only 17% of patients with CKD as iron deficient whereas approximately 50% were iron deficient based on the gold standard of bone marrow iron staining.24 Consistent with these findings, patients with iron studies that are within what is considered the normal range or “at goal,” may still show an increase in erythropoiesis to trials of iron therapy, whether they are on ESA therapy or not.24,25

Another major limitation of these parameters is that they do not differentiate between absolute and functional IDA. Transferrin, for example, is increased in both absolute and functional IDA. In addition, if functional iron deficiency exists due to a supply/demand mismatch, such as with ESA supplementation, then iron maybe stripped from transferrin faster than it can be mobilized from the iron stores, leading to a decrease in TSAT.10

Bone marrow biopsy is considered by many to be the gold standard for diagnosis of IDA.26 A study of 303 children in Malawi with iron deficiency concluded that the absence of iron fragments in a sample should be diagnostic of absolute iron deficiency, whereas the absence of erythroid progenitors (despite the presence of iron stores) should be diagnostic of functional iron deficiency.27 Estimates conclude, however, that up to 30% of bone marrow samples may be inaccurate or insufficient for diagnosis28 and the
number of fragments analyzed greatly affects the yield of a correct diagnosis.29 Other limitations include the invasiveness of the procedure and the burdens of cost and travel for patients. Given these limitations, there is a need for novel serum biomarkers to differentiate types of IDA in patients with CKD. Several biomarkers have been proposed; they are summarized in Table 1 and reviewed below.

- Serum ferritin: Ferritin is an acute-phase reactant and, as such, is frequently elevated in patients with CKD, irrespective of their iron stores.30,31 Increased ferritin levels in CKD are likely the result of underlying systemic inflammation because ferritin synthesis is responsive to inflammatory cytokines.32,33 Hence, the specificity of low ferritin is high for absolute iron deficiency, but normal or elevated ferritin levels to not exclude IDA in CKD.34,35

- Soluble transferrin receptor (sTfR): The transferrin receptor binds ferric iron and the complex is subsequently internalized into the cell. sTfR is then shed from the membrane of erythroid progenitor cells into the circulation.36 Hence, sTfR has been evaluated as a potential indicator of iron deficiency. A study of 71 patients dependent on dialysis found that sTfR did not detect occult iron deficiency. Rather, it positively correlated with hematologic parameters in the setting of EPO administration, indicating sTfR is a marker of erythropoiesis.36 Another study of 91 patients on dialysis showed similar results.37 Thus, the evidence does not support the use of sTfR in the evaluation of IDA in CKD.

- Percentage of hypochromic RBCs (HRC%) and reticulocyte Hgb content (CHR): Several other indirect measurements have been considered in the evaluation of IDA. HRC% and CHR both estimate Hgb content in RBCs, thereby reflecting the iron available for erythropoiesis in the recent timescale. HRC% and CHR are predictive of iron responsiveness, leading some to propose their use in the evaluation of IDA in CKD.38,39 HRC%, especially, is seen as a cost-effective measure for estimating iron responsiveness.39 However, both measurements are limited by testing requirements. HRC% must be tested within 6 hours of collection and CHR is time sensitive to the maturation of erythrocytes.40 Furthermore, CHR cannot be used in the setting of thalassemia, because thalassemia causes changes similar to iron deficiency.

- Hepcidin: Given its integral role in iron regulation, hepcidin has been evaluated as a marker of iron stores and iron responsiveness and to differentiate absolute and functional IDA.41 Hepcidin has been shown to correlate with ferritin levels in a subset of 61 patients with CKD from the Ferrinject assessment in patients with IDA and nondialysis-dependent CKD (FIND-CKD) trial.42 However, no reliable correlation was found between hepcidin and iron responsiveness.41 Similar findings have been reported in patients with CKD receiving dialysis.43 These data suggest the measurement of hepcidin levels is of limited utility in the evaluation of IDA in CKD.

- Plasma neutrophil gelatinase-associated lipocalin (NGAL): NGAL has been implicated in AKI, as an independent predictor of kidney-disease progression, and as a biomarker of inflammation.43,44 Additionally, NGAL affects sequestration of iron. In its free form, NGAL may increase the extracellular concentrations of iron, whereas the bound form of NGAL decreases it. The potential utility of NGAL as a biomarker of iron stores in CKD was evaluated in 419 patients with anemia, of whom 288 had CKD. An NGAL value of ≤394 ng/ml was found to correlate significantly with TSAT and to have a greater sensitivity and specificity in the detection of decreased iron stores in CKD than ferritin values of ≤500 ng/ml.45 Although these data are promising, the study did not evaluate the potential ESA effects on NGAL. Furthermore, two smaller studies of patients with CKD were unable to demonstrate that NGAL is an appropriate marker of decreased iron availability.46,47 Further research is needed before NGAL can be recommended as a reliable marker of iron deficiency in CKD.

Based on the current literature, the use of the traditional biomarkers of IDA is reasonable, especially considering the absence of other reliable biomarkers.

**Management**

The optimal management of iron deficiency in patients with CKD remains unclear. Only a few large-scale randomized trials had evaluated the safety of various iron formulations until recently. The Kidney Disease: Improving Global Outcomes (KDIGO) work group guidelines (2012) recommend balancing the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the potential risks of iron supplementation.1 For adult patients with CKD and anemia, KDIGO recommends a trial of iron repletion if the TSAT is ≤30% and the serum ferritin is ≤500 ng/ml. The European Renal Best Practice guideline (2013),48 on the other hand, recommends a trial of iron for TSAT levels of <20% and ferritin levels of <100 ng/ml to increase Hgb while avoiding ESAs with the goal of remaining below the ceiling of TSAT of 30% and ferritin of 500 ng/ml during supplementation. Considering the more recent evidence that many patients with CKD have ferritin levels >500 ng/ml,33 the most recent guidelines from the National Institute for Healthcare and Excellence (2015)49 and the Renal Association (2017)50 increased the ferritin ceiling to 800 ng/ml during iron supplementation.

**Risks of Iron Supplementation with Elevated Ferritin**

The concerns regarding iron overload are largely related to the potential for
free iron reactions, leading to damage from oxidative stress, increased tissue-iron deposition, and an increased risk of infection. To address whether chronic iron supplementation leads to increased tissue-iron deposition, a prospective study in France of 119 patients with CKD who were dialysis dependent used magnetic resonance imaging to quantify iron overload noninvasively. The authors reported no significant correlation between iron dosing and iron deposition in the liver. Importantly, cessation of IV iron supplementation resulted in a decline in iron deposition in the liver, suggesting that the intermittent administration of IV iron does not result in long-term iron overload. Although the reported findings are reassuring, the study was limited because it made no observations regarding patient mortality or CV disease. Additionally, the study participants received iron and ESA per the guidelines during the study period and, hence, the authors were unable to evaluate the safety of higher ceilings of ferritin.

Several studies have evaluated the safety of IV iron supplementation according to different TSAT and ferritin thresholds in patients with dialysis-dependent CKD and are summarized in Table 2. The Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) I and II trials investigated the safety of iron administration in patients with dialysis-dependent CKD with ferritin levels ranging from 500 ng/ml to 1200 ng/ml, with TSAT ≤25%. A total of 134 participants were randomized to either 125 mg of ferric gluconate or no treatment for 6 weeks, and then followed for 6 weeks after the completion of treatment. Of note, ferritin levels did not predict iron responsiveness. Rather, iron parameters showed greater improvement in the group receiving ferric gluconate and an associated significant decrease in EPO doses. After the additional 6-week follow-up period, the patients who had received ferric gluconate continued to require lower EPO doses. These data support the use of iron supplementation as an ESA-sparing strategy, even in patients with elevated serum ferritin levels.

The most compelling evidence in support of a more liberal approach to iron supplementation is derived from the Randomized Trial Comparing Proactive, High-Dose versus Reactive, Low-Dose IV Iron Supplementation in Hemodialysis (PIVOTAL).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Year</th>
<th>Population</th>
<th>n</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Safety</th>
<th>Additional</th>
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<tbody>
<tr>
<td>Coyne, et al.</td>
<td>DRIVE I</td>
<td>2007</td>
<td>Patients undergoing hemodialysis with Hgb =11 g/dl, ferritin 500–1200 ng/ml, TSAT ≤25%, and epoetin dosage ≥225 IU/kg per wk or ≥22,500 IU/wk</td>
<td>134</td>
<td>6 wk</td>
<td>No iron (control) versus 125 mg IV ferric gluconate</td>
<td>Patients receiving ferric gluconate had higher Hgb ((P=0.028)), more rapid Hgb response ((P=0.035))</td>
<td>No difference in adverse events</td>
<td>Ferritin levels ranged 500–1200 and had no correlation with outcomes</td>
</tr>
<tr>
<td>Kapoian, et al.</td>
<td>DRIVE II</td>
<td>2008</td>
<td>Same as DRIVE I</td>
<td>112</td>
<td>12 wk (6 wk from DRIVE I)</td>
<td>No iron (control) versus 125 mg IV ferric gluconate for the first 6 wk. For the additional 6 wk, treatment was per center</td>
<td>Ferric gluconate group had significantly lower EPO doses; 84% of the treatment arm maintained Hgb &gt;11.0 versus 68% of the control ((P&lt;0.05))</td>
<td>More adverse events in control group (IRR 1.73, P=0.041)</td>
<td></td>
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<tr>
<td>MacDougall, et al.</td>
<td>PIVOTAL</td>
<td>2019</td>
<td>Patients undergoing hemodialysis</td>
<td>2141</td>
<td>Median=2.1 yr</td>
<td>Iron sucrose: high dose (400 mg) given monthly versus low dose (0–400 mg) given reactively each mo based on ferritin &lt;200 mcg/L or TSAT &lt;20%</td>
<td>Composite outcome (nonfatal myocardial infarction, stroke, heart failure hospitalization, any-cause death) was 29% versus 32% ((P=0.04)) in the high-dose versus low-dose group; less ESA use in the high-dose group</td>
<td>Similar rates of infection and overall adverse events; vascular access thrombosis rates were 24% in the high-dose versus 21% in the low-dose group ((P=0.12)); but lower rates of fatal or nonfatal myocardial infarction were noted in the high-dose group (estimated treatment effect 0.69 [95% CI: 0.52–0.93])</td>
<td>Rates of stroke were similar for both groups but lower rates of fatal or nonfatal myocardial infarction were noted in the high-dose group</td>
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<tr>
<td>Agarwal, et al.</td>
<td>REVOKE</td>
<td>2015</td>
<td>Patients with stage 3 or 4 CKD and IDA</td>
<td>136</td>
<td>2 yr</td>
<td>Open-label ferrous sulfate 325 mg TID for 8 wk versus IV iron sucrose 200 mg every 2 wk (total dose 1 g)</td>
<td>Similar decline in eGFR; similar improvement in Hgb; similar ESA dose</td>
<td>Infections: (IRR 2.12) for IV versus oral iron groups ((P&lt;0.006)). CV events: (IRR 2.51) for IV versus oral iron groups ((P&lt;0.001))</td>
<td>Not powered for safety</td>
</tr>
<tr>
<td>Reference</td>
<td>Title</td>
<td>Year</td>
<td>Population</td>
<td>n</td>
<td>Follow-up</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Safety</td>
<td>Additional</td>
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<tr>
<td>Macdougall, et al.</td>
<td>FIND-CKD</td>
<td>2017</td>
<td>Patients with nondialysis-dependent CKD and IDA without ESA use</td>
<td>353</td>
<td>1 yr</td>
<td>Oral iron (ferrous sulfate 304 mg twice daily) versus FCM at high dose (500 or 1000 mg monthly based on ferritin) versus FCM at low dose (2 mg monthly based on ferritin)</td>
<td>Time to initiation of additional anemia therapy: the primary end point occurred in 23%, 32%, 32% in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively (HR, 0.65; 95% CI, 0.44 to 0.95; ( P = 0.026 ) for high-ferritin FCM versus oral iron)</td>
<td>No significant difference in adverse renal outcomes</td>
<td>Ferritin levels were significantly higher in the high-dose FCM group</td>
</tr>
<tr>
<td>Charytan, et al.</td>
<td>2013</td>
<td>Adult Patients with history of NDD-CKD of at least 3 mo or HD-CKD of at least 6 mo with IDA and no recent iron use</td>
<td>416 NDD-CKD, 97 HD-CKD</td>
<td>30 d</td>
<td>Standard medical care (provider determined: no iron, oral iron, or IV iron) versus FCM (15 mg/kg in NDD-CKD or 200 mg in HD-CKD)</td>
<td>Safety of high-dose FCM: no difference in safety events between groups; no difference in the proportion of patients with an increase of 1 g/dl in Hgb or Hgb &gt; 12 g/dl</td>
<td>Primary end point: high incidence of serious events in the standard care group (notably iron sucrose or ferrous gluconate), ( P &lt; 0.01 )</td>
<td>Not powered for secondary end points</td>
<td></td>
</tr>
<tr>
<td>Onken, et al.</td>
<td>REPAIR-IDA</td>
<td>2014</td>
<td>Patients with CKD and IDA with stable ESA dose (if applicable)</td>
<td>2584</td>
<td>56 d</td>
<td>FCM (15 mg/kg × 2 doses) versus IV iron sucrose (200 mg × 5 doses)</td>
<td>Composite safety outcome (all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina, CHF, arrhythmia, hypertension, hypotension); no significant difference; mean change in Hgb from baseline was higher in the FCM group</td>
<td>Composite (all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina, CHF, arrhythmia, hypertension, hypotension): no major difference; significant difference in number of transient hypertension in FCM group and hypotension in iron sucrose group</td>
<td>FCM noninferior for increases in TSAT, ferritin</td>
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IRR, incident risk ratio; TID, three times a day; NDD-CKD, non-dialysis dependent chronic kidney disease; HD-CKD, hemodialysis-dependent CKD; CHF, congestive heart failure.
is a randomized controlled trial of 2141 patients with dialysis-dependent CKD randomized to either high-dose iron sucrose (400 mg) given prescriptively each month versus a reactive, lower-dosing strategy that was adjusted based on ferritin or TSAT. Notably, the investigators set a ceiling of 700 ng/ml for ferritin and 40% for TSAT as hard stops for holding iron doses in the proactive, high-dose arm. After a mean follow-up of 2.1 years, the group that was randomized to the proactive, high-dose arm had a lower incidence of death, nonfatal CV events, and hospitalization, as well as significantly lower ESAs and transfusion requirements. Of note, there was no difference in infection rates between both study arms. Results of PIVOTAL are consistent with the results of DRIVE I and II and indicate that a more liberal approach to iron supplementation is safe and effective, specifically in patients undergoing dialysis. However, given that the median serum ferritin level in the United States is higher than the safety cutoff applied in PIVOTAL, further studies are needed to establish the safety of iron supplementation in patients with serum ferritin levels >700 ng/ml.62

Risks of IV versus Oral Iron Administration
Oxidative stress has been observed transiently in both humans and animals after iron infusion; however, the clinical significance of these findings is unclear. It has been postulated that oxidative stress, induced by IV iron, may lead to a higher risk of infection, atherosclerosis, and hospitalization. However, several observational studies on the topic have yielded conflicting results. In one analysis of >32,000 patients with dialysis-dependent CKD who were followed over 9 years, high doses of IV iron were found to associate with an increased risk of mortality, hospitalization, and CV events.63 Although other analyses have yielded similar results,64 their findings are at odds with those of several studies. For example, some have shown that the association between IV iron and mortality is attenuated after adjusting for co-morbidities.65 Other studies have shown more complex findings: IV iron use was associated with a significantly lower incidence of death in 58,058 patients with CKD on hemodialysis as long as the administered dosage of iron was ≤400 mg/mo, and with higher mortality if the dosage was >400 mg/mo.66 A larger observational study evaluated the potential association between IV iron and death in 72,114 patients with CKD on hemodialysis. After adjusting for hematocrit level and EPO dosing, the use of IV iron was associated with a 22% lower mortality.67 The largest analysis conducted, to date, evaluated 117,050 patients on hemodialysis with 776,203 unique iron exposure/follow-up periods with the goal of evaluating the safety of different IV-iron dosing strategies, including bolus versus maintenance and high (>200 mg/mo) versus low (≤200 mg/mo) dosages. They observed no consistent associations between any of the evaluated dosing strategies and CV events.68 Although such data may be reassuring, considering the nature and limitations of these observational studies, the long-term safety of IV iron remains unclear and caution should be applied when interpreting such studies.

Several randomized controlled trials have been conducted to evaluate the potential benefits and safety of IV iron (Table 3). The Randomized Trial to Evaluate IV and Oral Iron in CKD (REVOKE) was a single-center, randomized controlled trial of 136 patients with nondialysis-dependent CKD that compared IV iron sucrose to oral ferrous sulfate. The primary end point of the study was change in GFR. Secondary end points included albuminuria, Hgb response, and kidney disease–related quality of life. Although it was planned to last 2 years, the study was stopped early due to the higher incidence of adverse events in the IV iron group, including infection and heart failure.58 The findings of REVOKE contrast with the reported results of the multicenter FIND-CKD trial, in which 626 patients

Table 3. IV iron formulations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Molecular Weight (Da)</th>
<th>Maximum Daily Dose</th>
<th>Iron Concentration (mg/ml)</th>
<th>Test-Dose Required</th>
<th>Black Box Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran</td>
<td>265,000</td>
<td>100 mg</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Low mol wt iron dextran</td>
<td>165,000</td>
<td>100 mg</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sodium ferric gluconate complex</td>
<td>289,000–444,000</td>
<td>125 mg</td>
<td>12.5</td>
<td>No</td>
<td>No</td>
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<td>injection, United States Pharma-</td>
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<td>cepial</td>
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<tr>
<td>Ferumoxytol</td>
<td>750,000</td>
<td>510 mg</td>
<td>30</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Iron isomaltose</td>
<td>150,000</td>
<td>20 mg/kg</td>
<td>100</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>FCM injection</td>
<td>150,000</td>
<td>750 mg if weight &gt;50 kg (15 mg/kg if weight &lt;50 kg)</td>
<td>50</td>
<td>No</td>
<td>No</td>
</tr>
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</table>
with nondialysis-dependent CKD were randomized to receive ferric carboxymaltose (FCM) targeting one of two ferritin thresholds versus oral iron therapy. In contrast to REVOKE, FIND-CKD demonstrated no difference in the risk of infection, CV events, or kidney toxicity during 1 year of follow-up.\(^9\) When interpreting these conflicting results, several factors.\(^69,70\) First, neither study was adequately powered to evaluate safety outcomes. Second, REVOKE included patients at risk of rapid CKD progression, whereas FIND-CKD only included patients with stable CKD. As such, the patients included in REVOKE may have been at higher risk of infectious and CV adverse events than those included in FIND-CKD. Third, whereas REVOKE considered each event within a trial participant as a separate reportable event, FIND-CKD reported only one type of each event per participant even if there were multiple instances. FIND-CKD additionally only reported events up to the point that the trial therapy was changed, and so downstream events could not be directly attributed to their experimental intervention. Hence, it is difficult to reconcile the results of the two studies.

Two other studies were performed to evaluate the safety of IV iron as a primary end point. As shown in Table 2, the first study evaluated IV versus oral iron supplementation. A total of 508 patients with nondialysis-dependent CKD and dialysis-dependent CKD were randomized to receive either FCM or one of any other preparations, \(^72\) although their side effects differ due to inconsistencies with labeling agents.\(^52\) Although these data suggest an overall similar safety profile to both formulations, both studies are limited by the short duration of follow-up. As such, the safety of IV iron versus oral iron supplementation remains debatable, especially in patients with nondialysis-dependent CKD who are at high risk of CKD progression.

**Anaphylaxis with IV Iron**

One additional concern which has been noted with the administration of iron is anaphylaxis. Anaphylaxis is most commonly reported with iron dextran formulations, although this cannot be reliably confirmed due to inconsistencies with labeling agents.\(^52\) Although dextran confer a higher risk of anaphylaxis, most formulations of IV iron appear to have a better safety profile in this regard and most formulations do not require allergy testing before administration.\(^51\) A large retrospective cohort study of fee-for-service Medicare patients followed for 10 years found the anaphylaxis risk is estimated to range from 24 to 68/100,000 for all combined IV iron formulations (dextran, gluconate, sucrose, and ferumoxytol) and decreases with subsequent dosing.\(^71\) Although these data indicate that the incidence of anaphylaxis remains small, patients receiving IV iron therapy should be monitored closely.

**Iron Administration Ceilings**

Based on the current literature, we conclude that drawing a ceiling for iron supplementation for any patient with ferritin <500 ng/ml and TSAT <30% may lead to the underutilization of iron supplementation in a large portion of patients who would likely respond to treatment. A trial of iron may be considered for those with ferritin levels >500 ng/ml in whom an increase in Hgb level and/or decrease in ESA dose is desired. Beyond a ceiling of 800 ng/ml, however, clinicians should use their judgment to weigh the risks of alternate treatment, including the risk of higher ESA dose and the patient’s medical comorbidities, against the potential risks of iron supplementation. A TSAT ceiling of 40% may be considered a reasonable cutoff above which caution should be exercised before continuing iron repletion. For patients with CKD who are at high risk of CKD progression, a trial of oral iron supplementation is warranted before the consideration of IV iron.

**Iron Supplementation Formulations**

There is a variety of both IV and oral iron preparations available for use, each with their own risks and benefits.

Oral agents include ferrous sulfate, ferrous gluconate, ferrous fumarate, iron polysaccharide, and ferric citrate (FC). Ferrous preparations tend to be used most frequently as they are less expensive and more widely available than other preparations,\(^72\) although their side effects limit the daily total dose tolerated. Additionally, there is evidence that IV iron may be more effective than oral iron in general. This was first demonstrated by Macdougall et al.\(^73\) in a randomized controlled trial of 37 patients with CKD on ESAs comparing IV, oral, and no iron supplementation. Further studies have confirmed the superiority of numerous different IV iron formulations to the common oral therapies in both patients who are dialysis dependent and those with CKD stages 3–5, both for rapidity of improvement in Hgb and quality of life.\(^58,74–76\) Regardless of formulation, it appears that using smaller doses of IV iron with increased frequency is a more effective approach, than the use of larger doses less frequently, to maintain Hgb levels and decrease the dose of EPO.\(^51,58\) This approach of more frequent administration of smaller doses of IV iron is feasible and convenient in patients with CKD receiving intermittent hemodialysis but not in patients receiving peritoneal dialysis or in patients with nondialysis-dependent CKD.\(^51\) In patients with nondialysis-dependent CKD who do require IV iron supplementation, larger doses with decreased frequency...
may be preferred to reduce the number of venipunctures (to preserve future hemodialysis vascular access sites) and to minimize the burden of travel and the cost of the infusions.

Several IV iron formulations are available (reviewed in Table 3). Considering the large number of formulations available, the choice of IV iron formulation may be dictated not only by the safety profile but also by the cost and ease of use (single versus multiple infusions).

**NOVEL IRON THERAPIES**

The following is a summary of the novel iron therapies:

- **FC:** Iron replacement with an oral preparation like FC may be subject to a more physiologic regulation of iron absorption, thus potentially promising to avoid the side effects of iron overload that remain a concern with IV formulations.77,78 FC is approved as a phosphate binder in patients with ESKD. More recently, FC has been approved by the Food and Drug Administration (FDA) for the treatment of IDA in patients with CKD not on dialysis. This is based on recent data showing that FC improves Hgb (in addition to lowering phosphorus) in patients with CKD not on dialysis (stage 3–5).79,80 Considering the high pill burden in CKD, FC may represent an appealing approach for the treatment of hyperphosphatemia and IDA in CKD.

- **Ferric maltol:** Ferric maltol is approved for the treatment of patients with IDA and inflammatory bowel disease in the United Kingdom and the in the United States, having shown rapid correction of anemia with a relatively low side-effect profile.81 A phase 3 trial in the Study with Oral Ferric Maltol for the Treatment of IDA in Subjects with CKD (AEGIS-CKD) has been completed in patients with CKD stages 3–4 to evaluate the potential effects of ferric maltol on Hgb compared with placebo. The results of this study are still pending.

- **Ferric pyrophosphate citrate (FPC):** FPC was approved by the FDA in 2015 for use in patients on dialysis. It is a water-soluble, carbohydrate-free, complex iron salt administered via the dialysate to patients receiving hemodialysis. It donates iron directly to transferrin and may avoid iron sequestration in the reticuloendothelial macrophages.82 FPC has been compared with placebo in patients with ESKD receiving hemodialysis in the Continuous Replacement Using Iron Soluble Equivalents (CRUISE) 1 and 2 trials. FPC delivered via dialysate was found to better maintain Hgb, TSAT, and ferritin as compared with placebo, with significant reduction in ESA dosing.83

- **Liposomal/Sucrosomal iron:** Liposomal iron surrounds the ferric pyrophosphate core with a phospholipid bilayer and sucrosomal iron with an additional layer of sucrosomes (sucrester, a surfactant, and additional starchlike compounds).84 This allows for iron to bypass the gastrointestinal tract and be taken up by microfold cells through the lymphatic system, thus avoiding the downregulating effects of hepcidin and minimizing potential side effects.84 Preliminary data suggest that liposomal iron improves Hgb in patients with CKD while minimizing the risk of adverse events.85 Sucrosomal iron has similarly been shown to improve anemia in patients with celiac disease,86 patients undergoing bariatric surgery,87 and in patients with malignancy.88 Whether sucrosomal iron is efficacious or safe in patients with CKD has not been evaluated.

**NONIRON THERAPIES OF ANEMIA OF CKD**

There are several agents (outside of iron supplementation) that are currently under investigation for the treatment of anemia in CKD. Notably, agents that inhibit HIF prolyl-hydroxylases lead not only to increased production of EPO but also to increased iron store availability and increased iron uptake from the gastrointestinal tract. HIF prolyl-hydroxylase inhibitors (HIF-PHIs) are oral formulations that have been shown to increase Hgb levels in patients with CKD. For example, a 20-week phase 2b trial of vadadustat illustrated a significant improvement of Hgb compared with placebo in 138 patients with CKD (stage 3–5).89 More recently, roxadustat was found to increase Hgb levels in a 9-week phase 3 trial of 154 patients with anemia of CKD not on dialysis. Additional findings included a reduction in hepcidin levels and stable iron indices (despite restricted IV iron supplementation).90 In patients with ESKD on dialysis, 305 patients requiring ESA were randomized in a 2:1 ratio to receive either roxadustat or epoetin alpha. During the 26 weeks of follow-up, roxadustat increased Hgb and transferrin levels, maintained serum iron levels, and attenuated decreases in TSAT.91 Similar to the data in patients with CKD who were not on dialysis, roxadustat reduced hepcidin levels.91 These findings suggest that HIF-PHIs may improve iron utilization.92 There are currently at least six drugs from this family in various stages of clinical trials and investigation in the United States and abroad: roxadustat, vadadustat, daprodustat, molidustat, enarodustat, and desidustat.93 For example, phase 3 studies to evaluate major adverse CV outcomes with roxadustat have been completed and the results are forthcoming. The entry of this novel class in our therapeutic armamentarium is exciting. Although it is important to establish the long-term safety of HIF-PHIs, especially considering their potential to promote neoplastic growth and angiogenesis (particularly pertinent to diabetic retinopathy),95 these agents are likely to change the current algorithms for the treatment of anemia in patients with CKD including the utilization of iron supplementation.
CONCLUSIONS

Iron deficiency is a common and treatable cause of anemia in patients with CKD. Given the limitations of TSAT and ferritin in establishing iron deficiency in patients with anemia of CKD, the KDIGO guidelines recommend balancing the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the potential risks of iron supplementation. Multiple established agents exist for the treatment of IDA in CKD including several oral and IV formulations. For patients with stable CKD, IV formulations are acceptable and especially convenient for patients requiring hemodialysis. The dose and the frequency of IV iron administration should weigh patient comfort and accessibility.

DISCLOSURES

Dr. Pergola reports personal fees from Akebia, Astra-Zeneca, Kerry, Reata, ExThera, Vifor, Abbvie, and other from Renal Associates, PA (employer), during the conduct of the study. Dr. Kovesdy reports personal fees from Amgen, Sanofi-Aventis, Fresenius Medical Care, Kerry, Shire, Bayer, Abbott, Abbvie, Dr. Schar, Astra-Zeneca, and Takeda, outside the submitted work. Dr. Jalal reports research support from Keryx Inc, during the conduct of the study. All remaining authors have nothing to disclose.

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