Recent and Emerging Therapies for Iron Deficiency in Anemia of CKD: A Review

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Iron deficiency commonly contributes to the anemia affecting individuals with chronic kidney disease. This review describes diagnostic criteria for iron deficiency in chronic kidney disease, as well as mechanisms of functional and absolute iron deficiency and general treatment principles as delineated in the KDIGO (Kidney Disease: Improving Global Outcomes) guideline. Repletion of absolute iron deficits has progressed over time with the addition of better tolerated, more effective oral agents, including ferric citrate, ferric maltol, and sucrosomial iron. This article examines the structural characteristics and trial data enabling regulatory approval of these novel oral agents. Newer intravenous iron therapies, including ferric carboxymaltose and ferric derisomaltose, allow for fewer infusions and decreased risk of serious hypersensitivity reactions. Concerns about adverse effects such as cardiovascular events and infections are discussed. The potential risk of 6H syndrome (high FGF-23, hypophosphatemia, hyperphosphaturia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism) due to these intravenous agents is emphasized. The proposed pathophysiology of 6H syndrome and hypophosphatemia is described. Ferric pyrophosphate citrate enables administration of iron for repletion through dialysate. Relative merits, costs, and risks of various iron agents such as hypersensitivity and 6H syndrome/hypophosphatemia are summarized.

Pathophysiology of Iron Deficiency Anemia

Normal iron homeostasis depends on adequate absorption of iron from the diet. Absorbed iron replaces losses due to menstruation and sloughing of epithelial cells from the skin and intestines.[1] Iron in the body is tightly regulated because there are no natural mechanisms for its excretion. The mechanisms of iron absorption and internal distribution are summarized in Fig 1.

Functional Versus Absolute Iron Deficiency

In patients with chronic kidney disease (CKD), the unavailability of iron for hematopoiesis can be absolute or functional. Absolute iron deficiency occurs when the amount of storage iron in the liver, spleen, and marrow is minimal. This may stem from blood losses related to the dialysis procedure, gastrointestinal bleeding, or poor oral iron intake.[2] The prevalence of iron-deficiency anemia in the United States increased between 1999 and 2018, with the increase estimated to range between 10.5% and 106%, depending on age and sex. This has been attributed to a cultural dietary shift from beef to poultry-based food products over that time period.[3]

Functional iron deficiency is characterized by adequate iron stores, the gold standard for which is presence of stainable iron in bone marrow, but usually diagnosed in the clinical setting by blood tests as noted below.[4-6] Functional iron deficiency represents a supply/demand mismatch for iron to support erythropoiesis. On the supply side, inflammation leads to decreased iron availability primarily due to increased hepcidin concentration in plasma. On the demand side, erythropoiesis-stimulating agents (ESAs) used in patients with CKD accelerate red blood cell production and exceed the ability to sufficiently mobilize iron from stores. Functional iron deficiency due to ESA therapy can often be overcome with therapeutic iron supplementation, whereas anemia of inflammation may be more resistant to this intervention (Box 1).[7]

Diagnosis of Iron-Deficiency Anemia

Absolute iron deficiency in patients with CKD is defined by transferrin saturation (TSAT) <20% and ferritin level <100 ng/mL. Functional iron deficiency is defined by TSAT <20% and ferritin level >100 ng/mL in CKD without kidney replacement therapy (KRT) and >200 ng/mL in patients with CKD treated by dialysis. However, these parameters have been questioned and are an area of active review.[8] Because inflammation, which is highly prevalent in CKD, can increase ferritin and decrease transferrin concentrations in plasma, this compromises the applicability of these standard diagnostic tests. Alternative measures such as reticulocyte hemoglobin (Hb) content and percentage of hypochromic red blood cells have been proposed. However, limited availability of these assays has restricted their use in clinical practice, particularly in the United States.[9]

Principles of Management

The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guideline on anemia management in CKD suggests the treatment of anemia with iron supplementation in adults with CKD stage 3-5 when TSAT is <30% and ferritin level is <500 ng/mL.[10] The goal is to balance transfusion avoidance with the risks and side effects of iron therapy. The evidence base for these recommendations in adults is not robust. In pediatric patients with anemia who are not already receiving therapy, treating TSAT <20% and
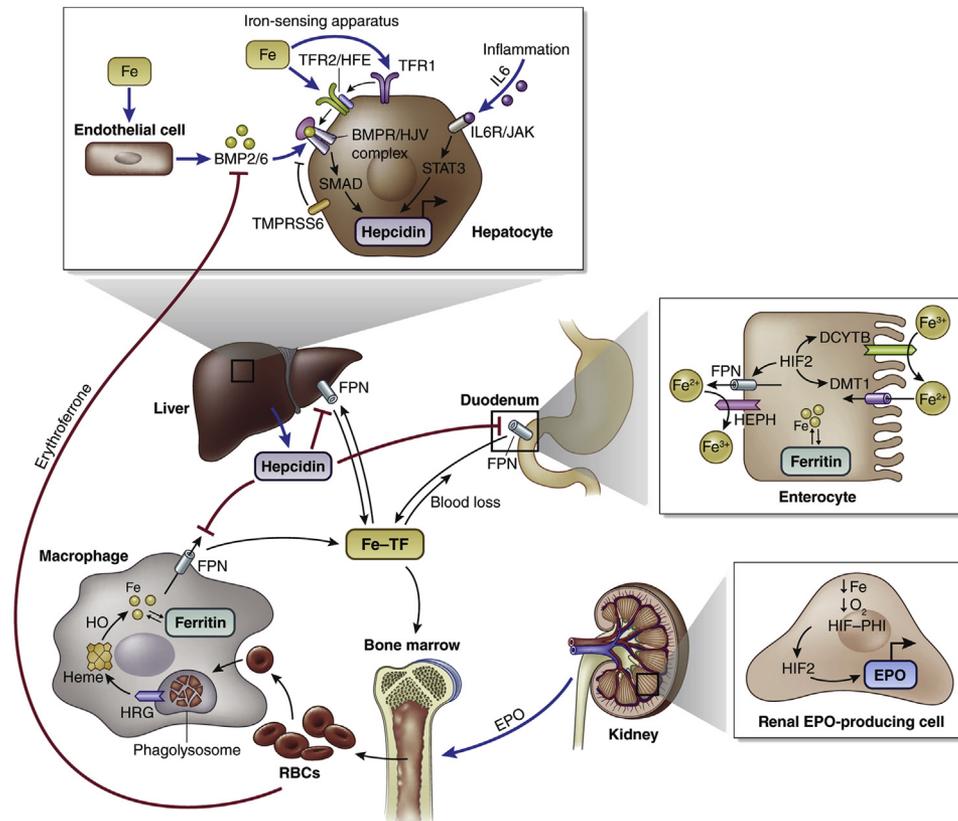
Figure 1. Direct and indirect regulation of systemic iron homeostasis. Iron (Fe) is provided mainly by reticuloendothelial macrophages that recycle iron from senescent red blood cells (RBCs), with a lesser contribution from dietary absorption and other body stores. Iron circulates in the plasma, predominantly bound to transferrin (TF), and is stored in cells in the form of ferritin. The liver hormone hepcidin controls systemic iron homeostasis by inducing degradation of the iron exporter ferroportin (FPN) to reduce iron entry into plasma from dietary sources and body stores. Iron deficiency and erythropoietic drive suppress hepcidin production to provide adequate iron for erythropoiesis and other essential functions. Iron and inflammation induce hepcidin to prevent iron overload and limit iron availability to pathogens. Iron induces hepcidin transcription by stimulating liver endothelial cells to produce bone morphogenetic proteins (BMPs) BMP2 and BMP6, which bind to the hepatocyte BMP receptor complex and coreceptor hemojuvelin (HJV) to activate SMAD transcription factors. Iron also induces hepcidin via the hepatocyte iron-sensing apparatus involving transferrin receptor 2 (TFR2), transferrin receptor 1 (TFR1), and homeostatic iron regulator protein (HFE). These pathways are all inhibited by iron deficiency, which also increases the activity of transmembrane serine protease 6 (TMPRSS6) to cleave HJV and further suppress hepcidin. Under conditions of accelerated erythropoietic activity, erythropoietin (EPO) induces erythroid progenitor cells to produce erythroferrone (ERFE), which suppresses hepcidin by functioning as a ligand trap to block the BMP signaling pathway. During inflammation, interleukin 6 (IL-6) and other inflammatory cytokines induce hepcidin transcription directly via a signal transducer and activator of transcription 3 (STAT3)–binding element in the hepcidin promoter. Hypoxia-inducible factors (HIFs), which are stabilized by low-oxygen (O_2) and low-iron conditions, contribute to iron homeostasis and erythropoiesis by regulating the production of EPO in the kidney, ferrireductase duodenal cytochrome B (DCYTB) and iron transporters FPN and divalent metal transporter 1 (DMT1) in the intestine, and the plasma iron carrier TF. Abbreviations: HEPH, hephaestin; HO, heme oxygenase; HRG, heme transporter HRG1. Image ©2021 Elsevier, Inc; reproduced from Babitt et al[8] with permission of the copyright holder.

ferritin level <100 ng/mL with iron is recommended in all patients with CKD stage 3-5. The evidence base for this recommendation is stronger than that in adults, but, noting that estimates of response are less likely to be accurate, KDIGO presents as an opinion that intravenous (IV) iron be avoided during active infection.[10]

A Cochrane Review of 28 studies with 2,098 participants in which oral and IV iron therapy were compared for patients with CKD[11] provided strong evidence that those receiving IV iron have increased ferritin (mean difference,

243.25 [95% CI, 188.74-297.5] ng/mL) and TSAT (mean difference, 10.20% [95% CI, 5.56%-14.83%]). The difference in Hb increase among patients treated with IV iron was also significant (mean difference, 0.90 [95% CI, 0.44-1.37] g/dL). Morbidity and cardiovascular mortality did not differ significantly between the 2 groups, but were reported in few studies. An updated meta-analysis[12] in 2016 showed that patients with stages 3-5 CKD (including those receiving dialysis [stage 5D]) treated with IV iron were more likely to exhibit an Hb increase >1 g/dL (risk

- Iron deficiency commonly contributes to anemia of chronic kidney disease and is amenable to treatment with newer oral and intravenous therapies
- Intravenous iron can lead to a number of rare but serious adverse effects, and hypophosphatemia is increasingly recognized as prevalent and potentially serious
- The choice of iron supplementation should be individualized to the patient and based on convenience, tolerance, cost, and the severity of iron deficiency

ratio, 1.61 [95% CI, 1.39-1.87]) than those treated with oral iron. Safety analysis showed similar rates of mortality and adverse events, although IV iron was associated with a higher risk of hypotension (risk ratio, 3.71 [95% CI, 1.74-7.94]) and lower risk of gastrointestinal adverse events (risk ratio, 0.43 [95% CI, 0.28-0.67]). The meta-analysis authors thus recommended increased use of IV iron for patients with CKD stages 3-5.[12]

The KDIGO guideline agrees that IV iron is generally more effective than oral iron for patient receiving hemodialysis (HD), but that oral iron is a reasonable alternative for patients with CKD who are not undergoing HD. For the latter group of patients, the choice between oral and IV iron is more nuanced. KDIGO advises clinicians to "select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost."[10] Although some studies have noted the potential for serious adverse effects to be greater with IV versus oral iron, considerations of adherence and effectiveness may encourage the use of IV formulations.[13]

Newer Oral Iron Agents

Although oral iron has been available for many years, its use has been limited in part by gastrointestinal side effects, including dyspepsia and constipation.[8] Some of the dyspepsia is thought to arise from gastric acid interacting with the ferrous form (ie, Fe^{2+}), which is more basic than ferric iron (Fe^{3+}). Conversion of Fe^{2+} to Fe^{3+} by gastric acid facilitates its absorption even though the Fe^{3+} must be reduced back to Fe^{2+} by ferrireductase (duodenal cytochrome B [DCYTB]) before absorption by the divalent metal transporter 1 (DMT1) channel in the small bowel. That is the rationale for administering Fe^{2+} supplements on an empty stomach when gastric acid will not be buffered by food. Novel iron formulations use Fe^{3+}, which does not require administration on an empty stomach and causes less dyspepsia, and the bioavailability of which is not decreased by agents that decrease stomach acidity such as H_2 blockers and proton pump inhibitors.

Ferric Citrate

Ferric citrate is a novel oral iron preparation in which Fe^{3+} is complexed to a polymer of tricarboxylic acid (citrate) and water. Originally introduced as a phosphate binder, ferric citrate subsequently obtained US Food and Drug Administration (FDA) approval as a treatment for iron-deficiency anemia in patients with CKD without KRT. Ferric citrate was compared with placebo in 232 patients with CKD and iron-deficiency anemia who were not receiving KRT in whom therapy with iron salts such as ferrous sulfate had failed. A substantially higher percentage of those treated with ferric citrate (52.1%) versus placebo (19.1%; P < 0.001) exhibited the primary endpoint of a 1-g/dL increase in Hb level at any time during the 16-week randomization period. There was slightly more gastrointestinal toxicity, both diarrhea (24% vs 19%) and constipation (22% vs 15%), in ferric citrate versus placebo recipients, respectively.[14] A pooled analysis of the 232-patient phase 3 trial with a 149-patient phase 2 trial demonstrated that more patients treated with ferric citrate exhibited an Hb level >10 g/dL (47.8% vs 18.6% with placebo). This analysis also identified a higher rate of gastrointestinal side effects in the ferric citrate arm.[15] A reanalysis of the phase 3 trial showed that patients with more severe iron deficiency experienced a greater increase in Hb level.[16] A randomized trial of 60 patients with CKD who were not receiving KRT found ferric citrate to be more effective in increasing TSAT and ferritin level at 12 weeks. However, the ferric citrate group was prescribed 1,260 mg of elemental iron per day, compared with 195 mg/d in the ferrous sulfate group, so the differences may not be surprising even accounting for the 3- to 4-fold lower bioavailability of ferric iron.[17,18] Hb levels, as well as a number of other parameters (fibroblast growth factor 23 [FGF-23], intact parathyroid hormone, and erythroferrone), were not significantly different between the 2 groups.[19]

In patients with CKD undergoing dialysis, ferric citrate is indicated for phosphate binding but is used on an off-label basis as an iron supplement. A phase 3 randomized controlled trial of ferric citrate versus sevelamer carbonate and/or calcium acetate in 441 prevalent HD recipients over 1 year demonstrated higher median ferritin levels in the ferric citrate arm, with an average mean difference of 282 ng/mL (P < 0.001). TSAT increased in the ferric citrate arm by 9.5% (P < 0.001). ESA dose, IV iron requirements, and Hb level were all favorably affected in the ferric citrate arm to a statistically significant degree, with no increase in adverse events.[20] Although the price of ferric citrate is higher than those of other phosphate binders and oral iron therapies, economic analyses suggest that the reduction in ESA and IV iron requirements would result in a net savings by implementing these therapies.[21,22] Ferric citrate reduced serum phosphate levels among patients with CKD without KRT who had increased baseline serum phosphate concentrations (≥4.5 mg/dL)

but did not reduce serum phosphate levels among patients with baseline serum phosphate concentrations within the population reference range. Ferric citrate reduced FGF-23 concentrations to a statistically significant degree (P < 0.001) versus placebo.[23] A meta-analysis of 16 studies of ferric citrate use in patients with CKD demonstrated significant increases in Hb level, TSAT, and ferritin level versus the comparator.[24]

Ferric Maltol

Ferric maltol consists of one Fe^{3+} ion complexed to 3 maltol moieties. This structure protects the Fe^{3+} ion while passing through the stomach and provides high bioavailability when the complex is dissociated at the enterocyte, where Fe^{3+} is reduced to Fe^{2+} and then absorbed via DMT1. As such, a lower dose of iron has been shown to be efficacious with this agent: 30 mg twice daily.[25] In a placebo-controlled study of 168 patients with CKD without KRT studied for 16 weeks, ferric maltol increased Hb level by 0.5 ± 0.122 g/dL, compared with a change of -0.02 ± 0.165 g/dL in the placebo arm (P = 0.0149).[26] In addition to data presented for use in patients with iron-deficiency anemia–secondary inflammatory bowel disease, these results led to US FDA approval in 2019.[27]

Sucrosomial Iron

The sucrosome is a novel drug-delivery method that has been applied to oral iron repletion. Sucrose esterified with fatty acids and combined with lecithin forms a phospholipid bilayer encasing ferric pyrophosphate.[28] The bilayer is further coated with tricalcium phosphate and starch, permitting it to pass through the stomach acid. Downstream, it is endocytosed through Peyer's patch microfold cells.[25] The efficacy of sucrosomial iron 30 mg/d was evaluated in a 3-month open-label randomized controlled trial in 99 patients with CKD without KRT in comparison with IV sodium ferric gluconate 125 mg per week until a total dose of 1,000 mg was administered. At 3 months, the proportions of patients who exhibited increases in Hb level of 0.6 g/dL were 56.2% with sodium ferric gluconate and 43.5% with sucrosomial iron (P < 0.05). Fewer adverse events attributed to treatment were seen in the sucrosomial

iron group (3.1% vs 34.5%; P < 0.001).[25,29] Sucrosomial iron (as SiderAL) is available over the counter in the United States through its manufacturer's website and other online vendors.

Summary of Novel Oral Irons

Each of the novel oral iron agents has improved gastrointestinal tolerability relative to Fe^{2+} formulations. Sucrosomial iron is a reasonable first choice because of its lower overall cost and availability without a prescription. Ferric maltol is next in cost, and ferric citrate is the costliest but also offers phosphate binding capability (Table 1).

Newer IV Iron Agents

The number of IV iron agents has increased steadily in the past few years. Older agents such as iron dextran (1974), sodium ferric gluconate (1999), and iron sucrose (2000) have been joined by ferumoxytol in 2009 and, more recently, ferric carboxymaltose and ferric derisomaltose (also known as iron isomaltoside). Concerns about oxidative stress induced by rapid iron release,[30,31] manifested by adverse reactions including cardiovascular events, motivated the development of newer compounds.[32-35]

Modern formulations contain iron enveloped by a carbohydrate moiety that minimizes iron release within the circulation.[8,30,36] The newer agents have reduced rates of anaphylaxis compared with iron dextran, but ongoing concerns remain surrounding hypersensitivity reactions, cardiovascular events, and hypophosphatemia (Table 2).[36,37]

Ferumoxytol

Because it was approved more than a decade ago, ferumoxytol is not considered a newer IV iron agent and will not be discussed in detail in this review. However, it is important to point out that ferumoxytol was the first IV iron agent to decrease the incidence of anaphylaxis compared with iron dextran and to decrease the intravascular release of free iron compared with sodium ferric gluconate and iron sucrose. Because the adverse reactions to free iron in the circulation are dose-related, the

Table 1. Oral Therapies for Iron Repletion in CKD

Characteristic	Ferrous Sulfate	Ferrous Fumarate	Ferrous Gluconate	Ferric Citrate	Ferric Maltol	Sucrosomial Iron
Side effect						
Dyspepsia	++	++	++	+	+	+
Constipation	+	+	+	+	+	+
Available over the counter	Yes	Yes	Yes	No	No	Yes
Phosphate binder	No	No	No	Yes	No	No
Approximate minimum annual cost, USD	$10.80[a]	$237.60[a]	$37.60[a]	$8,294.40[b]	$7,200.00[b]	$720.00[b]

Based on information from Lexicomp.[63] Abbreviation: CKD, chronic kidney disease.
[a]Based on daily iron repletion dose.
[b]Based on recommended dose.

Table 2. Newer (Third-Generation) Intravenous Iron Formulations

Agent	Molecular Weight, Da	Maximum Weekly Dose	Minimum Infusion Time, min	[Fe], mg/mL	Black Box Warning	Severe Hypersensitivity	Hypophosphatemia
Ferumoxytol	731,000	510 mg	15	30	Yes	0.2%	0.4%
Ferric carboxymaltose	150,000	750 or 1,000 mg	15	50	No	1.6%	∼40%
Ferric derisomaltose	150,000	1,000 mg or 20 mg/kg if <50 kg	15	100	No	0.3%	3.5%

No test dose is required for any of the 3 agents. Table based on information from Glaspy et al,[56] Balakrishnan et al,[64] and Lexicomp.[63]

maximum FDA-approved single dose of sodium ferric gluconate is 125 mg,[38] although it is commonly administered on an off-label basis in doses of 250 mg.[39] The maximum FDA-approved single doses of iron sucrose are 100 mg in patients undergoing maintenance dialysis, 200 mg in patients with CKD not treated with KRT, and 300-400 mg in peritoneal dialysis recipients.[40] For patients with CKD without KRT or undergoing home dialysis, such a limitation requires several visits to an infusion center to administer a 1,000-mg repletion dose of IV iron. This also means more venipunctures for those infusions, which puts future vascular access at risk. Ferumoxytol is approved for 510-mg administration by infusion or slow IV push over a period of 15 minutes. It has been reported that 1,020 mg ferumoxytol can be safely administered over a period of 15 minutes, allowing for iron repletion in a single visit.[41,42]

Ferric Carboxymaltose

Initially approved by the FDA in 2013, ferric carboxymaltose is composed of ferric oxyhydroxide surrounded and tightly bound by carboxymaltose[30,36,43] Ferric carboxymaltose is dosed at 15 mg/kg on day 0 and day 7 for individuals ≤50 kg in weight. The original FDA approval was 2 doses of 750 mg for individuals >50 kg in weight, but, in 2021, the FDA approved a single 1,000-mg dose in such individuals as an alternative.[44] Ferric carboxymaltose was compared in 2 cohorts of patients with iron-deficiency anemia versus other standard iron therapies based on Hb level increase between day 0 and day 35.[43,45] In cohort 1, ferric carboxymaltose 1,500 mg increased Hb level by a mean of 1.57 g/dL, compared with 0.80 g/dL with oral ferrous sulfate (P < 0.001). In cohort 2, ferric carboxymaltose 1,500 mg increased Hb level by a mean of 2.90 g/dL, compared with 2.16 g/dL with IV iron sucrose 1,000 mg (P < 0.001). Serious adverse events were not significantly different with ferric carboxymaltose versus the comparators.

In the REPAIR-IDA trial, among 2,584 patients with iron-deficiency anemia and CKD without KRT, mean Hb increases at 56 days were 1.13 g/dL in the ferric carboxymaltose (750 mg × 2 doses) group and 0.92 g/dL in the iron sucrose (200 mg × 5 doses) group, meeting criteria for noninferiority (95% CI, 0.13-0.28).[46] Serious adverse events were similar between groups; ferric carboxymaltose

recipients had more hypertensive episodes, whereas iron sucrose recipients had more hypotension. Hypophosphatemia was identified at greater frequency in the ferric carboxymaltose arm.[46]

The FIND-CKD trial studied ferric carboxymaltose for 56 weeks in patients with CKD without KRT, with a primary endpoint of initiation of other anemia intervention (ESA, other iron therapy, or transfusion) or 2 consecutive Hb measurements <10 g/dL.[47] Ferric carboxymaltose treatment was targeted to high ferritin (400-600 ng/mL) or low ferritin (100-200 ng/mL) compared with ferrous sulfate in a 1:1:2 ratio. The percentages of participants who reached the primary outcome were 23.5% in the ferric carboxymaltose high-ferritin arm, 32.2% in the ferric carboxymaltose low-ferritin arm, and 31.8% in the ferrous sulfate arm. The hazard ratio for the primary endpoint was 0.65 (95% CI, 0.44-0.95; P = 0.026) for high-ferritin ferric carboxymaltose versus oral iron. No difference in cardiovascular or infectious adverse events was noted.[47]

Ferric Derisomaltose

Iron isomaltoside was initially approved in Australia in 2017 and later by the US FDA in 2020 after being renamed ferric derisomaltose.[48] Compositionally, ferric derisomaltose is ferric oxyhydroxide encased in derisomaltose. The FERWON group studied ferric derisomaltose administered as a single 1,000-mg dose versus iron sucrose given in as many as 5 doses of 200 mg over a period of 2 weeks.[49,50] FERWON-IDA included 1,512 patients with diverse etiologies of iron-deficiency anemia, whereas FERWON-NEPHRO examined 1,538 patients with CKD without KRT. Both FERWON trials were randomized at a 2:1 ratio of ferric derisomaltose to iron sucrose, with coprimary endpoints of efficacy at increasing Hb level at 8 weeks and serious or severe hypersensitivity reactions. Efficacy was nearly identical between the 2 agents, increasing Hb level by 2.5 g/dL in both arms of FERWON-IDA and by 1.22 g/dL in both arms of FERWON-NEPHRO. Hypersensitivity events were also insignificantly different, with a pooled relative risk difference 0.1% higher with ferric derisomaltose versus iron sucrose. An analysis of 5 of these studies (N = 5,247) noted that the rate of moderate to severe hypersensitivity reactions was low across all current IV iron formulations excluding iron dextran, at

0.2%-1.7%. The differences between agents were small, and confidence intervals overlapped.[51-53] Another meta-analysis (N = 8,599) examining the risk of serious hypersensitivity reactions among IV iron recipients showed a low rate overall, but lower rates with ferric derisomaltose than with ferric carboxymaltose or iron sucrose.[54]

The ferric derisomaltose arms in the combined FER-WON studies had 63 events in 50 (2.5%) patients versus 48 events in 41 (4.1%) patients in the iron sucrose arms (P = 0.018). Driven by hypertension, congestive heart failure, and atrial fibrillation, the time to first adverse cardiovascular event was also longer with ferric derisomaltose versus iron sucrose (P = 0.014). Although unexpected given the short study duration (8 weeks), this differential could be due to slower mobilization of iron and consequent lesser oxidative stress in the ferric derisomaltose recipients.[36]

The PHOSPHARE-IDA paired randomized controlled trials studied ferric carboxymaltose and ferric derisomaltose with respect to hypophosphatemia occurring between baseline and day 35 in patients with iron-deficiency anemia and normal kidney function.[53] Serum phosphate level <2.0 mg/dL occurred with both agents, but significantly more often with ferric carboxymaltose than ferric derisomaltose (trial A, 75.0% vs 7.9% [P < 0.001]; trial B, 73.7% vs 8.1% [P < 0.001]). A separate systematic review and meta-analysis showed analogous results for hypophosphatemia (47% in ferric carboxymaltose vs 4% in ferric derisomaltose; P < 0.001). Normal kidney function,

low baseline serum ferritin level, and low TSAT were identified as predictors for hypophosphatemia.[55,56]

6H Syndrome

The 6H syndrome (high FGF-23, hypophosphatemia, hyperphosphaturia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism) seen with various IV iron formulations but most prominent with ferric carboxymaltose is thought to occur as a result of impaired cleavage (inactivation) of the phosphatonin FGF-23.[57,58] Longer-term complications of hypophosphatemic osteomalacia and fractures have also been described (Fig 2).[59] Clinicians will need to weigh the relative risks, costs, and availability of the various IV iron formulations when selecting therapy (Table 3).

Ferric Pyrophosphate Citrate

Ferric pyrophosphate citrate offers the option to administer iron directly via dialysate bicarbonate containers or a bicarbonate central delivery system and was FDA-approved for use in patients receiving HD in 2015.[60] The iron dose administered with each dialysis is 5-7 mg, which approximates the iron loss with each HD treatment. The CRUISE paired trials compared ferric pyrophosphate citrate versus placebo over 48 weeks and found that Hb levels were maintained with ferric pyrophosphate citrate, whereas they decreased by 0.4 g/dL with placebo (P < 0.001).[61] Ferritin and TSAT were more stable in the ferric pyrophosphate citrate arm, along with decreased ESA and IV iron requirements. Because some dialysis providers are
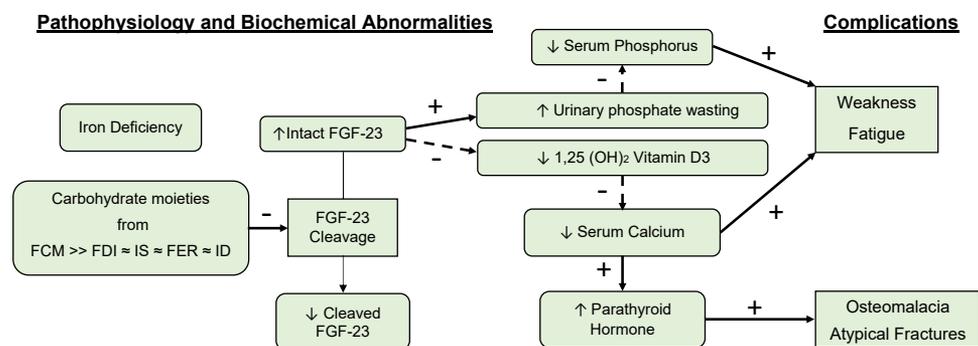

Figure 2. 6H syndrome (high fibroblast growth factor 23 [FGF-23], hypophosphatemia, hyperphosphaturia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism). In the setting of iron deficiency, FGF-23 transcription is increased. Normally, this has no substantial adverse consequences because FGF-23 is cleaved proportionally to synthesis to the inactive form. However, higher levels of intact FGF-23 develop in the presence of certain IV iron formulations. It is speculated that the carbohydrate moieties of the iron formulations inhibit the cleavage of FGF-23. The extent of this apparent inhibition, and consequent hypophosphatemia, appears to be greatest with ferric carboxymaltose (FCM), substantially less with ferric derisomaltose (FDI), lesser still with iron sucrose (IS), and extremely uncommon with ferumoxytol (FER) and iron dextran (ID). Estimates of relative incidence of hypophosphatemia are limited by lack of head-to-head comparisons across agents and heterogeneity among studies in thresholds of hypophosphatemia when reported. Increased FGF-23 leads to enhanced urinary phosphate wasting, lowering serum phosphorus and leading to weakness and fatigue. Increased FGF-23 also reduces 1,25-dihydroxyvitamin D levels, resulting in decreased serum calcium. Low calcium may contribute to weakness and fatigue and, more importantly, causes increased parathyroid hormone. Increased rates of osteomalacia and atypical fractures have been reported principally with ferric carboxymaltose to date. (Based on information from Kassianides et al,[57] Blumenstein et al,[36] and Glaspy et al.[56])

Table 3. Pros and Cons of Parenteral Iron Formulations

Agent	Pros	Cons
Iron dextran	Lowest cost, can give 1,000 mg in 1 dose (off label), low risk of 6H syndrome	High rate of hypersensitivity, requires test dose, requires 1.5 h of infusion and observation
Ferric gluconate	Low risk of severe hypersensitivity, low cost, low risk of 6H syndrome	Takes 4-8 doses to administer 1,000 mg, administered over 1 h, risk of hypotension
Iron sucrose	Low risk of severe hypersensitivity, low cost, low risk of 6H syndrome	Takes 3-5 doses to administer 1,000 mg
Ferumoxytol	Low incidence of 6H syndrome, takes 2 doses to administer 1,000 mg	Has black box warning for hypersensitivity, higher cost
Ferric carboxymaltose	Highest total US approved dose (1,500 mg in 2 doses), 1,000 mg in 1 dose also US approved, low risk of severe hypersensitivity	Highest incidence of 6H syndrome/ hypophosphatemia, higher cost
Ferric derisomaltose	1,000 mg in 1 dose is US approved, low risk of severe hypersensitivity	Hypophosphatemia (4%), higher cost, limited availability (?)
Ferric pyrophosphate citrate	Low risk of severe hypersensitivity, given through dialysate, low risk of 6H syndrome	In-center hemodialysis patients only; for iron maintenance, not repletion; risk of hypotension

Abbreviation: 6H syndrome, high fibroblast growth factor 23, hypophosphatemia, hyperphosphaturia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism.

concerned regarding the infection risk associated with iron in the bicarbonate central delivery system and because some dialysis machines use solid bicarbonate concentrate, an IV form of ferric pyrophosphate citrate was developed and approved by the FDA in 2020. The IV form is infused over the course of the HD treatment (pre- or post-membrane) and provides 6.75 mg iron in a prefilled syringe. Ferric pyrophosphate citrate can be infused using the machine's heparin pump and, if the patient is receiving heparin, can be safely mixed with the heparin.[62]

Conclusions

Functional and absolute iron deficiency often contribute to anemia in patients with CKD, and iron repletion is required for effective Hb synthesis. Newer oral agents may provide increased iron bioavailability and fewer side effects than traditional iron salts, perhaps decreasing the need for IV iron therapy in some patients with CKD without KRT receiving home dialysis. For patients with milder degrees of iron deficiency (eg, TSAT >15% and ferritin >50 ng/mL), we propose starting with an inexpensive oral ferrous salt unless the patient reports previous intolerance to such agents. If the patient does not show a response in 2-3 months or is intolerant of Fe^{2+}, it is reasonable to switch to a newer ferric oral iron supplement or IV iron preparation. If the patient has more severe iron deficiency (TSAT <15% or ferritin <50 ng/mL), we recommend proceeding directly to an IV iron agent. Newer IV iron formulations are associated with fewer anaphylactic reactions than iron dextran and decreased free iron that may contribute to acute reactions and long-term vascular injury. Because these IV iron preparations can be given in larger single doses than ferric gluconate or iron sucrose, they are better suited for patients with CKD without KRT and those receiving home dialysis to decrease visits to infusion centers and venipuncture. Nonetheless, caution with respect to nuanced risks of IV iron

formulations remains prudent because of acute reactions and hypophosphatemia. Newer IV iron agents are expensive and may not be approved by some prescription drug plans. In such cases, we prefer to prescribe 1,000 mg of iron dextran in a single infusion than to subject the patient to multiple smaller infusions of sodium ferric gluconate or iron sucrose. It remains to be determined how a shift away from in-center HD for treatment of kidney failure, as well as more effective therapies to slow the rate of CKD progression, as proposed by the Advancing American Kidney Health Initiative, will accelerate the development and uptake of iron therapies designed to decrease patient travel to infusion centers while maintaining or improving tolerance and safety.

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